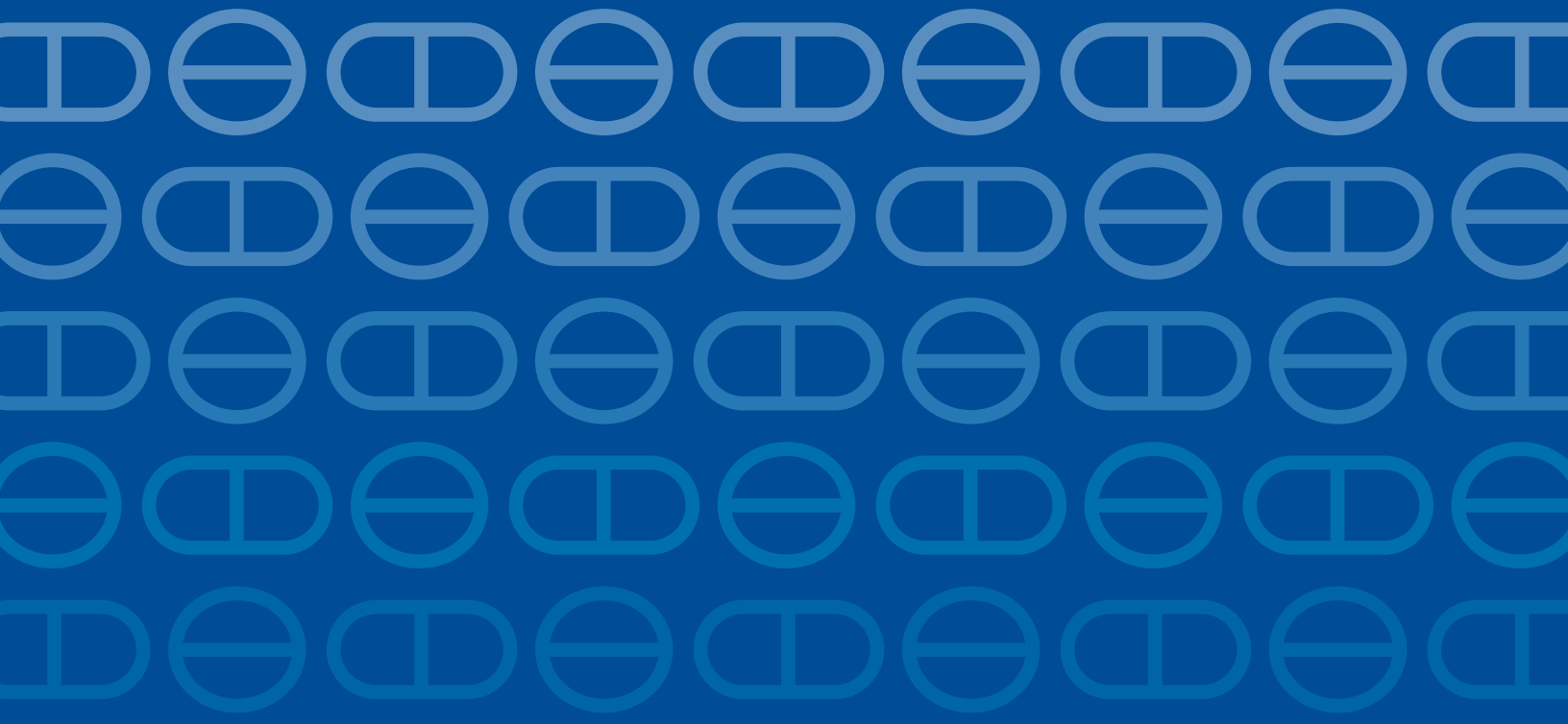
PACE Pharmaceutical Assistance Contract for the Elderly

Alosa Health
Balanced information for better care

Preventing cardiovascular disease

Evidence-based recommendations on risk, lipid-lowering drugs, aspirin, and lifestyle



Preventing cardiovascular disease:

Evidence-based recommendations on risk, lipid-lowering drugs, aspirin, and lifestyle

Principal Consultants: Alex Chaitoff, M.D., Jacob Mirsky, M.D., Prihatha Narasimmaraj, M.D., Ross Pollack, M.D.

Series Editors: Benjamin N. Rome, M.D., M.P.H. (principal editor), Dae Kim, M.D., M.P.H., Sc.D., Jerry Avorn, M.D., Ellen Dancel, PharmD, M.P.H.

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

Alosa Health

Preventing cardiovascular disease

Evidence-based recommendations on risk, lipid-lowering drugs, aspirin, and lifestyle

Activity Overview:

The goal of the educational program is to provide primary care clinicians with a review of evidence-based practices for the prevention of cardiovascular disease, such as the role of lipid-lowering therapy, lifestyle interventions, and the limited role for aspirin.

The educational program has several components, which include:

- Written evidence report (print monograph)
- Summary document of top 4-5 key messages
- "Academic detailing" educational sessions in physicians' offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
- Reference cards for easy access to key materials
- Patient education information (brochure/tear off sheets)

This program works to synthesize the current clinical information on this topic into accessible, non-commercial, evidence-based educational material, which is taught interactively to providers by specially-trained clinical educators.

Target Audience:

The educational program is designed for clinicians practicing internal medicine, primary care, family medicine, and geriatrics, and nurses and other health care professionals who deliver primary care.

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Calculate the 10-year risk of cardiovascular disease using a validated tool
- Identify recommended lipid-lowering therapies based on risk assessment
- Describe the role of a coronary artery calcium score to help clarify need for a statin
- Understand the role of lipid-lowering therapies in adults over age 75 years
- Formulate a plan for lifestyle changes with patients and link with programs when available
- Recognize that for most patients, particularly older adults, the risks of aspirin for primary prevention outweigh the benefits.

Disclosure Policy:

All individuals in a position to control the content of this activity have been asked to disclose any relationship they have with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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Faculty and Planners:

Alexander Chaitoff M.D., M.P.H., is a Clinical Fellow in Medicine at Harvard Medical School and an internal medicine resident at Brigham and Women's Hospital. Dr. Chaitoff has no relevant financial relationships to disclose.

Jacob Mirsky, M.D., is an Instructor of Medicine at Harvard Medical School and a primary care clinician at Massachusetts General Hospital. Dr. Mirsky has no relevant financial relationships to disclose

Prihatha Narasimmaraj, M.D., is a Clinical Fellow in Medicine at Harvard Medical School and an internal medicine resident at Brigham and Women's Hospital. Dr. Narasimmaraj has no relevant financial relationships to disclose

Ross Pollack, M.D., is a Clinical Fellow in Medicine at Harvard Medical School and an internal medicine resident at Brigham and Women's Hospital. Dr. Pollack has no relevant financial relationships to disclose

Benjamin N. Rome, M.D., M.P.H., is an Instructor in Medicine at Harvard Medical School, a health policy researcher in the Division of Pharmacoepidemiology and Pharmacoepidemiology and a primary care clinician at Brigham and Women's Hospital. Dr. Rome has no relevant financial relationships to disclose.

Jerry Avorn, M.D. is a Professor of Medicine at Harvard Medical School and Chief emeritus of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. An internist, he has worked as a primary care physician and geriatrician and has been studying drug use and its outcomes for over 35 years. Dr. Avorn has no relevant financial relationships to disclose.

Dae Kim, M.D., Sc.D., is an Associate Professor of Medicine, Harvard Medical School and a geriatrician at Hebrew SeniorLife and Beth Israel Deaconess Medical Center and researcher on frailty. Dr. Kim has no relevant financial relationships to disclose.

Dawn Whitney, M.S.N./Ed., R.N. is a Clinical Educator at Alosa Health. She is a lecturer in the School of Nursing and Health Sciences at the University of Massachusetts - Boston and Bouvé College of Health Sciences at Northeastern University. She has no relevant financial relationships to disclose.

Ellen Dancel, Pharm.D., M.P.H., is the Director of Clinical Materials Development at Alosa Health. Dr. Dancel has no relevant financial relationships to disclose.

Reviewers:

Thomas A. Gaziano, M.D., M.Sc., is an Associate Professor of Medicine at Harvard Medical School and a cardiologist at Brigham and Women's Hospital. Dr. Gaziano receives research funding from Novartis.

All other individuals including course directors, planners, reviewers, faculty, staff, etc., who are in a position to control the content of this educational activity have reported no relevant financial relationships with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death and morbidity globally.[1] The vast majority (92%) of patients who develop CVD have one or more modifiable risk factors.[2] As a result, strategies to prevent cardiovascular disease by mitigating these risk factors represent a major opportunity to reduce morbidity and mortality.

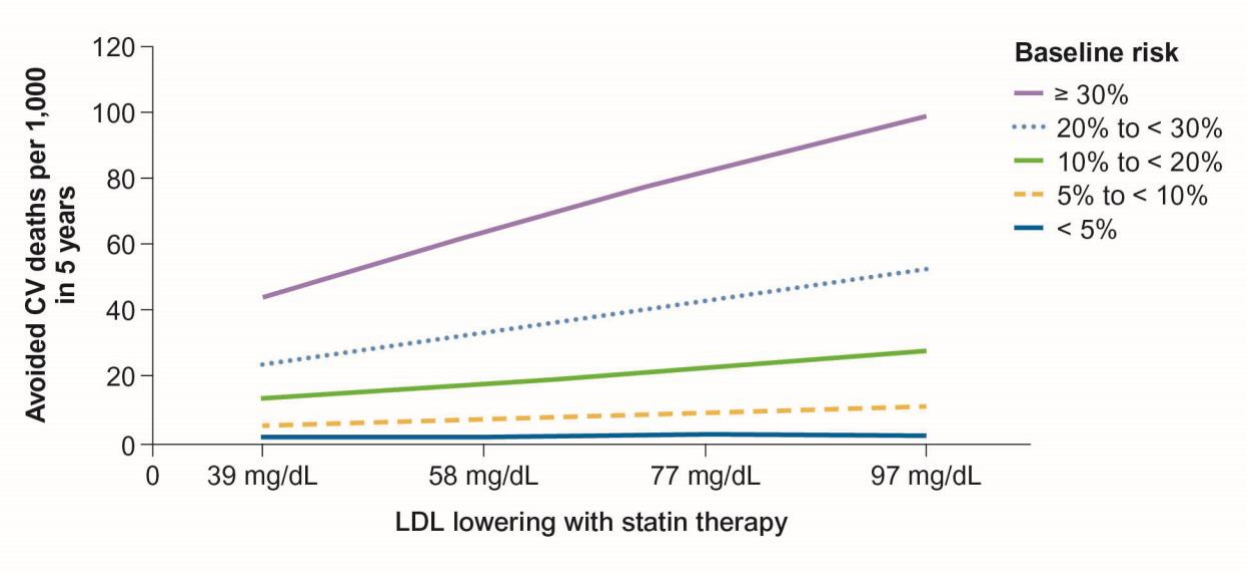
These strategies include non-pharmacologic lifestyle modifications, including smoking cessation, diet, and exercise. Additionally, behavioral and pharmacologic therapies to improve control of hypertension and diabetes are important for preventing cardiovascular outcomes associated with these diseases. In addition, some pharmacologic therapies have been used solely for the purpose of preventing cardiovascular disease. Traditionally, aspirin was commonly used for its anti-platelet effect, but in recent years evidence has made clear that the bleeding risk of taking a daily aspirin may outweigh the small benefit in cardiovascular risk reduction in primary prevention. Meanwhile, lipid-lowering statins have shown benefits in cardiovascular risk reduction and are now a mainstay strategy for preventing CVD.

This document will review the evidence for pharmacologic and non-pharmacologic strategies to prevent cardiovascular disease. First, we will review the strategies for estimating individual risk of developing CVD, which is essential for assisting patients in choosing among the various available strategies. Second, we will review the evidence for lipid-lowering medications, the evidence suggesting limited benefits for aspirin, and the evidence for diet and exercise. This evidence document will not address smoking cessation or treatment for hypertension and diabetes, as these are addressed in other Alosa modules. See **AlosaHealth.org** for more information.

Estimating Risk of CVD

Understanding a patient's individual risk of CVD is essential for selecting preventive interventions with a favorable risk/benefit profile. For example, treatment with a statin is far more effective for preventing cardiovascular deaths if targeted toward patients with high underlying risk (Figure 1 on next page). As a result, calculating a patient's individual risk is a crucial first step in determining strategies for CVD prevention.

Figure 1: Efficacy of statin therapy on vascular deaths is closely associated with pre-intervention cardiovascular risk[3]



Based on a review of the evidence, the 2019 American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines on the primary prevention of cardiovascular disease **recommend cardiovascular risk assessment for all adults aged 40-75**.[3] For adults aged 20-39 years, CVD risk screening is also reasonable. Risk factors should be reassessed **at least every 4-6 years** and more frequently in higher risk individuals.

Evidence supporting the use of risk assessment tools

Risk assessment can be done informally by evaluating individual risk factors known to be associated with CVD. However, this approach is prone to error and bias and may not provide enough detail for the patient and clinician deciding on preventive therapies. Fortunately, there are several validated tools that combine multiple risk factors into a single numeric estimate of patient's individual CVD risk. These tools provide useful information to patients and clinicians when choosing strategies to reduce cardiovascular risk. The 2019 AHA/ACC guidelines for the primary prevention of CVD recommends the use of formal 10-year atherosclerotic cardiovascular disease (ASCVD) risk calculators, specifically the ACC/AHA Pooled Cohort Equation (PCE).

Using formal risk assessment tools like the PCE has been shown to lead to cardiovascular risk reduction. A 2017 Cochrane review on the use of risk scoring for primary prevention provides the most comprehensive assessment of the efficacy of formal CVD risk prediction formulas for preventing CVD.[4] This meta-analysis included trials that compared the use of formal risk assessment tools versus usual care (informal clinician assessment of cardiovascular risk) on several measures of CVD risk, therapies, and outcomes.

The evidence demonstrates that compared to usual care, using CV risk tools was associated with:

- More patients **initiating or intensifying lipid lowering (**relative risk [RR] 1.47; 95% CI: 1.15-1.87) or **anti-hypertension** therapies (RR 1.51; 95% CI: 1.08-2.11)

- A modest reduction in **cholesterol levels** (0.1 mmol; 95% CI: 0.2-0.0 mmol) and **systolic blood pressure readings** (2.77 mm Hg; 95% CI: 4.16-1.30 mmHg)
- A higher likelihood of **smoking cessation** (RR 1.38; 95% CI: 1.13-1.69).

There was no observable effect of risk assessment tools in terms of patient's adherence to medications or exercise. Importantly, there was **no reduction in the incidence of CVD** (10-year incidence 5.4% vs 5.3% without risk assessment (RR 1.01; 95% CI: 0.95-1.08)**,** although only three trials measured this outcome and the quality of the evidence was poor. Overall, these findings suggest that risk tools can lead to important improvements in patient's adherence to pharmacologic and behavioral CV risk reduction strategies.

Pooled cohort equation

The most-commonly used, best-validated, and widely recommended risk assessment tool in the U.S. is the pooled cohort equation (PCE).[5] The PCE was developed by a working group of the ACC/AHA in 2013 to identify patients at high risk of CVD who may benefit from the use of statins for primary prevention.[6] The PCE utilized several population-based cohorts of largely Non-Hispanic White and African American populations. It calculates risk stratified by sex and race (White vs. Black).

The PCE is available free online at **tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/.**

The variables included in the PCE include:

- age (40-75 years)
- sex
- race (i.e., White, Black, other)
- blood pressure
- cholesterol (total, HDL, LDL)
- diabetes status
- smoking
- treatment for hypertension

The PCE has been validated in several U.S.-based cohorts of patients and performs well in discriminating risk of CVD, especially for those with intermediate risk, where decisions about therapies (e.g., statins) are typically being made.[5] In modern cohorts of patients, the PCE may overestimate risk, particularly for those with the highest estimated risk. This may be explained by higher use of statins and other preventive therapies in modern cohorts, compared to those in which the PCE was developed.

As with any risk assessment tool, there may be discrepancies between the observed and predicted outcomes, particularly when used within homogenous populations with restricted risk distributions. Specifically, the PCE may overestimate the risk of CVD in East Asian[7-9] and Hispanic white populations.[10] The risk of CVD amongst South Asian populations may be underpredicted by the PCE.[11] The U.K. based QRISK2 risk assessment tool may be more accurate in this population although was developed from a population living in the U.K. rather than U.S.[12] PCE underestimates risk in individuals with HIV who are at borderline and intermediate risk.[13] A similar effect has been demonstrated in patients with sarcoidosis.[14] The PCE also underpredicted the risk of CVD among patients from disadvantaged communities.[15]

Recent results suggest that the PCE may more broadly overestimate the risk of ASCVD across a diverse modern cohort of patients without established CVD. This may be due to increased use of statins and

other primary prevention interventions in more modern cohorts, compared to those in which the PCE was created.[16]

Alternatives to the pooled cohort equation

The PCE is just one of multiple predictive tools for CVD risk assessment. The most commonly used of these alternatives are the Framingham General CVD risk profile[17] and the Reynolds Risk score.[18] The Framingham General CVD risk profile performed similarly to the PCE according to a recent meta-analysis although both tools overestimated the risk of CVD particularly in patients at higher socioeconomic status.[19,20] The Reynolds Risk score may be slightly more accurate for patients from higher socioeconomic status and with lower overall risk of CVD.[10]

While no tool for evaluating CVD is perfect, the PCE offers several advantages over other tools. First, it predicts only hard outcomes (i.e., cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke). Second, it has been validated in several randomized and non-randomized trials of a wide population of U.S. patients. Third, it is freely available to use and requires only information that is typically easily available from the patient or the patient's chart. Fourth, it has been widely recommended and adopted over the past several years, and it has even been incorporated into many electronic health records. As a result, we recommend the PCE over other risk assessment tools in nearly all cases.

Summary of risk assessment tools

Ultimately, risk assessment tools are meant to be a helpful component of assessing risk and deciding on preventive therapies, and clinicians should use these tools while recognizing their limitations.

For example, there are limited data to support the use of risk assessment tools in individuals younger than 40 and those older than 75. The PCE does not calculate risk for adults who are not 40-75 years old. Importantly, risk assessment tools should **NOT** be used for patients with established CVD or for decision making on secondary prevention.

Patient-centered care around cardiovascular risk assessment is essential in the primary care office. We recommend the use of the PCE for most patients presenting to the primary care providers office. Individual practices may incorporate alternative risk assessment algorithms and the provider should be aware that each risk assessment tool has limitation. Decisions on therapies for primary prevention of CVD should incorporate multiple factors, of which the risk assessment algorithms are an important element.

BOTTOM LINE: Assessing individual CVD risk is important for deciding on strategies to prevent CVD. Formal risk assessment tools, like the Pooled Cohort Equation (PCE), are preferred over informal risk assessment and should be used every 4-6 years for patients aged 40-75 years.

Incorporating additional risk factors for CVD

The PCE and other risk tools do not include all known risk factors for CVD. As a result, it may be important to consider additional risk factors when stratifying risk and selecting preventive strategies, particularly for patients who are deemed intermediate risk by the PCE (10-year ASCVD risk 7.5% to < 20%). For this purpose, the AHA/ACC guidelines recommend the use of additional "risk-enhancing" factors in decisions on the appropriate intensity of therapies.

- family history of premature CVD
- metabolic syndrome
- chronic kidney disease
- history of preeclampsia or premature menopause (age <40 years)
- chronic inflammatory disorders (e.g., rheumatoid arthritis, lupus, chronic infections like HIV)
- high risk race/ethnicity (South Asian ancestry)
- elevated triglycerides >174 mg/dL
- apolipoprotein B >129, hsCRP >2.0 mg/L
- ankle brachial index <0.9
- lipoprotein(a) >50 mg/dL
- Coronary artery calcium score (>0)

Each of these factors has been found to be independently associated with risk of CVD, after adjusting for traditional risk factors included in the PCE (Table 1).[21]

Table 1: Relative risk for ASCVD by risk-enhancer factor after adjustment for traditional risk factors

Condition	RR/OR/HR for ASCVD (95% CI)
Parental premature CVD (<55M, <65F)[22]	Male: 2.0 (1.2-3.1) Female: 2.0 (0.9-3.1)
Parental stroke[23]	Outcome (All stroke): OR 3.79 (1.90-7.58); no adjustment for LDL
Metabolic syndrome[24]	2.42 (1.20-4.88) men only, includes patients with DM
CKD (CVD mortality)[25]	eGFR 45-59: 1.38 eGFR 30-44: 2.42 eGFR 15-29: 3.29
Rheumatologic Disease[26] Not adjusted for lipids, included T2DM as outcome	RA: 2.01 (1.73-2.34) Ankylosing Spondylitis: 1.56 (1.13-2.14) Psoriasis: 1.28 (1.07-1.53) Vasculitis: 1.54 (1.12-2.12) SLE: 6.36 (4.37-9.25)
HCV/HIV co-infection vs. HIV alone[27]	2.91 (1.19-7.12)
Early menopause (<40)[28]	1.32 (1.16-1.51)
Pre-eclampsia[29]	2.28 (1.87-2.78)
Ankle arm index (<0.9)[30]	2.03 (1.22-3.37)
Hypertriglyceridemia*[31]	1.37 (1.31-1.42) adjusted for HDL-C, non-HDL-C: 0.99 (094-1.05)
hsCRP*[32]	1.37 (1.27-1.48)
Lipoprotein (a)*[33]	1.13 (1.09-1.18)
Apolipoprotein B*[34]	1.43 (1.35-1.51) vs 1.25 (1.18-1.33) for LDL-C
Coronary artery calcium (CAC) score (>99)[35]	5.0 (2.1-12.1), relative to CAC=0

*HR calculated with respect to 1 standard deviation increase in lab value

Coronary artery calcium score

For patients with intermediate risk of CVD according to the PCE, several risk factors can be used to further stratify risk. One of the tools that has strong evidence for further stratifying patient risk is the coronary artery calcium (CAC) score.

CAC scoring utilizes a non-contrast, low radiation exposure axial CT-scan to assess the total calcium burden of the coronary arteries (Table 2). This should not be confused with other forms of coronary artery imaging, such as CT angiography, which are used for diagnostic purposes in symptomatic patients and require higher doses of radiation and use of intravenous contrast.[36]

Table 2: Categorization of disease burden by coronary artery calcium score

CAC Score (Agatston Units)	Disease burden
0	No identifiable disease
1-99	Mild disease
100-399	Moderate disease
>399	Severe disease

The CAC score can improve the discriminatory accuracy of standard risk assessment tools.[37,38] Patients with a CAC score of 0 have a much lower risk of developing CVD than patients with a CAC score greater than zero (Table 3).[39] As a result, the CAC can be used to guide preventive strategies for select patients who have intermediate risk of CVD according to the PCE**.** For example, a CAC score of zero suggests that it may be reasonable to withhold statin therapy.

Table 3: Risk of coronary events associated with increasing CAC score after adjustment for standard risk factors[39]

	Major coronary event			Any coronary event		
CAC score	Risk per 1,000 persons	HR (95% CI)	P Value	Risk per 1,000 persons	HR (95% CI)	P Value
0	2	**1.00**		4	**1.00**	
1-100	14	**3.89 (1.72-8.79)**	<0.001	23	**3.61 (1.96-6.65)**	<0.001
101-300	32	**7.08 (3.05-16.47)**	<0.001	54	**7.73 (4.13-14.47)**	<0.001
>300	38	**6.84 (2.93-15.99)**	<0.001	80	**9.67 (5.20-17.98)**	<0.001

Limitations of the CAC score

There are several limitations to CAC scoring. For example, among patients younger than 40 years who develop obstructive coronary artery disease confirmed by angiogram, many have a CAC score of zero.[40] Among older patients, particularly men over age 65, the prevalence of CAC score zero declines rapidly, limiting the utility of the test for this population (Figure 2).[41] Furthermore, CAC scores are not validated to assess the ongoing efficacy of statin therapy as score may increase over time with stabilization (increased calcification) of coronary artery plaques.[42] Finally, cost and limited insurance coverage can limit patient access to this tool.[43]

Figure 2: Prevalence CAC scores by age and gender[41]

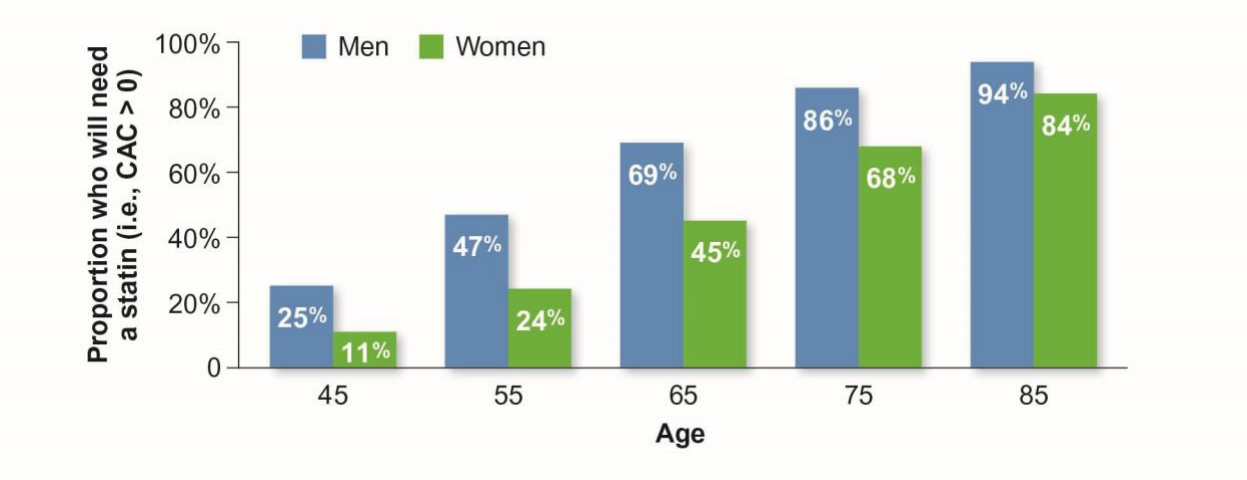


Figure 2 shows the distribution of CAC scores stratified by age and gender from a cohort of about 16,000 patients in Munich, Germany, without known CVD or symptoms of exertional dyspnea or chest pain.[41]

Potential uses of the CAC

The most validated use of CAC is among patients with intermediate risk according to the PCE (10-year ASCVD risk 7.5% to < 20%) to determine whether statin therapy is recommended. Several risk factors may be used to clarify the risk for these patients, but the CAC is among the strongest predictors of CVD and may be helpful particularly for patients who wish to avoid statin therapy and for whom much of their CVD risk is driven by age rather than modifiable risk factors.[21]

There are other proposed uses for the CAC. For example, among older patients who are more likely to experience adverse effects from both lipid lowering and blood pressure lowering therapies, the CAC can be used to determine the patients for whom aggressive lipid and blood pressure control is likely to be unnecessary.[38]

Here is a list of patients who might benefit from knowing if their CAC score is zero:[21]

- patients reluctant to initiate statin who wish to understand their risk and potential for benefit more precisely
- patients concerned about need to reinstitute statin therapy after discontinuation for statin-associated muscle symptoms
- older patients (men 55-80 years of age; women 60-80 years of age) with low burden of modifiable risk factors who question whether they would benefit from statin therapy
- middle-aged adults (40-55 years of age) with PCE-calculated 10-year risk of ASCVD 5% to <7.5% (borderline risk)

In each case, the clinician and patient should discuss whether a CAC score is necessary to make decisions about preventive therapy. If use of the PCE and consideration of other risk factors (e.g., family history, chronic inflammatory diseases) can provide sufficient information to make informed decisions about statin therapy and other preventive strategies, a CAC score may be unnecessary.

BOTTOM LINE: The coronary artery calcium (CAC) score is strongly predictive of CVD, but it may only be useful in a select group of patients for whom decisions are unable to be made based on the calculated 10-year ASCVD risk score and other risk factors.

Statins for primary prevention

While many classes of lipid-lowering medications have been studied for preventing CVD, statins have shown the greatest benefits. Statins inhibit HMG-CoA reductase, a key enzyme in cholesterol synthesis. Through this inhibition, statins lower serum levels of cholesterol, particularly low-density lipoprotein (LDL).

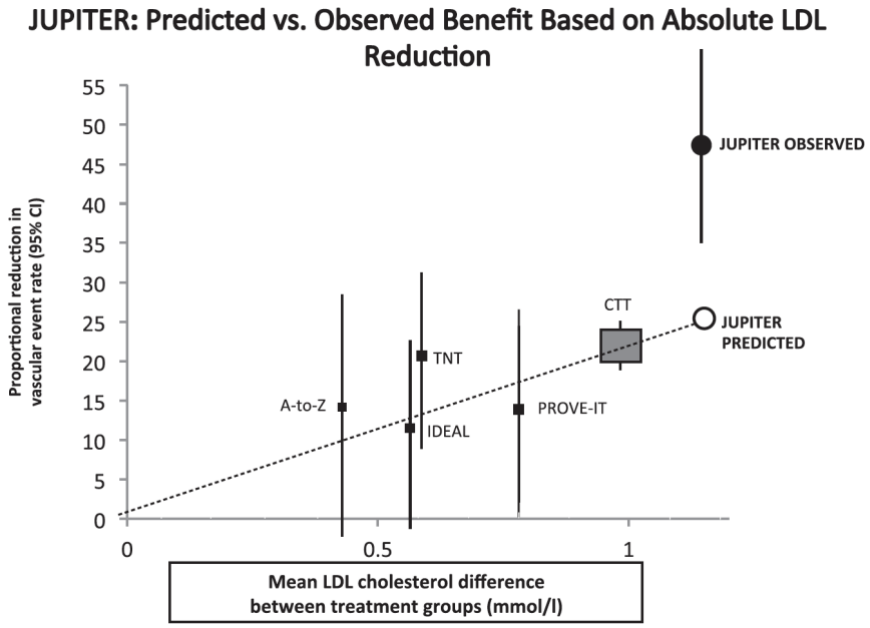
Even beyond their lipid-lowering effects, statins have been found to exert pleiotropic effects that are protective against CVD, including decreasing vascular inflammation and oxidative stress, improving endothelial function, stabilizing atherosclerotic plaques, and inhibiting thrombogenesis. These protective effects appear to be at least partially independent of statins' effects on lowering LDL cholesterol. As a result, statins have been shown to be beneficial in terms of reducing CV risk even among patients with average LDL cholesterol levels.[44]

Effectiveness of statins

One of the earliest trials to demonstrate the benefits of statins for primary prevention was the **AFCAPS/TexCAPS study** (1998), which enrolled patients without ASCVD and near-average LDL levels (mean LDL 150 mg/dL) and found that lovastatin therapy reduced incidence of first CV event by 37%, compared to placebo.[45] Importantly, risk reduction was observed regardless of baseline LDL, suggesting that there was no useful LDL threshold to guide which patients would most benefit from a statin.[45] These benefits have been replicated in several additional trials, including **WOSCOPS** (1995) and **HOPE-3** (2016).[46,47]

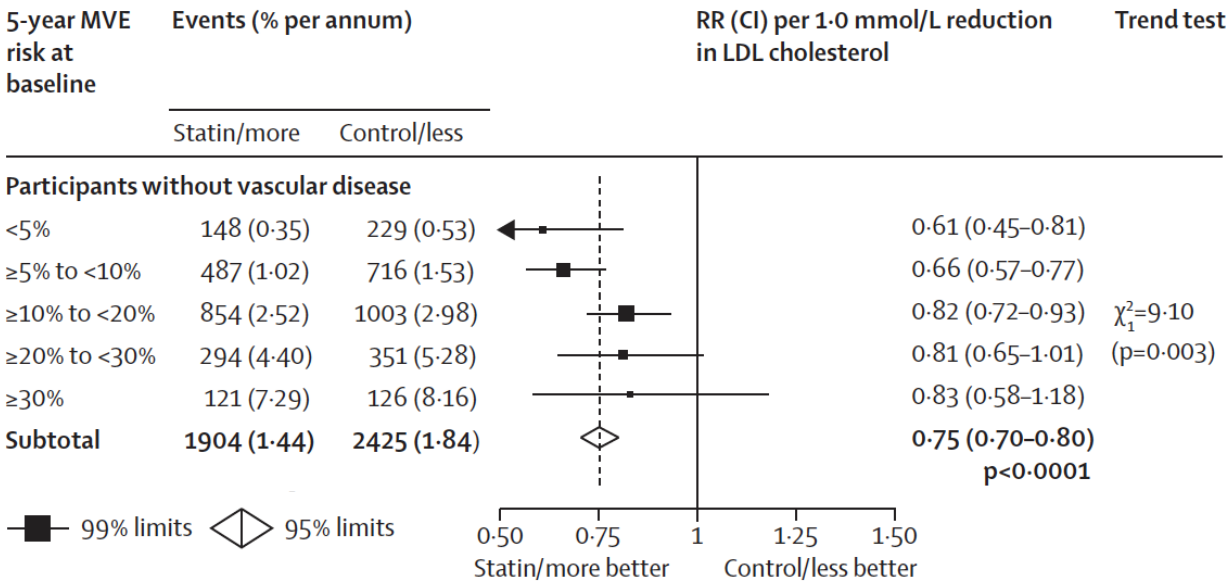
The landmark **JUPITER trial** (2008) enrolled patients without ASCVD with average LDL levels (<130 mg/dL) and elevated high-sensitivity C-reactive protein (hs-CRP), an inflammatory biomarker associated with elevated CV risk.[48] At median follow-up of 1.9 years, patients taking rosuvastatin 20 mg had fewer first-time CV events (HR 0.56; 95% CI: 0.46-0.69) than placebo.[48] Moreover, the magnitude of this effect was greater than predictions based on absolute LDL reductions derived from prior trial data (Figure 3).[44] These data suggest that the benefits of statins extend beyond their lipid-lowering effect.

Figure 3: Predicted vs. observed reduction in vascular event rate from JUPITER trial[44]



A 2012 meta-analysis by the Cholesterol Treatment Trialists' Collaborators of 22 statin trials (including six primary prevention trials) showed decreased major vascular events and improved all-cause mortality with statins compared to placebo regardless of baseline CVD risk.[3] While the absolute risk reduction with statin therapy is greater among individuals with high underlying risk, relative risk reduction was noted even patients at low baseline risk of CVD, suggesting that statins are effective for primary CVD in adults at any level of CVD risk.[3]

Figure 4: Decreased major vascular events in patients on statins across baseline risk[3]



BOTTOM LINE: Statins are effective at lowering the risk of cardiovascular disease for patients regardless of baseline risk, although the absolute reduction in risk is greatest for patients with higher baseline risk.

Risks of statins

In addition to being effective, statins have become a widely used tool for preventing CVD in part because they are safe and well-tolerated by a majority of patients. However, statins have been associated with skeletal muscle, metabolic, neurologic, and other possible side effects that should be incorporated into the risk-benefit discussions deciding on a statin for primary prevention.[49]

Statin-associated muscle symptoms

Statin-associated muscle symptoms are the most common statin side effect, estimated to occur in up to 10% of patients on statin therapy. Most commonly, these muscle symptoms present as myalgias, but rarely they can be associated with marked creatine kinase (CK) elevations and clinical rhabdomyolysis.[49] Preclinical studies suggest a possible mechanism for these symptoms, because statins decrease mitochondrial function, attenuate energy production, and alter muscle protein degradation.[50]

Rhabdomyolysis is a rare, but potentially fatal, complication of statin use. The prevalence of rhabdomyolysis with current statin usage is 0.01%.[51] In some cases, rhabdomyolysis is triggered by use of high doses of statins or by statin accumulation due to interactions with concomitant medications that compete with the cytochrome p450 system.

Table 4: Prevalence of statin-associated muscle symptoms[51]

Symptom	Prevalence
Myalgia	3-10%
Myopathy	0.1-0.2%
Rhabdomyolysis	0.01%

Statin-associated muscle symptoms are most common early in the course of treatment. Among patients who develop statin-associated muscle symptoms, 90% develop symptoms in the first 6 months of statin therapy or after a dose up-titration, and of these, 75% occur in the first 10-12 weeks.[51]

Physically active patients appear to experience muscle symptoms more often than inactive patients.[50] Higher doses of a statin increase the risk of muscle symptoms, although the absolute risk seen in clinical trials (as opposed to observational or registry data) is low.[52] Other risk factors for statin-associated muscle symptoms are shown in Table 5.

Table 5: Risk factors for statin-associated muscle symptoms[53]

Endogenous factors	Exogenous factors
Age >80 years Female Asian ethnicity Low BMI, frail History of existing muscle pain or elevated creatine kinase Family history of myopathy or myopathy with statin therapy Neuromuscular diseases Severe renal disease Acute/decompensated liver disease Hypothyroidism (untreated) Diabetes Genetic polymorphisms	Alcohol abuse Illicit drug use Drug interactions e.g., fibrates, amiodarone, verapamil, warfarin, macrolides, and more Surgery with severe metabolic demands Heavy and/or unaccustomed exercise

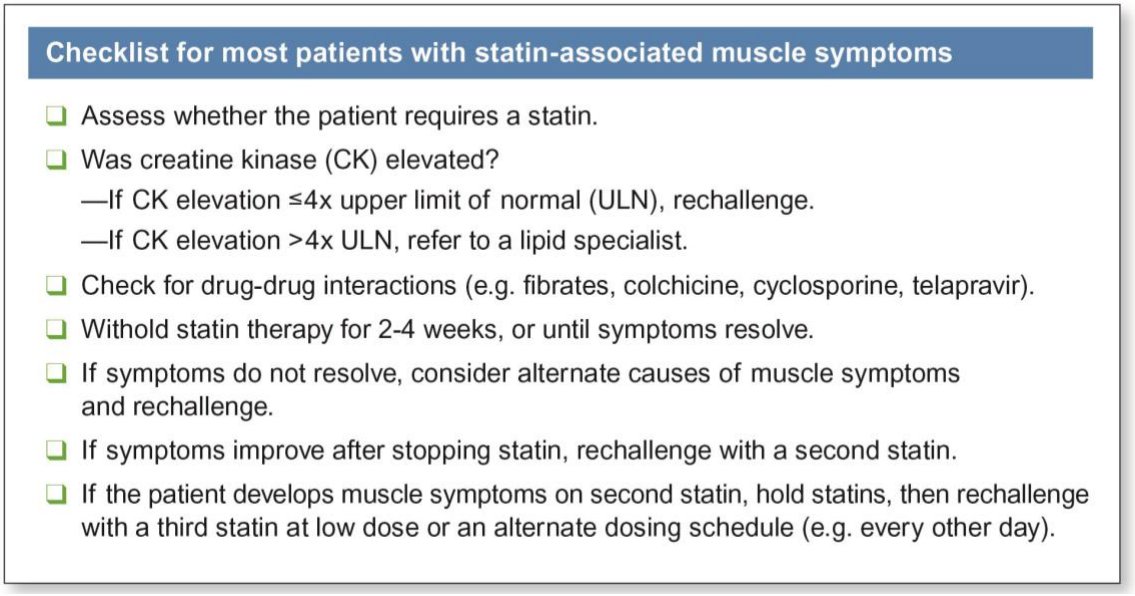
While statin-associated muscle symptoms are a known side effect, there is also a proven component of placebo effect that may contribute to these symptoms. For example, the **GAUSS-3 trial** (2016) enrolled 511 adult patients with history of statin intolerance and employed a 24-week crossover procedure with atorvastatin or placebo to identify patients who developed symptoms.[54] Fifty-one percent of patients who received atorvastatin before placebo experienced muscle symptoms with atorvastatin alone, compared to 34% of patients who received placebo before atorvastatin who experienced symptoms with atorvastatin alone.[54] In both crossover groups, atorvastatin was associated with an increased incidence of muscle symptoms (HR 1.34; 95% CI: 1.05-1.71 for patients who received atorvastatin first and HR 1.96; 95% CI: 1.44-2.66 for patients who received placebo first). Notably, 26.5% of patients experienced intolerable muscle symptoms with placebo but not with atorvastatin.[54] Similarly, the **SAMSON trial** (2021) employed an n-of-1 design to compare 60 patients' symptoms with atorvastatin, placebo, and no treatment and found that both statins and placebo were associated with significantly higher mean symptom intensity than no treatment, though no difference in symptom intensity between atorvastatin and placebo.[55]

Overall, these results suggest that at least some component of muscle symptoms related to statins is caused by a "nocebo effect" (defined as the expectation of negative effects with any treatment, even if placebo).

They also suggest that even among patients who experience statin-associated muscle symptoms, it is safe to re-try a statin because some patients will not have recurrent symptoms. Among patients with statin-associated muscle symptoms who discontinue therapy, over 90% are ultimately able to tolerate the same statin or a different statin with careful reintroduction and monitoring.[49]

Evaluation of patients' comorbidities can be helpful in identifying factors that may predispose patients to statin-associated myopathy, including hypovitaminosis D, hypothyroidism, or drug interactions.[49] Switching to an alternate statin (pravastatin is the only moderate-intensity statin associated with lower rates of muscle toxicity, as fluvastatin and pitavastatin are no longer routinely used), reducing the daily dose, or using intermittent dosing options (preferably with a statin with a longer half-life) can be used to maximize adherence.[49] According to a 2015 meta-analysis of 302 patients, coenzyme Q-10 is not effective at reducing statin-associated muscle symptoms.[49]

Figure 5: Checklist for managing statin intolerance



Diabetes

Statins have been associated with increased insulin resistance and with a small increase in onset of type 2 diabetes, which was first observed in two trials (JUPITER and AFCAPS/TexCAPS) in which 342 of 12,205 subjects (2.8%) on statins developed diabetes compared to 290 (2.4%) on placebo (RR 1.18; 95% CI: 1.01-1.39).[56] The significance of this finding was primarily driven by patients enrolled in JUPITER, which used higher doses of statins than AFCAPS/TexCAPS.[56] Based on this trial data, a 2021 cohort study of 83,022 Veterans Affairs (VA) patients matched statin users and non-users to measure progression of diabetes (i.e., initiating a new diabetes medication or increasing the dose of an existing one, or incident hyperglycemia or diabetic ketoacidosis).[57] A greater proportion of statin users experienced diabetes progression than non-users (56% vs. 48%; adjusted OR 1.37; 95% CI: 1.35-1.40; p<0.001).[57] However, this analysis is limited by the potential for residual confounding between statin users and non-users, especially because guideline-based therapy would recommend that nearly all patients with type 2 diabetes receive treatment with a statin.

Even with these possible risks, statin therapy still carries proven morbidity and mortality benefits among patients with diabetes or who are at risk of diabetes that outweigh any possible worsening in glycemic control. Specifically, statins significantly reduce cardiovascular events and death in these patients. Thus, withholding a statin due to a small risk of precipitating new diabetes or worsening existing diabetes is not recommended. However, it is reasonable to be watchful of diabetes progression in patients newly started on statin therapy; individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines.[58] Those who develop diabetes during statin therapy should typically remain on their statin for primary CVD prevention.[58]

Cognitive impairment

Concerns have been raised about the association between statin use and memory loss or cognitive impairment. However, the **PROSPER trial** (2002) and several subsequent meta-analyses of randomized controlled trials (RCTs) have not shown evidence of long-term adverse cognitive side effects with statin

therapy.[49,59,60] Despite these reassuring trial data, statin-associated "brain fog" symptoms have been reported clinically; the FDA has acknowledged that statins may be associated with cognitive impairment in rare cases, though causality has not been demonstrated.[61]

While concerns about cognition should not prevent use of statins for primary prevention, if symptoms develop that are intolerable to patients this may necessitate statin discontinuation. There is no evidence to suggest that switching from a lipophilic statin to a hydrophilic statin for these patients is likely to mitigate symptoms.[49]

BOTTOM LINE: Statins are generally well-tolerated, but muscle symptoms are reported by up to 10% of patients. The vast majority of cases are mild and occur early in the course of treatment, and most patients with these symptoms are able to tolerate the same statin at a lower dose or a different statin with careful reintroduction and monitoring.

Statins may be associated with a slight increase in risk of new or progressive type 2 diabetes, though this is more than offset by the cardiovascular benefits of statins. There is no strong evidence to suggest that statins increase the risk of cognitive impairment.

Using statins for primary prevention

Statins should be used for primary cardiovascular prevention in patients where the benefits outweigh risks. The 2013 ACC/AHA guidelines on cholesterol management in primary prevention shifted the paradigm of cholesterol management by focusing on reduction of CVD rather than lipid-lowering effect alone.[58] The 2019 ACC/AHA guidelines continue to uphold these recommendations, which rely on 10-year assessment of absolute ASCVD risk in patients between age 40-75 (determined by the PCE).[58] The guidelines also introduced the use of "risk-enhancing factors" to guide decision-making in borderline- or intermediate-risk adults.[58]

The 2019 ACC/AHA cholesterol guidelines recommend statin treatment in three clinical scenarios where the benefits of LDL-lowering therapy are believed to outweigh risks:[58]

Patients with LDL levels ≥190 mg/dL

Patients with primary severe elevations of LDL (≥190 mg/dL) have a high lifetime risk of ASCVD and have increased risk of genetic hyperlipidemia. Patients in whom a secondary cause of hyperlipidemia is suspected should be first assessed and treated for reversible causes (e.g., obesity, medications, hypothyroidism, nephrotic syndrome) before pursuing genetic testing. Treatment with a statin is recommended for this group of patients regardless of whether other cardiovascular risk factors are present.

Diabetic patients age 40-75 years

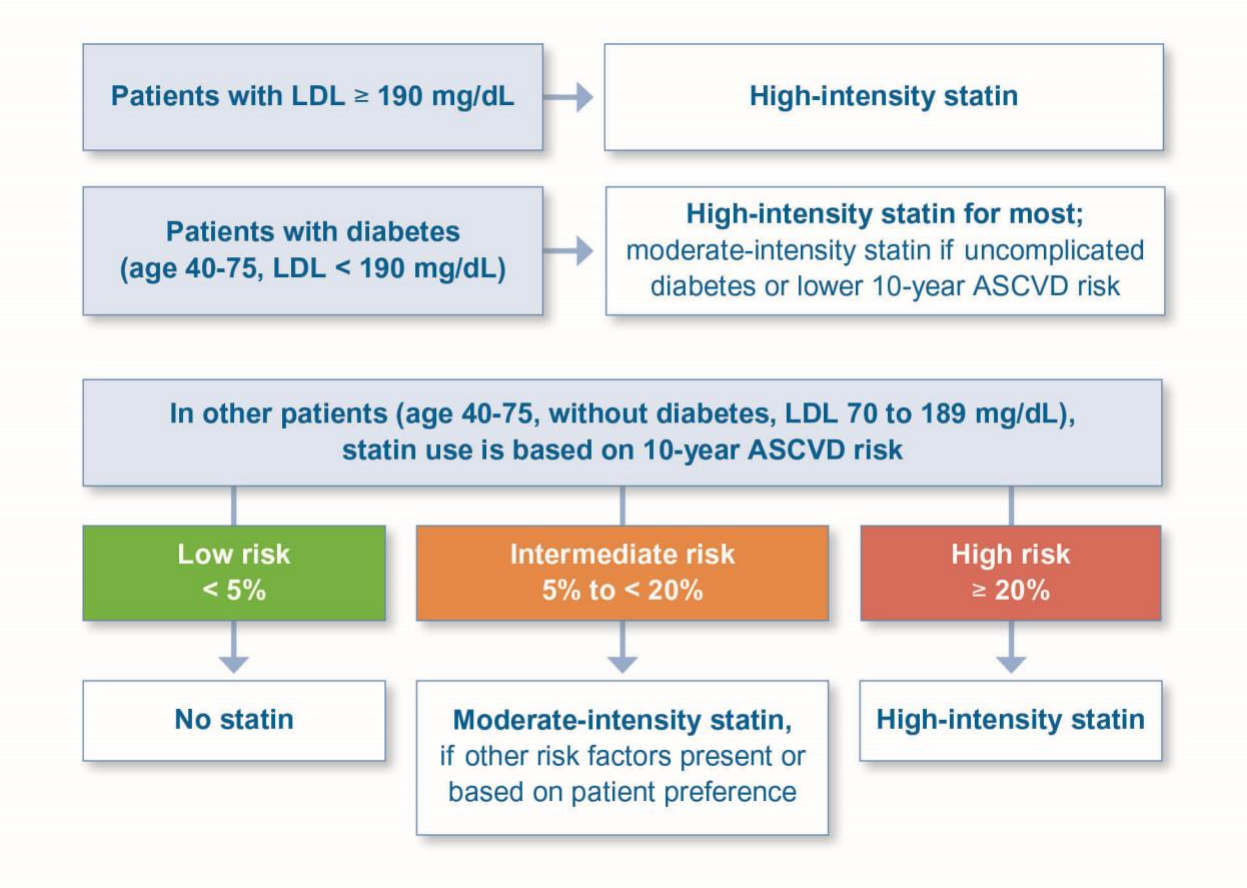
Diabetes is a strong predictor of CVD, and in most of these patients, statins are recommended regardless of whether other risk factors are present. The guidelines suggest statin use for patients aged 40-75 years old. Individuals younger than 40 years or older than 75 years may also benefit from statin therapy, although this population has not been traditionally included in randomized controlled trials. In these patients, the consideration of additional risk factors is warranted.

Patients age 40-75 years with 10-year ASCVD risk >5% and LDL < 190mg/dL

For all other patients aged 40-75 years, the decision to use a statin for primary CVD prevention depends on a more global assessment of risk factors. As discussed in the earlier section (see page XX), these risk factors are best assessed using a tool to combine multiple risk factors, such as the PCE. Patients with an estimated 10-year ASCVD risk above 5% should be considered for statin therapy. The 5% or greater risk threshold is lower than that used in prior guidelines but is thought to represent a more meaningful balance of the benefits vs. low risks of statin therapy.

For patients with a 10-year ASCVD risk between 5% and <20%, other risk factors not included in the PCE (summarized in Table 1, including the CAC score) can help guide statin decision-making (Figure 6). Individuals younger than 40 years or older than 75 years may also benefit from statin therapy if ASCVD risk is high, although this population has not been traditionally included in randomized controlled trials. In these patients, the consideration of additional risk factors and risks of therapy is warranted.

Figure 6: Recommendations for statins as primary CVD prevention[58]



Statin intensity

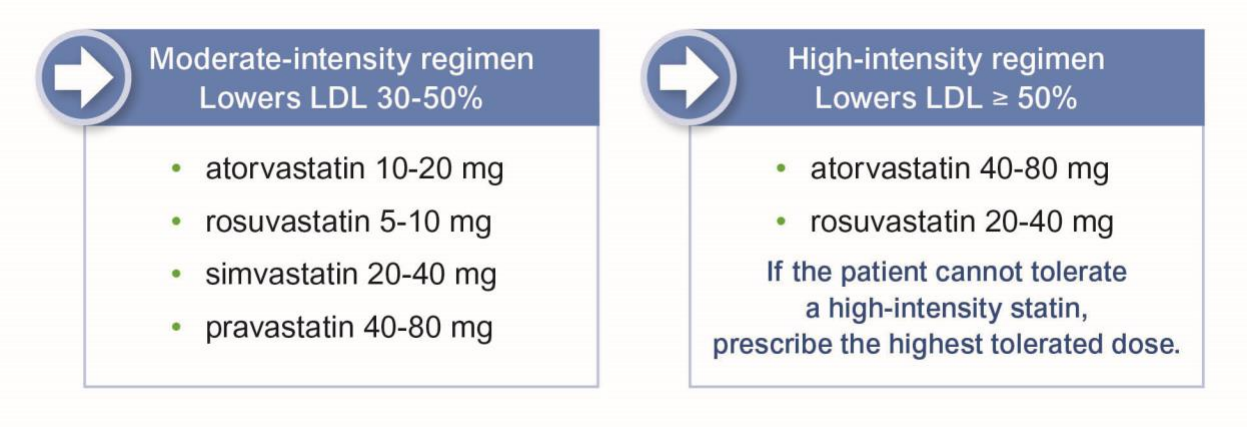
The 2019 ACC/AHA guidelines recommend initiation of a moderate- or high-intensity statin contingent on risk group (Figure 7). Patients with severe hyperlipidemia (LDL ≥ 190 mg/dL), most patients with diabetes, and patients with 10-year risk ASCVD ≥ 20% should receive a high-intensity statin, because these patients are considered highest risk.[58] High-intensity statin use is associated with fewer CV events than

moderate-intensity statins in secondary prevention, despite a small difference in achieved LDL level; this finding has been extrapolated to statins for primary prevention.[62]

Clinical trials of statins for patients with diabetes have studied moderate-intensity statins. However, high-intensity statins reduce cardiovascular risk more than moderate-intensity statins, and because diabetes is a strong risk factor for ASCVD, the ACC/AHA guidelines recommend a high-intensity statin for patients with long-standing diabetes (≥10 years) or those with any end-organ complications (e.g. nephropathy/proteinuria, retinopathy, neuropathy, or vascular disease). [58]

Patients recommended to initiate statin therapy based on the 2019 ACC/AHA guidelines who do not fall in the above two risk groups are recommended to initiate a moderate-intensity statin.[58] This includes patients with uncomplicated diabetes and non-diabetic patients with a 10-year ASCVD risk of 5-20%. Low-intensity statins are not routinely recommended, though for elderly or frail patients who cannot tolerate moderate-intensity statins, they may still confer some benefit compared to no statin therapy.[62]

Figure 7: Moderate- and high-intensity statin regimens



LDL goal on statin therapy

While the 2003 US guidelines (NCEP ATP III) originally established a goal LDL< 100 mg/dL for patients using statins for primary prevention, the ACC/AHA guidelines have removed this threshold and instead shifted the focus towards maximally tolerated dose of moderate- to high-intensity statin therapy without a specific LDL goal.[58] A goal LDL < 100 mg/dL is recommended only for patients with severe baseline hypercholesterolemia (i.e., LDL ≥ 190 mg/dL).[58]

Monitoring LDL levels after initiating statin therapy remains useful for identifying "suboptimal responders." Several studies have found that 40-50% of patients have a suboptimal LDL response to statin therapy, including a British prospective cohort study (n=165,411) showing that 50% of primary prevention patients had less than a 40% reduction in baseline LDL at 24 months, and subsequently experienced higher CV event risk.[63]

The most likely cause for suboptimal response is nonadherence or inadequate adherence.[63] A small percentage of patients may experience suboptimal responses based on genetic loci that modulate statin responsiveness, though this effect is modest in genome-wide association studies.[63] Based on these considerations, the ACC/AHA guidelines recommend monitoring lipid panels 4-12 weeks after starting

therapy to assess response and adherence, with further monitoring based on clinician discretion.[58] We believe it is reasonable to annually monitor lipids to assess adherence and re-assess CVD risk.

Of note, while observational studies of patients with very low LDL levels have shown increased rates of diabetes, hemorrhagic stroke, cataract development, these associations have not been corroborated by trial data and should be interpreted with caution.[64] Decreasing statin dose or stopping statin therapy based on a "too-low" LDL level is not recommended.

BOTTOM LINE: Statins are recommended as primary cardiovascular prevention for adults age 40-75 with diabetes, LDL ≥190, or a 10-year ASCVD risk ≥5%. There is no specific LDL goal for most patients; a high-intensity statin is recommended in most cases, except patients at lower risk, such as uncomplicated diabetes or ASCVD risk 5-20%. Monitoring LDL levels after initiation of statin therapy is primarily recommended to assess adherence.

Statins in older adults

Discontinuing statins in older adults

Current recommendations on discontinuation of statins in older adults are limited. The 2019 ACC/AHA guidelines suggest it is reasonable to stop statins in adults older 75 years "when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits".[58] No European guidelines provide recommendations on stopping statins in older adults.[65] Given the previous lack of guidance on how to weigh risks and benefits, individual decisions are largely left up to shared decision-making between clinicians and patients.

Recent observational data has shown that stopping statins for primary prevention can be associated with elevated CV risk and mortality. A 2021 retrospective cohort study of around 29,000 Italian patients (mean age 76.5 years, 20% of cohort had pre-existing ischemic heart disease) matched patients who discontinued statins but continued other medications (including antihypertensives, antidiabetic, or antiplatelet medications) and controls who did not discontinue any medications.[66] Patients in the statin discontinuation group experienced increased risk of hospital admissions for heart failure (RR 1.24; 95% CI: 1.07-1.43), any cardiovascular outcome (RR 1.14; 95% CI: 1.03-1.26), and all-cause mortality (RR 1.15; 95% CI: 1.02-1.30) over mean follow-up of 20 months.[66]

A 2019 retrospective cohort study of over 120,000 French patients over age 75 with no history of ASCVD found that stopping statins was associated with a higher risk of hospital admissions for CV events (HR 1.33; 95% CI: 1.21 – 1.75).[67] Risk factors for statin discontinuation in this study included hospital admission, admission to skilled nursing home, diagnosis of metastatic solid tumor, and initiation of enteral or oral feeding, which suggests that patients with increased frailty or shorter life expectancy were more likely to stop statin therapy.[67] Lastly, a 2021 observational cohort study of over 27,000 Danish primary prevention patients (median age 79 years) found that CV event rates were higher in patients who discontinued statins than those who continued (HR 1.32; 95% CI: 1.18 – 1.48) at median follow up of 5.5 years.[68]

Although the nature of observational studies is subject to bias and confounding, these data raise some concerns about stopping statins based on advanced age alone.

Initiating statins for primary prevention in older adults

Few statin trials include patients over age 75, though this group may still benefit from statin initiation for primary prevention. There is evidence that the benefits of statin therapy begin 2-5 years after initiation, and a 2021 meta-analysis of statin RCTs showing that 2.5 years of statin therapy was needed to avoid 1 major adverse cardiovascular event for 100 patients on a statin.[69] The 2019 ACC/AHA guidelines recommend statins for primary prevention in high-risk individuals over age 75 years in the absence of life-limiting illness.[58]

A 2019 meta-analysis of 22 statin RCTs (n=134,537) by the Cholesterol Treatment Trialists' Collaborators did not observe significantly decreased major vascular events in patients above 75 years without vascular disease on statin therapy (RR 0.92; 95% CI: 0.77-0.99), though this analysis was limited by the small number of patients included in this subgroup analysis (n=561).[70]

A 2020 retrospective cohort study of over 327,000 VA patients over age 75 without ASCVD observed decreased all-cause mortality (HR 0.75; 95% CI: 0.74-0.76) and CV mortality (HR 0.80; 95% CI: 0.72-1.16) among patients who initiated statins during the study period compared to non-statin users.[71] These observational data may be subject to confounding and bias, but they provide some evidence that statins may offer benefits for many patients over 75 years. Importantly, measures of frailty were included in the above VA study and should be used – rather than age alone – to aid in determining which patients would benefit from statin therapy.

BOTTOM LINE: Statins should not be discontinued based on advanced age alone. Individuals over 75 years of age at high CVD risk may benefit from initiating a statin.

Non-statin LDL-lowering medications

In addition to statins, several other classes of lipid-lowering medications exist. Many of these medications are used among patients with known CVD to reduce risk of recurrent events. However, the evidence for any non-statin lipid-lowering medications in primary prevention of CVD is limited.

Ezetimibe

Ezetimibe (Zetia, generics) blocks cholesterol absorption in the gastrointestinal (GI) tract and can reduce LDL level by 10-20% when used as monotherapy. Ezetimibe was first studied for secondary CVD prevention in the **IMPROVE-IT trial** (2015), which showed that ezetimibe in conjunction with a moderate-intensity statin lowered ASCVD risk by 2% in patients treated for secondary prevention over 7 years.[72]

Data on ezetimibe's utility in primary prevention is limited to one Japanese open-label study comparing ezetimibe to no treatment in patients without ASCVD and LDL level ≥ 140 mg/dL.[73] Although ezetimibe was associated with a 34% decrease in incidence of sudden cardiac death, MI, coronary revascularization, or stroke, interpretation of this study was limited by issues with under-enrollment and underpowering, protocol violations, and significant loss to follow-up.[73] Additionally, the generalizability of this study is limited as no patients were on statin therapy.[73]

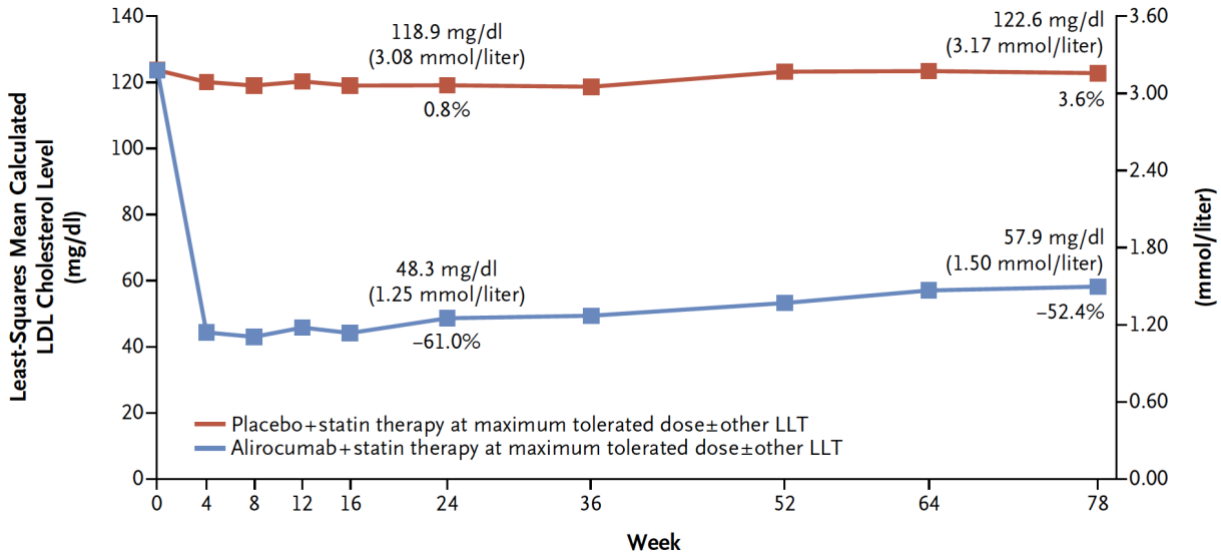
Ezetimibe is generally well-tolerated but does have some known side effects, including upper respiratory infection, fatigue, and sinusitis.[74] Ezetimibe combined with statin therapy has been associated with LFT elevations >3x ULN (1.3% in combination therapy vs 0.4% in statin monotherapy).[74]

PCSK9 Inhibitors

Proprotein convertase subtilisin kexin 9 (PCSK9) is a protease produced predominately in the liver that facilitates the breakdown of hepatocyte LDL receptors and causes decreased clearance of LDL cholesterol.[75] PCSK9 inhibitors, evolocumab (Repatha) and alirocumab (Praluent), are monoclonal antibodies that are injected subcutaneously to inhibit PCSK9 and significantly lower serum LDL levels (approximately 50-60% reduction when used as monotherapy or in conjunction with statins).[75]

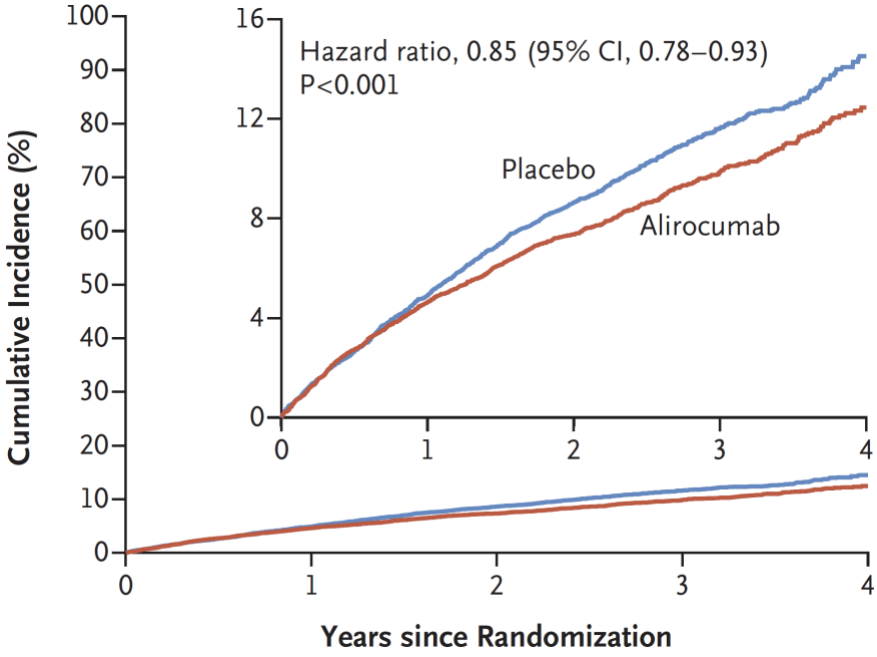
PCSK9 inhibitors have primarily been studied for secondary CVD prevention in patients on maximal statin therapy. The **ODYSSEY LONG TERM trial** randomized 2,341 patients at high risk for cardiovascular events who were already receiving statins to alirocumab (150 mg) or placebo every 2 weeks.[76] The trial observed a mean 62% decrease in LDL levels at 24 weeks; 79% of patients achieved an LDL level < 70 mg/dL during this time frame (Figure 8).[76]

Figure 8: Alirocumab reduced LDL by 60% in patients on statin therapy[76]



A follow up study, **ODYSSEY OUTCOMES**, randomized 18,924 patients with acute coronary syndrome in the past one year already receiving maximally tolerated statins to alirocumab (75 mg) or placebo every 2 weeks.[77] At four years, cumulative incidence of the primary composite end point (death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, and unstable angina) was significantly lower in the alirocumab group (12.5%) compared to the placebo group (14.5%), (HR 0.85; 95% CI: 0.78-0.93) (Figure 9).[77]

Figure 9: Alirocumab decreased incidence of CV events in patients on statins for secondary prevention[77]



The **ODYSSEY FHI and FHII trials** also studied alirocumab in patients with heterozygous familial hyperlipidemia who had not achieved <100 mg/dL in primary prevention or <70 mg/dL in secondary prevention.[78] Over 80% of enrolled patients were on high-dose statins at baseline.[78] At week 24, patients in the treatment group experienced a mean LDL reduction of 58% (FHI) and 54% (FHII) which was sustained through week 78.[78]

The **ODYSSEY LONG TERM trial** of alirocumab compared to placebo injection showed relatively low rates of adverse events, although rates were higher with alirocumab: injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%).[76] In the **OSLER trial** of evolocumab, the most common adverse events were nasopharyngitis (12.2% with evolocumab vs. 9.8% with standard therapy), upper respiratory tract infection (7.7% vs. 7.6%), influenza (7.1% vs. 5.2%), arthralgia (6.9% vs. 4.3%) and back pain (6.5% vs. 5.4%).[79]

Both alirocumab and evolocumab are approved by the FDA for use in secondary prevention (patients with clinical ASCVD who require additional lowering of LDL cholesterol beyond statin therapy) and in primary prevention for patients with heterozygous familial hypercholesterolemia (HeFH). With the exception of this high-risk population, the high price, method of administration via biweekly or monthly subcutaneous injections, and side effect profile make PCSK9 inhibitors less desirable for primary prevention for most patients.

BOTTOM LINE: Ezetimibe and PCSK9 inhibitors have evidence supporting their use in lowering LDL and reducing risk of ASCVD. Ezetimibe may have utility in patients in whom statin therapy is limited by statin-associated side effects. Except for patients with familial hyperlipemia, use of

PCSK9 inhibitors for primary prevention is prohibited by cost, method of use, and side effect profile.

Triglyceride-lowering medications

An independent association between ASCVD event rates and elevated triglycerides (TG) has been observed, which has been theorized to be due to an elevation in remnant cholesterol particles causing increased atherosclerotic events.[21]

Statins are the first-line management for high triglycerides, as high-intensity statins can lower triglyceride levels up to 30%.[21] It is also critical to address secondary causes of hypertriglyceridemia, including lifestyle causes, systemic disorders, and triglyceride-raising medications.[21]

According to the 2019 ACC/AHA guidelines, elevated serum triglycerides (≥ 175 mg/dL) should be considered a risk-enhancing factor that can favor of initiation of statin therapy, especially in borderline risk cases.[58] Other medications that have been studied as TG-lowering therapies are discussed below.

Icosapent ethyl

Icosapent ethyl (Vascepa) is a high-dose marine-derived omega-3 fatty acid that has been studied as a triglyceride-lowering therapy in high-risk patients. The **REDUCE-IT trial** (2019) compared icosapent ethyl to a mineral oil placebo in 8,179 patients with elevated triglycerides on statin therapy.[80] Approximately one-third of enrolled patients were high-risk primary prevention patients, defined by: age ≥50 years, diagnosis of diabetes, and the presence of one additional CV risk factor (cigarette smoking, hypertension, HDL ≤40 mg/dL for males or ≤50 mg/dL for females, hs-CRP > 0.3 mg/dL, CrCl <60 mL/min, retinopathy, micro- or macroalbuminuria, or ankle-brachial index <0.9).[80] At 1 year, median TG levels were reduced by 18% in the icosapent ethyl group and rose by 2.2% in the placebo group.[80] At median follow-up of 4.9 years, icosapent ethyl reduced the primary combined CV endpoint by 4.8% (HR 0.75; 95% CI: 0.68-0.83; p<0.001).[80] A modest increase in hospitalizations for atrial fibrillation was also observed (3.1% vs. 2.1%, p=0.004).[80]

Interpretation of the REDUCE-IT trial results for primary prevention patients is limited by several considerations. First, the majority of trial patients (70%) had established ASCVD. Second, varying evidence suggests that the mineral oil control may have increased CV risk in the control group and thus overestimated the effect of icosapent ethyl.[81] This may be reflected in the discordance between the magnitude of absolute event reduction (4.8%) and the relatively modest decrease in triglyceride levels observed in the treatment group (18%).[81] An alternative interpretation is that icosapent ethyl exerts a pleiotropic effect on CV risk reduction beyond its triglyceride-lowering effect.

The **STRENGTH trial**, which sought to follow up on the outstanding questions raised in the REDUCE-IT trial, compared a high-dose omega-3 formulation (similar to icosapent ethyl) to corn oil placebo in approximately 13,000 statin-treated patients at high risk of ASCVD events.[81] No difference in the primary composite endpoint was observed at 38 months (HR 0.99; 95% CI: 0.90-1.09), so the trial was stopped early for futility.[81] Of note, the STRENGTH trial also observed increased incidence of atrial fibrillation in the treatment group (2.2% vs 1.3%, HR 1.69; 95% CI: 1.29-2.21), though the mechanism for this association is unknown.[81]

Icosapent ethyl is currently approved by the FDA for a very limited population of primary prevention patients – those on maximally tolerated statin therapy, with triglyceride levels ≥150 mg/dL, and with a diagnosis of diabetes plus two additional CV risk factors.

Of note, over-the-counter fish oil preparations (lower dose and different formulation than icosapent ethyl) do not have any evidence for primary prevention; in an RCT of approximately 25,000 patients, patients experienced no reduction in CV events compared to placebo over 5.3 years.[82]

Fibrates

Fibrates (e.g., gemfibrozil, fenofibrate) alter gene expression in target cells, and activate a gene that increases HDL levels and decreases triglyceride levels. Fibrates can reduce LDL cholesterol by 5-20% and serum triglyceride levels up to 50-70%.[83] However, they do not have strong evidence in CV risk reduction. A meta-analysis of 18 fibrate trials (n=45,000) conducted over a mean of 4.1 years found no effect on all-cause or CV mortality.[84] Additionally, fibrates (especially gemfibrozil) are associated with risk of muscle toxicity, which increases for patients on statins.[84]

As a result, fibrates may play a role for patients with severely elevated triglycerides (e.g., for reducing risk of pancreatitis), but their use for CVD prevention is limited.

Niacin

Nicotinic acid (niacin or vitamin B3) binds to a receptor on adipocytes, inhibiting lipolysis and release of fatty acids. At doses of 1500-2000 mg daily, niacin can reduce LDL cholesterol by 5-25% and triglycerides by 20-35%.[21] No study has shown that niacin improves CV outcomes, and it is associated with several adverse side effects including flushing, pruritis, GI effects, hepatotoxicity, nephrotoxicity, and increased insulin resistance.[85]

BOTTOM LINE: For patients with elevated triglycerides and ASCVD risk, statins remain first-line therapy. If triglycerides remain ≥150 mg/dL despite maximum statin therapy, icosapent ethyl may be considered for primary prevention in select high-risk patients. Fibrates and niacin are not recommended in primary prevention due to no evidence of benefit.

Aspirin for primary CVD prevention

For more than a century, aspirin has been one of the most widely-used and widely-studied drugs in the clinician's armamentarium. It is an inexpensive, easily-available agent with analgesic, anti-inflammatory, and antipyretic effects. Aspirin also has antiplatelet properties, which is the basis for its use in patients with, or at risk for, cardiovascular disease.[86]

Using aspirin to prevent CVD was popularized after the 1989 Physicians' Health Study, which randomized 22,071 participants to receive aspirin 325 mg every other day versus placebo and reported a 44% reduction in the risk of MI (but no reduction in risk of mortality from cardiovascular causes). However, subsequent trials in the 1990s through 2014 provided largely mixed results, so prescribing this classic drug, or guiding patients in their over-the-counter use of this drug, became a more complicated endeavor. Data from 10 trials suggested that patients varied widely in the benefits they might receive from aspirin

therapy, in their inherent vulnerabilities to the risks posed by aspirin, in their use of other medications that may directly or indirectly alter aspirin's risk/benefit profile, and in their comorbidities and past medical histories.

The inherent challenges of recommending aspirin for primary prevention are embodied in the multiple different recommendations the U.S. Preventive Services Task Force (USPSTF) has made over the decades. Initially in 1996, aspirin for primary prevention was given a "C" rating (not enough evidence to make a recommendation).[87] In 2002 and 2009, the USPSTF revised their rating to an "A" for most individuals for whom the perceived benefit of treatment outweighed possible bleeding risks.[88,89] Then, in 2016, the USPSTF again revised their rating to a "B" for adults aged 50-59 with increased cardiovascular disease risk (recommend aspirin use) and a "C" for adults aged 60-69 with elevated risk (consider aspirin use after shared-decision making).[90] Finally, most recently in October 2021, the USPSTF has again revised their rating of aspirin for primary prevention to a "C" for adults aged 40-59 with increased cardiovascular disease risk (consider aspiring use after shared-decision making) and a "D" (do not recommend) for those 60 and older.[91]

Even as the USPTF guidelines have been adopted to account for newer evidence, many patients continue to take aspirin. For example, based on data from 14,328 adults in the 2017 National Health Interview Survey, 23.4% of adults aged ≥40 years (about 29 million persons) reported taking aspirin daily for CVD prevention, about 6.6 million of whom were doing so without a clinician's recommendation.[92] The rate of aspirin use was much higher in older adults: 44.6% of adults aged 70-79 years, and 46.2% of adults aged ≥80 years used daily aspirin for primary prevention (an estimated 9.5 million adults).[92] A more recent study from 2021 showed that, through 2018, 42% of adults over 60 were still using aspirin for primary prevention.[93] Primary care providers (PCPs) can make a difference by identifying such patients and educating them about appropriate use of aspirin.[94]

Modern trials of aspirin for primary prevention

As recently as 2016, the preponderance of evidence seemed to suggest that low-dose aspirin (e.g., 81 mg/day) conferred a net benefit for the primary prevention of cardiovascular disease, and a number of guidelines used these data as the basis for their recommendations.[95,96]

In 2018, however, two large, long-term, high-quality randomized trials showed no ASCVD benefits for aspirin in primary prevention, while simultaneously demonstrating small, but significant, increased risk for major bleeding (Table 6).[97,98] A third 2018 trial in patients with diabetes found a modest CVD benefit, but with similarly increased bleeding risks.[99] Some of the differences in results from the three recent trials compared to older primary prevention trials may be explained by the fact that the older trials were conducted at a time when smoking was common, blood pressure control was suboptimal, and aggressive lipid lowering was rare.[100]

Table 6: Trials published in 2018 comparing aspirin vs. placebo for primary prevention of ASCVD[97-99]

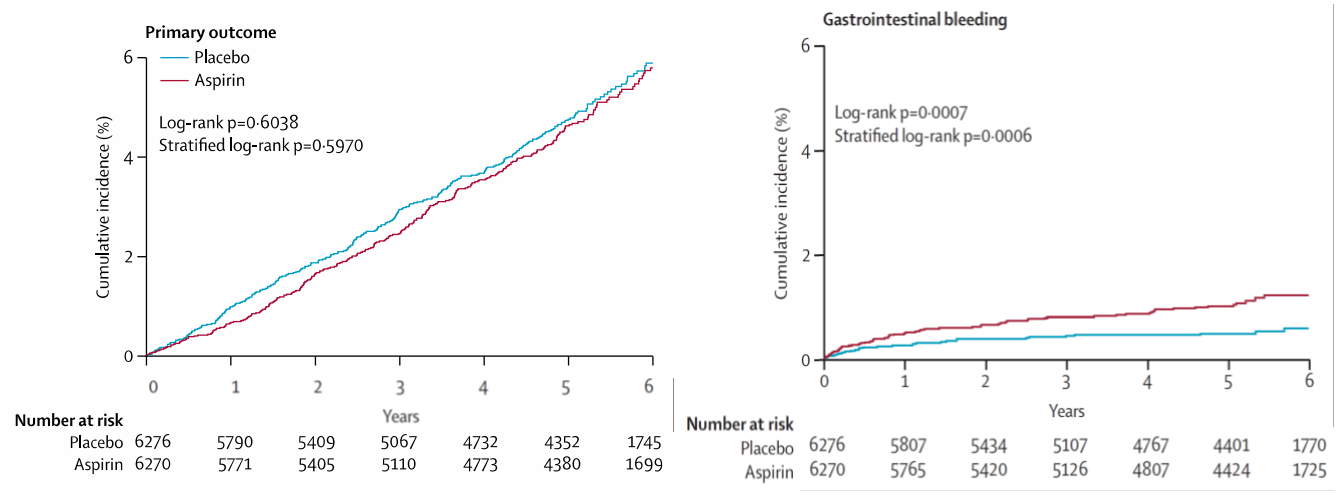
RCT	Patient population	Size	Follow-up	Mean age	CV effect (95% CI)	Major bleeding	
						Relative risk (95% CI)	Actual risk difference
ASPREE	Healthy older adults	19,114	4.7 years (median)	74	No difference	**HR 1.38 (1.18-1.62)**	2.4 extra events/ 1000 person-years
ARRIVE	"moderate" CV risk	12,546	5 years (median)	64	No difference	**HR 2.11 (1.36-3.28)**	0.5%
ASCEND	Diabetes	15,480	7.4 years (mean)	63	**RR 0.88 (0.79-0.97)**	**RR 1.29 (1.09-1.52)**	0.9%

HR – hazard ratio; RR – rate ratio

The **ASPREE trial** randomized 19,114 community-dwelling older adults (mean age 74 years, 44% male) to aspirin 100 mg/day vs. placebo.[98] No significant difference in CV events was observed after a median follow-up of 4.7 years (HR 0.95; 95% CI: 0.83-1.08), but aspirin was associated with a significantly increased risk of major bleeding (HR 1.38; 95% CI: 1.18-1.20).

The **ARRIVE trial** enrolled 12,546 patients (70% male) thought to be at moderate risk for CVD based on a mean 10-year ASCVD risk score of 17%.[97] The observed ASCVD risk of trial participants was lower, with extrapolated 10-year risk of 8.4% to 8.8% based on 5 years of follow-up (Figure 10). The trial randomized patients to 100 mg daily aspirin vs. placebo, and, as with ASPREE, no statistically significant difference in the rate of major CV events was observed (HR 0.96; 95% CI: 0.81-1.13). There was, however, a significantly increased risk of GI bleeding (HR 2.11; 95% CI: 1.31-3.28).

Figure 10: Primary and GI bleeding outcomes in ARRIVE[97]



The **ASCEND trial** randomized 15,480 patients with diabetes (any diabetes type, 62% male) but no evidence of CVD to aspirin 100 mg/day vs. placebo with mean follow-up of 7.4 years.[99] Serious vascular events occurred less frequently in the aspirin group vs. the placebo group (8.5% vs. 9.6%, P=0.001), but the incidence of major bleeding was also higher with aspirin: 4.1% vs. 3.2%, P=0.003). In subgroup

analyses, the CVD benefits of aspirin were only significant in patients aged 60 and younger. The risks of major bleeding, however, were significantly higher for patients older than 60 years, suggesting that the risk/benefit equation in this population favors younger patients.

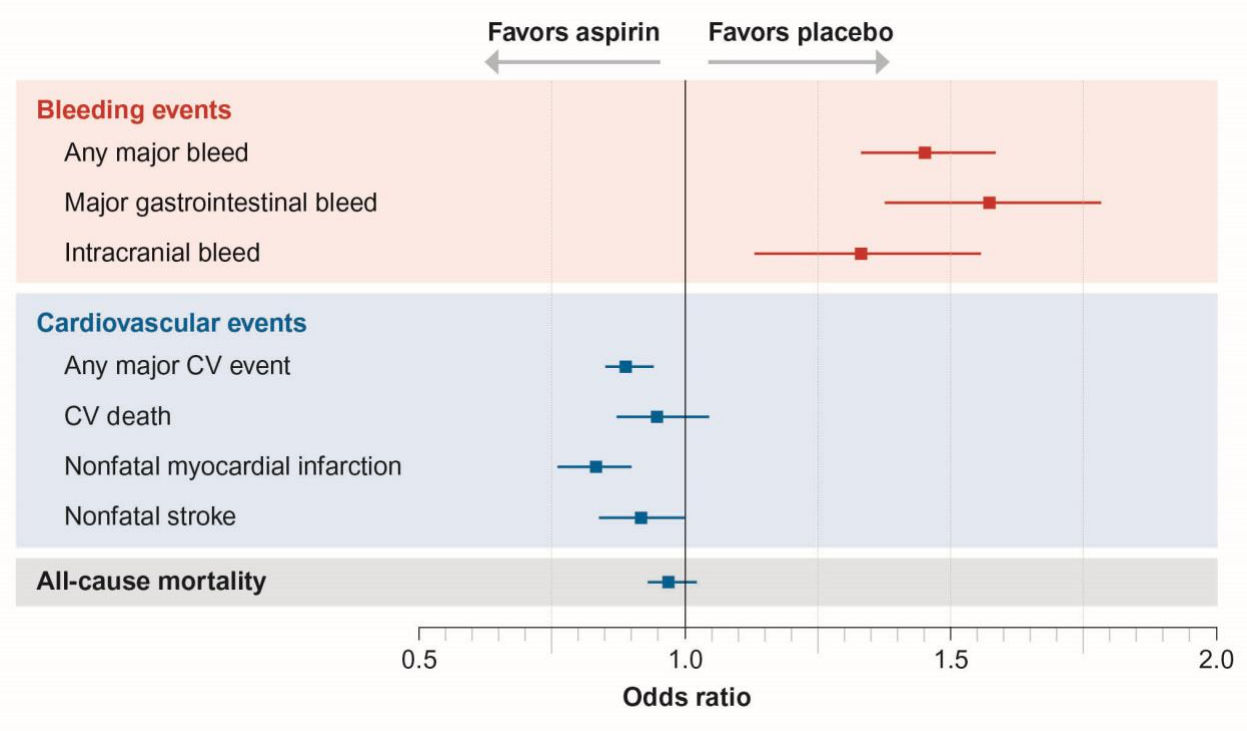
Summarizing decades of conflicting evidence

A 2019 meta-analysis combined data from 13 previous trials over four decades, including all those summarized above. With regards total cardiovascular events (cardiovascular death or non-fatal stroke or myocardial infarction), aspirin provided modest benefit over placebo (60.2 per 10,000 participant-years with aspirin and 65.2 per 10,000 participant-years with placebo, HR 0.89; 95% CI: 0.84-0.94) The number needed to treat to prevent 1 cardiovascular event was 241. However, this benefit was driven by a reduction in risk of non-fatal myocardial infarction, and there was no benefit with regards to cardiovascular mortality or overall mortality.

Moreover, aspirin was associated with substantial increased risk of bleeding (23.1 per 10,000 participant-years vs. 16.4 per 10,000 participant years, HR 1.43; 95% CI: 1.30-1.56.[101] The number of patients needed to treat to result in 1 bleeding event was 210. The results were similar for major gastrointestinal bleeding and intracranial bleeding.

More recently, the 2021 USPSTF guideline committee completed their own meta-analysis and reached the same conclusion at Zheng et al (Figure 11).[91]

Figure 11: Cardiovascular and bleeding outcomes from primary prevention trial meta-analysis [22]



With the new trials shifting the totality of evidence, the 2019 ACC/AHA guidelines for primary prevention of CVD with aspirin state that “aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit,” cautious language that is mirrored in the 2021 USPSTF draft guidelines.[58,91]

Prescribers can consider discussing the risks and benefits of aspirin for primary prevention with younger patients at high risk for CVD calculated by the PCE but low risk for bleeding, or patients with diabetes. When discussing risks and benefits of aspirin with patients, consider posing the following questions:[102]

- *How concerned are you about having a heart attack or stroke, or developing cancer?*
- *Have you ever had problems with bleeding?*
- *Are you concerned about the risk of bleeding while on aspirin?*
- *Could you tolerate minor bleeding or bruising as a side effect?*
- *How do you feel about medication side effects in general?*
- *How do you feel about taking daily aspirin for years?*

Assessing patients for aspirin-associated risks

Most trials of aspirin for primary prevention excluded individuals at high risk of bleeding, i.e., people with a history of GI bleeding, history of peptic ulcer disease, concomitant use of non-steroidal anti-inflammatory medications (NSAIDs) or anticoagulation. Despite these exclusions, aspirin was associated with a heightened risk of bleeding in nearly every trial.[22]

The primary adverse effect of aspirin is GI bleeding, the risk of which is dose dependent. The increased risk of GI bleeding exists even with low doses of aspirin. Even doses <100 mg daily increase the risk of GI bleeding approximately 2-fold relative to patients not on aspirin, while doses ≥300 mg increase the risk 4-fold.[103] In contrast, the benefit of aspirin is less dose-dependent, which is why, in the U.S., low-dose aspirin (81 mg) is typically the recommended dose for antiplatelet indications.

The risk of GI bleeding increases with age, and men have a higher risk of bleeding compared to women.[103] Patients concomitantly taking NSAIDs or other antiplatelet medications and patients with peptic ulcer disease also have a higher risk of GI bleeding.

Prevention of GI bleeding is important in high-risk individuals who would benefit from the CV benefits of aspirin. Buffered or enteric-coated aspirin does not reduce the risk of GI bleeding compared to plain tablets.[104] For patients who need to take an aspirin despite high bleeding risk (e.g. secondary CV prevention), the risk should be mitigated using a proton pump inhibitor (PPI). In patients with healed peptic ulcer disease, restarting aspirin with a PPI decreased the risk of recurrent bleeding.[103] Patients treated with aspirin and a PPI had lower bleeding rates than patients treated with clopidogrel alone.[105] A PPI should also be prescribed for patients with a history of GI bleeding, those taking dual antiplatelet therapy, and those concomitantly taking anticoagulant medications. Eradication of Helicobacter pylori infection also reduced the risk of aspirin-induced bleeding in affected patients.[106]

BOTTOM LINE: Aspirin should not be routinely prescribed for primary prevention. For older patients (age 60 and over), those with low CVD risk, or those with increased bleeding risk, aspirin for primary prevention should be avoided or discontinued. For patients <60 years of age, with high CV risk, and diabetes, clinicians should discuss risks and benefits with patients to decide on whether to use aspirin for primary prevention.

Lifestyle interventions for primary cardiovascular prevention

Beyond pharmacologic therapy, lifestyle interventions play an important role in preventing cardiovascular disease. According to the landmark 2004 **INTERHEART study** (a case-controlled study of over 30,000 individuals from every inhabited continent),[107] lifestyle factors, such as diet and exercise, contributed to nearly 60% of excess population attributable risk of developing cardiovascular disease.[108,109] Other studies have consistent findings: many risk factors for cardiovascular disease can be modified by nonpharmacologic means, and these risk factors contribute significantly to the risk of developing cardiovascular disease.[110,111]

This section will describe the evidence for using nonpharmacologic approaches to reduce cardiovascular disease risk. Each section will include a discussion of how a disease associated with excess cardiovascular risk (e.g., hypertension, diabetes, or hyperlipidemia) is impacted by nonpharmacologic approaches to risk factor mitigation (e.g., diet, exercise, weight-loss, or other approaches). Finally, the evidence for how these nonpharmacologic approaches may directly impact cardiovascular disease risk itself (e.g., myocardial infarctions) will be discussed.

Impacts of non-pharmacologic interventions on risk factors for cardiovascular disease

Hypertension

Large cohorts and meta-analyses of trials suggest that hypertension may be the strongest driver of cardiovascular disease.[110] While pharmacologic therapy plays an important role in treating hypertension, there is high quality evidence that multiple nonpharmacologic interventions can lower blood pressure. A low-sodium and high fruit/vegetable diet, exercise, weight loss, and reducing alcohol intake have strong evidence of being associated with lowering blood pressures to a similar degree as monotherapy antihypertensive medication initiation.

The strongest evidence for dietary approaches to reducing hypertension are in low-sodium and high fruit/vegetable diets. Perhaps the most famous trial is the 1997 **Dietary Approaches to Stop Hypertension (DASH) diet study**. This study demonstrated that, among individuals with hypertension, just eight weeks of following a diet rich in fruits, vegetables low-fat dairy products, and reduced sodium could lower systolic (11.4 mm Hg) and diastolic blood pressure (5.5 mmHg), compared with a control diet.[110] While the DASH diet contained multiple components, a Cochrane meta-analysis of interventional studies included 195 studies involving over 12,000 individuals found that sodium reduction to an average of 1.5 grams per day reduced systolic/diastolic blood pressure by 5.7/2.9 mm Hg among White individuals with hypertension, 6.6/2.9 mm Hg among Black individuals, and 7.8/2.7 mm Hg among Asian individuals.[111]

There is also strong interventional study data that exercise can significantly reduce blood pressure. In one network meta-analysis of 391 trials, among individuals with hypertension, there were no differences in between the systolic-lowering effects of medications and exercise.[112] This same meta-analysis estimated that exercise reduced systolic blood pressure by approximately 9 mmHg. This finding is consistent across multiple populations; for example, trials in specific populations, such as among African-American men[113]

with severe hypertension and individuals with resistant hypertension,[114] also confirm multiple forms of exercise reduce blood pressure.

Moreover, multiple trials suggest that reduced alcohol consumption is associated with significant reductions in blood pressure, though those reductions are most likely to be seen among individuals who use more alcohol. For example, one meta-analysis of 36 trials, which included 2,865 participants, found that, among individuals who drank fewer than two alcoholic drinks a day, further reduction in alcohol use was not associated with significant reductions in blood pressure. However, among individuals who drank more than two alcoholic drinks per day, a reduction in intake was associated with a 5.5/4.0 reduction in systolic/diastolic blood pressure.[115]

Finally, there evidence that weight loss can lead to lower blood pressures. For example, in a Cochrane meta-analysis of 8 trials involving 2,100 individuals suggested that those assigned weight-loss diets (an aggregate of many different dietary interventions across trials) had a 4.5/3.2 mmHg reduction in systolic/diastolic blood pressure compared to controls, though the authors note the evidence is largely low-quality.[116] A separate meta-analysis included 25 trials (4,874 participants) and assessed how weight loss, regardless of method to obtain said weight loss, impacted blood pressure. This trial found an average weight reduction of 5.1 kg led to reduced systolic/diastolic blood pressure by 4.4/3.6 mmHg. Put another way, there was approximately a 1 mmHg reduction in systolic and diastolic blood pressure for every kilogram of weight lost. This effect was larger among the subgroup of patients taking antihypertensive drugs, highlights the complementary nature of pharmacologic and nonpharmacologic approaches to improving blood pressure control.[117]

Interventions that combine multiple nonpharmacologic approaches to reducing hypertension have the strongest evidence for reducing blood pressure. Specifically, the **PREMIER trial** published in 2003 found that multiple comprehensive lifestyle modification coaching sessions (which included multiple diet, exercise, weight loss goals, and alcohol use education) lowered systolic blood pressure an average of 4.4 mmHg more than traditional advice-only counseling alone.[118]

Other nonpharmacologic approaches to blood pressure reduction do not have the same strength of evidence to suggest consistent blood pressure lowering effects. For example, in a meta-analysis of 23 observational studies, smoking status was not clinically significantly associated with average blood pressure.[119] Additionally, though there are plausible biologic reasons to connect stress and blood pressure and observational studies link stress and hypertension,[120] clinical trials have not generally shown stress-reduction techniques to lower blood pressure.[121,122] However, though these data should be interpreted with caution given generally small sample sizes and limited stress reduction techniques studied.

Type 2 diabetes mellitus

While less prevalent than hypertension, diabetes is a major contributor to the burden of cardiovascular disease.[123] Overall, the evidence suggests that nonpharmacologic interventions may have limited ability to impact diabetes control, and on average pharmacologic approaches to controlling diabetes will often have larger effect sizes than nonpharmacologic approaches. However, at least in the short term, low carbohydrate diet, exercise, and weight loss (by any means) have been shown to impact diabetes incidence and control.

Concerning diet, most studies assess how a low-carbohydrate diet impact diabetes progression, usually compared to a low-fat diet. For example, in one meta-analysis of 36 trials, glycated hemoglobin declined

by an average of 1.4% in the short term among individuals who ate low-carbohydrate diets compared with low-fat diets; however, this difference nearly and then completely disappeared after 1-2 years of follow up.[124] In a separate meta-analysis of 23 trials, those on low-carbohydrate diets (compared with "other" diets) had a higher rate of diabetes remission (defined as glycated hemoglobin <6.5%; 57% versus 31%); however, once again long-term data (i.e., 12 month data) did not show any reduction in risk of having diabetes.[125] Taken in totality, these trials suggest that a low-carbohydrate diet likely improved control of diabetes in the short term, but whether because of physiologic changes or difficulty maintaining a diet long-term, low-carbohydrate diets are likely insufficient to maintain control of diabetes over a period of years.

Trials suggest that any amount of exercise can be modestly helpful in managing diabetes. For example, in a meta-analysis of 47 trials examining the effect of physical exercise advice and structured physical exercise programs on glycated hemoglobin, structured training (both aerobic and anaerobic) was associated with decreases in glycated hemoglobin (−0.67%, 95% CI: −0.84% to −0.49%). Studies that advised patients to increase physical activity without providing a structured program did not result in reduced glycated hemoglobin.[126]

Finally, weight loss has been associated with prevention of diabetes. For example, in one observational study, which included 1,079 participants, for every 5 kg of weight loss, there was a 16% reduction in the risk of developing diabetes (after adjusting for age and physical activity).[127] Similarly, in a cohort study of 33,184 individuals, weight gain over a ten year period was linearly associated with incidence of diabetes (OR 1.05 per 1% change in body weight; 95% CI: 1.04-1.06).[128] There are fewer studies showing how often non-surgical weight loss can lead to sustained remission of diabetes, but one is the **DiRECT trial**.[129] This open-label, cluster-randomized, controlled trial, of 272 participants was conducted at primary care sites within the United Kingdom and compared how a structured weight-loss program vs advice impacted weight loss and diabetes control. It found that those in the intervention group lost more weight (5.4 kg; 95% CI: 4.0-6.9) and had a lower mean difference in glycated hemoglobin (0.44% less; 95% CI: 0.13-0.76) compared with the control group despite the intervention group using fewer anti-hyperglycemic agents. Sustained weight loss at 24 months, when it could be achieved, was tied to sustained remission of diabetes.

Other lifestyle factors have been associated with risk of diabetes, but there is less evidence about how intervening upon them may impact diabetes risk. For example, numerous population-based studies suggest that tobacco use is associated with likelihood of being diagnosed with diabetes;[130] however, other studies suggest smoking cessation may not actually reduce the risk of developing diabetes in these patients.[130] Alternatively, multiple studies have shown that among individuals with diabetes, glycated hemoglobin levels are often lower among individuals using alcohol,[131] while interventional studies have shown that initiating the use of moderate amounts of alcohol can actually decrease fasting plasma glucose levels among individuals with diabetes.[132] While smoking and frequent consumption of alcohol may have numerous deleterious effects on health, their impact specifically diabetes incidence and control remains less clear.

Hyperlipidemia

While decisions about pharmacologic therapy targeting lipids (e.g. statins) are now based on composite risk more so than low-density lipoprotein (LDL) level alone, lipid levels remain an independent risk factor cardiovascular disease.[133] Non-pharmacologic approaches can modestly improve lipid levels, but the effect is far less than pharmacologic approaches (i.e. statins).

Starting doses of statins reduces LDL by 21-43%,[134] substantially more than even the most aggressive nonpharmacologic approach. For example, a meta-analysis found that high soluble fiber diets (2-10 g/day) may be able to lower LDL by up to 18%, but many studies show limited or no impact of diet on LDL. The average reduction in LDL in this meta-analysis of 67 studies was only 2.2 mg/dL.[135] Similarly, a trial exploring the impact of dietary portfolio (i.e., highly targeted instructions for eating foods with proven lipid-lowering effects) reduced a LDL by an average of 13.8%.[136]

Similarly, exercise can modestly impact cholesterol values. In a meta-analysis of 25 trials examining the effects of aerobic exercise on HDL levels found that at least 120 minutes/week of exercise increased HDL by approximately 4%.[137] Exercise is also generally associated with decreased LDL levels, though the effect appears to be partly modified by body weight. For example, in a meta-analysis of 95 studies of the effects of exercise on body weight and LDL, when body weight did not change, LDL levels decreased less than when body weight did decrease (3.3 mg/dL vs 11.2 mg/dL, respectively); alternatively, when body weight increased, LDL levels correspondingly increased by 3.0 mg/dL.[138] This ability of weight loss to impact LDL levels has been suggested by several other studies. For example, in a study of 100 patients experiencing obesity who were randomized to two weight-loss diet interventions, individuals with elevated total cholesterol level at baseline (mean total cholesterol 261 mg/dL) had both reduced weight and a 14.9% reduction in total cholesterol after 51 months.[139]

Other nonpharmacologic approaches seem to have even smaller effects on cholesterol levels. For example, one meta-analysis of 44 studies suggested that alcohol use might be associated with small increases in HDL, it was not significantly associated with LDL level.[140] Similarly, a trial of 1,504 current smokers found that smoking cessation did modestly increase HDL levels, but it also did not significantly change LDL.[141] Ultimately, reducing alcohol intake and smoking cessation have numerous benefits but they may have relatively small impacts on hyperlipidemia.

Based on the totality evidence, a high-fiber and plant-sterol rich diet, regular exercise, and weight loss, improve hyperlipidemia. While the effects are lower than the lipid-lowering benefits offered by statins, these non-pharmacologic interventions may still play an important role in cardiovascular risk reduction.

Impact of non-pharmacologic interventions on cardiovascular disease incidence

In addition to impacting the risk factors for cardiovascular disease, non-pharmacologic interventions have also been shown to modify the likelihood of developing cardiovascular disease itself. Because of the long timeframe over which cardiovascular disease develops, most supporting data supporting come from a combination of observational studies and interventional trials. Overall, there is strong evidence that smoking cessation, exercise, and diet, especially a Mediterranean diet, lower the risk of developing cardiovascular disease.

While most of the data concerning the benefits of not smoking and cardiovascular disease are largely from observational studies, the results are overwhelming. In a meta-analysis of 141 cohort studies, the pooled relative risk for coronary heart disease was 1.65 (95% CI: 1.53-1.78) for smoking even just one cigarette per day.[142] There is also a strong association seen between smoking cessation and reduced risk of future cardiovascular events. For example, in a cohort of 8,770 heavy smokers followed for 25 years, those who quit had a 39% reduction in the hazard of having a cardiovascular event compared with those who continued to smoke.[143]

Similarly, most of the data showing associations between regular exercise and cardiovascular disease reduction come from observational studies, but the effect sizes are similarly large. For example, a cohort study of 479,856 adults found that those who met the guideline recommended amount of exercise at the beginning of the study period had lower all-cause and cardiovascular-specific mortality after a medial follow-up period of 8.75 years.[144] Two other well-known cohort studies, the Harvard Alumni Health Study and the Nurses Health Study, found a dose-dependent association between exercise and cardiovascular disease risk in men and women, respectively.[145,146]

There is strong observational and interventional evidence that high-fiber diets (i.e. those rich in fruits/vegetables) and low-sodium diets reduce risk of cardiovascular events. For example, a meta-analysis of 22 cohort studies found that total dietary fiber intake was inversely associated with risk of cardiovascular disease (risk ratio 0.91 per 7 g/day; 95% CI: 0.88-0.94).[147] With regard to the benefits of a low-sodium diet, in a cohort study of over 3,000 individuals followed from the **TOHP I and TOHP II trials**, a >1 year comprehensive low-sodium diet counseling program was associated with a 25% lower risk of cardiovascular disease (relative risk 0.75; 95% CI: 0.57-0.99, P=0.04) up to ten years after the intervention.[148]

The highest quality evidence that a dietary intervention can reduce cardiovascular disease comes from the **PREDIMED trial**, which studied 7,447 adults at high cardiovascular risk. The study found that a Mediterranean diet was associated with an approximately 30% reduced risk of cardiovascular events during median 4.8 years follow-up.[149]

In 2021, the American Heart Association published comprehensive dietary advice.[150] While some of the recommendations are based on expert opinion, several of the recommendations are supported by evidence that diet can improve cardiovascular risk factors and reduce incidence of cardiovascular disease. These recommendations suggest:

- Adjust energy intake and expenditure to achieve and maintain a healthy body weight
- Eat plenty of fruits and vegetables, choose a wide variety
- Choose foods made mostly with whole grains rather than refined grains
- Choose healthy sources of protein
  - Mostly protein from plants (legumes and nuts)
  - Fish and seafood
  - Low-fat or fat-free dairy products instead of full-fat dairy products
  - If meat or poultry are desired, choose lean cuts and avoid processed forms
- Use liquid plant oils rather than tropical oils (coconut, palm, and palm kernel), animal fats, (e.g., butter and lard), and partially hydrogenated fats
- Choose minimally processed foods instead of ultra-processed foods
- Minimize intake of beverages and foods with added sugars
- Chose and prepare foods with little or no salt
- If you do not drink alcohol, do not start; if you choose to drink alcohol, limit intake

While it is accepted that high levels of alcohol consumption are associated increased cardiovascular risk, the effect of modest alcohol consumption is less clear. In an analysis of 83 prospective studies, which included 599,912 current alcohol users, the lowest risk of mortality was observed among those drinking approximately 100g per week of alcohol; however, alcohol consumption was roughly linearly associated with coronary artery disease (HR 1.06; 95% CI: 1.00-1.11), heart failure (HR 1.09; 95% CI: 1.03-1.15), and fatal hypertensive disease (HR 1.24; 95% CI: 1.15-1.33).[151] By contrast, a separate meta-analysis of

84 observational studies found that the lowest risk for coronary heart disease mortality was in individuals who consume 1-2 drinks per day.[152]

Data supporting an association between weight loss and risk of cardiovascular disease is inconsistent. In a meta-analysis of 54 randomized trials, which included over 30,000 individuals with obesity, weight loss was associated with decreased all-cause mortality but not a reduction in cardiovascular events or cardiovascular-specific mortality.[153] Similarly, for other nonpharmacologic interventions, such as stress reduction, no large, reliable studies have assessed how stress reduction impacts cardiovascular disease risk, though numerous studies have outlined the deleterious effects of stress on the cardiovascular system.[154] As such, the absence of conclusive evidence of the ability of these nonpharmacologic interventions to impact cardiovascular disease directly should not necessarily be taken to mean there is evidence for the absence of an effect.

Finally, one nonpharmacologic intervention for which there is no evidence of benefit is over-the-counter supplements. A review of 24 trials of omega-3 fatty acid supplements found less than 10% of them showed any signal of benefit (note this does not include prescription omega-3 supplements studied in the STRENGTH or REDUCE-IT trials).[155] Moreover, there is some evidence of harm in taking some supplements. For example, in a meta-analysis of seven studies, taking antioxidant vitamins (versus not) was associated with an increased risk of both all-cause (7.4% vs 7.0%) and cardiovascular-specific (3.4% vs 3.1%) mortality.[156] This finding was also replicated in a separate similar meta-analysis.[157]

Summary

Several nonpharmacologic interventions have been shown to impact both the risk factors associated with cardiovascular disease and cardiovascular disease itself. The interventions with the best evidence include a diet rich in fruits/vegetables, low animal fats, high in fiber, and low in sodium; a mix of aerobic and anaerobic exercise; and smoking cessation. Multiple other nonpharmacologic approaches to reducing cardiovascular disease are also likely to benefit patients, including minimizing alcohol use and maintaining a healthy weight, though data is more limited.

BOTTOM LINE: There is strong evidence that non-pharmacologic interventions reduce risk of cardiovascular disease, including a diet high in fiber, low in animal fat, and low in sodium; a mix of aerobic and anaerobic exercise; and smoking cessation.

Implementing non-pharmacologic interventions to reduce risk of cardiovascular disease

Several national guidelines and societies strongly support lifestyle change to prevent ASCVD. The U.S. Preventive Services Taskforce recommends “offering or referring adults with cardiovascular disease risk factors to behavioral counseling interventions to promote a healthy diet and physical activity (2020, Grade B).” [158] The ACC/AHA similarly recommend that adults, “should be routinely counseled in healthcare visits to optimize a physically active lifestyle… [and] a diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish” to decrease ASCVD risk factors (2019, Class I).[58]

While these recommendations are based on strong evidence of benefit, the evidence for their effectiveness comes is best supported by trials which provide substantial support and multiple touch points to engage patients and reinforce these behavior changes. The US Preventive Services Taskforce acknowledges that the basis of recommending behavioral interventions comes from studies with a median of 12 patient contacts, with an estimated six hours of total contact time, over 12 months. Studies of interventions that offer behavioral advice without these supports often fail to show any benefit.

This poses a challenge to implementing behavioral interventions in a typical primary care office. The purpose of this section is to address these concerns and provide evidence and tools to implement non-pharmacologic approaches for cardiovascular prevention in a typical primary care setting.

Behavior change in primary care

Although lifestyle modifications are at the foundation of recommendations to prevent ASCVD, clinicians aren't routinely trained on healthy lifestyle changes and have limited time to do so in clinical practice.[159,160] As a result, clinicians rarely discuss physical activity or nutrition with patients.[161]

The first step for addressing lifestyle changes in primary care is to **assess** a patient's current lifestyle factors. There are several simple tools that can be used in the primary care setting to accomplish this assessment.

For exercise, a patient can be asked a two-question screener:

1. *"How many days a week do you engage in moderate to strenuous exercise, such as a brisk walk?"*
2. *"On average, how many minutes per day do you exercise at this level*?"

For nutrition, a patient can be asked to recall their dietary intake:

- "*Tell me everything you ate and drank in the past 24 hours."*

Further inquiry of dietary quality can be probed by specifically asking patients to reflect on foods with dietary quality that is high (e.g., fruits, vegetables, whole grains, and plant-based proteins) or low (e.g., processed foods, "fast food," meat products, sugar-sweetened beverages).

If time permits, patients can fill out a comprehensive lifestyle assessment tool, available online from the American College of Lifestyle Medicine: **ihacares.com/assets/pdfs/Lifestyle%20Medicine/ACLM-LLUH_short_form_english_2019.pdf.**

General strategies for behavior change

There are several frameworks for understanding behavior change in the primary care setting, several of which are discussed below.

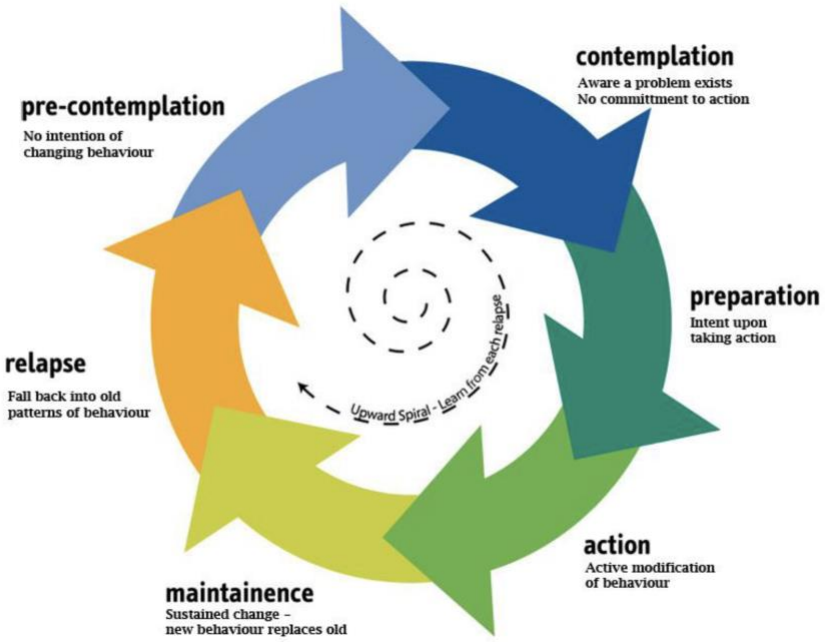
Transtheoretical model

Perhaps the most foundational of all behavior change models is the **Transtheoretical Model**, which clarifies five "stages of change" that can be identified by a clinician: [162]

- **precontemplation**: no thoughts about making a change
- **contemplation**: thinking about making a change
- **preparation**: planning to make a change
- **action**: making changes
- **maintenance**: keeping changes

There is also a designation for **relapse**, if change is interrupted. By applying this framework to patient care, providers can target unique interventions to each stage that are specific to individual health behaviors.

Figure 12: The Transtheoretical Model of behavior change[162]



5 A's framework

For patients who are considering behavior change, the **5 A's framework** can be a useful tool for engaging patients in the office setting.[163,164] The "5 A's" framework has been adapted from the smoking cessation literature to apply to any behavior change. Table 8 describes the five steps and how to use them.

Table 8: the 5 A's applied to exercise[163]

Stage	Area of Focus	Example Questions for Patients
Assess	Beliefs, behaviors, knowledge, and readiness to change	*"How do you feel about exercising?"* *"On a scale of 1-10, with 1 being not ready and 10 being very ready, how ready are you to start exercising?"*
Advise	Current recommendations (based on individual health)	*"Can I share some information with you about exercise? The current national guidelines recommend 150 minutes of moderate aerobic physical activity weekly."*
Agree	Goals based on patient's interest and confidence	*"Based on your desire to exercise more, you are committing to walk for 15 minutes 3 times a week."*
Assist	Identify potential barriers and ensure social support for change	*"Is there anyone who you can walk with to keep you motivated and engaged?"*
Arrange	Follow-up, assistance, support, referral	*"Let's set up a follow-up appointment in 3 months to check in on how things are going."*

Motivational Interviewing

Motivational interviewing is a, "person-centered method of guiding to elicit and strengthen personal motivation for change."[165] Motivational Interviewing theorizes the importance of internal motivations and promotes patients toward "Change Talk" (e.g., "I need to exercise more") and away from "Resistance Talk" (e.g., "I'm too busy to go to the gym"). Like the "5 A's," there are several steps in Motivation Interviewing:

- engage patients to elicit patient perspectives (e.g., **"**What would you like about exercising more?")
- focus on possible directions ("Can I share with you some health benefits of swimming?")
- evoke "change talk" ("How were you successful at starting up a swimming plan in the past?")
- plan for commitments ("What will you do to start swimming again?").

Although most of the evidence showing benefit of Motivational Interviewing is from outside the primary care setting, one research study has demonstrated the efficacy of a brief curriculum for and written assessment of Motivational Interviewing skills in primary care.[166]

It is important to identify possible barriers to change and develop solutions in partnership with patients.[167] Some examples of questions that can elicit potential barriers include,

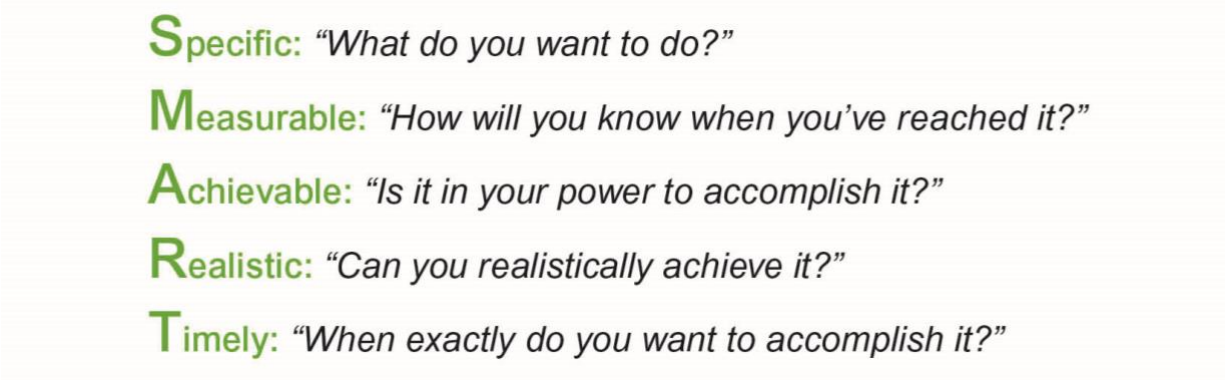
- *"What might get in the way of you walking in the morning before work?"*
- *"What might make it hard for you to walk in the morning before work?"*

Once barriers are clarified, it can then be helpful to focus on facilitators of change. These include resources that will support lifestyle modifications, including local resources (e.g., gyms, cooking classes, libraries, food pantries and meal-delivery services, YMCA and YWCA, worksite wellness programs, Walk with a Doc, and local park) as well as virtual resources (e.g., American College of Lifestyle Medicine tools and resources; Health and wellness coaches; wearable devices such as FitBit; and apps such as Noom, Headspace, and MyFitnessPal).

SMART Goals

Clarifying barriers and facilitators allow for the creation of realistic behavior change goals. A popular method for goal setting is to agree on "SMART Goals" (Figure 13), which are specific, measurable, attainable, relevant, and timely.[168] For example, a non-SMART goal of "I want to exercise more" can be converted into a SMART goal that is much more likely to generate results, such as, "I will walk for 30 minutes on Tuesdays and Thursdays before I leave for work." SMART goals are supported by the U.S. Preventive Services Taskforce, American Diabetes Association, American Heart Association, Chronic Disease Self-Management Program, and Chronic Care Model.

Figure 13: setting SMART goals



In order for know whether SMART goals are achieved, it is critical for patients to self-monitor their behaviors.[167] It is important for primary care providers to encourage patient to track targeted behaviors to monitor success as well as obstacles. A provider can consider with the patient the question, *"How will you be able to know if you are reaching your goals?"*, and request that patients bring records to follow-up visits.

BOTTOM LINE: To implement behavior change interventions in primary care, clinicians should utilize frameworks, including the transtheoretical model of change, the 5 A's, motivational interviewing, and SMART goals.

Specific strategies for behavior change to prevent cardiovascular disease in primary care

Although there is strong evidence for the benefits of lifestyle changes in preventing cardiovascular disease, there is limited research into primary care-based strategies for facilitating such changes. Instead,

practitioners can use well-established strategies for communicating important behavioral insights (Table 9).

Table 9: Suggestions for behavior change for nutrition and physical activity

Topic	Goal	Specifics
Nutrition	Provide simple insights on the benefits of plant-predominant diets	• Start filling a plate with vegetables, fruits, and grains to "crowd out" other foods • Eat the Rainbow resources (Figure 14) • Use MyPlate for patient-friendly schematic for well-balanced, plant-predominant diet (Figure 15)
Physical Activity	Write an "exercise prescription" [169]	• Highlight CDC guidelines for aerobic exercise and strengthening activities (Figure 16) • Tips and tools available at **exerciseismedicine.org**

When extra support is needed to facilitate behavior changes, patients can be referred to dieticians and exercise physiologists or fitness trainers. Dietician consultations in adult primary care are effective for improvement dietary quality, diabetes outcomes, and weight loss.[170] Insurance coverage for these services may vary. For example, patients with Medicare may have coverage for nutrition therapy services by a dietician if they have diabetes, chronic kidney disease, or a kidney transplant within the prior 36 months (https://www.medicare.gov/coverage/nutrition-therapy-services).

Figure 14: Eat the Rainbow

Figure 15: Dietary guidelines for a balanced diet[171]

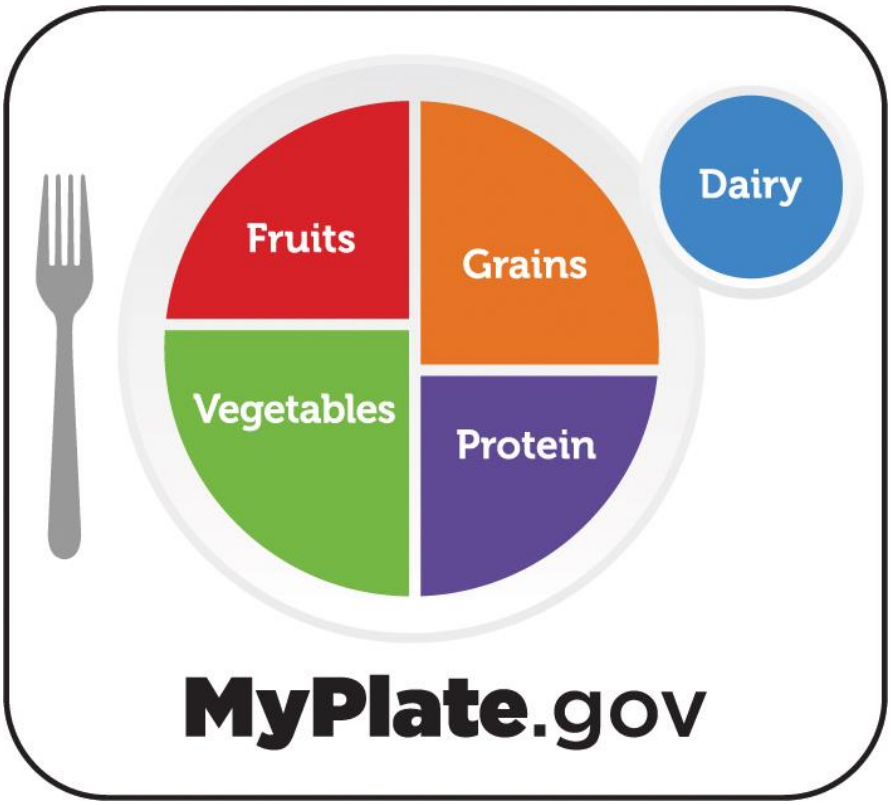


Figure 16: Exercise recommendations for adults[172]

Putting it all together

This evidence document has summarized the latest evidence for pharmacologic and non-pharmacologic strategies to prevent cardiovascular disease. The use of these strategies must always be tailored to each patient, based on individual risk of developing cardiovascular disease balanced against the risks of treatment. Because cardiovascular disease is common and the risks of treatment are small, many adults will be eligible for preventive therapy, either via lifestyle changes alone or in combination with a medication (typically a statin).

- For all adults 40-75 years old, risk of cardiovascular disease should be assessed every 4-6 years using a risk tool such as the Pooled Cohort Equation (PCE).
- Statins should be used in primary prevention for adults age 40-75 years with diabetes, an LDL ≥ 190, or a 10-year ASCVD risk of ≥5%.
- The intensity of statin should be determined based on risk; for most patients there is no specific LDL goal, but lipids should be monitored on therapy to assess for adherence.
- For adult older than age 75 years, statins still offer benefits and should not be discontinued based on age alone.
- Other lipid-lowering medications have a very limited role for primary prevention.
- Aspirin is not recommended for primary prevention of CVD in most patients.
- For adults older than age 60 years or at high risk of bleeding, aspirin should be discontinued if being used for primary prevention alone.
- Non-pharmacologic lifestyle interventions should be used to reduce risk of cardiovascular disease, including a diet high in fiber, high in fruits/vegetables, low in animal fat, and low in sodium; a mix of aerobic and anaerobic exercise; and smoking cessation.
- Clinicians should use existing tools and frameworks to promote behavior change and utilize available community and virtual resources.

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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This material was produced by Benjamin Rome, M.D., M.P.H., Instructor in Medicine (principal editor); Dae Kim, M.D., Sc.D., Associate Professor of Medicine; Jerry Avorn, M.D., Professor of Medicine; Jacob Mirsky, M.D., Instructor in Medicine; Alex Chaitoff, M.D., Clinical Fellow in Medicine; Prihatha Narasimmaraj, M.D., Clinical Fellow in Medicine; Ross Pollack, M.D., Clinical Fellow in Medicine; all at Harvard Medical School; Dawn Whitney, R.N., M.S.N., Lecturer at Northeastern University and University of Massachusetts, Boston; and Ellen Dancel, Pharm.D., M.P.H., Director of Clinical Materials Development at Alosa Health. Drs. Avorn, Chaitoff, Narasimmaraj, Pollack, and Rome are physicians at the Brigham and Women's Hospital, Dr. Mirsky is at Massachusetts General Hospital, and Dr. Kim practices at the Beth Israel Deaconess Medical Center and Hebrew Senior Life, all in Boston. None of the authors accepts any personal compensation from any drug company.

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