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Ohio Cardiovascular and Diabetes Health Collaborative

Atherosclerotic Cardiovascular Disease Risk Reduction:
Management of Lipids

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Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in the U.S. for people with diabetes mellitus (DM). In 2015, the annual cost of ASCVD was $126 billion with approximately $37.3 billion of this cost associated with DM.[1-3]

The management of elevated lipids in patients with and without DM is similar, with the major exception being the recommendation for statin therapy in all patients over age 40 with DM.[3,4] For individuals with DM, the American Diabetes Association (ADA) recommends yearly assessment of risk factors including obesity, hypertension, dyslipidemia, and smoking; family history for premature coronary disease or chronic kidney disease; and the presence of albuminuria.[3] The following document summarizes the management of lipids for prevention of ASCVD in patients with and without DM based on current guidelines.[3-5]

For individuals with DM, the American Diabetes Association (ADA) recommends yearly assessment of risk factors including obesity, hypertension, dyslipidemia, and smoking; family history for premature coronary disease or chronic kidney disease; and the presence of albuminuria.

Primary and Secondary ASCVD Prevention

Primary Prevention

In adults 40 to 75 years of age without ASCVD, the first step in developing a primary prevention strategy is to assess the long-term ASCVD risk using pooled cohort equations (PCEs).[4] The American Heart Association (AHA) guidelines (Figure 1) recommend using risk enhancing factors in individuals with borderline (5% to 7.5%) or intermediate (7.5% to < 20%) 10-year ASCVD risk by PCE (Table 1).
In patients where the risk-benefit of statin therapy is borderline or not clear, a coronary artery calcium (CAC) score may be helpful (Table 2).[4,6-8]

Patients with DM are considered to be at high risk for ASCVD and will benefit from moderate intensity statin therapy for primary prevention. Additional DM-specific risk enhancers and primary prevention therapy recommendations for patients with DM, based on age and risk considerations, are summarized in Table 1 and Table 3a, respectively.

Secondary Prevention

Patients with established ASCVD, independent of presence of DM, are at high risk for recurrent events (Figure 2). Recent acute coronary syndrome (within the past 12 months), history of myocardial infarction, history of ischemic stroke, and symptomatic peripheral artery disease, are considered major ASCVD events, regardless of DM status. Additional high-risk conditions include being age 65 years and older, heterozygous familial hypercholesterolemia, history of prior coronary revascularization, DM, hypertension, chronic kidney disease (eGFR 15-59 ml/min/1.73 m^2), congestive heart failure, current smoking, and persistently elevated LDL-C ≥ 100 mg/dL. Patients with multiple major ASCVD events or one major ASCVD event plus multiple high-risk conditions are considered to be "very high-risk" patients.[4] The recommendations for secondary prevention are based on age and risk considerations and are summarized in Table 3b.

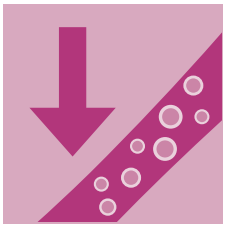
ASCVD Risk Reducing Interventions

Lifestyle

Medical therapy to reduce long-term cardiovascular risk should include counseling for nutrition, physical activity, smoking cessation, and psychosocial care of patients with and without DM.[9] Major cardiovascular guidelines from the ADA,[3] AHA,[4] and American Association of Clinical Endocrinology (AACE),[5] recommend promoting healthful eating patterns to achieve and maintain ideal body weight and to attain individualized glycemic, blood pressure, and lipid goals. Lifestyle modifications including a Mediterranean-style diet,[10, 11] or DASH diet rich in polyunsaturated and monosaturated fats;[12,13] weight loss of 5% or more of total body weight in individuals who are overweight or obese;[14] and 150 minutes or more of moderate to vigorous intensity aerobic activity per week can improve blood glucose as well as lipids.[15] To maximize the likelihood of success, nutrition plans should consider an individual's personal preferences as well as social and demographic factors including food insecurity and access.[9]

Statins as a LDL–Cholesterol Lowering Therapy

Statins, or hydroxymethylglutaryl coenzyme A (HMG-CoA) inhibitors, lower cholesterol by inhibiting the rate-limiting step of endogenous cholesterol production. In addition to lifestyle interventions, statin therapy remains the cornerstone of lipid management in all patients. Statins reduce the risk of ASCVD events and cardiovascular mortality in patients with and without DM, both for primary and secondary prevention. A meta-analysis by Cholesterol Treatment Trialist Collaborators[16] of major statin primary and secondary prevention trials (N = 169,138) demonstrated that for every 39 mg/dL reduction in LDL-C, there was a 22% reduction in relative risk of major vascular events and a 10% reduction in all-cause mortality. The effect was significant in patients with different demographic and baseline factors.



Intensity of statin therapy. The 2018 AHA/ACC lipid guidelines[4] define lipid-lowering treatment targets for statin therapy to reduce LDL cholesterol: ≥ 50% reduction as high intensity, 30% to 49% reduction as moderate intensity, and < 30% reduction as low intensity (Table 4). The 2020 AACE lipid guidelines[5] defines lipid-lowering treatment targets based upon LDL targets. These approaches are compared in Table 5.

Side effects and new-onset diabetes mellitus. The incidence of statin-associated side effects is low with most patients being able to tolerate side effects by either lowering the dose or selecting an alternative statin. The most frequent side effect associated with statin use is muscle symptoms such as myalgia (1% to 5% in randomized clinical trials and 5% to 10% in observational studies),[4] myositis/myopathy, rhabdomyolysis, or statin-associated autoimmune myopathy.[17, 18] Elevation of liver transaminases is infrequent and statin therapy rarely leads to hepatic failure. Statin use has been shown to increase the risk of new-onset DM in a dose dependent manner. The incidence is more frequent in the presence of other risk factors like body mass index ≥ 30 kg/m^2, fasting glucose ≥ 100 mg/dL, metabolic syndrome and A1C ≥ 6%.[19-22] The AHA guidelines[4] recommend continuing treatment with statin therapy in patients with increased DM risk or new-onset DM with emphasis on net clinical benefit.

Statin therapy and ezetimibe. Ezetimibe is a cholesterol absorption inhibitor that blocks the cholesterol transport Nieman Pick C1-Like 1 (NPC1L1) protein to inhibit intestinal and biliary absorption of cholesterol. Ezetimibe is generally used as an adjunct to statin therapy in very high-risk patients or in patients intolerant of statins. The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IM-PROVE-IT),[23] involving 18,144 participants with acute coronary syndrome (27.2% with DM), found that adding ezetimibe therapy (10 mg/day) to simvastatin (40 mg/day) led to an incremental lowering of LDL-C and resulted in 2% absolute risk reduction in the primary endpoint of death from cardiovascular causes, major coronary event, or non-fatal myocardial infarction (MI) (34.7% vs. 32.7%, p = 0.016).

Statin therapy and PCSK9 inhibitors. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, are human monoclonal antibodies that bind to PCSK9 receptors and reduce the degradation of LDL receptors. Their use is generally reserved for secondary prevention in very high-risk patients with LDL-C ≥ 70 mg/dL on maximally tolerated lipid-lowering therapy.[4] Evolucumab[24] and alirocumab,[25] both administered subcutaneously, on a background of maximally tolerated statin therapy was shown to reduce the risk of composite of cardiovascular death, myocardial infarction, stroke hospitalization of unstable angina, or coronary revascularization (Hazard Ratio [HR], 0.85; 95% Conference Interval [CI], 0.79 to 0.92).[24] The cost effectiveness of PCSK9 inhibitors is low, ranging from $141,700 to $450,000 per quality-adjusted life year added.[26]

Bempedoic Acid. The recently FDA-approved agent, bempedoic acid, inhibits ATP citrate lyase and cholesterol synthesis upstream of HMG-CoA reductase, the rate-limiting step of cholesterol biosynthesis.[27] Its effect is additive when used with ezetimibe but less than additive when added to a statin. In a recent clinical outcome trial, bempedoic acid was shown to reduce the primary CVD composite outcome but not stroke or cardiovascular or all-cause mortality.[28] High-sensitivity C-reactive protein was also reduced. It was associated with lower levels of myalgias compared to statins but nonsignificant increased rates of gout and cholelithiasis. Bempedoic acid increases simvastatin and pravastatin levels, and these statins should not be used in doses above 20 mg/day, and 40 mg/day respectively.

Hypertriglyceridemia Treatment

Statin Therapy and Fibrate

The effect of hypertriglyceridemia on cardiovascular risk is unclear; however, patients with severe hypertriglyceridemia (levels ≥ 500 mg/dL) need to be evaluated for secondary causes. Hypertriglyceridemia in patients with DM is often very responsive to improved DM control. To reduce the risk of pancreatitis, treatment of severe hypertriglyceridemia consists of the combination of diet, lifestyle, and statin therapy (especially if ASCVD risk is elevated). If there is persistent hypertriglyceridemia, add fibric acid derivatives or omega-3 fatty acids.[3] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial,[29] involving 5,518 patients with type 2 DM, the combination of fenofibrates with simvastatin as compared to simvastatin alone showed no difference in the composite end point of non-fatal MI, non-fatal stroke, and death from cardiovascular causes (p = 0.32).

Statin Therapy and Omega-3 Fatty Acids

The omega-3 fatty acid icosapent ethyl is a highly purified eicosapentaenoic acid (EPA) that has been shown to lower triglyceride (TG) levels. In the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT),[30] which followed patients with established cardiovascular disease or DM and other risk factor, icosapent ethyl was shown to reduce ischemic events including cardiovascular death, with triglyceride levels of 135 to 499 mg/dL, on a background of optimal statin therapy. Risk reduction was shown to be independent of triglyceride lowering and suggests a mechanism specific to EPA rather than TG reduction.

Statin Therapy and Niacin

In addition to elevated LDL cholesterol, low levels of high-density lipoprotein (HDL) is an independent predictor of risk for cardiovascular disease. However, no benefit of niacin added to a statin was seen in two recent trials.[31,32] Current ADA[3] and AHA[4] guidelines do not recommend combination therapy with a statin and niacin.

Table 1. Risk Enhancing Factors for Clinician-Patient Risk Discussion

Family history of premature ASCVD (males <55 years; females <65 years)
Primary hypercholesterolemia (LDL-C 160-189 mg/dL; non-HDL-C 190-219 mg/dL)
Metabolic syndrome*
Chronic kidney disease (eGFR 15-59 mg/min/1.73m^2 with or without albuminuria)
Chronic inflammatory conditions like psoriasis, rheumatoid arthritis, or HIV/AIDS
History of premature menopause (before age 40 years)
History of pregnancy-associated conditions such as preeclampsia
High-risk race/ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers 1. Persistently elevated primary hypertriglyceridemia (≥175 mg/dL) 2. Elevated high-sensitivity C-reactive protein (≥2 mg/dL) 3. Elevated lipoprotein(a) ≥50 mg/dL 4. Elevated apolipoprotein B ≥130 mg/dL 5. Ankle-brachial index <0.9
Additional Diabetes-Specific Risk Enhancers 1. Long duration of diabetes (≥10 years for type 2 diabetes and ≥20 years for type 1 diabetes) 2. Albuminuria (≥30 mcg/mg) 3. Neuropathy 4. Retinopathy
*Presence of any three - increased waist circumference, elevated triglycerides ≥175 mg/dL, elevated blood pressure, elevated glucose, and low HDL-C

ASCVD = atherosclerotic cardiovascular disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

Adapted from 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[4]

Table 2. Role of Coronary Artery Calcium Score in Influencing Statin Use

Proposed Decision-Making Approach to Selective Use of Coronary Artery Calcium (CAC) Measurement for Risk Prediction Using 10-year Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimate Plus CAC Score to Guide Statin Therapy

Patient's 10-year ASCVD risk estimate	<5%	5%-7.5%	>7.5%-20%	>20%
Consulting ASCVD risk estimate+risk enhancers+CAC				
If CAC score =0	Statin not recommended	Statin not recommended	Statin not recommended	**Recommended statin**
If CAC score >0	Statin not recommended	**Consider for statin**	**Recommended statin**	**Recommended statin**
Does CAC score modify treatment plan?	☒ CAC not effective for this population	☑ CAC can reclassify risk up or down	☑ CAC can reclassify risk up or down	☒ CAC not effective for this population

Adapted from *Coronary calcium score and cardiovascular risk*[8]

Table 3a. Primary Prevention of Atherosclerotic Cardiovascular Disease (ASCVD) in Patients with Diabetes

Age Group	Additional Considerations	Recommendation	COR
20-39 years	Long duration (≥10 years for type 2 diabetes and ≥20 years for type 1 diabetes), albuminuria ≥30 mcg/mg, eGFR <60 ml/min/m^2, retinopathy, neuropathy, and ankle-brachial index <0.9	May be reasonable to initiate statin therapy	IIb
40-75 years	Regardless of estimated 10-year ASCVD risk	Moderate intensity statin therapy	I
40-75 years	LDL-C of 70-189 mg/dL	Assess 10-year risk using race and sex specific pooled cohort equations	IIa
>75 years	Already on statin therapy	Continue with statin therapy	IIa
>75 years	Not on statins	Clinician-patient discussion of risk/ benefits	IIb
Any age	Multiple ASCVD risk factors	High intensity statin therapy to reduce LDL-C by ≥50%	IIa
Any age	ASCVD risk ≥20%	Add ezetimibe to statin therapy if a high-intensity statin cannot be tolerated or does not lower LDL-C, as expected, by ≥50%	IIb

ASCVD = atherosclerotic cardiovascular disease (ASCVD); COR = class (strength) of recommendation; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol

Adapted from AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[4]

Table 3b. Secondary Prevention of Atherosclerotic Cardiovascular Disease (ASCVD)

Age Group	Additional Considerations	Recommendation	COR
≤75 years	No contraindications	High intensity statin therapy to reduce LDL-C by ≥50%	I
	High intensity statin therapy contraindicated/ side effects	Moderate intensity statin therapy	I
	Very high risk on maximally tolerated statin, LDL-C>70 mg/dL	Add ezetimibe	I
	Very high risk patients with LDL-C>70 mg/dL despite maxmally tolerated LDL-C lowering therapy	Add PCSK9 inhibitor after discussion	IIa
	Clinical ASCVD on maximally tolerated statin, LDL-C>70 mg/dL	Consider adding ezetimibe	IIb
>75 years		High intensity or moderate intensity statin after discussion with the patient	IIa

ASCVD = atherosclerotic cardiovascular disease; COR = class (strength) of recommendation; LDL-C = low-density lipoprotein cholesterol

Adapted from 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[4]

Table 4. Statin Therapy Dosing for LDL-Cholesterol Reduction

High Intensity (≥50% reduction in LDL Cholesterol)	**Moderate Intensity** (30%-49% reduction in LDL Cholesterol)	**Low Intensity** (<30% reduction in LDL Cholesterol)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40-80 mg	
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg bid	
	Pitvastatin 1-4 mg	

Adapted from 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[4]

Table 5. Comparison of AACE/ACE and AHA/ACC Approaches to Lipid Management

AACE/ACE Risk Categories and LDL-C Goal

Categories		LDL-C Goal
Extreme Risk	Progressive ASCVD including unstable anigna Established clinical ASCVD plus DM or CKD ≥3 or HeFH History of premature ASCVD (<55 year, male; <65 years, female)	<55 mg/dL
Very High Risk	Established clinical ASCVD or recent hospitalization for ACS, carotid, or peripheral vascular disease, or 10-year risk >20% Diabetes with ≥1 risk factor(s)* CKD ≥3 with albuminuria HeFH	<70 mg/dL
High Risk	≥2 risk factors and 10-year risk 10%-20% Diabetes or CKD ≥3 with no other risk factors	<100 mg/dL
Moderate Risk	<2 risk factors and 10-year risk <10%	<100 mg/dL
Low Risk	No risk factors	<130 mg/dL

Risk Factors* Advancing age, elevated non-HDL-C, elevated LDL-C, DM, HTN, CKD, smoking, family history of ASCVD

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol

Adapted from American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease[5]

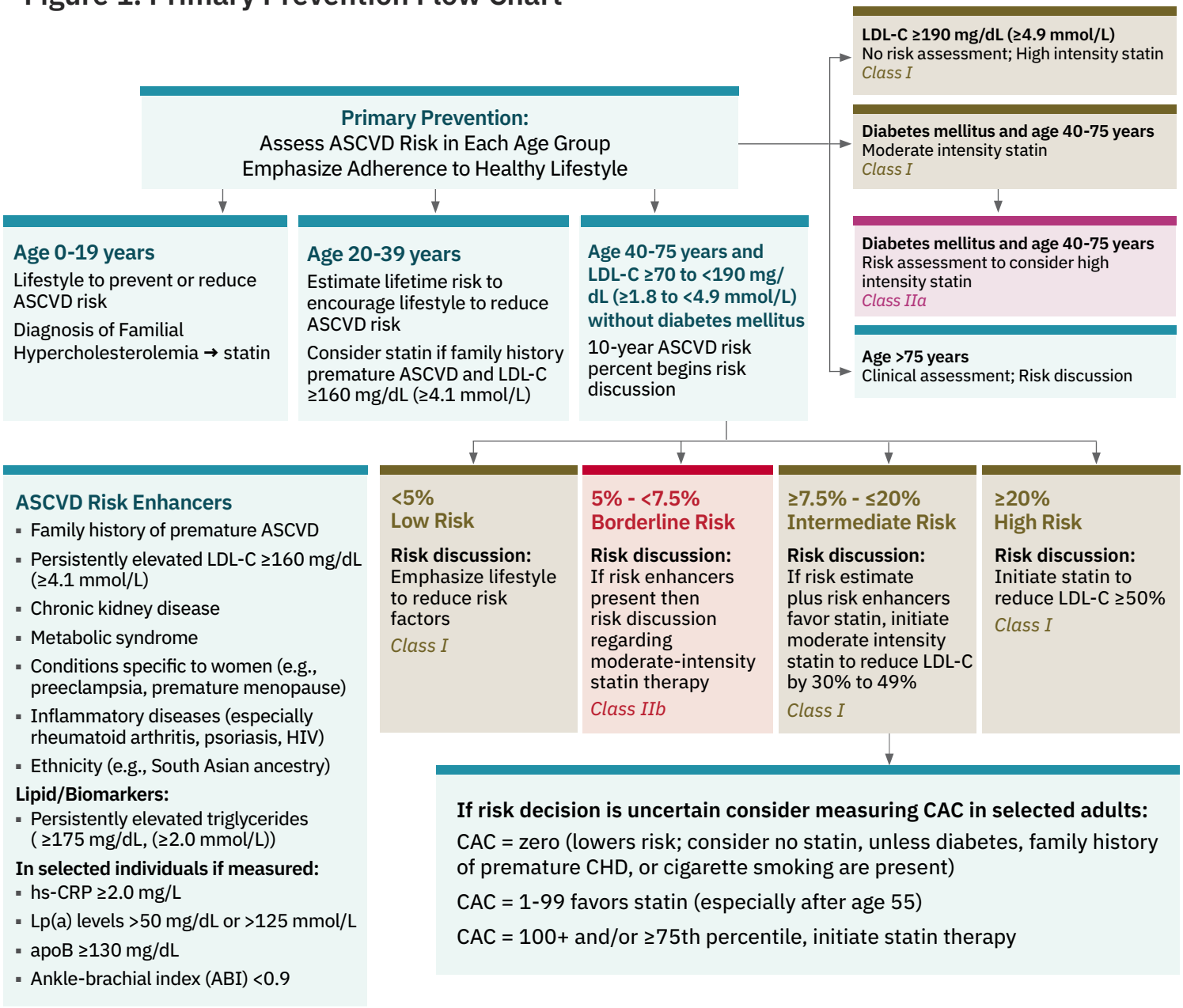
AHA/ACC Categories and LDL-C Goal/Recommendation

Categories		LDL-C Goal/Recommendation	Comments
Primary Prevention ***Mostly for age 40-75 years***			
ASCVD High Risk >20%		High intensity statin (LDL-C reduction ≥50%)	
ASCVD Intermediate Risk (≥7.5% to <20%)		Moderate intensity if risk enhancers^	
ASCVD Borderline Risk (5% to <7.5%)		Risk discussion if risk enhancers^	
ASCVD Low Risk (5%)		Lifestyle changes	
LDL-C ≥190 mg/dL		High intensity statin (LDL-C reduction ≥50%)	
Diabetes Mellitus	Ages 20-39	Consider statin therapy if risk enhancers^ present	
	Ages 40-74	Moderate intensity statin (LDL-C reduction 30%-49%)	
Secondary Prevention			
ASCVD Very High Risk	Multiple major ASCVD events (recent ACS, history of MI, history of ischemic stroke, symptomatic peripheral artery disease) and multiple high risk conditions*	High intensity statin (LDL-C reduction ≥50% and LDL-C <70 mg/dL)	Consider adding PCSK9i to ezetimibe and maximal statin if LDL-C ≥70 mg/dL
ASCVD Not At Very High Risk	Age ≤75 years	High intensity statin (LDL-C reduction ≥50% and LDL-C <70 mg/dL)	If LDL-C ≥70 mg/dL can add ezetimibe
	Age >75 years	Moderate or high intensity statin	

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PCSK9i = PCSK9 inhibitor

Adapted from 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[4]

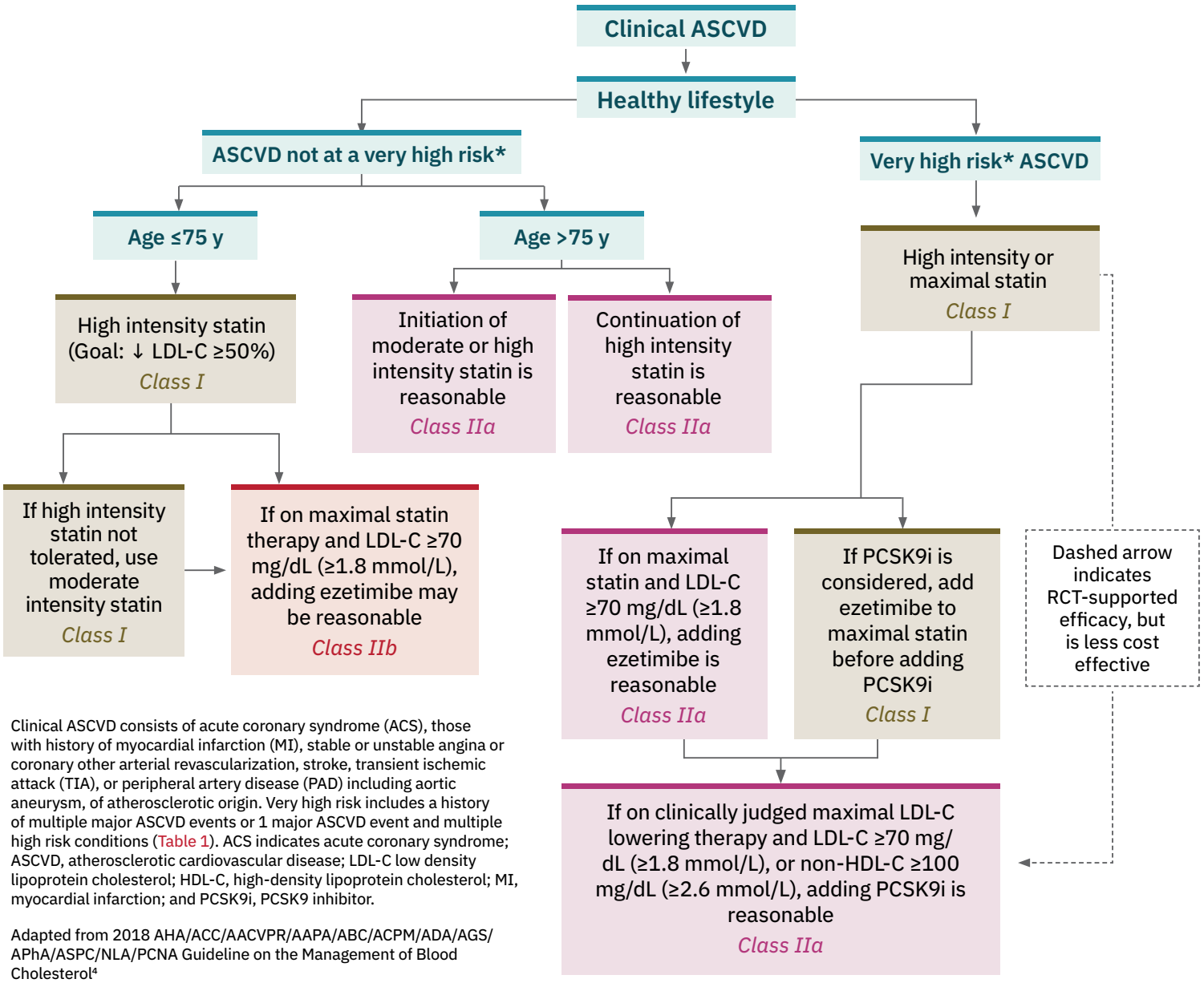
Figure 1. Primary Prevention Flow Chart



apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a), = lipoprotein (a)

Adapted from 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[4]

Figure 2. Secondary Prevention Flow Chart



Clinical ASCVD consists of acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, of atherosclerotic origin. Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high risk conditions (Table 1). ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; LDL-C low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; and PCSK9i, PCSK9 inhibitor.

Adapted from 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[4]

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