Metabolic Syndrome: A Focus on Hypertension, Dyslipidemia, and Obesity: Module 1

Michigan Center for Clinical Systems Improvement

(Mi-CCSI)

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Objectives

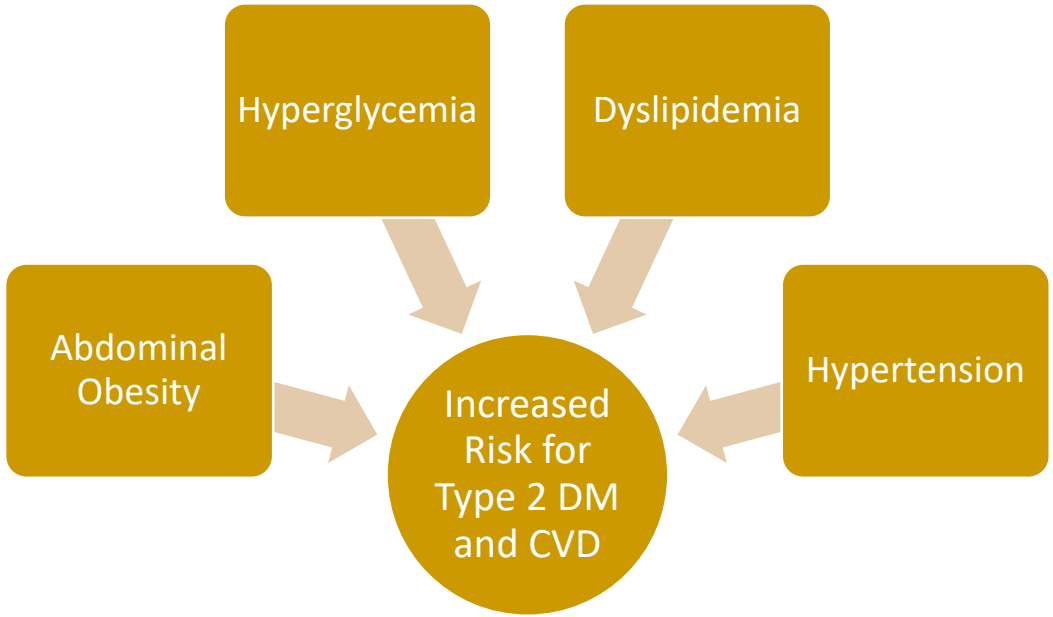
At the conclusion of this presentation, the participant will be able to:

1. Describe the concept of the metabolic syndrome and its implications.
2. Identify the role obesity plays in the pathophysiological processes associated with the metabolic syndrome.
3. List treatment targets and treatment strategies for hypertension and dyslipidemia.

Metabolic Syndrome

Metabolic Syndrome

- Also sometimes referred to as *insulin resistance syndrome* or *syndrome X*
- The co-occurrence of metabolic risk factors for both type 2 diabetes mellitus (DM) and cardiovascular disease (CVD) suggest the existence of a *metabolic syndrome*



Meigs JB. Metabolic syndrome (insulin resistance syndrome or syndrome X). In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2020.

Metabolic Syndrome

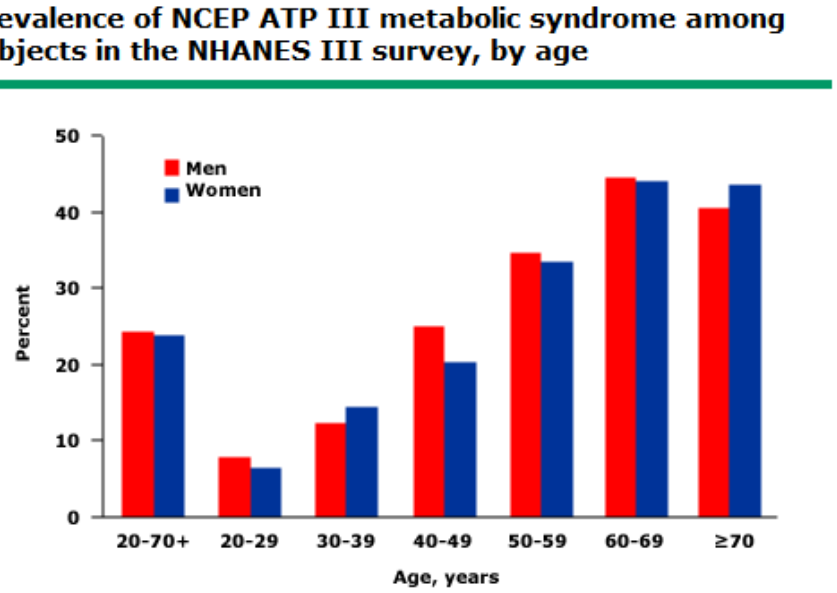
- Definition from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)

Presence of Three of the Following Five Traits
Abdominal obesity, defined as a waist circumference ≥102 cm (40 in) in men and ≥88 cm (35 in) in women
Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
Serum high-density lipoprotein (HDL) cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL cholesterol
Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure
Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose

Meigs JB. Metabolic syndrome (insulin resistance syndrome or syndrome X). In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2020.

Metabolic Syndrome

- Based on data from the National Health and Nutrition Examination Survey (NHANES) III survey, prevalence is increasing
  - 22% in a 1988-1994 cohort
  - 34.5% in a 1999-2002 cohort
- Patients with metabolic syndrome are at increased risk of type 2 DM and CVD
  - Metabolic syndrome has also been associated with fatty liver disease, chronic kidney disease, obstructive sleep apnea and multiple other disorders



Meigs JB. Metabolic syndrome (insulin resistance syndrome or syndrome X). In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2020.

Risk Factors for Metabolic Syndrome

Obesity

- In the NHANES III study, metabolic syndrome was present in only 5% of normal weight individuals, but 22% and 60% of overweight and obese individuals, respectively
- In a cohort of the Framingham Heart Study, an increase in weight of ≥ 2.25 kg (~ 5 lbs) over 16 years was associated with a 21-45% increase in risk
- A large waist circumference alone identifies 46% of individuals who will develop metabolic syndrome within 5 years

Other Factors

- Parental history
- Age, race, and sex
- Postmenopausal status
- Smoking
- Low household income
- Diet (excess carbohydrates or soft drink and sugar-sweetened beverage consumption)
- Physical inactivity and poor cardiorespiratory fitness
- Atypical antipsychotic medications, especially clozapine

Meigs JB. Metabolic syndrome (insulin resistance syndrome or syndrome X). In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2020.x

Metabolic Syndrome

- The Endocrine Society suggests evaluation at three-year intervals for individuals with one or more risk factor

Meigs JB. Metabolic syndrome (insulin resistance syndrome or syndrome X). In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2020.x

Metabolic Syndrome

Two major therapeutic goals

1. Treat underlying causes (overweight/obesity and physical inactivity) by intensifying weight management and increasing physical activity

2. Treat cardiovascular (CV) risk factors if they persist despite lifestyle modification

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Metabolic Syndrome

Two major therapeutic goals

1. Treat underlying causes (overweight/obesity and physical inactivity) by intensifying weight management and increasing physical activity
   - Reduce body weight by 7-10% during year one and continue weight loss thereafter until BMI < 25 kg/m^2
   - Complete at least 30 minutes (preferably ≥ 60 minutes) of continuous or intermittent moderate intensity exercise 5 times per week, but preferably daily
   - Reduce the intake of saturated fat, trans fat, and cholesterol
2. Treat CV risk factors if they persist despite lifestyle modification
   - Glycemic control in patients with DM
   - Treatment of HTN
   - Lowering of serum cholesterol according to recommended guidelines

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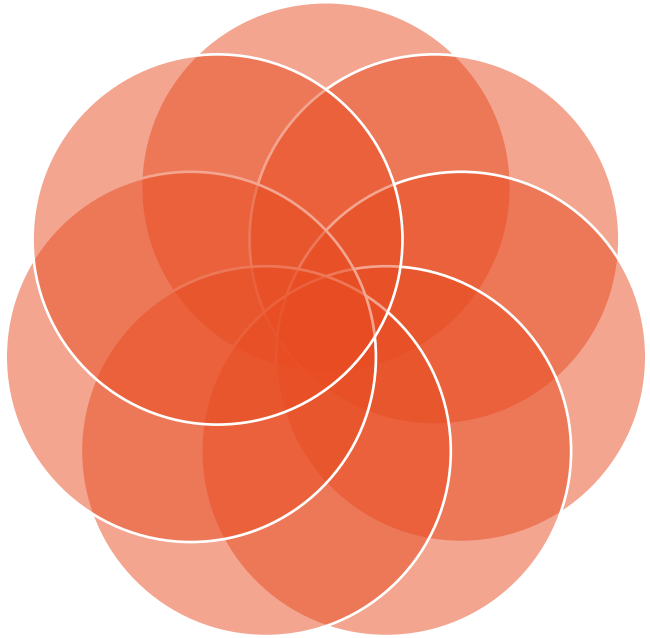
Obesity

Obesity



Perreault L. Obesity in adults: Prevalence, screening, and evaluation. In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2020.

Obesity

- BMI screening should be done for all adult patients as a component of the routine physical
  - BMI = (weight/2.205)/(height/39.37)^2
- Waist circumference should also be measured for those with a BMI between 25 and 35 kg/m^2
- Overall risk status should be evaluated for patients with BMI ≥ 25 kg/m^2 or a waist circumference ≥ 35 (women) or ≥ 40 (men) inches

Classification	BMI (kg/m^2)
Underweight	< 18.5
Normal weight	≥ 18.5 to 24.9
Overweight	≥ 25 to 29.9
Class I Obesity	30 to 34.9
Class II Obesity	35 to 39.9
Class III Obesity	≥ 40

Perreault L. Obesity in adults: Prevalence, screening, and evaluation. In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2020.

Health Consequences of Obesity

- Obesity has surpassed smoking as the number one cause of preventable disease and disability
- > 230 comorbidities and complications of obesity have been identified
- Individuals that are overweight or obese have a higher risk of HTN, hypercholesterolemia, and DM compared to normal weight individuals

Perreault L. Overweight and obesity in adults: Health consequences. In: UpToDate, Kunins L (Ed), UpToDate, Waltham, MA, 2020.

Hypertension

Epidemiology

- Treatment of HTN is the most common reason for an office visit and for the use of chronic prescription medications in non-pregnant adults in the United States
- Nearly half of adults older than 20 years of age in the United States have HTN
- 53% of adults already on anti-hypertension medications have a blood pressure (BP) that remains above goal
- Higher prevalence with increasing age and in non-Hispanic black populations

Basile J and Bloch MJ. Overview of hypertension in adults. In: UpToDate, Forman JP and Kunins L (Eds), UpToDate, Waltham, MA, 2020.

Egan BM. The prevalence and control of hypertension in adults. In: UpToDate, Forman JP and Kunins L (Eds), UpToDate, Waltham, MA, 2020.

Classification

Classification	Systolic (mm Hg)*	Diastolic (mm Hg)*
Normal BP	< 120	< 80
Elevated BP	120-129	< 80
HTN Stage 1	130-139	80-89
HTN Stage 2	≥ 140	≥ 90

** If there is a disparity in category between the systolic and diastolic values, the higher value determines the stage*

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Ambulatory and Self-Measured BP Monitoring

- Ambulatory BP monitoring (ABPM) is performed using a device that is worn by the patient that takes BP measurements over a 24- to 48-hour period
  - Records BP at preset intervals
- Self-measured BP (SMBP) is done by the patient over a limited time period using proper technique
- Indications for ABPM and/or SMBP
  - Diagnosing white coat and masked HTN
  - Confirming a new diagnosis of hypertension
  - Evaluating the effectiveness of therapy
  - Confirming that BP is not controlled when resistant hypertension is suspected
- All-cause mortality and the risk of cardiovascular events correlate more closely with 24-hour, daytime, or nighttime ABPM than with the office-based blood pressure measurement.

Townsend RR and Cohen J. Out-of-office blood pressure measurement: Ambulatory and self-measured blood pressure monitoring. In: UpToDate, Forman JP and Kunins L (Eds), UpToDate, Waltham, MA, 2020.

Classification

Townsend RR and Cohen J. Out-of-office blood pressure measurement: Ambulatory and self-measured blood pressure monitoring. In: UpToDate, Forman JP and Kunins L (Eds), UpToDate, Waltham, MA, 2020.

Classification of white coat and masked hypertension [1-3]

Classification	Alternative name(s)	Antihypertensive treatment status	Office (ie, clinic) blood pressure	Mean out-of-office blood pressure
White coat hypertension	Untreated white coat hypertension; isolated office hypertension	Not taking antihypertensive medication	At or above threshold for hypertension	Below threshold for hypertension
White coat effect	Treated white coat hypertension	Taking antihypertensive medication	Above goal blood pressure	At or below goal blood pressure
Masked hypertension	Untreated masked hypertension	Not taking antihypertensive medication	Below threshold for hypertension	At or above threshold for hypertension
Masked uncontrolled hypertension	Treated masked hypertension	Taking antihypertensive medication	At or below goal blood pressure	Above goal blood pressure

References:

1. *Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension 2018; 71:e13.*
2. *Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018; 39:3021.*

ABPM

- More predictive of target-organ damage and CV events than office BP readings
- Preferred method for confirming the diagnosis of HTN
- May also be considered for:
  - Suspected episodic HTN
  - Determining response to therapy in patients known to have substantial white coat effect
  - Hypotensive side effects in response to therapy
  - Resistant HTN
  - Autonomic dysfunction

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Screening and Diagnosis of Hypertension

- Simple and quick to perform at each office visit
- At a minimum
  - Annually for adults with previously normal BP
  - Semi-annually for adults with risk factors for hypertension or if their previous systolic BP was 120-129
- A diagnosis can be made without further confirmatory readings when the patient presents with:
  - Hypertensive urgency or emergency
  - Initial screening BP ≥160/≥100 mm Hg and known target end-organ damage
- For all other patients, diagnosis requires integration of home or ABPM

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Primary (Essential) HTN

- The pathogenesis of primary HTN is poorly understood
- Risk factors include:

Age	Obesity	Race	Family history
Reduced nephron number	High-sodium diet	Excessive alcohol consumption	Physical inactivity

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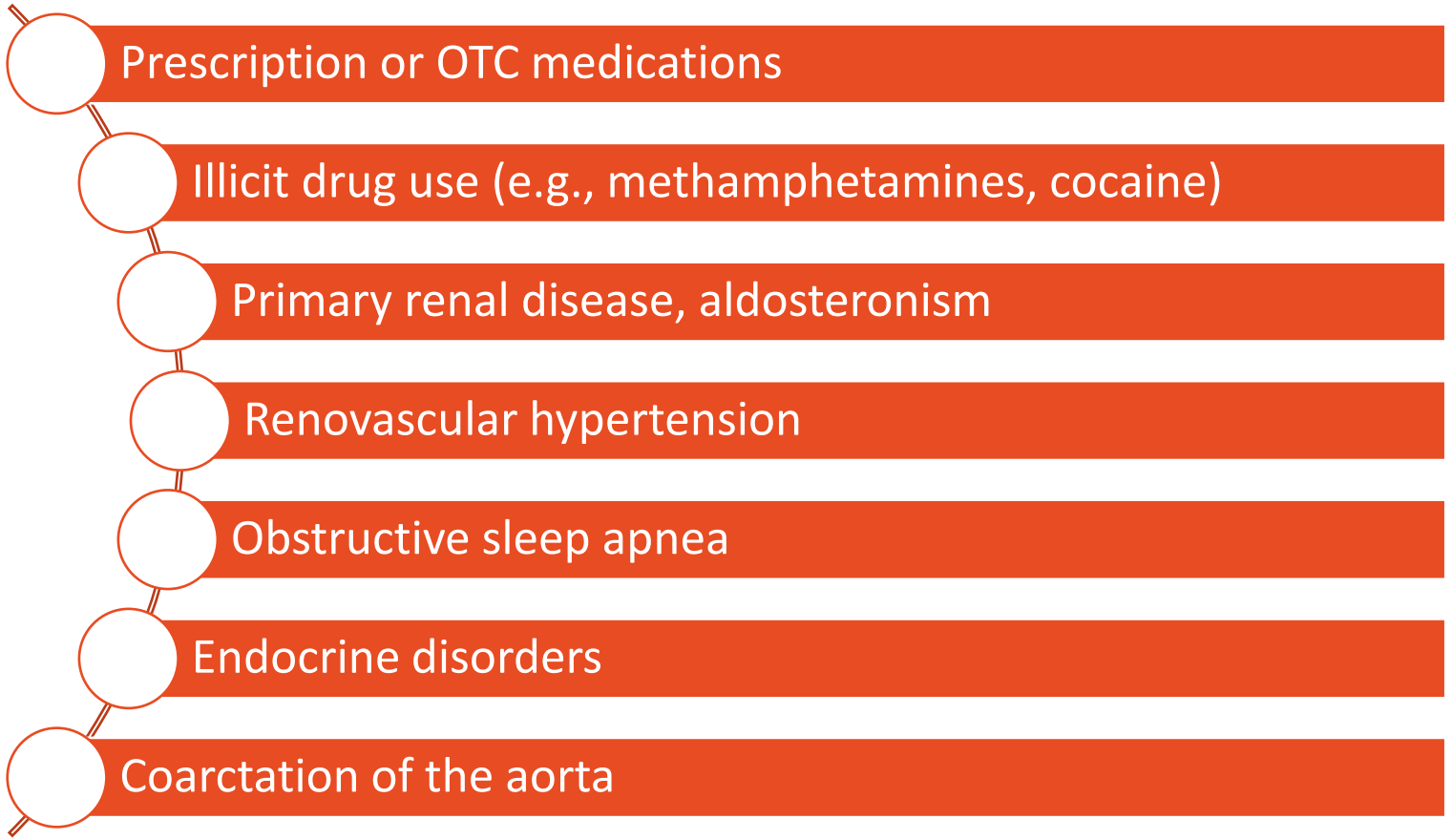
Secondary HTN



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Medication-Induced (Secondary) HTN

- Examples (not an all-inclusive list):
  - Oral contraceptives, particularly those containing higher doses of estrogen
  - Non-steroidal anti-inflammatory agents (NSAIDs), especially with chronic use
  - Antidepressants, including tricyclics (TCA), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors
  - Corticosteroids
  - Decongestants, such as phenylephrine and pseudoephedrine
  - Some weight-loss medications
  - Stimulants, including methylphenidate and amphetamines
  - Atypical antipsychotics, including clozapine and olanzapine

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Complications of HTN

- HTN is the most important modifiable risk factor for premature CVD
- The risk of a CV event increases as BP increases, with risk beginning to rise (for all age groups) with blood pressures > 115/75
- The risk of death from heart disease or stroke doubles for every 20 mm Hg higher systolic and 10 mm Hg higher diastolic BP
- Specific CV complications include left ventricular hypertrophy, heart failure, ischemic stroke, intracerebral hemorrhage, ischemic heart disease, chronic kidney disease and end-stage renal disease

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Approach to Treatment

- Comprehensive lifestyle modification should be prescribed to all patients with elevated BP or hypertension
- Not all patients with HTN require pharmacologic therapy
- Pharmacologic therapy should be initiated in the following circumstances:
  - Out-of-office daytime SBP ≥135 or DBP ≥85
  - Average office BP ≥ 140/90 if out-of-office readings not available
  - Out-of-office SBP ≥130 or DBP ≥80 (or average office SBP ≥130 or DBP ≥80) who have one or more of the following features
    - Established clinical cardiovascular disease
    - Type 2 diabetes mellitus
    - Chronic kidney disease
    - Age 65 years or older
    - An estimated 10-year risk of atherosclerotic cardiovascular disease of at least 10%
- Data is limited on the risks and benefits of initiating drug therapy in patients who have stage 1 hypertension and who are either > 75 years of age OR who have elevated risk of atherosclerotic cardiovascular disease (≥10%) but not clinical cardiovascular disease, diabetes, or chronic kidney disease

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Treatment Targets

Goal blood pressure according to baseline risk for cardiovascular disease and method of measuring blood pressure

	Routine/conventional office blood pressure (manual measurement with stethoscope or oscillometric device)*	Unattended AOBPM, daytime ABPM, or home blood pressure ¶
Higher-risk population Δ		
▪ Known ASCVD ◇ ▪ Heart failure ▪ Diabetes mellitus ▪ Chronic kidney disease ▪ Age ≥65 years § ▪ Calculated 10-year risk of ASCVD event ≥10% ¥	125 to 130/<80	120 to 125/<80
Lower-risk ‡		
▪ None of the above risk factors	130 to 139/<90	125 to 135/<90

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Initiating Therapy

- Therapy selection for specific drug classes is based on:
  - Evidence of decreased CV risk
  - BP lowering efficacy
  - Safety
  - Tolerability
  - Patient-specific ”compelling” indications
- Single-agent therapy is unlikely to be sufficient in most patients with a baseline BP 15 mm Hg or more above goal
- Initial therapy consists of two first-line agents from different classes for any patient whose BP is more than 20 mm Hg systolic or 10 mm Hg diastolic above goal

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“Compelling” Indications

Indication or Contraindication	ACE Inhibitor or ARB	Beta Blocker	Diuretic	Aldosterone Antagonist	Calcium Channel Blocker
Heart Failure with Reduced Ejection Fraction	✔	✔	✔	✔	
Post-Myocardial Infarction	✔	✔		✔	
Proteinuric Chronic Kidney Disease	✔				
Angina Pectoris		✔			✔
Atrial Fibrillation Rate Control		✔			✔ *
Atrial Flutter Rate Control		✔			✔ *

* Non-dihydropyridine

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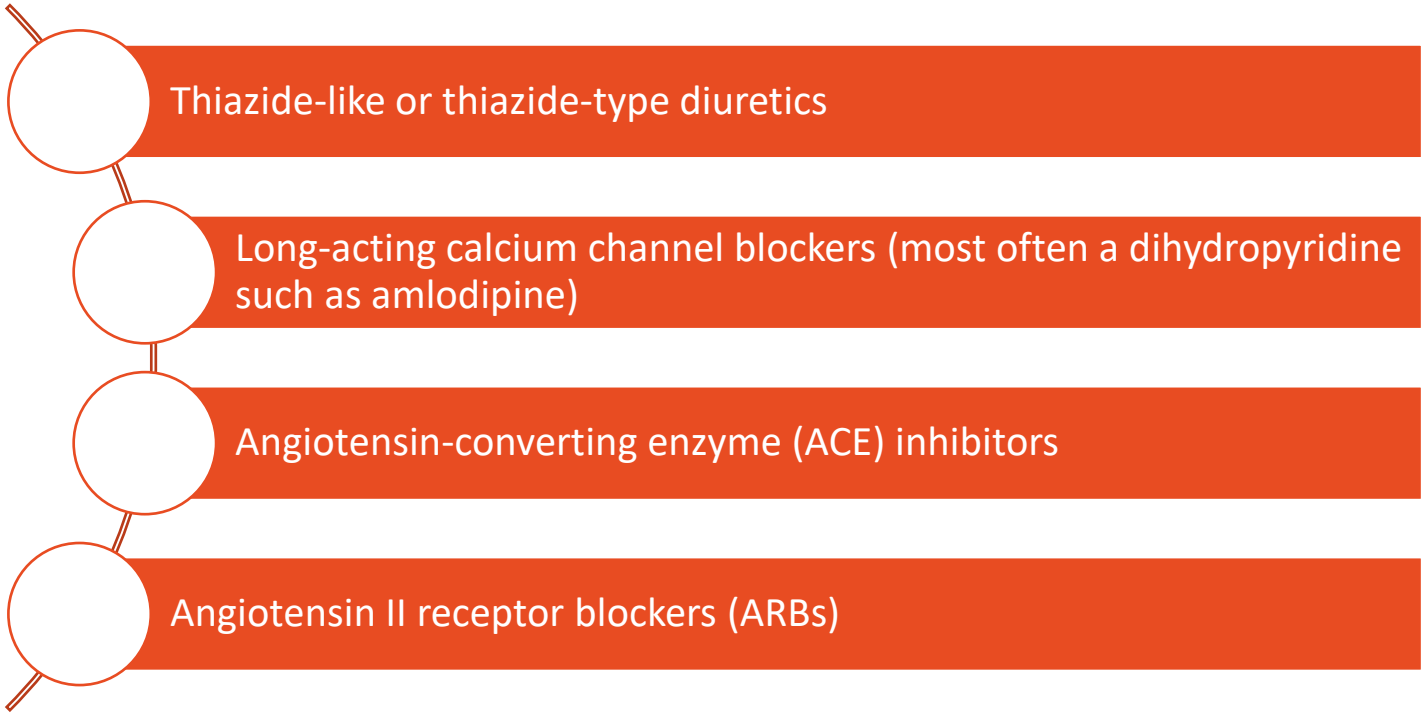
Initiating Therapy

- In the absence of a “compelling” indication, select initial therapy from among the following four drug classes



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Mann, JFE. Choice of drug therapy in primary (essential) hypertension. In: UpToDate, Forman JP (Ed), UpToDate, Waltham, MA, 2020.

Initiating Therapy

- Two agents:
  - Long-acting ACE inhibitor or ARB + long-acting dihydropyridine calcium channel blocker
  - Alternatively, ACE inhibitor or ARB + thiazide diuretic (less beneficial when HCTZ is used)
- If BP remains uncontrolled, despite the use of two agents:
  - ACE inhibitor or ARB + long-acting dihydropyridine calcium channel blocker + thiazide-like diuretic (chlorthalidone preferred)

Mann, JFE. Choice of drug therapy in primary (essential) hypertension. In: UpToDate, Forman JP (Ed), UpToDate, Waltham, MA, 2020.

Thiazide-Like or Thiazide-Type Diuretics

- Thiazide-like products are preferred over thiazide-type diuretics:
  - Superior potency at similar dose levels
  - Longer duration of action
  - Improved relative efficacy in reducing the risk of cardiovascular events and HF
- Monitoring for hypokalemia is important, especially at the initiation of therapy and following dose changes
- Beneficial effects on bone mineral density and decreased rates of hip or pelvic fractures as compared to agents from other classes

Thiazide-like	Thiazide-type
• **Chlorthalidone: 12.5-25 mg one daily; titrate, as needed, based on patient response (doses > 25 mg/day may result in risks of adverse events that outweigh the benefits)** • Indapamide: 1.25 once daily; titrate (at 4 week intervals) up to 5 mg once daily, as needed, based on patient response	• Hydrochlorothiazide (HCTZ): 12.5-25 mg once daily, titrate up to a dose of 50 mg once daily, as needed, based on patient response

Mann, JFE. Choice of drug therapy in primary (essential) hypertension. In: UpToDate, Forman JP (Ed), UpToDate, Waltham, MA, 2020.
Lexicomp Online Database. Hudson (OH): Lexicomp Inc.: 2020. Referenced June 2020.

Calcium Channel Blockers

- Amlodipine, a long-acting dihydropyridine agent, is the most used product in this class
- Non-dihydropyridine agents, verapamil and diltiazem, particularly useful for
  - Rate control in patients with atrial fibrillation
  - Control of angina in patients with coronary disease and normal left ventricular systolic function
  - Patients with obstructive airway disease

Mann, JFE. Choice of drug therapy in primary (essential) hypertension. In: UpToDate, Forman JP (Ed), UpToDate, Waltham, MA, 2020.
Page RL, et al. Drugs That May Cause or Exacerbate Heart Failure. A Scientific Statement From the American Heart Association. Circulation 2016;134:e32-69.
Colucci WS. Drugs that should be avoided or used with caution in patients with heart failure. In: UpToDate, Gottlieb SS (Ed), UpToDate, Waltham, MA, 2019.

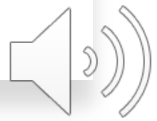
Calcium Channel Blockers

Class	Drug	Initial Dose	Beyond Initial Therapy
Dihydropyridine (DHP)	**Amlodipine**	**2.5-5 mg once daily**	**Titrate (at 1-2 week intervals) to a max of 10 mg once daily**
	Nifedipine extended release	30-60 mg once daily	Titrate (at 1-2 week intervals) to a dose range between 30-90 mg once daily
Non-Dihydropyridine (Non-DHP)	Diltiazem 12-hour formulation	60-120 mg twice daily	Titrate (at 7-14 day intervals) to a dose range between 240-360 mg/day in two divided doses
	Diltiazem 24-hour formulation	120-240 mg once daily	Titrate (at 7-14 day intervals) to a dose range between 120 -360 mg once daily
	Verapamil immediate-release	40-80 mg three times daily	Titrate (at weekly intervals) to a dose range between 120-360 mg/day in three divided dose (max 480 mg/day in 3 divided doses)
	Verapamil extended-release	120-180 mg once daily	Titrate (at weekly intervals) to a dose range between 120-360 mg/day in 1-2 divided doses (max 480 mg/day in 1-2 divided doses)
	Verapamil extended-release (delayed onset)	100-200 mg once daily at bedtime	Titrate (at weekly intervals) to a dose range between 100-300 mg once daily at bedtime (max 400 mg once daily at bedtime)

Mann, JFE. Choice of drug therapy in primary (essential) hypertension. In: UpToDate, Forman JP (Ed), UpToDate, Waltham, MA, 2020.
Lexicomp Online Database. Hudson (OH): Lexicomp Inc.: 2020. Referenced June 2020.

Angiotensin-Converting Enzyme Inhibitors

- First-line for patients with:
  - HF
  - Asymptomatic LV dysfunction
  - History of ST elevation MI or non-ST elevation MI who have had an anterior infarction, diabetes, or systolic dysfunction
  - Proteinuric CKD



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Angiotensin-Converting Enzyme Inhibitors

Drug	Dose Comparison (Bold Indicates Recommended Starting Dose)					
Benazepril		5 mg QD	**10 mg QD**	20 mg QD or divided BID	40 mg QD or divided BID	80 mg QD or divided BID
Captopril			**25 mg BID or TID**	50 mg BID	100 mg BID	200 mg BID
Enalapril	2.5 mg QD	**5 mg QD**	10 mg QD or divided BID	20 mg QD or divided BID	40 mg QD or divided BID	
Fosinopril			**10 mg QD**	20 mg QD or divided BID	40 mg QD or divided BID	80 mg QD or divided BID
Lisinopril		5 mg QD	**10 mg QD**	20 mg QD	40 mg QD	80 mg QD
Quinapril		5 mg QD	**10-20 mg QD**	20 mg QD or divided BID	40 mg QD or divided BID	80 mg QD or divided BID
Ramipril		1.25 mg QD	**2.5 mg QD or divided BID**	5 mg QD or divided BID	10 mg QD or divided BID	20 mg QD or divided BID

QD: once daily
BID: twice daily

ACE Inhibitor Antihypertensive Dose Comparison Pharmacist's Letter. Last Updated November 2016. Accessed June 26, 2020.

Angiotensin II Receptor Blockers (ARBs)

- Indications and efficacy are similar to those of ACE inhibitors
- May be of particular utility in patients unable to tolerate ACE inhibitors due to cough

Medication	Initial Dose	Usual Target or Maintenance Dose
Azilsartan	80 mg once daily	80 mg once daily
Cadesartan	16 mg once daily	8-32 mg daily in 1-2 divided doses
Eprosartan	600 mg once daily	400-800 mg daily in 1-2 divided doses
Irbesartan	150 mg once daily	150-300 mg once daily
Losartan	50 mg once daily	50-100 mg once daily
Olmesartan	20 mg once daily	20-40 mg once daily
Telmisartan	40 mg once daily	40-80 mg once daily

Mann, JFE. Choice of drug therapy in primary (essential) hypertension. In: UpToDate, Forman JP (Ed), UpToDate, Waltham, MA, 2020.
Comparison of Angiotensin Receptor Blockers (ARBs). Pharmacist's Letter. Last Updated September 2018. Accessed June 26, 2020.

Resistant Hypertension

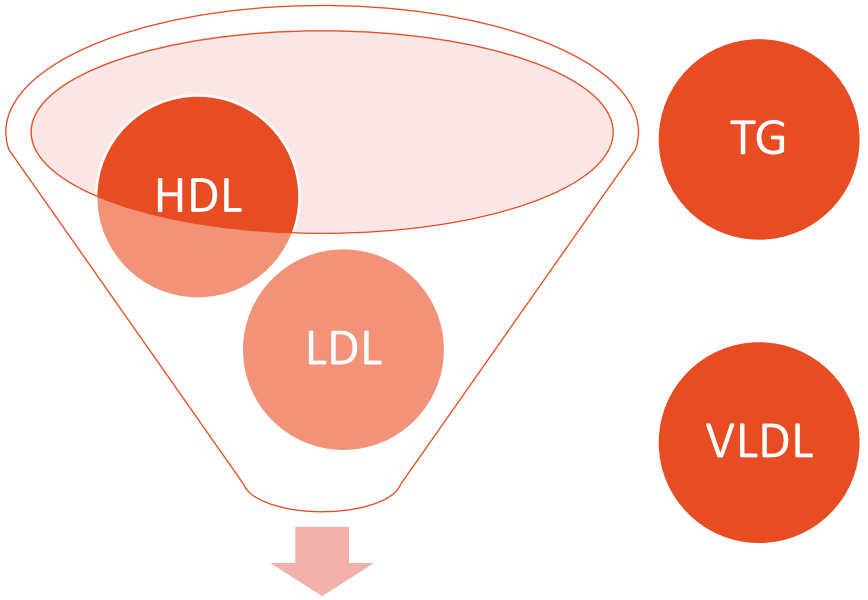
- Hypertension is deemed resistant when
  - BP remains above goal despite the use of three anti-hypertensive agents from different classes, one of which is a diuretic **OR**
  - BP is controlled with four or more anti-hypertensive medications
- More likely to be related, at least in part, to a secondary cause
- Consideration should be given to “compelling indications” when selecting therapy classes
- If the patient does not have a compelling indication, the preferred three drug regimen is
  - ACE inhibitor or ARB + long-acting dihydropyridine calcium channel blocker + thiazide-like diuretic (chlorthalidone preferred)
- If BP remains uncontrolled add spironolactone
- Consider a vasodilating beta-blocker, long-/centrally-acting agent, or direct vasodilator for patients that remain hypertensive after the addition of spironolactone

Townsend RR. Treatment of resistant hypertension. In: UpToDate, Forman JP (Ed), UpToDate, Waltham, MA, 2020.

Dyslipidemia

Screening

- Baseline lipid profile at initiation of care with an adult primary care provider
- Subsequent screening is dependent on cardiovascular risk
  - Higher: between the ages of 25-30 for males and 30-35 for females
  - Lower: age 35 for males and 45 for femailes
- Assess CVD risk and repeat measurement every three-five years depending on risk



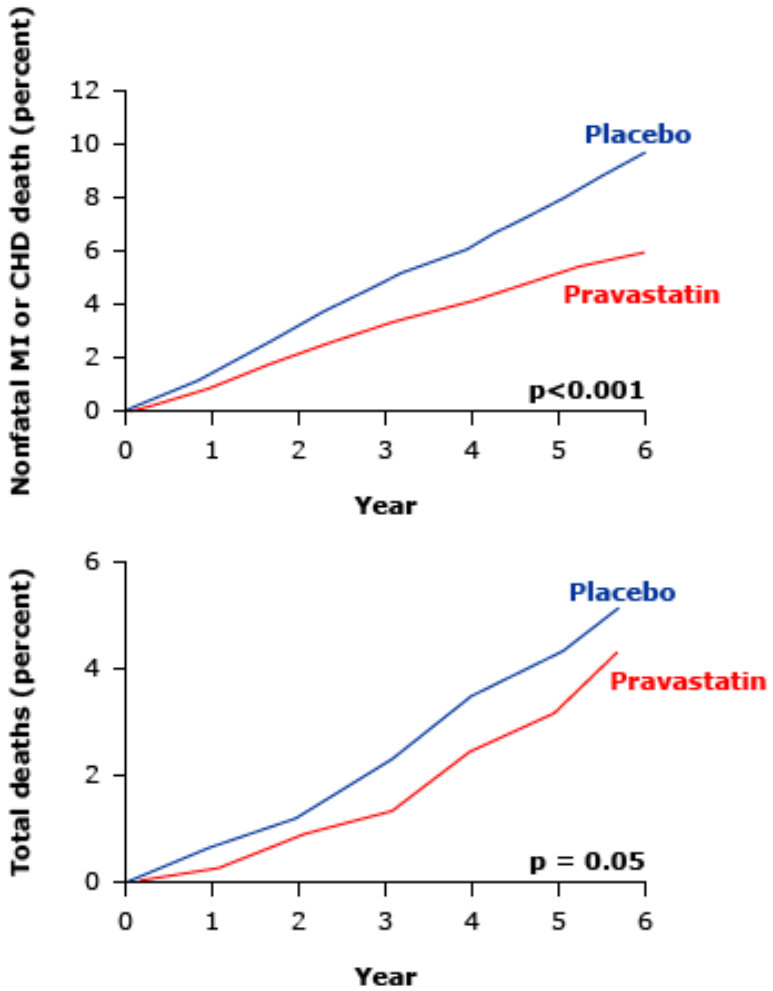
Vijan S. Screening for lipid disorders in adults. In: UpToDate, Givens J (Ed), UpToDate, Waltham, MA, 2020.

Management of LDL-C

Pignone M. Management of elevated low density lipoprotein-cholesterol (LDL-C) in primary prevention of cardiovascular disease. In: UpToDate, Saperia GM (Ed), UpToDate, Waltham, MA, 2020.
Rosenson RS et al. Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease. In: UpToDate, Saperia GM(Ed), UpToDate, Waltham, MA, 2020.

Primary Prevention

- Numerous studies have correlated LDL-C lowering with a reduction in risk for CVD
  - In particular, myocardial infarction
- Benefit from LDL-C lowering with statin therapy at all levels of cardiovascular risk and regardless of pre-treatment levels



Pignone M. Management of elevated low density lipoprotein-cholesterol (LDL-C) in primary prevention of cardiovascular disease. In: UpToDate, Saperia GM (Ed), UpToDate, Waltham, MA, 2020.

Approach to Treatment

- Decision to treat should be based on global CVD risk
  - ASCVD Risk Estimator Plus via the American College of Cardiology
- Balance cost and the potential for side effects with benefit
- All patients should undergo lifestyle modification
- Statins are the agent of choice for primary prevention
  - Ezetimibe is not well-studied in patients without cardiovascular disease
  - PCSK9 inhibitors have not been adequately studied for primary prevention in patients without familial hypercholesterolemia

Pignone M. Management of elevated low density lipoprotein-cholesterol (LDL-C) in primary prevention of cardiovascular disease. In: UpToDate, Saperia GM (Ed), UpToDate, Waltham, MA, 2020.

Statin Therapy

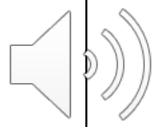
- Impacts
  - Competitive inhibition of HMG CoA reductase, the rate limiting step in cholesterol biosynthesis
  - Modest (5%) HDL cholesterol raising properties
  - 20-40% fall in triglyceride levels
- Efficacy
  - Reduction in the risk of MI and cardiovascular mortality
  - No increase in non-cardiovascular mortality has been seen

Pignone M. Management of elevated low density lipoprotein-cholesterol (LDL-C) in primary prevention of. cardiovascular disease. In: UpToDate, Saperia GM (Ed), UpToDate, Waltham, MA, 2020.
Rosenson RS. Statins: Actions, side effects, and administration. In: UpToDate, Givens J (Ed), UpToDate, Waltham, MA, 2020
Rosenson RS and Baker SK. Statin muscle-related adverse events. In: UpToDate, Given J (Ed), UpToDate, Waltham, MA, 2020.

Statins and Muscle Side Effects

- 2-11% of patients taking statins experience myalgias or myopathy
  - Severe myonecrosis (0.5%) and clinical rhabdomyolysis (0.1%) are much rarer
  - More likely to occur in patients with acute or chronic renal failure, obstructive liver disease, or hypothyroidism
  - Less common with pravastatin and fluvastatin
- Usually begin weeks to months after therapy initiation and can occur in the absence of CK elevations
- The risk of muscle injury is significantly higher when a statin that is extensively metabolized by CYP3A4 is taken in combination with a drug that interferes with CYP3A4
  - Lovastatin, simvastatin, and atorvastatin are metabolized by CYP3A4
  - Pravastatin, fluvastatin, and rosuvastatin are preferred when a patient is receiving a drug that strongly inhibits CYP3A4

Strong inhibitors
Atazanavir
Ceritinib
Clarithromycin
Cobicistat and cobicistat-containing coformulations
Darunavir
Idelalisib
Indinavir
Itraconazole
Ketoconazole
Lopinavir
Mifepristone
Nefazodone
Nelfinavir
Ombitasvir-paritaprevir-ritonavir
Ombitasvir-paritaprevir-ritonavir plus dasabuvir
Posaconazole
Ritonavir and ritonavir-containing coformulations
Saquinavir
Telithromycin
Tucatinib
Voriconazole



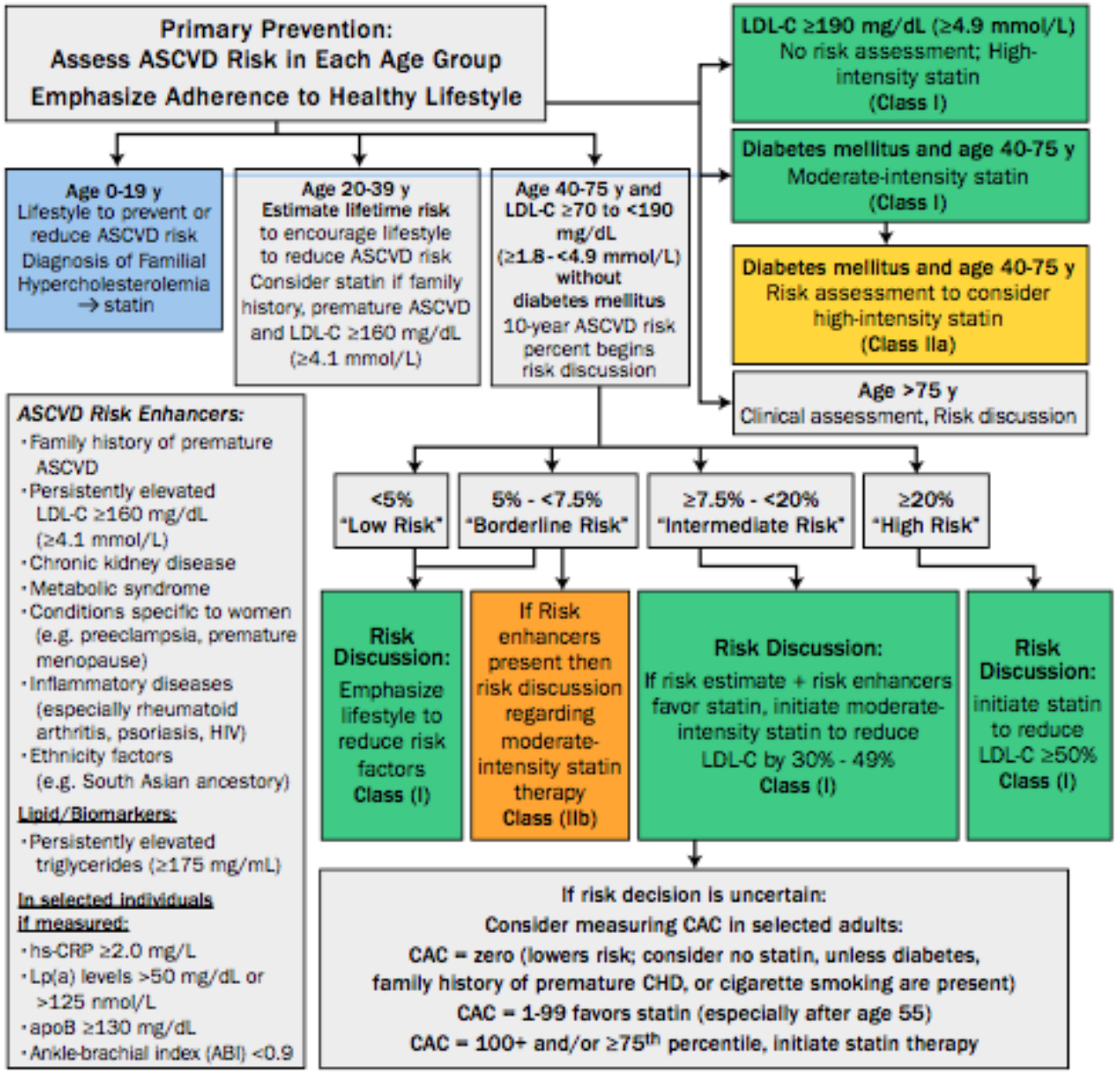
Rosenson RS and Baker SK. Statin muscle-related adverse events. In: UpToDate, Given J (Ed), UpToDate, Waltham, MA, 2020.

Daily Adult Statin Doses

Statin	Low-Intensity (LDL reduction < 30%)	Moderate-intensity (LDL reduction 30-50%)	High-Intensity (LDL reduction ≥50%)
Atorvastatin		10-20 mg	40-80 mg
Fluvastatin	20-40 mg	80 mg (XL) or 40 mg twice daily	
Lovastatin	20 mg	40-80 mg	
Pravastatin	10-20 mg	40-80 mg	
Rosuvastatin		5-10 mg	20-40 mg
Simvastatin	10 mg	20-40 mg	

Statin Dose Comparison. Pharmacist's Letter. Last Updated April 2018. Accessed June 30, 2020.

Primary Prevention



2018 Guideline on the Management of Blood Cholesterol. Guidelines Made Simple. American College of Cardiology. Available from: https://www.acc.org/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Guidelines/2018/Guidelines-Made-Simple-Tool-2018-Cholesterol.pdf. Last updated: June 2019. Accessed June 30, 2020.

Approach to Therapy - Secondary Prevention

- All patients with known CVD should be counseled on proven lifestyle interventions and receive high-intensity statin therapy, regardless of baseline LDL-C level
  - Remeasure LDL-C within 6-8 weeks of therapy initiation
- If the patient has not achieved the expected 50% reduction in LDL-C or if LDL-C remains ≥ 70 mg/dL, consider
  - Patient non-adherence
  - Addition of a second drug
- When adding additional therapy, consider ezetimibe prior to PCSK9 inhibitor therapy in most cases

Rosenson RS et al. Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease. In: UpToDate, Saperia GM (Ed), UpToDate, Waltham, MA, 2020.

Ezetimibe

- Cholesterol absorption inhibitor
  - Impairs the absorption of dietary and biliary cholesterol at the brush border of the small intestine
- Dosing: 10 mg orally once daily
- LDL-C reduction of approximately 17% when used as monotherapy
  - One in eight patients experience a 36% reduction
- An additional 14% reduction in LDL-C, beyond what was expected with simvastatin alone, was seen in one trial that evaluated co-administration of both medications
- Generally well tolerate
- An option for patients unable to tolerate any statin therapy

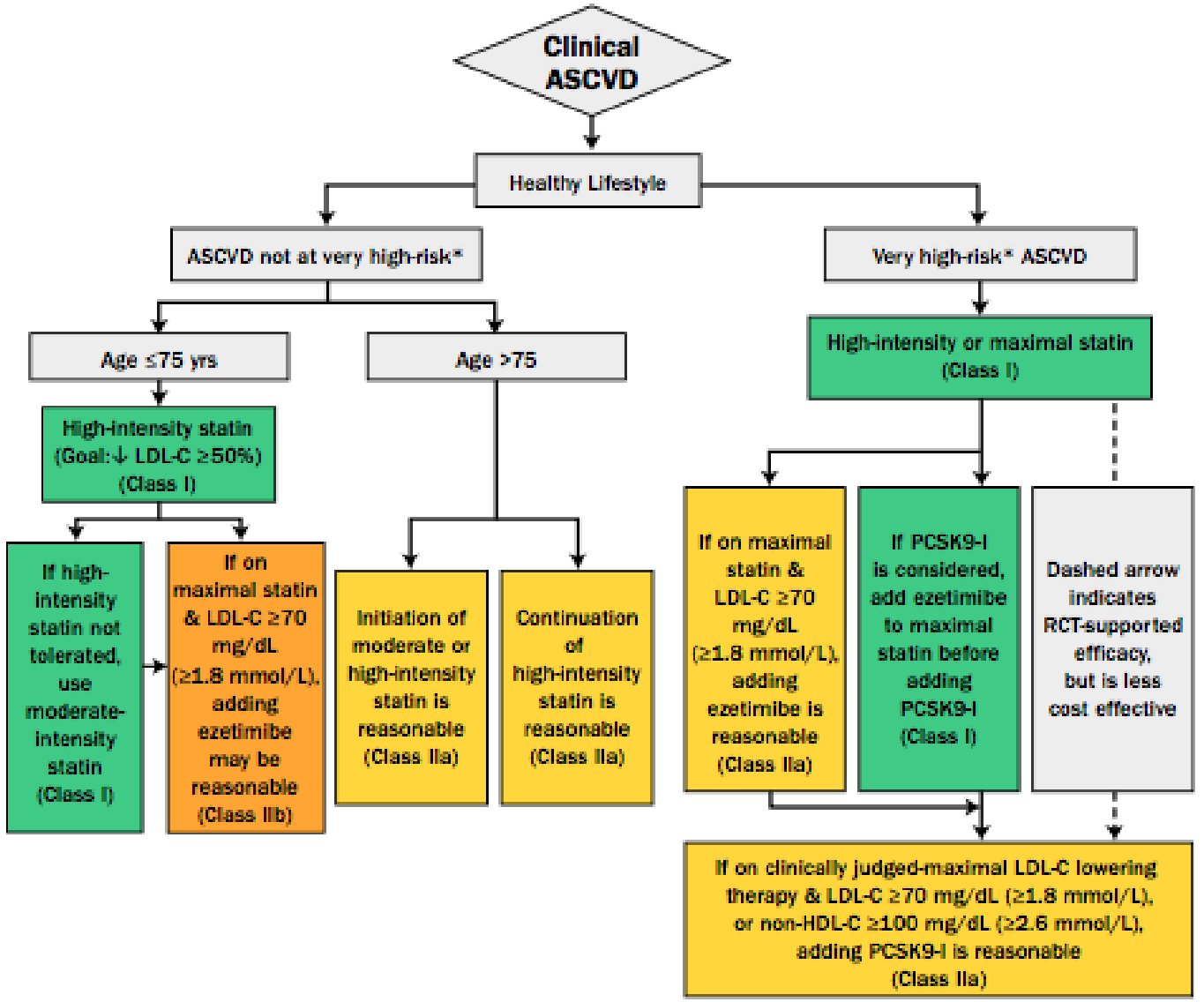
Rosenson RS. Low density lipoprotein cholesterol lowering with drugs other than statins and PCSK9 inhibitors. In: UpToDate, Saperia GM (Ed), UpToDate, Waltham, MA, 2020.
Rosenson RS et al. Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease. In: UpToDate, Saperia GM (Ed), UpToDate, Waltham, MA, 2020.

PCSK9 Inhibitors

- Injectable products administered subcutaneously
- Injection-site reactions are the most common side effects
- Use is associated with lower rates of myocardial infarction and stroke

Stroes ESG et al. PCSK9 inhibitors: Pharmacology, adverse effects, and use. In: UpToDate, Saperia GM (Ed), UpToDate, Waltham, MA, 2020.

Secondary Prevention in Patients with Clinical ASCVD



*Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4 on following page).

2018 Guideline on the Management of Blood Cholesterol. Guidelines Made Simple. American College of Cardiology. Available from: https://www.acc.org/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Guidelines/2018/Guidelines-Made-Simple-Tool-2018-Cholesterol.pdf. Last updated: June 2019. Accessed June 30, 2020.

Top 10 Take-Home Messages from Current Guidelines

1. In all individuals, emphasize heart-healthy lifestyle across the life-course.
2. In all patients with clinical ASCVD, reduce LDL-C with high-intensity or maximally tolerated statin therapy.
3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of non-statins to statin therapy.
4. In patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL), without calculating 10-year ASCVD risk, begin high-intensity statin therapy.
5. In patients 40-75 years of age with diabetes and LDL-C ≥ 70 mg/dL, start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

2018 Guideline on the Management of Blood Cholesterol. Guidelines Made Simple. American College of Cardiology. Available from: https://www.acc.org/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Guidelines/2018/Guidelines-Made-Simple-Tool-2018-Cholesterol.pdf. Last updated: June 2019. Accessed June 30, 2020.

Top 10 Take-Home Messages from Current Guidelines

1. In adults 40-75 years of age evaluated for primary ASCVD prevention, have a clinician-patient risk discussion before starting statin therapy.
2. In adults 40-75 years of age without diabetes and LDL-C levels ≥ 70 mg/dL, at a 10-year risk of ≥ 7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.
3. In adults 40-75 years of age without diabetes and 10-year risk of 7.5-19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see #7).
4. In adults 40-75 years of age without diabetes and with LDL-C levels ≥70 mg/dL- 189 mg/dL, at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.
5. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4-12 weeks after statin initiation or dose adjustment, repeated every 3-12 months as needed.

2018 Guideline on the Management of Blood Cholesterol. Guidelines Made Simple. American College of Cardiology. Available from: https://www.acc.org/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Guidelines/2018/Guidelines-Made-Simple-Tool-2018-Cholesterol.pdf. Last updated: June 2019. Accessed June 30, 2020.

Thank you!