جامعة بيرزيت
BIRZEIT UNIVERSITY

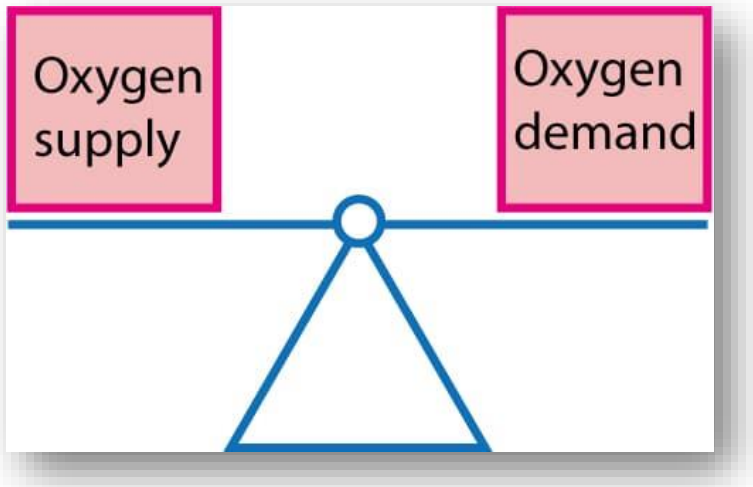
Stable Ischemic Heart Disease

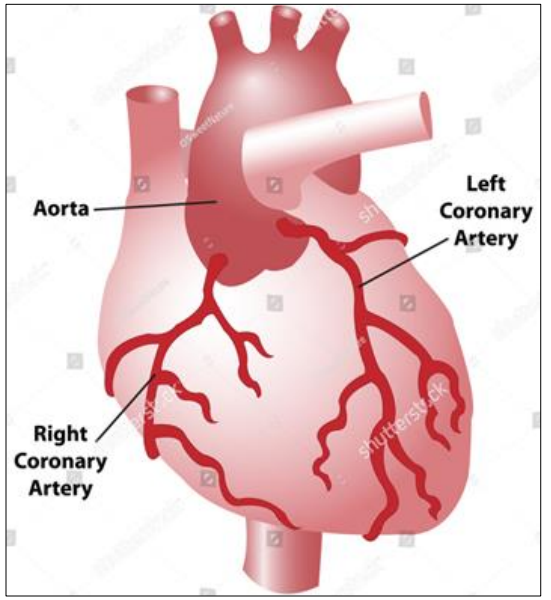
20/03/2025

BADER REMAWI

Physiology

- The heart is perfused through the coronary arteries (arise from aortic arch)
- Balance between myocardial O_2 supply and O_2 demand (MVO_2)

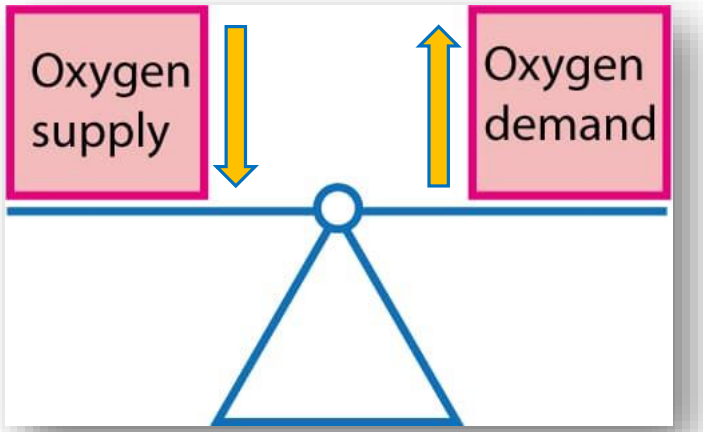


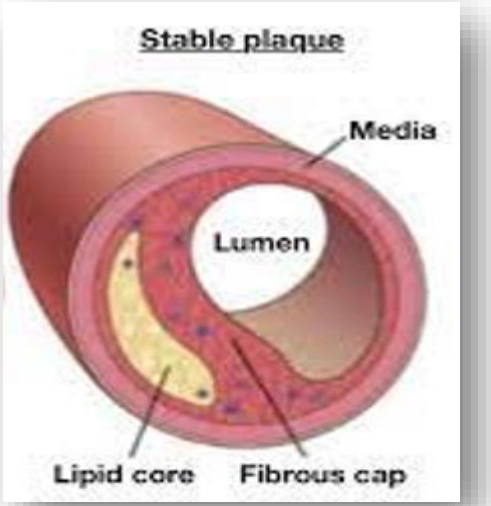


Pathophysiology

- Imbalance between myocardial O_2 supply and O_2 demand
  - Failure to maintain adequate coronary blood flow to meet the metabolic demands of myocytes (ischemia)

- Etiology:
  - Atherosclerotic plaque (unruptured) in coronary arteries (most common etiology)
  - Vasospastic coronary arteries (Variant/Prinzmetal's angina)
  - Both





Pathophysiology

- Determinants of myocardial O_2 supply:
  - Coronary blood flow (plaques, collaterals…)
  - Oxygen carrying capacity and extraction
  - Heart rate and systole
  - Vasospasm…

- Determinants of myocardial O_2 demand:
  - Heart rate (chronotropy)
  - Myocardial contractility (inotropy)
  - Arterial blood pressure
  - Exertion, emotion, mental stress…

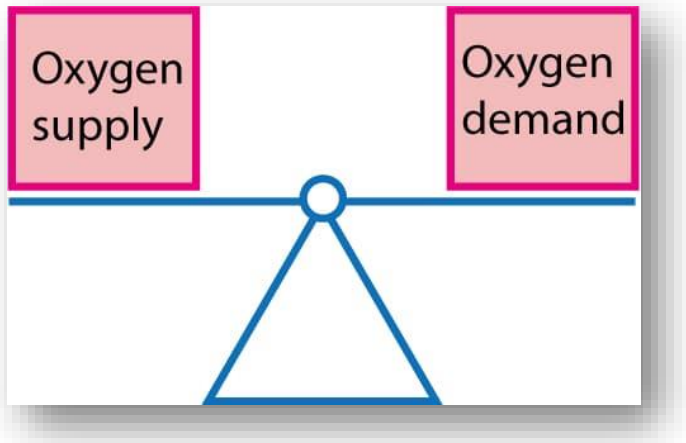


TABLE 33-3

Grading of Angina Pectoris by the Canadian Cardiovascular Society Classification System

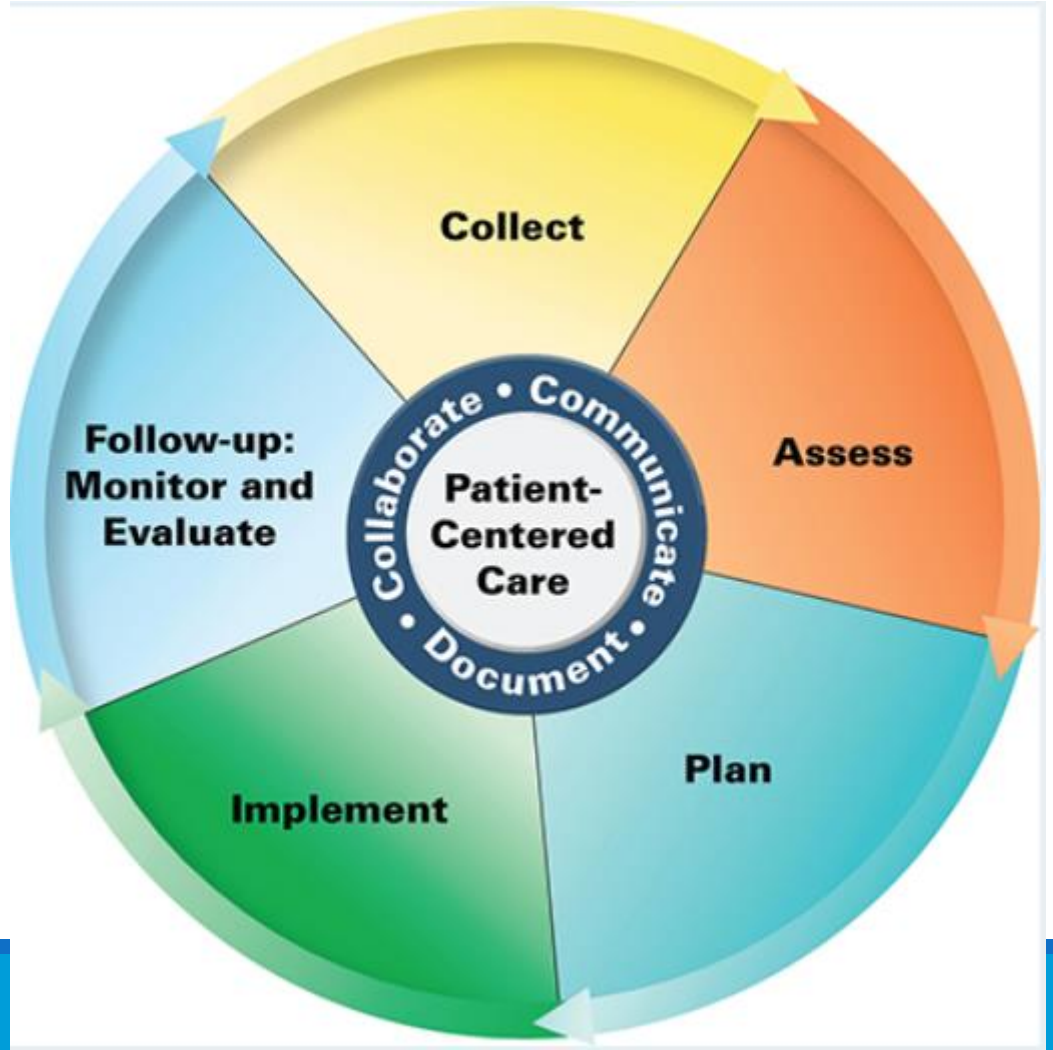
Class	Description of Stage
Class I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
Class II	Slight limitation or ordinary activity. Angina occurs on walking or climbing stairs rapidly, on walking uphill, on walking or stair climbing after meals, in cold, in wind, under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition
Class III	Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace
Class IV	Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest

TABLE 33-2

PQRST Approach to Assessment of a Patient's Chest Pain

Factor	Presentation in Stable Ischemic Heart Disease
Precipitating factors	Typically brought on by some level of exercise or exertion
Palliative measures	Relieved by rest with or without sublingual nitroglycerin in 5-10 minutes
Quality of the pain	Described as a continuous squeezing, heaviness, or tightness
Region	Substernal
Radiation	Left or right arm, back, down into the abdomen, up into the neck
Severity	While pain is subjective, those who have pain report a 5 or higher on a 10-point scale
Temporal pattern (timing)	Pain lasts less than 20 minutes and is usually relieved in 5-10 minutes

Patient care process



Patient care process

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Description of chest discomfort and/or related symptoms (eg, precipitating factors, palliative measures, quality, location, radiation, and severity)
- Patient medical (personal and family) and social histories (eg, tobacco/ethanol use), dietary habits (eg, intake of foods high in sodium, cholesterol, and/or saturated fat), and physical activity (eg, frequency and duration of moderate-intensity aerobic activity)
- Current medications including over-the-counter (OTC) medications (eg, aspirin-containing medications), herbals/dietary supplements
- History of allergy or intolerance to previous medications
- Objective data
- Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
    - Labs: serum creatinine (SCr), potassium (K^+), hemoglobin (Hgb), platelets, liver function tests (LFTs), lipid profile, blood glucose, A1c
    - Diagnostic testing results

Patient care process

Assess

- Description of chest discomfort to determine differential diagnosis and classification of angina symptoms
- Presence of provoking factors (eg, exertion, mental/emotional stress, tachyarrhythmia, high adrenergic state including the use of stimulant medications, and exposure to cold)
- Presence/control of risk factors for SIHD (eg, hypertension, dyslipidemia, diabetes, smoking, and obesity)
- Presence/control of SIHD-related complications (eg, myocardial infarction [MI], heart failure [HF], and stroke)
- Adverse drug reactions from current/previous medications used to treat/prevent angina symptoms or major adverse cardiac events (MACE)
- Previous/recent revascularization procedures (eg, percutaneous coronary intervention [PCI] with/without stenting, and coronary artery bypass graft [CABG] surgery)
- Contraindications to medications to treat/prevent angina symptoms and/or prevent MACE
- Barriers that may impair adherence to the care plan

Patient care process

Plan*

- Initiate/modify drug therapy to treat and prevent angina symptoms, prevent MACE, and address risk factors for SIHD including specific drug(s), dose, route, frequency, and duration (see Fig. 33-2, Tables 32-6 and 32-7)
- Monitoring parameters: efficacy (eg, signs and symptoms of angina and SIHD-related complications) and adverse drug reactions; frequency and timing of follow-up
- Patient education: the purpose of treatment, lifestyle modifications, planned procedures, and drug-specific information (eg, indication, dose, route, frequency, adverse drug reactions; see Table 33-8)
- Self-monitoring for worsening angina symptoms, signs and symptoms of SIHD-related complications, adverse drug reactions, when to seek emergency medical attention
- Address barriers to adherence to medications and lifestyle modification
- Referrals to other providers (eg, primary care provider, endocrinologist, dietician, and smoking cessation)

Patient care process

Implement*

- Provide patient education regarding all elements of the treatment plan as described above
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, every 1-2 months until goals achieved, then every 6-12 months)

Follow-up: Monitor and Evaluate

- Frequency and severity of chest discomfort, sublingual nitroglycerin use, exercise tolerance, presence/control of SIHD risk factors, and presence/control of SIHD-related complications
- Presence of adverse drug reactions and drug-drug interactions
- Patient adherence to treatment plan using multiple sources of information

** Collaborate with the patient, caregivers, and other healthcare professionals.*

ACC/AHA grading system

The American College of Cardiology and American Heart Association Evidence Grading System

Recommendation Class
I. Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective
II. Conditions for which there is conflicting evidence or a divergence of opinion that the usefulness/efficacy of a given procedure or treatment is useful and effective
a. The weight of evidence/opinion is in favor or usefulness/efficacy
b. Usefulness/efficacy is less well established by evidence/opinion
III. Conditions for which there is evidence or general agreement that a given procedure or treatment is not useful/effective and in some cases may be harmful

ACC/AHA grading system

The American College of Cardiology and American Heart Association Evidence Grading System

Level of Evidence
A. Data derived from multiple randomized clinical trials with large numbers of patients
B. Data derived from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries
C. Expert consensus was the primary basis for the recommendation

Treatment strategies

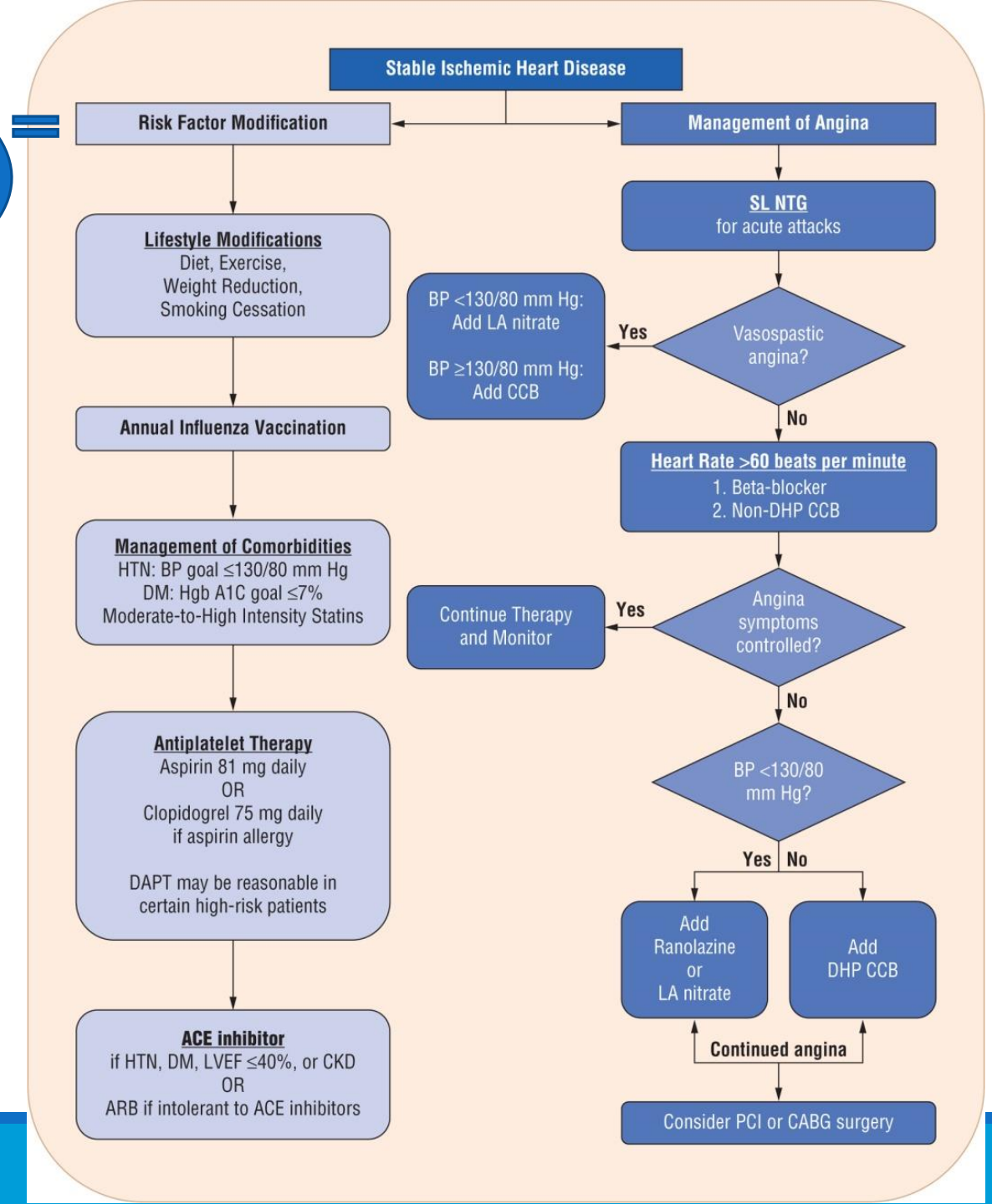
- **Two complementary strategies for SIHD treatment**

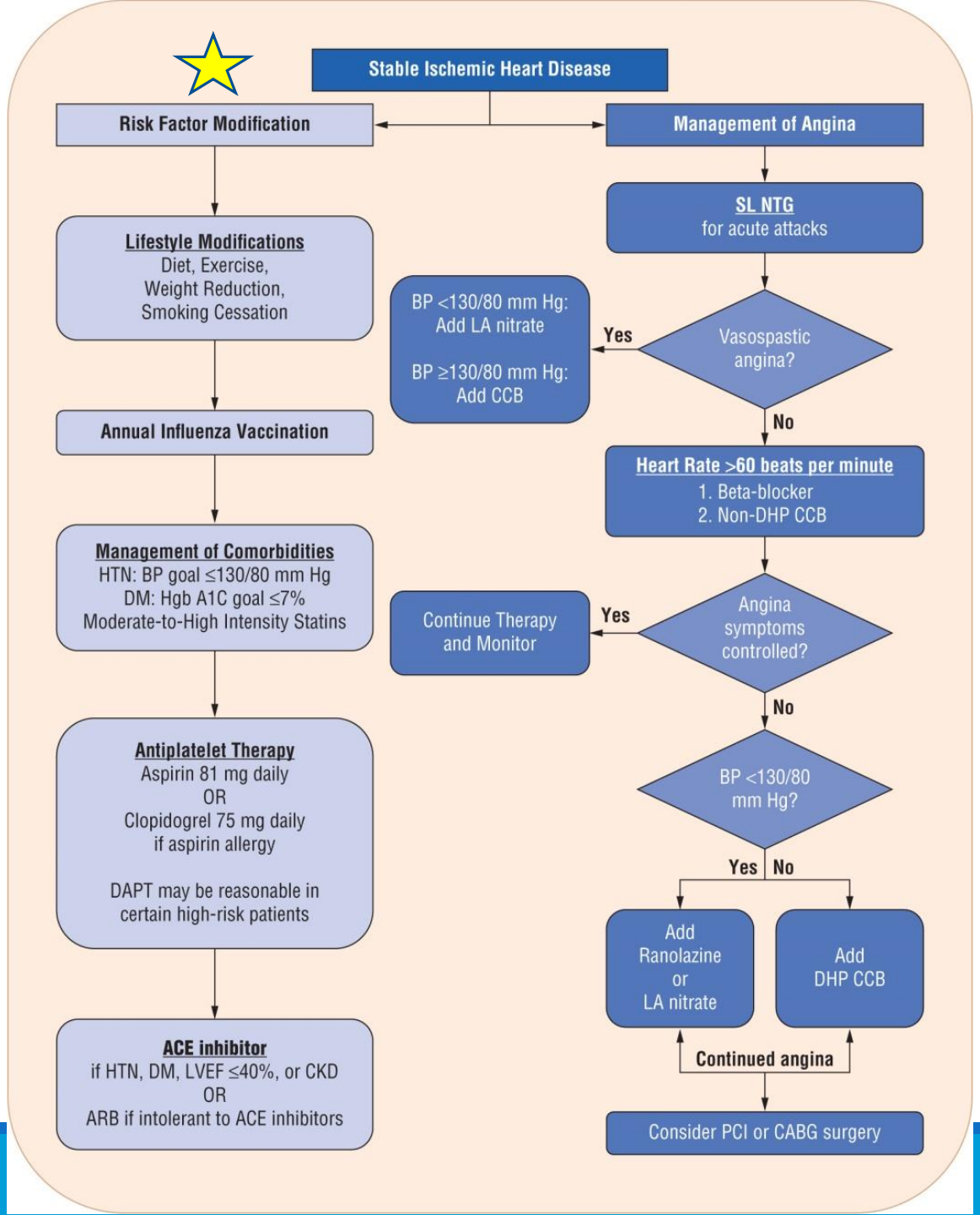
- 1) Slowing progression of atherosclerosis + Preventing complications (MI, HF, stroke, death)
  - Risk-factor modification + Vasculoprotection therapies *(improve survival, but do not relieve symptoms!)*

- 2) Reducing the number of ischemic episodes + Increasing the amount of angina-free exertion
  - Antianginal therapies *(relieve symptoms, but do not improve survival!)*

Guideline-Directed Medical Therapy (GDMT)

GDMT reduces mortality risk and MI rates in SIHD





Treatment strategies
Risk factor modification

Lipid Management
Class I
1. Lifestyle modifications, including daily physical activity and weight management, are strongly recommended for all patients with SIHD. 2. Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), *trans*-fatty acids (to <1% of total calories), and cholesterol (to <200 mg/day). 3. In addition to therapeutic lifestyle changes, a high-intensity statin should be prescribed with a goal of achieving a ≥50% decrease in LDL-C, in the absence of contraindications or documented adverse drug reactions. 4. In patients with contraindications or intolerant to high-intensity statin therapy, moderate-intensity statins should be used, if tolerated, with a goal of achieving a 30%-49% decrease in LDL-C.
Class IIa
1. In patients older than 75 years, moderate- or high-intensity statin therapy should be used after considering the potential benefits (risk reduction) and risks (adverse drug reactions, drug-drug interactions, patient frailty). 2. For patients with an LDL-C >70 mg/dL (1.81 mmol/L) on maximally tolerated statin therapy and at very high risk for CV events, the addition of ezetimibe is reasonable. 3. For patients with an LDL-C >70 mg/dL (1.81 mmol/L) or a non-HDL-C level ≥100 mg/dL (≥2.59 mmol/L) on maximally tolerated LDL-C lowering therapy (statin plus ezetimibe) and at very high risk for CV events, the addition of a PCSK-9 inhibitor is reasonable depending on benefit, risk, cost, and patient preference.

Treatment strategies
Risk factor modification

Blood Pressure Management
Class I
1. All patients should be counseled about the need for lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products. 2. In patients with SIHD with BP 130/80 mm Hg or higher, antihypertensive drug therapy should be instituted in addition to or after a trial of lifestyle modifications. 3. The specific medications used for the treatment of HTN in SIHD patients should be based on compelling indications (eg, prior MI, angina, and HFrEF) and may include β-blockers, ACE inhibitors, or ARBs with the addition of other drugs, such as thiazide diuretics, dihydropyridine calcium channel blockers, or aldosterone antagonists, if needed to achieve a goal of BP less than 130/80 mm Hg. 4. For patients with angina and persistent uncontrolled HTN, it is recommended to add dihydropyridine CCBs to β-blockers.
Class IIa
1. For patients who have had an ACS, it is reasonable to continue β-blockers long-term if needed for treatment of HTN.

Treatment strategies
Risk factor modification

Diabetes Management
Class I
1. Among patients with type 2 DM who have established ASCVD or indicators of high-risk, established kidney disease, or HF, a sodium-glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen independent of A1c, metformin use, and in consideration of patient-specific factors.
Class IIa
1. For selected individual patients, such as those with a short duration of diabetes mellitus and a long life expectancy, a goal A1c of 7% (0.07; 53 mmol/mol) or less is reasonable. 2. A goal A1c <8% (0.08; 64 mmol/mol) is reasonable for certain patients according to age, history of hypoglycemia, the presence of microvascular or macrovascular complications, or presence of coexisting medical conditions.
Class IIb
1. Initiation of pharmacotherapy interventions to achieve target A1c might be reasonable.

Treatment strategies
Risk factor modification

Physical Activity
Class I
1. For all patients, the clinician should encourage 30-60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week, supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, and household work) to improve cardiorespiratory fitness and move patients out of the least-fit, least-active, high-risk cohort (bottom 20%). 2. For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription. 3. Medically supervised programs (cardiac rehabilitation) and physician-directed, home-based programs are recommended for at-risk patients at first diagnosis.
Class IIa
1. It is reasonable for the clinician to recommend complementary resistance training at least 2 days per week.

Treatment strategies
Risk factor modification

Weight Management
Class I
1. BMI and/or waist circumference should be assessed at every visit, and the clinician should consistently encourage weight maintenance or reduction through an appropriate balance of lifestyle, physical activity, structured exercise, caloric intake, and formal behavioral programs when indicated to maintain or achieve a BMI between 18.5 and 24.9 kg/m^2 and a waist circumference less than 102 cm (40 in.) in men and less than 88 cm (35 in.) in women (less for certain racial groups). **2. The initial goal of weight loss therapy should be to reduce body weight by approximately 5%-10% from baseline. With success, further weight loss can be attempted if indicated.**

Treatment strategies
Risk factor modification

Smoking Cessation Counseling
Class I
1. Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home should be encouraged for all patients with SIHD. Follow-up, referral to special programs, and pharmacotherapy are recommended along with a systematic strategy for smoking cessation (Ask, Advise, Assess, Assist, Arrange, Avoid).

Alcohol Consumption
Class IIb
1. In patients with SIHD who use alcohol, it might be reasonable for nonpregnant women to have one drink (4 ounces [~120 mL] of wine, 12 ounces [355 mL] of beer, or 1 ounce [30 mL] of spirits) a day and for men to have one or two drinks per day unless alcohol is contraindicated (such as in patients with a history of alcohol abuse or dependence or with liver disease).

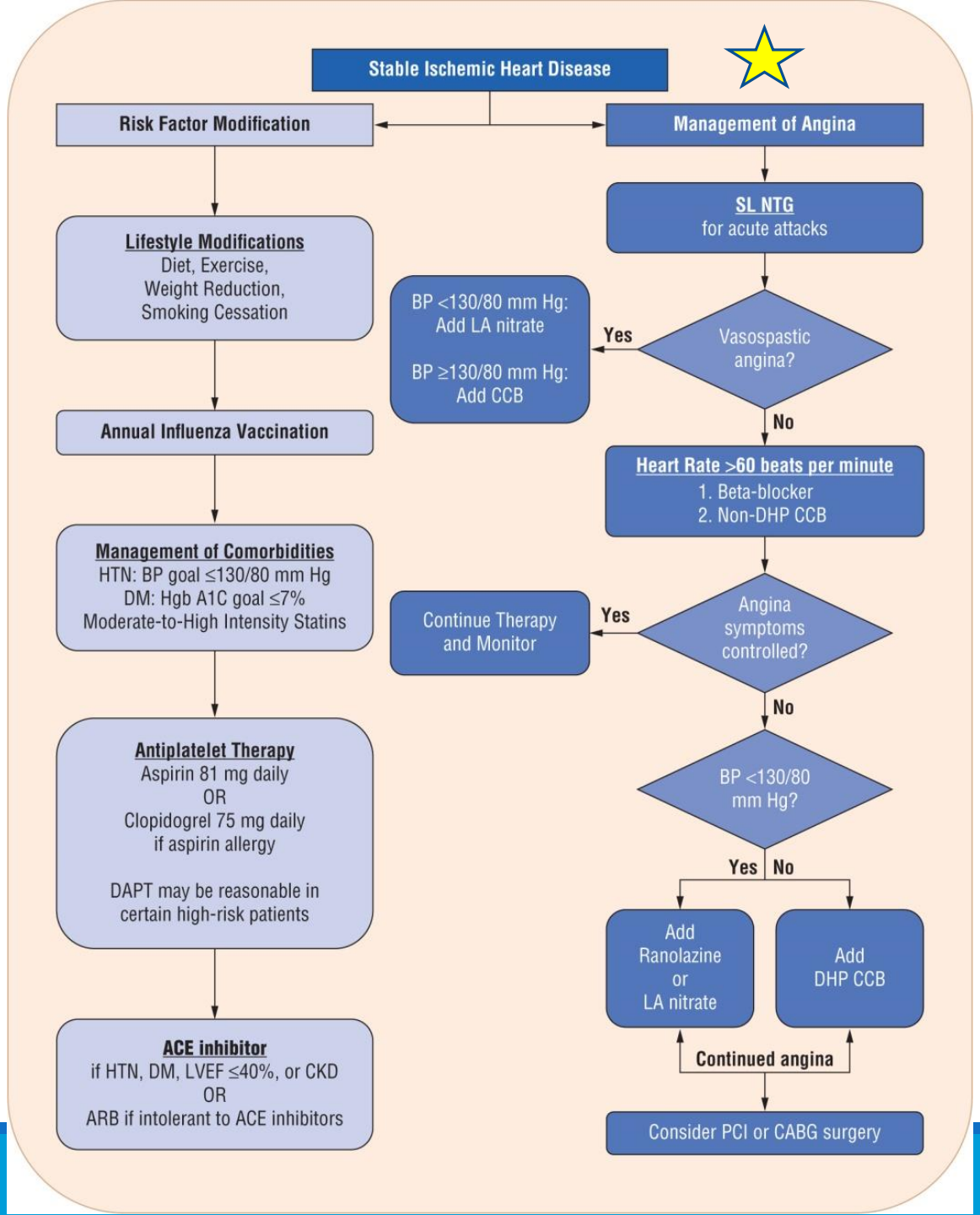
Treatment strategies
Risk factor modification

Influenza Vaccination
Class I
1. Annual influenza vaccinations are recommended for patients with SIHD.

Avoiding Exposure to Air Pollution
Class IIa
1. It is reasonable for patients with SIHD to avoid exposure to increased air pollution to reduce the risk of cardiovascular events.

Treatment strategies
Risk factor modification

Management of Psychological Factors
Class IIa
1. It is reasonable to consider screening SIHD patients for depression and to refer or treat when indicated.
Class IIb
1. Treatment of depression has not been shown to improve cardiovascular disease outcomes but might be reasonable for its other clinical benefits.



Treatment strategies
Management of symptoms

Class I

1.β-Blockers should be prescribed as initial therapy for the relief of symptoms in patients with SIHD (LOE B).

2.Calcium channel blockers or long-acting nitrates should be prescribed for the relief of symptoms when β-blockers are contraindicated or cause unacceptable adverse drug reactions in patients with SIHD (LOE B).

3.Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for the relief of symptoms when initial treatment with β-blockers is unsuccessful in patients with SIHD (LOE B).

4.Sublingual nitroglycerin or nitroglycerin spray is recommended for the immediate relief of angina in patients with SIHD (LOE B).

Class IIa

1.Treatment with a long-acting non-dihydropyridine calcium channel blocker (verapamil or diltiazem) instead of a β-blocker as initial therapy for relief of symptoms is reasonable in patients with SIHD (LOE B).

2.Ranolazine can be useful when prescribed as a substitute for β-blockers for the relief of symptoms in patients with SIHD if initial treatment with β-blockers leads to unacceptable adverse drug reactions or is ineffective or if initial treatment with β-blockers is contraindicated (LOE B).

3.Ranolazine in combination with β-blockers can be useful when prescribed for relief of symptoms when initial treatment with β-blockers is not successful in patients with SIHD (LOE A).

***Antianginal therapies are relatively equivalent in their ability to reduce ischemic episodes**

Treatment strategies
Management of symptoms

- In patients with a history of MI or HF, the use of β-blockers also provide a *survival* advantage

- To decrease MVO_2, the goal of β-blocker or non-DHP CCB is to:
  - Lower resting HR to 50 - 60 bpm
  - Lower exercise HR to < 100 bpm
- Some patients cannot tolerate HR in this range (especially elderly)
  - Goal resting HR: as low as tolerated above 50 bpm

- Combination of DHP CCB with non-DHP CCB:
  - Not common, but acceptable for SIHD patients with contraindications or intolerance to β-blockers
  - Different Ca channel targets
  - Monitor for peripheral edema and signs/symptoms of reduced cardiac output

Treatment strategies
Management of symptoms: **Vasospastic angina**

- β-blockers are less useful in vasospastic angina
  - May worsen angina probably due to unopposed α1-adrenergic receptor stimulation
- High doses of LA nitrates are typically needed for adequate symptom control
  - May not be tolerated
- CCBs are dosed less frequently than LA nitrates
  - Nifedipine, verapamil, & diltiazem are equally effective for initial management of coronary vasospasm
- Acceptable to combine CCBs with LA nitrates

Desired outcomes of treatment

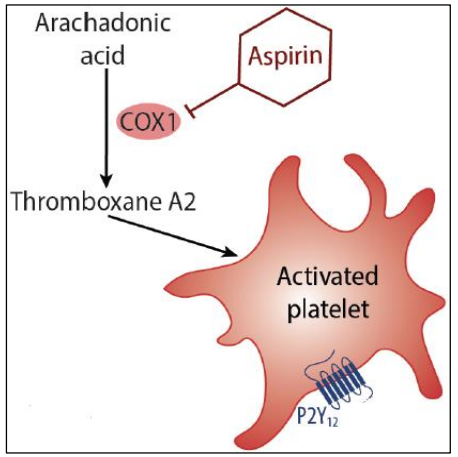
- Reducing the risk of CV events and mortality
- Complete, or nearly complete, elimination of chest pain
- Return to normal activities (functional capacity of CCS Class-I angina)

Pharmacotherapy to reduce mortality
Antithrombotics: **Aspirin**

- Small ASA doses (~ 30 mg QD) effectively inhibit COX-1
- ASA maintenance doses > 75 - 100 mg provide little additional antiplatelet activity

- <u>ACC/AHA recommendations</u>:
  - ASA 75 - 162 mg QD (Class I)
  - Aspirin should be continued indefinitely in absence of CIs

- ASA *may* have non-platelet-mediated effects → Clinical benefits?
  - Attenuating the synthesis of cytokines (e.g. IL-2, IL-6, IFN) in leukocytes
  - Preventing leukocyte rolling
  - Preventing macrophage-induced endothelial activation



Pharmacotherapy to reduce mortality
Antithrombotics: **Aspirin**

- **Aspirin non-responsiveness**: Lack of response to ASA antiplatelet effects
- Rate ~ 24% (range 0% - 57%)
- Causes:
  - Structural changes to COX-1
  - Temporary blockade of COX-1 active site
    - e.g. Concomitant administration of NSAID (naproxen, ibuprofen) results in competition in binding to the site of action
    - ASA antiplatelet effect is impaired when ibuprofen is given 2 hours before aspirin
    - ASA antiplatelet effect is retained when ASA is given first
- Consequences:
  - Lack of clinical benefit
  - Increased risk of ischemic events
  - Increased risk of recurrent CV events

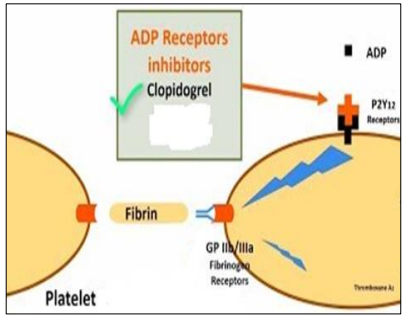
Pharmacotherapy to reduce mortality
Antithrombotics: **Aspirin**

- No difference in ASA non-responsiveness between different ASA doses:
  - 81 mg vs. 162 mg vs. 325 mg (daily doses)
  - Low dose (75 - 150 mg) vs. Moderate dose (160 - 325 mg) vs. High dose (500 - 1,500 mg) (daily doses)

- Management of ASA non-responsiveness:
  - Routinely testing patients is NOT recommended (low incidence overall)!
  - Increasing ASA dose does NOT impact responsiveness!
  - Change to or add an alternative antiplatelet (the only effective strategy)

Pharmacotherapy to reduce mortality
Antithrombotics: **Clopidogrel**

- **Indication:** Alternative, second-line, antiplatelet to prevent MI and death in CAD patients who cannot take ASA (allergy, intolerance, contraindication)
- **Dose:** 75 mg QD
- Highly variable patient responsiveness to clopidogrel
- **Clopidogrel non-responsiveness**: Lack of response to clopidogrel antiplatelet effects (rate 5% - 44%)
- Causes of non-responsiveness:
  - Poor adherence 'even a small number of missed doses' (most common cause)
  - Polymorphisms in CYP 2C19 (responsible for converting clopidogrel to its active metabolite)
  - Drug interactions with CYP 2C19 (e.g. proton pump inhibitors)
- Consequences of non-responsiveness: Poor clinical outcomes
- Management of non-responsiveness: Unclear; address underlying etiology



Pharmacotherapy to reduce mortality
Antithrombotics: **DAPT**

- ACC/AHA recommendation:
  - ASA (75 - 162 mg daily) + Clopidogrel (75 mg daily) might be reasonable in certain high-risk SIHD patients (Class IIb, LOE B recommendation)

- Benefits of DAPT (ASA + $P2Y_{12}$ inhibitor) in IHD:
  - After PCI with coronary stent placement
  - After ACS treatment

- DAPT increases the risk of moderate-major bleeding compared to ASA monotherapy

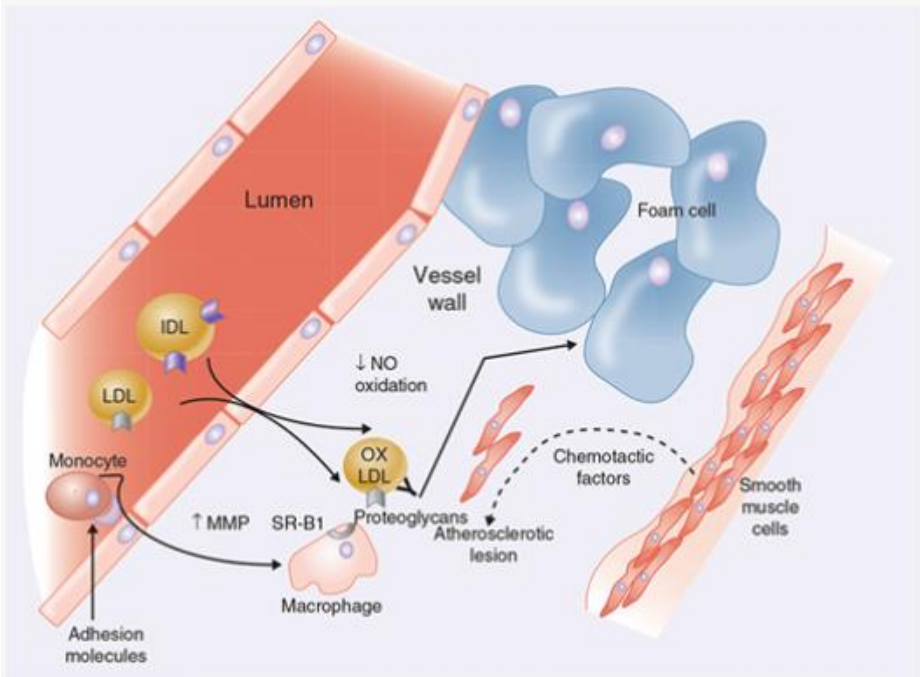
Pharmacotherapy to reduce mortality
Antithrombotics: **Rivaroxaban + ASA**

- Rivaroxaban 2.5 mg BID + ASA low-dose vs. ASA alone:
  - Combination provided a 24% relative reduction in CV death, MI, and stroke (greatest benefit in patients with polyvascular disease, HF, DM, or moderate-severe renal insufficiency)
  - Combination caused a significant increase in major bleeding
- Rivaroxaban + ASA combination is recommended by the American Diabetes Association (ADA)

Pharmacotherapy to reduce mortality
ACE inhibitors

- Stabilize coronary plaque
- Restore or improve endothelial function
- Inhibit vascular smooth muscle cell growth
- Decrease macrophage migration
- Prevent oxidative stress
- Inhibit platelet aggregation (antithrombotic properties)
- Augment the endogenous fibrinolytic system

Role in ASCVD



Pharmacotherapy to reduce mortality
ACE inhibitors

- In patients with ASCVD; ACE inhibitors significantly reduce the risk of CV death, MI, or stroke
- Benefits were seen even with a *minimal* reduction in BP!

- ACC/AHA recommendations:
  - ACE inhibitors should be used in all SIHD patients who have HTN, DM, HFrEF, or CKD unless contraindicated (Class I, LOE A)
  - ACE inhibitors should be used in all SIHD patients who have other vascular diseases “ischemic stroke, PAD…” (Class IIa, LOE B)

- ACE inhibitors are also appropriate following MI

Pharmacotherapy to reduce mortality
ARBs

- Alternative to ACE inhibitors if patients cannot tolerate them

- ACEi + ARB combination:
  - Does not provide added benefit
  - Significantly increases the risk of hypotension, syncope, and renal dysfunction
  - Should be avoided

- ACC/AHA recommendations:
  - ARBs should be used in all SIHD patients who have HTN, DM, HFrEF, or CKD if they are intolerant to ACEi (LOE A)
  - ARBs should be used in all SIHD patients who have other vascular diseases if they are intolerant to ACEi (LOE B)

Pharmacotherapy to reduce mortality
Lipid management

- High LDL-C → Increase in coronary events

- Statins significantly lower LDL-C:
  - Decrease CV events (MI, stroke)
  - Decrease the need for coronary revascularization (PCI, CABG)

- For every 40 mg/dL reduction in LDL-C:
  - 10% reduction in all-cause mortality
  - 20% reduction in cardiac mortality

- High dose/potency statin regimens are more effective than Low dose/potency statin regimens

Pharmacotherapy to reduce mortality
Lipid management

- Non-statin antilipemic agents:
  - Add-on therapy to maximally tolerated high-intensity statin
  - For patients with clinical ASCVD who have LDL ≥ 70 mg/dL or do not achieve 50% LDL reduction
  - Options: Ezetimibe, PCSK9-inhibitors, Bile-acid sequestrates

- Lifestyle modifications:
  - Diet low in saturated fat and cholesterol → reduces LDL-C by 10% - 15%
  - Plant sterols/stanols (2 g/d) → reduce LDL-C by 5% - 15%
  - Soluble fibers (> 10 g/d) → reduces LDL-C by 3% - 5%
  - 4.5 kg weight loss → reduces LDL-C by 5% - 8%
  - Regular physical exercise → does not reliably reduce LDL-C (improves cardiac fitness, facilitates weight loss)

Pharmacotherapy to reduce mortality
Blood pressure management

- High BP → Increased risk of CV events and vascular death

- Risk of vascular death increases linearly over the BP range (115/75 mm Hg - 185/115 mm Hg)
- Risk of vascular death doubles for every 20 mmHg increase in SBP or 10 mmHg increase in DBP

- Lifestyle modifications
- HTN medications in SIHD patients:
  - **β-Blockers:** Lower BP + Control angina symptoms
  - **ACE inhibitors:** Lower BP + Reduce CV risk
  - **DHP CCBs:** Lower BP + Control angina symptoms
  - **Thiazide diuretics:** Lower BP

Most SIHD patients will receive these agents for HTN treatment

Add-on therapy for further control of BP and angina symptoms

Add-on therapy for further control of BP

Pharmacotherapy to reduce mortality
Diabetes management

- DM is a strong risk factor for CVD development
- Patients with type 1 DM have 10-fold increased risk of having a CV event
- Patients with type 2 DM have 2-6-fold increased risk of CV death

- Intensive glycemic therapy:
  - Goal HbA1c < 7%
  - Reduces microvascular complications (retinopathy, nephropathy, neuropathy)
  - Reduces macrovascular complications (ischemic events)
  - In high-risk patients (e.g. DM with preexisting CVD), intensive therapy is less effective in reducing macrovascular complications and causes more adverse events (severe hypoglycemia, mortality)

- AHA/ACC recommendations:
  - HbA1c < 7% for patients with short-duration DM and long-life expectancy (Class IIa, LOE B)
  - HbA1c < 8% for frail or high-risk patients (Class IIa, LOE C)

Pharmacotherapy to reduce mortality
Diabetes management

- Metformin:
  - Drug of first choice for type 2 DM patients, including those with SIHD
  - Effect on CV events is debated

- Sulfonylureas:
  - Similar reduction in A1c as Metformin
  - High risk of hypoglycemia and weight gain
  - Effect on CV events is debated

- Newer DM therapies vs. Standard DM therapy:
  - SGLT-2 inhibitors & GLP-1 agonists reduce death risk by 20% and 12%, respectively (including CV mortality)
  - Risk of adverse events leading to discontinuation in GLP-1 agonists > SGLT-2 inhibitors

Pharmacotherapy to reduce mortality
Diabetes management

- ADA guideline recommendations:
  - Agents shown to reduce CV events should be used as part of the glucose-lowering regimen, regardless of glycemic control
  - These agents should be added to metformin therapy in patients with DM type 2 and ASCVD
  - Examples: SGLT-2 inhibitors (empagliflozin, canagliflozin); GLP-1 agonists (liraglutide)

Pharmacotherapy to reduce mortality
Smoking cessation

- Tobacco use → Increased risk of CVD
- Smoking is probably the most important cause of *preventable* CVD and death
- Smokers lose ~ 10 years of life expectancy compared to non-smokers
- Early smoking cessation → ~ 90% reduction in mortality + improved quality of life

- <u>How cigarette smoking promotes and accelerates ASCVD</u>:
  - Increases platelet adhesion
  - Elevates fibrinogen concentrations
  - Causes endothelial dysfunction
  - Alters serum lipids
  - Causes vasoconstriction

Pharmacotherapy to reduce mortality
Smoking cessation

- Clinicians' advice about smoking cessation significantly increases the likelihood of patient quitting

- 6 A's framework:
  - Ask each patient about tobacco use at every visit
  - Advise each smoker to quit
  - Assess each smoker's willingness to make a quit attempt
  - Assist each smoker in making a quit attempt by offering medication and referral for counseling
  - Arrange for follow-up
  - Avoid exposure to environmental tobacco smoke

Pharmacotherapy to reduce mortality
Smoking cessation

- All smoking cessation medications (OTC, prescriptions) are more effective than placebo
- Smoking cessation medications have no evidence of CV adverse events

- First-line medications for tobacco dependence in adults:
  - Nicotine replacement therapy
    - Available as OTC & in several dosage forms to fit patient needs: patch, tablet, gum, lozenge, nasal spray
  - Varenicline: $\alpha_4\beta_2$ nicotinic receptor partial agonist
  - Sustained-release Bupropion: NDRI

- Non-pharmacologic smoking cessation methods:
  - As important as pharmacotherapy
  - Self-help programs, telephone counseling, behavioral therapy, exercise

Pharmacotherapy to reduce mortality
Influenza vaccination

- Patients with CV disease who develop seasonal influenza → High risk for complications & death

- Influenza vaccination in patients with CAD → Lower rates of ischemic events
  - Greatest benefit in those with a recent ACS

- <u>Guidelines recommendation</u>:
  - All patients with SIHD should receive an annual influenza vaccination to prevent morbidity and mortality

Pharmacotherapy to reduce symptoms
β-Blockers: **MOA**

- Commonly used in SIHD management
- Reduce episodes of myocardial ischemia

- MOA:
  - Competitive inhibition of catecholamines effects on cardiac β_1-adrenoceptors → Reduction in myocardial chronotropy (heart rate) and inotropy (contractility)
  - Competitive inhibition of catecholamines effects on renal β_1-adrenoceptors → Reduction in Renin release → Reduction in arterial BP

  } Decreased O_2 Demand

  - Reduction in HR → Prolonging diastole filling time → Increasing myocardial perfusion

  } Increased O_2 Supply

Pharmacotherapy to reduce symptoms
β-Blockers: **Agents**

- All β-blockers appear equally effective for SIHD treatment:
  - Non-selective β-blockers (propranolol…)
  - β_1-selective blockers (atenolol, metoprolol, bisoprolol)…
  - β-Blockers with combined α_1 and β-blockade (labetalol, carvedilol…)

Selection depends on:
- Comorbid diseases
- Preferred dosing frequency
- Cost

- β_1-selective agents:
  - Preferred in COPD, PAD, DM, Dyslipidemias, Sexual dysfunction
  - Lose their selectivity at higher doses

- β-Blockers with intrinsic sympathomimetic activity (ISA):
  - Antagonists (competing with endogenous catecholamines) with
    Partial agonist activity (causing slight-moderate activation of β-receptor)
  - Do not affect resting HR; Modestly lower exercise HR
  - Not used in CAD; increase MVO2

Pharmacotherapy to reduce symptoms
β-Blockers: **ADRs**

- **CV adverse drug reactions**
  - Most ADRs of β-blockers are an extension of their pharmacologic activity
  - Bradycardia, hypotension, heart block

- **Impaired glucose metabolism**
  - Greater effect with non-selective β-blockers
  - Decreased glycogenolysis + Decreased glucagon secretion → Hypoglycemia
  - Blunt the counter-regulatory effects of catecholamines during hypoglycemia: tremor, tachycardia, nervousness

- **Altered serum lipids**
  - Greater effect with non-selective β-blockers; usually transient
  - Inhibiting lipases in fat cells → Reducing TGs breakdown → Increased TGs
  - Decreased HDL (no impact on LDL)

Pharmacotherapy to reduce symptoms
β-Blockers: **ADRs**

- **CNS adverse drug reactions**
  - Fatigue, depression, insomnia, general malaise
  - Usually mild; but a common reason for treatment discontinuation

- **Impotence** (reported in ~ 1% of men receiving β-blockers)

- **Bronchospasm in patients with history of airway disease**
  - All patients should receive a β-blocker following MI unless there is an absolute contraindication
  - COPD patients with SIHD who have never experienced ACS/MI:
    - May be treated with β_1-blocker if there are compelling reasons to use it over another antianginal agent
    - However, if COPD is moderate-severe, β-blockers may increase the risk of hospitalization

- **Fluid overload in patients with HFrEF**

Pharmacotherapy to reduce symptoms
β-Blockers: **Absolute contraindications**

- Preexisting bradycardia
- Second or third-degree atrioventricular (AV) block
- Hypotension
- HFrEF with unstable fluid status
- History of uncontrolled reactive airway disease (asthma)
- Severe peripheral arterial disease (critical limb ischemia)
- DM with frequent hypoglycemia episodes

Non-DHP CCB are the preferred second-line choice if β-blockers are contraindicated/discontinued

Pharmacotherapy to reduce symptoms
β-Blockers: **Abrupt withdrawal**

- If BBs need to be discontinued, doses should be tapered over 2 - 3 weeks to prevent abrupt withdrawal

- Mechanism:
  - During β-blocker therapy, myocardial β-receptors become up-regulated
  - Abrupt withdrawal of β-blocker → New receptors, and previously blocked receptors, are now stimulated by endogenous catecholamines

- Consequences:
  - Significant increase in MVO2
  - Induced ischemia (and possibly MI)

- If β-blockers cannot be tapered:
  - Instruct patients to avoid exertion as much as possible
  - Instruct patients to manage angina episodes with SL nitroglycerin

Pharmacotherapy to reduce symptoms
CCBs: **MOA**

- CCBs effectively reduce the frequency and duration of angina episodes in SIHD

- <u>MOA</u>:
  - Reduction in myocardial chronotropy and inotropy
  - Reduction in arterial vasospasm
  - Reduction in arterial BP

  } Decreased O_2 Demand

  - Coronary vasodilation
  - Reduction in myocardial chronotropy

  } Increased O_2 Supply

  - CCBs inhibit Ca entry into myocardium and vascular smooth muscle → Inhibiting the activation of actin-myosin complex → Inhibiting muscle contraction

Pharmacotherapy to reduce symptoms
CCBs: **Agents**

- DHP CCBs:
  - e.g. nifedipine, amlodipine, isradipine, felodipine
  - Primarily block Ca receptors in vascular smooth muscle cells (e.g. arterioles)
  - Minimal effect on the myocardium

- Non-DHP CCBs:
  - e.g. verapamil (phenylalkylamine), diltiazem (benzothiazepine)
  - Primarily block Ca entry in the myocardium
  - Minimal effect on vascular smooth muscle
  - Verapamil impact on myocardium > Diltiazem (intermediate effect)

Pharmacotherapy to reduce symptoms
CCBs: **ADRs**

- **Reflex tachycardia**
  - Results from arterial dilation by DHP CCBs
  - Common with *short-acting* DHP CCBs; avoid in SIHD, ACS, HTN, hypertensive crisis
  - Reflex tachycardia from *longer-acting* DHP CCBs can be prevented with concurrent BB
- **Peripheral edema**
  - Most DHP CCBs are contraindicated in HFrEF
  - Amlodipine and Felodipine are considered safe in HFrEF and concomitant SIHD or HTN
- **Hypotension**
- **Headache**
- **Gingival hyperplasia**

More common with DHP CCBs

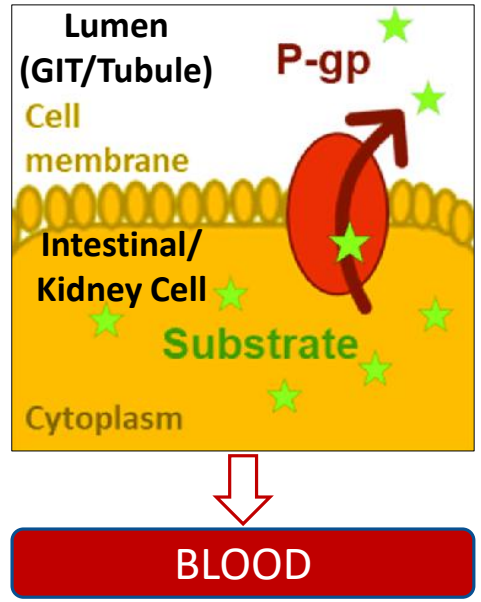
Pharmacotherapy to reduce symptoms
CCBs: **ADRs**

- **Bradycardia, hypotension, AV block, LV depression**
  - Similar pharmacodynamic effects to β-blockers → Similar CV contraindications
  - Non-DHP CCBs should be avoided in HFrEF due to negative inotropic effects
  - Impairment of LV function: Nifedipine > Amlodipine, Felodipine
- **Constipation**
  - Common with verapamil (~ 8% of patients)

More common with Non-DHP CCBs

Pharmacotherapy to reduce symptoms
CCBs: **PK/PD**

- CCBs undergo hepatic metabolism via CYP 3A4 and other isoenzymes
- Non-DHP CCBs inhibit the clearance of other CYP 3A4 substrates
  - e.g. carbamazepine, cyclosporine, lovastatin, simvastatin, benzodiazepines
- Non-DHP CCBs (Verapamil > Diltiazem) inhibit P-glycoprotein mediated drug efflux
  - e.g. digoxin, cyclosporine
  - Digoxin levels must be closely monitored if used concomitantly with Verapamil
- Agents that induce the CYP 3A4 can reduce the effectiveness of all CCBs
- Non-DHP CCBs in combination with other negative chronotropic agents
  - Monitor for the development of bradycardia or heart block
  - e.g. β-blockers, digoxin, amiodarone

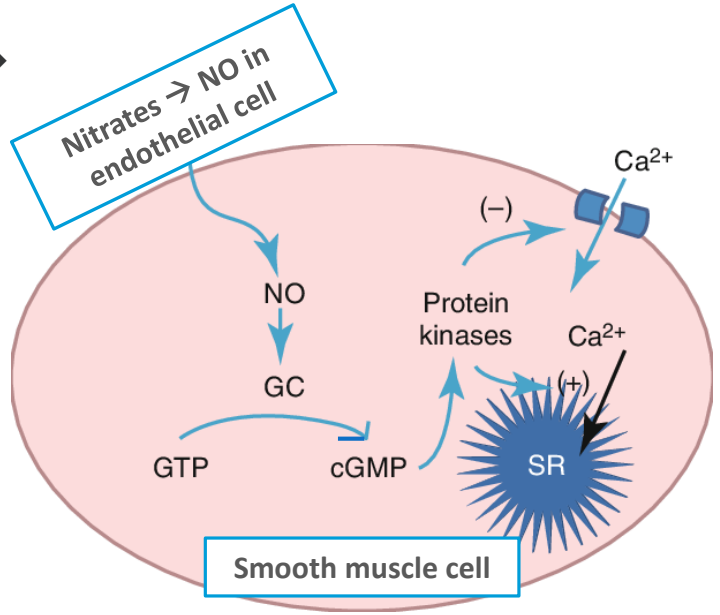


Pharmacotherapy to reduce symptoms
Nitrates: **MOA**

- Organic nitrates are prodrugs
  - Nitrate *--- denitration --->* Nitric Oxide 'NO' (Endothelium-Derived Relaxing Factor 'EDRF')

- <u>MOA</u>:
  - NO activates soluble Guanylate Cyclase (GC) in the vascular endothelium →
  - Increased production of cyclic Guanosine Monophosphate (cGMP) →
  - Reduction in cytoplasmic Ca →
  - Vasodilation

  - Anti-platelet effects (aggregation inhibitor)? (negligible clinical impact)



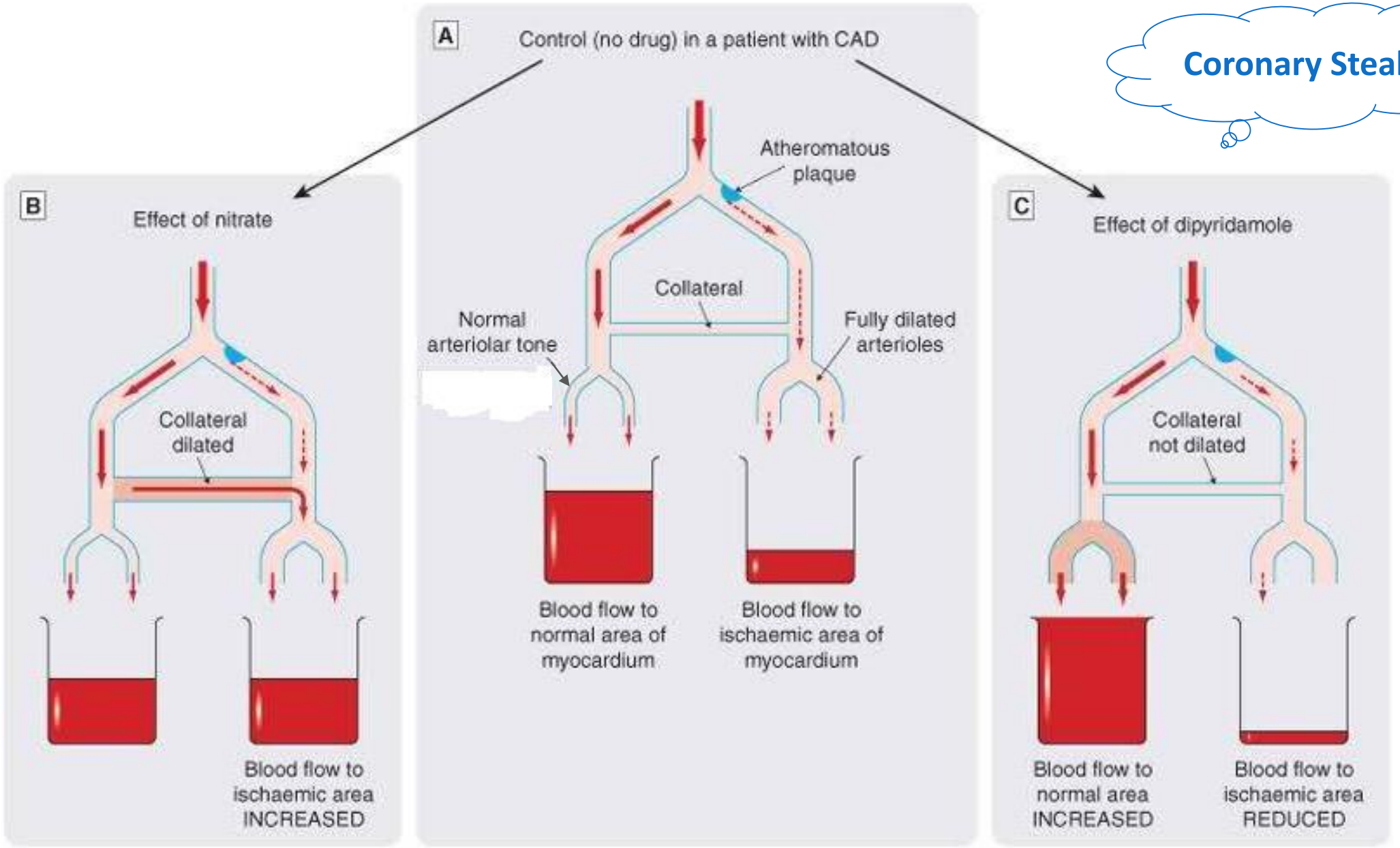
Pharmacotherapy to reduce symptoms
Nitrates: **MOA**

- Venodilation:
  - Predominant effect
  - Leads to reduced preload and MVO_2

- Arteriodilation:
  - Occurs with high doses
  - Leads to reduced afterload and MVO_2
  - Can cause reflex tachycardia and increased MVO_2 (may negate antianginal benefits)
  - Combination with β-blockers or non-DHP CCB prevents reflex tachycardia

- Coronary artery dilation:
  - Vasodilates stenotic vessels AND intracoronary collaterals
  - Leads to enhanced blood flow and myocardial oxygen supply to ischemic areas

Coronary Steal



Pharmacotherapy to reduce symptoms
Nitrates: **MOA**

- Nitrates do not cause *coronary steal* like other vasodilators
  - e.g. dipyridamole, sodium nitroprusside

- Coronary steal:
  - Vasodilation in *normal* non-atherosclerotic coronary vessels (microcirculation)
  - No vasodilation in *diseased* atherosclerotic coronary vessels or collaterals

- Consequences:
  - Blood flow is shifted away (stolen) from atherosclerotic to non-atherosclerotic coronary vessels

- Nitrate-induced coronary vasodilation:
  - Predominately in epicardial vessels and collaterals
  - Minimal effect on coronary microcirculation

Pharmacotherapy to reduce symptoms
Nitrates: **ADRs**

- **Headache**
  - Usually resolves after 2 weeks of chronic nitrate therapy
  - Acetaminophen is effective during the initial weeks of nitrate therapy
- **Skin erythema and inflammation**
  - Occurs with transdermal nitroglycerin
  - Initiate therapy with smaller doses and rotate the application site to mitigate risk
- **Postural hypotension** (usually not severe)
- **Syncope**
- **Nausea**
- **Flushing**

Pharmacotherapy to reduce symptoms
Nitrates: **Agents**

- Nitrate formulations:
  - For acute anginal attacks
  - For chronic use

Product	Onset (minutes)	Duration	Initial Dose
Nitroglycerin			
IV	1-2	3-5 minutes	5-10 µg/min
Sublingual*	1-3	30-60 minutes	0.3-0.4 mg
Oral	40	3-6 hours	2.5-6.5 mg three times a day
Ointment	20-60	2-8 hours	0.5-1 in. (1.3-2.5 cm)
Patch	40-60	>8 hours	0.2-0.4 mg/hour (1 patch)
Isosorbide dinitrate			
Immediate release	20-40	4-6 hours	5-20 mg three times a day
Sustained release	60	8 hours	40 mg once daily
Isosorbide mononitrate			
Immediate release	30-60	6-8 hours	20 mg twice a day
Extended release	30-60	12-24 hours	30-60 mg daily

* Sublingual nitroglycerin exists in three different formulations: tablets, spray, and powder packets.

Pharmacotherapy to reduce symptoms
Nitrates: **Agents (SL NTG)**

- All CAD patients should have access to SL NTG
- Patient education to ensure proper SL NTG use
- SL route avoids GI absorption and hepatic first-pass metabolism
- SL NTG 300 - 400 µg typically provides relief of angina within 5 minutes of administration
- SL NTG can relieve symptoms even if patients are chronically taking long-acting nitrates
- ADRs (flushing, headache, postural hypotension) can appear rapidly with SL NTG
  - Inform patients about this

Education Point	Rationale
Keep in original dark glass container	SL NTG will interact with plastic and can lose potency when exposed to light
Do not store in a larger plastic vial with a child-resistant safety cap	During an episode of angina, you do not want the patient struggling to figure out how to open the safety cap
Do not store in the bathroom	SL NTG will degrade in moisture and tablets will lose their integrity and potency
Keep SL NTG close by at all times; may need multiple vials	SL NTG does not do any good to the patient if they do not have it with them at the time of an episode of angina. The patient should consider having one at home, at work, in the garage, etc.
The patient should be sitting down and resting while taking the tablet	While SL NTG tablets are small, the dose is not. It is likely the patient will have some flushing, may get a headache, and even become a little light-headed. They need to know this can happen.
Describe how to use a sublingual tablet	The SL NTG is administered under the tongue in order to provide rapid absorption and avoid first-pass metabolism. The patient needs to keep the tablet under the tongue until dissolved. Avoid swallowing the tablet.
Once opened, tablets need to be refilled every 6 months and spray every 3 years	Due to the instability of SL NTG tablets, they are typically only good for 6 months after the bottle is opened. Shelf-life of the spray is longer. Patients need to be advised to refill SL NTG even if all doses have not been taken.
Remove the cotton plug from the bottle	Larger quantity bottles commonly have a cotton plug. During an episode of angina, you do not want the patient to be struggling with trying to get the cotton plug out of the bottle.
May be taken in advance of events known to cause chest pain (2-5 minutes in advance)	SL NTG can be used to prevent episodes of angina if taken before partaking in an exertional event known to precipitate angina/chest discomfort. This dose provides up to 30 min. protection
Contact 911 if first SL NTG does not relieve angina	Most episodes of angina are relieved within 5-10 minutes of rest and a single SL NTG. If pain persists, the episode may be an acute coronary syndrome, not stable ischemic heart disease. This requires rapid medical attention.

Pharmacotherapy to reduce symptoms
Nitrates: **Tolerance**

- Nitrate tolerance can develop with chronic long-acting nitrate therapy
  - May start to develop 24 hours - 1 week of nitrate therapy

- Not an "all or none" phenomenon:
  - Reduced responsiveness (antianginal effect) in some patients
  - No responsiveness at all in other patients

- Mechanism of tolerance:
  - Exact mechanism unknown
  - Chronic nitrate administration → Oxidative stress → Dysfunction of mitochondrial aldehyde dehydrogenase (responsible for converting nitrates to NO) → Reduced NO levels → Reduced/lost antianginal effect

Pharmacotherapy to reduce symptoms
Nitrates: **Tolerance**

- Tolerance cannot be overcome with higher nitrate doses
- **Preferred management strategy:** 10-14-hour nitrate-free interval every day
- **Rationale:** Although nitrate tolerance develops rapidly, it is also reversed rapidly
- **Drawback:** Lack of 24-hour anti-ischemic coverage → Risk for angina episodes
- **Solution:** Provide the nitrate-free interval during sleeping nighttime hours (lower MVO_2)
- **Problems:**
  - 20% - 30% of SIHD patients experience nocturnal angina episodes
  - Angina episodes and MI commonly occur in the morning hours, immediately before or after awakening
- **Recommendation:** LA nitrates should not be routinely used as monotherapy in SIHD patients because of:
  - Lack of 24-hour coverage
  - Lack of protection against circadian-related ischemic events
  - Potential for reflex tachycardia
- **Evidence:** Patients taking intermittent transdermal NTG did not experience rebound ischemia during the nitrate-free interval when β-blockers or diltiazem were concurrently used

Pharmacotherapy to reduce symptoms
Nitrates: **Tolerance**

- Transdermal NTG patches and ISMN are the most commonly prescribed chronic nitrates
  - Less frequent dosing than ISDN

- To provide an adequate nitrate-free interval:
  - ISDN TID preparation should be dosed 4 - 5 hours apart (not Q 8 hours)
  - ISMN BID preparation should be dosed 7 hours apart (not Q 12 hours)
  - ISMN ER/QD preparation provides 12 hours of nitrate exposure → Follow by a 12-hour nitrate-free interval
  - Transdermal NTG patches: on in am & off in pm (e.g. apply at 8 am, remove at 8 pm)

Patients working night shifts need to adjust the administration time of nitrates

Product	Onset (minutes)	Duration	Initial Dose
Nitroglycerin			
IV	1-2	3-5 minutes	5-10 µg/min
Sublingual*	1-3	30-60 minutes	0.3-0.4 mg
Oral	40	3-6 hours	2.5-6.5 mg three times a day
Ointment	20-60	2-8 hours	0.5-1 in. (1.3-2.5 cm)
Patch ★	40-60	>8 hours	0.2-0.4 mg/hour (1 patch)
Isosorbide dinitrate			
Immediate release	20-40	4-6 hours	5-20 mg three times a day
Sustained release	60	8 hours	40 mg once daily
Isosorbide mononitrate ★			
Immediate release	30-60	6-8 hours	20 mg twice a day
Extended release	30-60	12-24 hours	30-60 mg daily

Pharmacotherapy to reduce symptoms
Ranolazine: **MOA**

- Does not impact HR, BP, inotropic state, or coronary blood flow
  - Little affinity for α_1, β_1, and β_2 adrenoreceptors
  - Minimal Ca channel blocking activity

- MOA:
  - Exact mechanism unknown!
  - Na channel blocker
  - Reduces myocardial oxygen consumption
  - Improves myocardial function and perfusion
  - Beneficial anti-ischemic effects when ranolazine is added to BB, Non-DHP CCB, or DHP CCB

- Antihyperglycemic effect:
  - Reduces A1c by 0.6% - 0.7% in patients with or without DM, without causing hypoglycemia
  - Good choice in diabetics?

Pharmacotherapy to reduce symptoms
Ranolazine: **PK**

- Available as a sustained-release BID preparation
- Half-life ~ 7 hours

- Ranolazine dose of 1,000 mg BID improves exercise tolerance more than dose of 500 mg BID
- Recommendation:
  - Initiate patients on 500 mg BID
  - Increase dose to 1,000 mg BID within the next 1 - 2 weeks if tolerated

- Several clinically important drug interactions:
  - Primarily metabolized by CYP3A4 (70%-85%) and CYP2D6 (10%-15%)
  - Substrate for *P*-glycoprotein

Pharmacotherapy to reduce symptoms
Ranolazine: **PK**

- Concurrent use of *potent* CYP3A4 inhibitors and inducers with ranolazine is contraindicated

- Potent CYP3A4 inhibitors:
  - Significantly increase ranolazine concentrations
  - e.g. ketoconazole, itraconazole, protease inhibitors, clarithromycin

- Potent CYP3A4 inducers:
  - Significantly decrease ranolazine concentrations
  - e.g. phenytoin, phenobarbital, carbamazepine, rifampin, rifabutin, rifapentine, St. John's wort

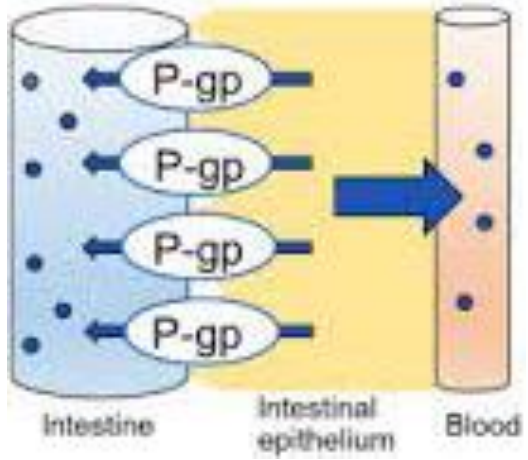
- Concurrent use of *moderate* CYP3A4 inhibitors with ranolazine is allowed
  - Still, ranolazine dose should not exceed 500 mg BID
  - e.g. diltiazem, verapamil, erythromycin, fluconazole

Pharmacotherapy to reduce symptoms
Ranolazine: **PK**

- Ranolazine is a CYP3A4 inhibitor:
  - May inhibit simvastatin metabolism
  - Simvastatin dose should not exceed 20 mg QD

- Ranolazine is an intestinal and renal P-gp inhibitor:
  - Competes with digoxin for intestinal and renal P-gp
  - Increases digoxin plasma concentrations
  - Digoxin dose may need to be reduced

- Potent P-gp inhibitors:
  - May increase ranolazine concentrations and ADRs
  - Ranolazine dose should be reduced
  - e.g. cyclosporine



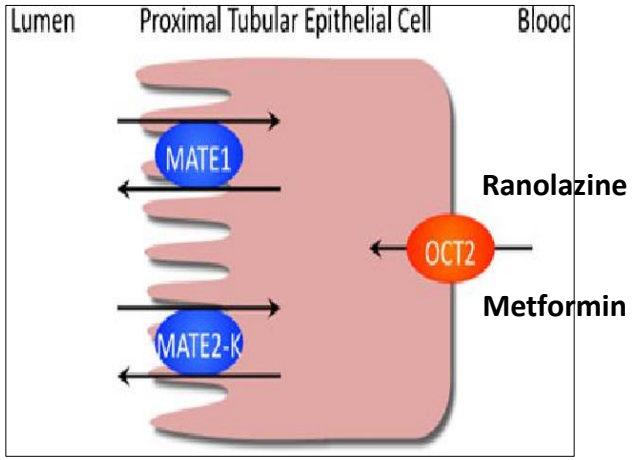
Pharmacotherapy to reduce symptoms
Ranolazine: **PK**

- Ranolazine and Metformin compete for renal clearance through the Organic Cation Transporter 2

- Consequences:
  - Increased metformin concentrations
  - Increased risk of lactic acidosis

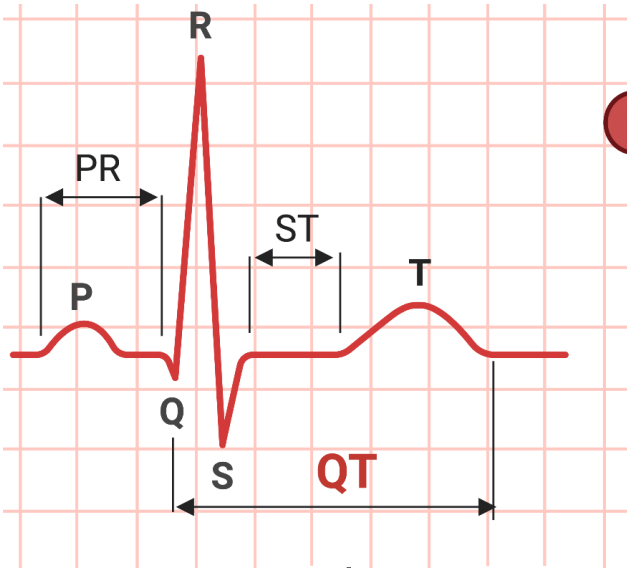
- Clinical relevance:
  - Only when full-dose drugs are combined (both doses 1,000 mg BID)

- Recommendations:
  - Reduce metformin dose to 850 mg BID
  - No need to decrease metformin dose if patient on ranolazine 500 mg BID



Pharmacotherapy to reduce symptoms
Ranolazine: **ADRs**

- Benign ADR profile compared to LA nitrates
  - More expensive
- Most common ADRs:
  - Constipation, Nausea, Dizziness, Headache
- Modest prolongation of QTc:
  - Prolongation by 15 msec or less
  - More severe with higher doses
  - Patients should not exceed Ranolazine 1,000 mg BID
  - Caution in patients receiving concomitant QTc-prolonging agents



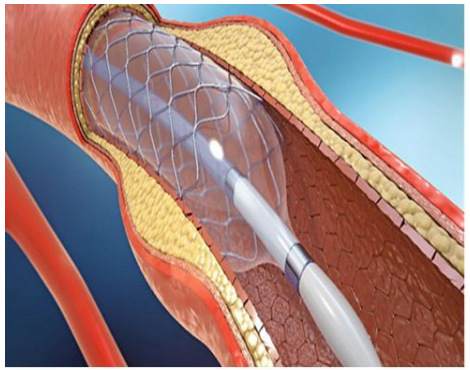
2 **Normal QTc:**
Men:
470 milliseconds or less

Women:
480 milliseconds or less

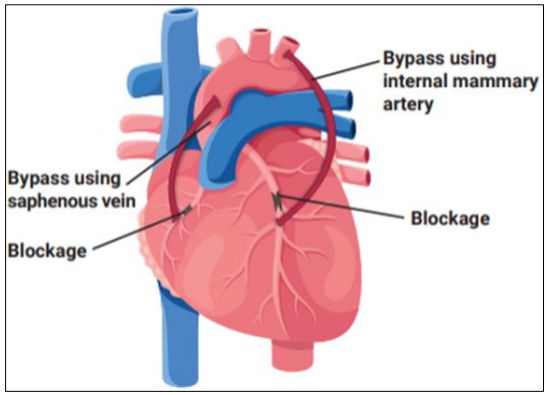
msec = millisecond

Non-pharmacologic therapy

- Surgical revascularization:
  - Percutaneous coronary intervention (PCI)
  - Coronary artery bypass grafting (CABG) surgery “less common”



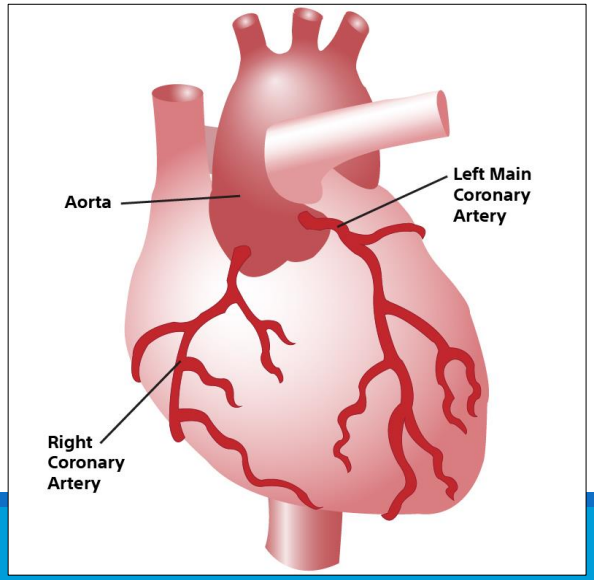
- MOA:
  - Increases myocardial oxygen supply in vessels with critical stenosis (highly effective)
  - **PCI:** opening the stenotic vessel
  - **CABG:** using alternative transplanted vessels to bypass the stenosis



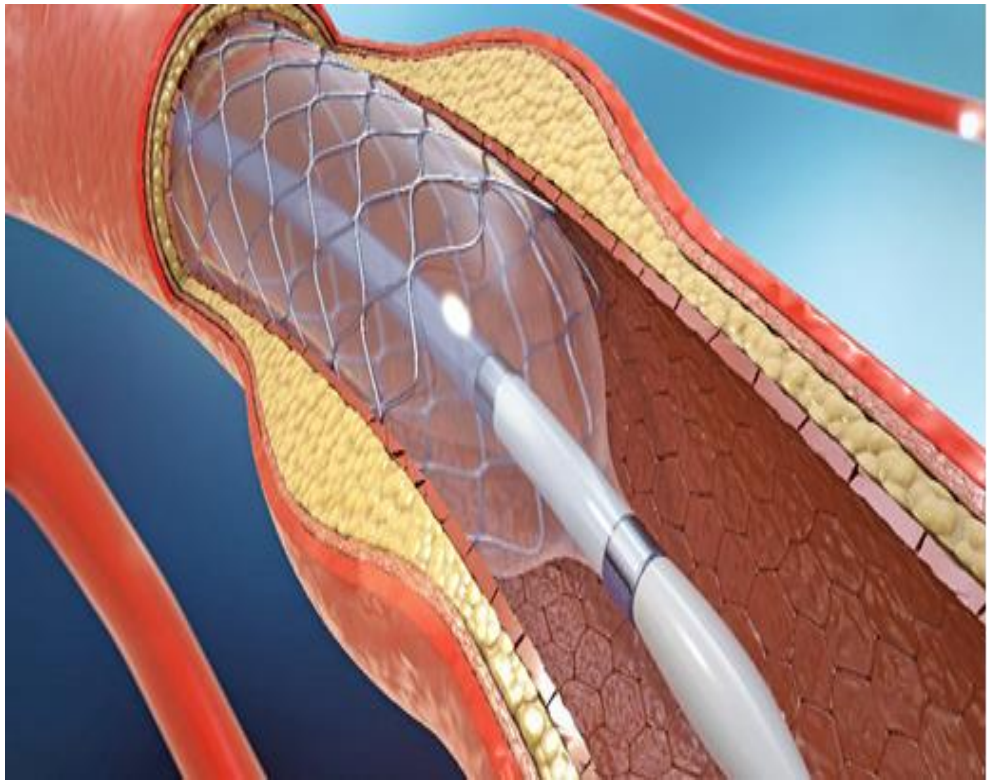
Non-pharmacologic therapy

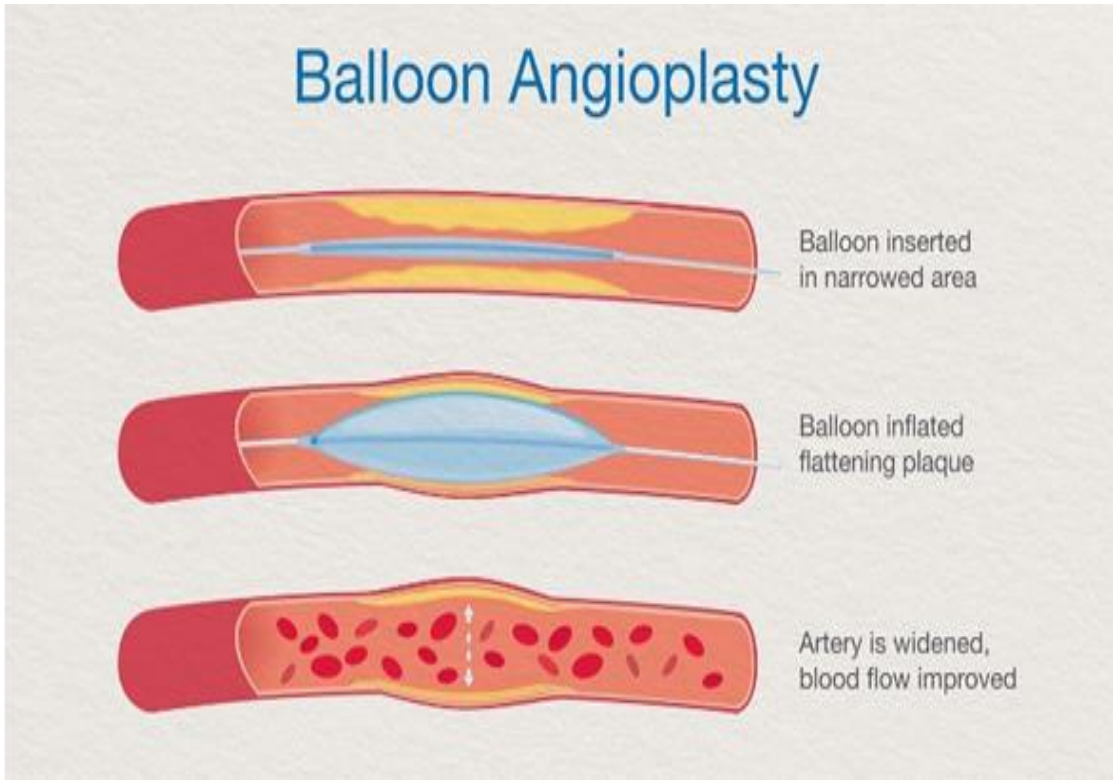
- Goals of revascularization:
  - Primary goal: prolong life (CABG > PCI; CABG > Medical management)
  - Secondary goal: eliminate/reduce refractory symptoms

- Recommended over medical therapy as *initial* management of SIHD in select patients:
  - Significant stenosis of the left main coronary artery
  - Multivessel disease
  - LV dysfunction
  - Refractory angina



Non-pharmacologic therapy
PCI: **Procedure**





Balloon angioplasty ± Stent placement (other less common intracoronary procedures may be performed)
PCI in SIHD = Elective PCI (mostly completed in 30 - 60 minutes)
Catheter is guided into coronary arteries through either the femoral or radial artery

Non-pharmacologic therapy
PCI: **Indications**

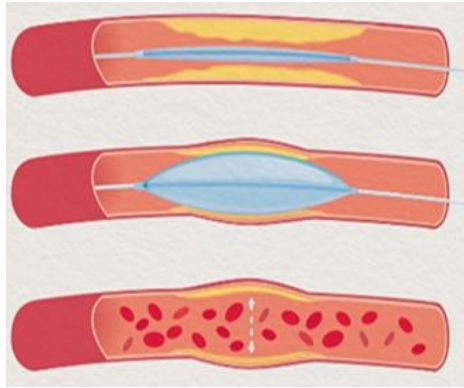
- No study to date has demonstrated that PCI in SIHD improves survival
- PCI with GDMT does not lower the risk of death and MI compared to GDMT alone
- PCI cannot be supported as the initial management strategy in most SIHD patients
- PCI should be reserved for SIHD patients with refractory angina after receiving optimal GDMT

Non-pharmacologic therapy
PCI: **Complications**

- Abrupt vessel closure
- Restenosis
- Thrombosis

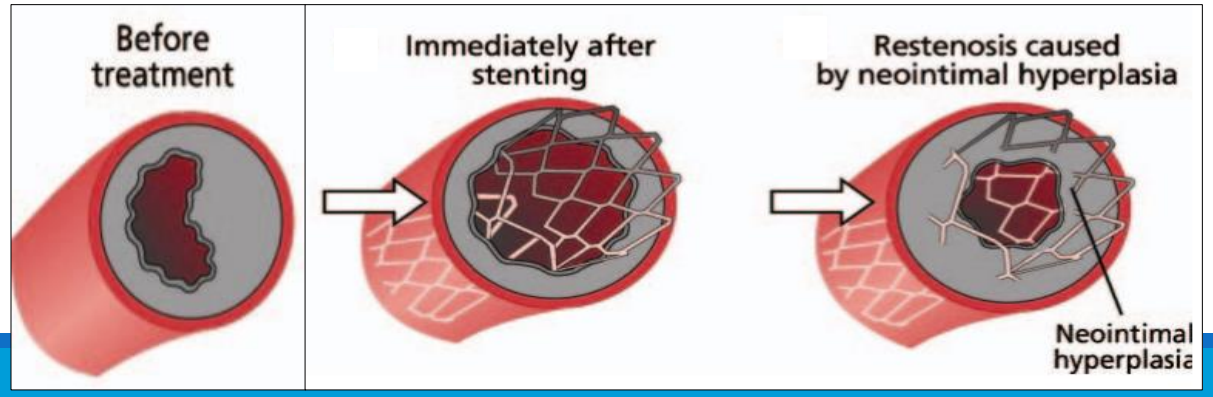
Non-pharmacologic therapy
PCI: **Complications (Abrupt vessel closure)**

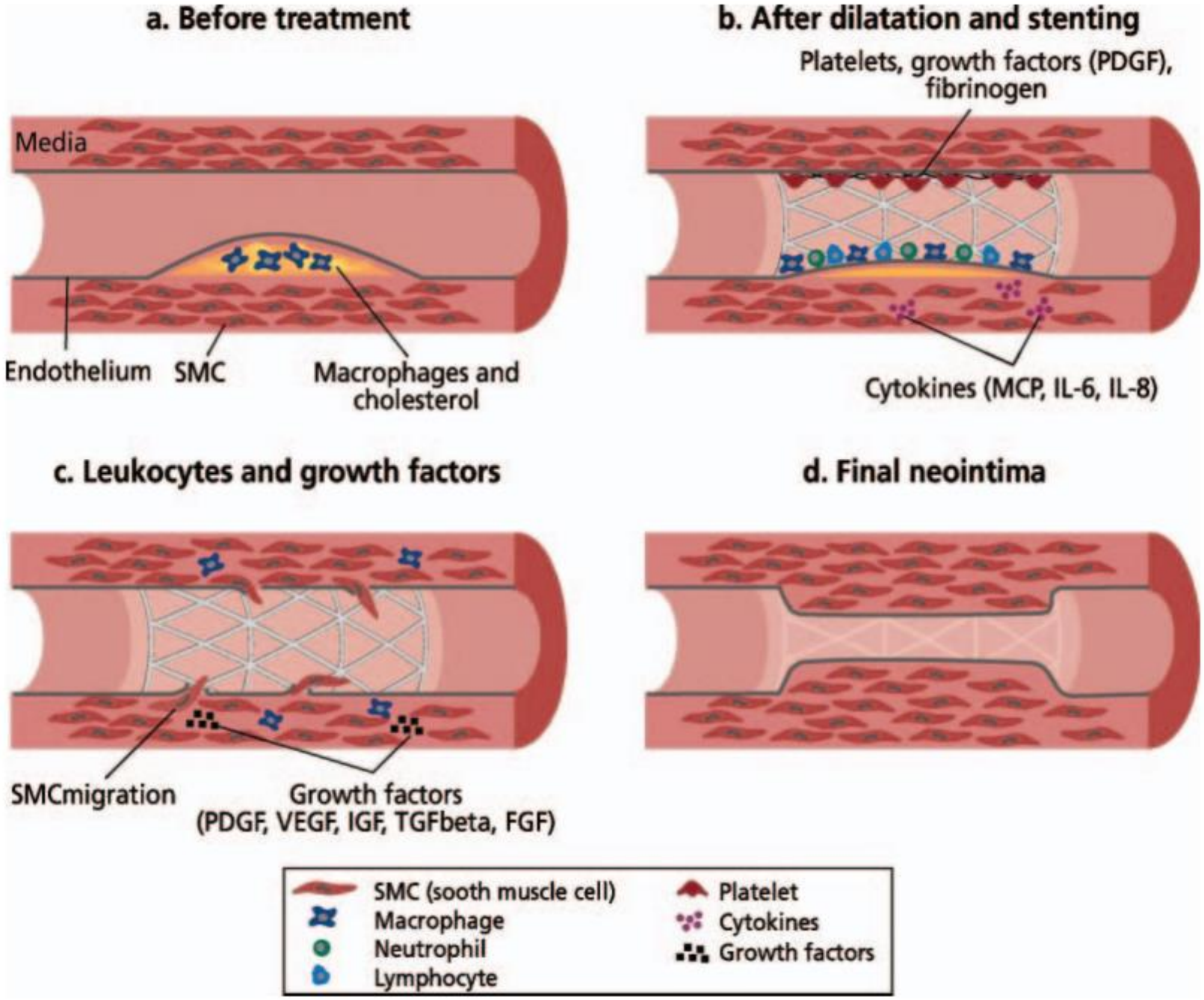
- Potential complication of balloon angioplasty
- Provoked by physical disruption of the plaque on the vessel walls
- Intracoronary stents can be applied to reduce the risk of abrupt vessel closure
- Stents are made of stainless steel or other metals
- Balloon angioplasty + Stent placement do not prevent death/MI more effectively than balloon angioplasty alone



Non-pharmacologic therapy
PCI: **Complications (Restenosis)**

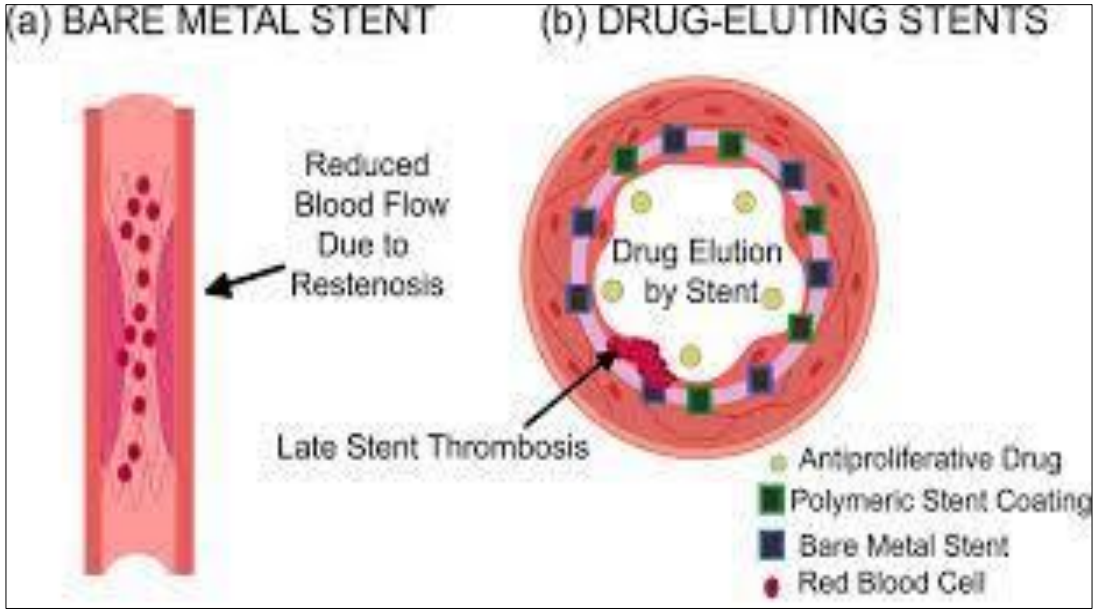
- > 50% diameter loss in the vessel lumen at the site of intervention
- Most often occurs within the first 3 - 6 months following the procedure
- Pathophysiology:
  - Physical damage of the cells lining the vessel →
  - Complex cascade of various growth factors and cytokines →
  - Promoted smooth muscle cell proliferation (neointimal hyperplasia)
- Leads to recurrent symptoms and the need for another revascularization procedure





Non-pharmacologic therapy
PCI: **Complications (Restenosis)**

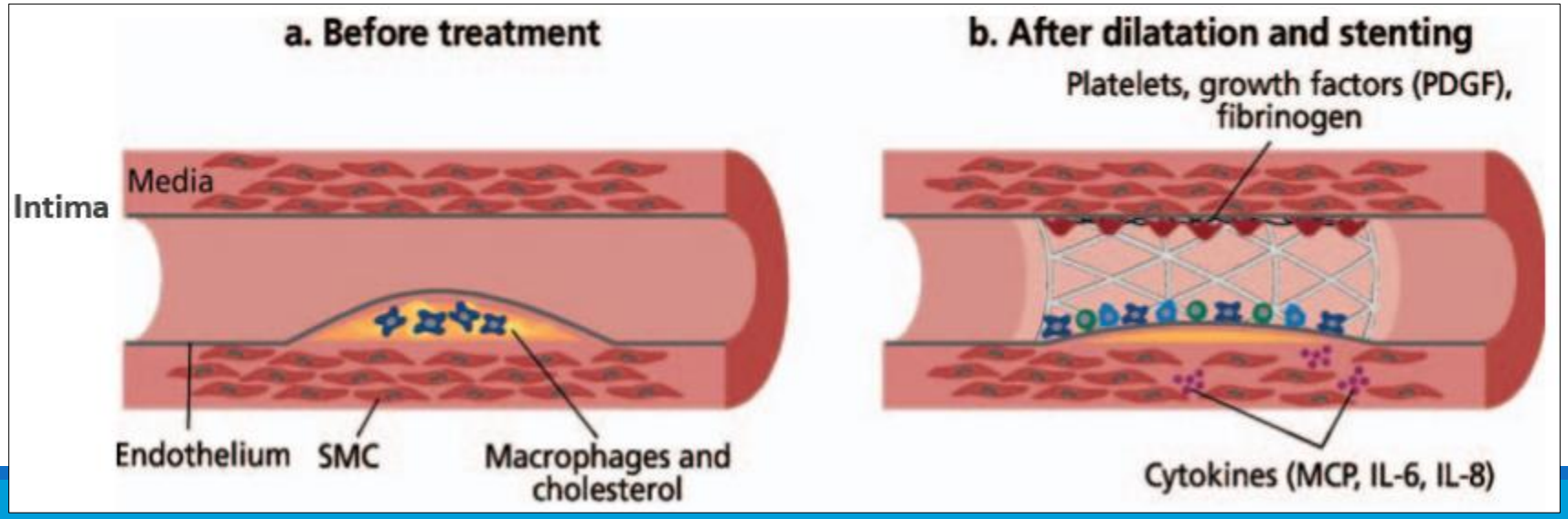
- To reduce the risk of restenosis:
  - Anti-proliferative therapy (Drug-eluting stents ‘DES’)
  - These drugs prevent neointimal hyperplasia; reducing restenosis rates to 5% - 10%
  - DES are coated with sirolimus, paclitaxel, zotarolimus, or everolimus



Non-pharmacologic therapy
PCI: **Complications (Thrombosis)**

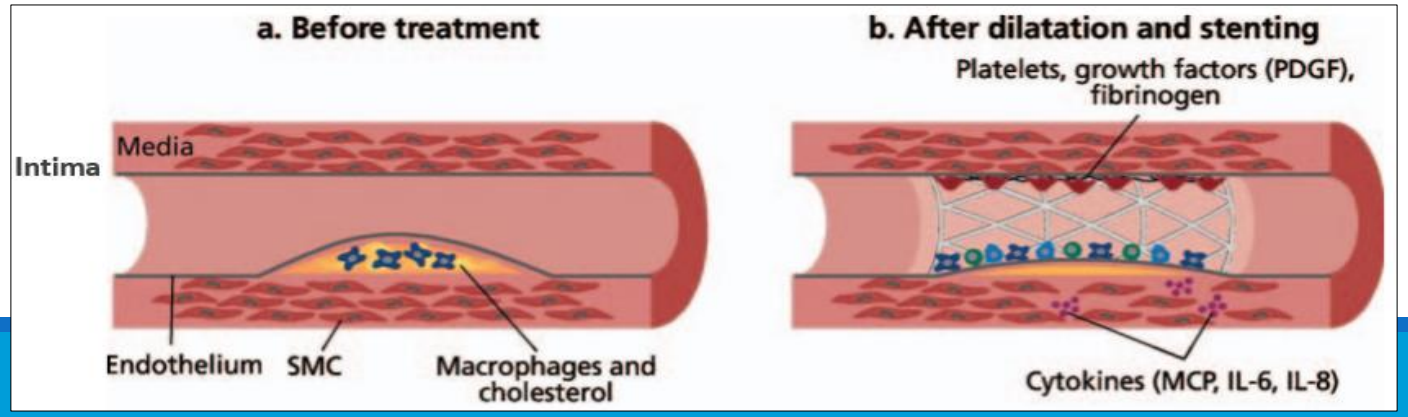
- Uncommon, but catastrophic (leads to large MI or death in two-thirds of cases)

- Pathophysiology:
  - The exposed stent induces platelet adhesion, activation, and thrombus formation
  - The physical damage on the atherosclerotic plaque induces platelet recruitment and activation



Non-pharmacologic therapy
PCI: **Complications (Thrombosis)**

- Risk for stent thrombosis remains until a thin layer of endothelial tissue grows around the stent ***(re-endothelialization)***
- Re-endothelialization typically occurs in 2 - 4 weeks after BMS deployment
- Re-endothelialization is significantly prolonged with the use of DES
  - Antiproliferative drugs prevent smooth muscle, neointimal, and endothelial cell growth →
  - Stent is exposed to platelets for a longer period →
  - Increased risk of stent thrombosis



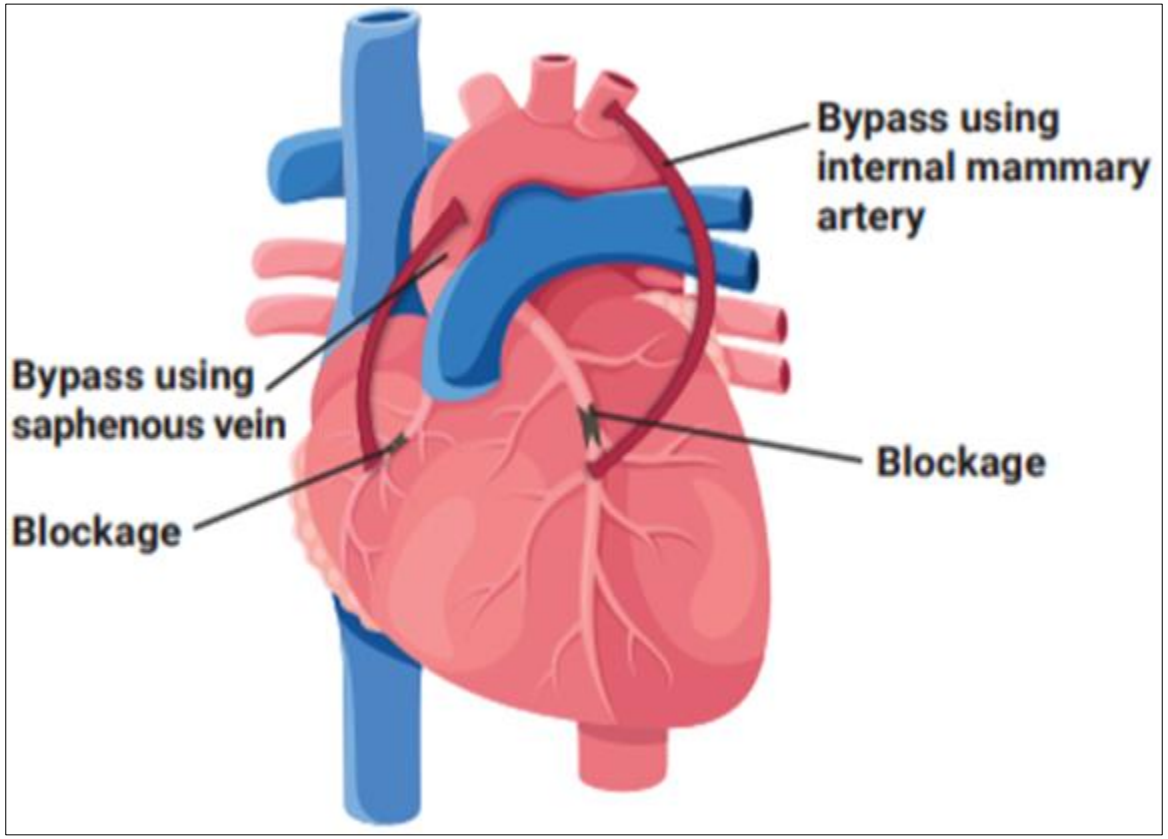
Non-pharmacologic therapy
PCI: **Complications (Thrombosis)**

- To reduce the risk of thrombosis:
  - Antithrombotic therapy (antiplatelets; mainly DAPT)
  - Stent should not be placed if the patient will not tolerate or comply with the recommended duration of DAPT

- Recommendations before PCI:
  - All patients should receive Aspirin LD (if no CI)
    - Aspirin-naïve patients: ASA 325 mg, 2 - 24 hours before PCI
    - Patients already on chronic ASA therapy: take an additional 75 - 325 mg before PCI
  - All patients receiving a stent should also receive a $P2Y_{12}$ inhibitor LD (e.g. clopidogrel 300 - 600 mg)

- Recommendations after PCI:
  - Chronic treatment with Aspirin 81 mg QD + $P2Y_{12}$ inhibitor MD
    - DAPT duration in BMS: Minimum 1 month (2 weeks if high risk of bleeding); then ASA monotherapy
    - DAPT duration in DES: Minimum 6 months (3 months if high risk of bleeding or develop significant bleeding); then ASA monotherapy
    - Long DAPT duration is reasonable in patients who tolerate therapy and have low risk of bleeding
    - It is reasonable to continue with $P2Y_{12}$ inhibitor monotherapy after DAPT

Non-pharmacologic therapy
CABG: **Procedure**

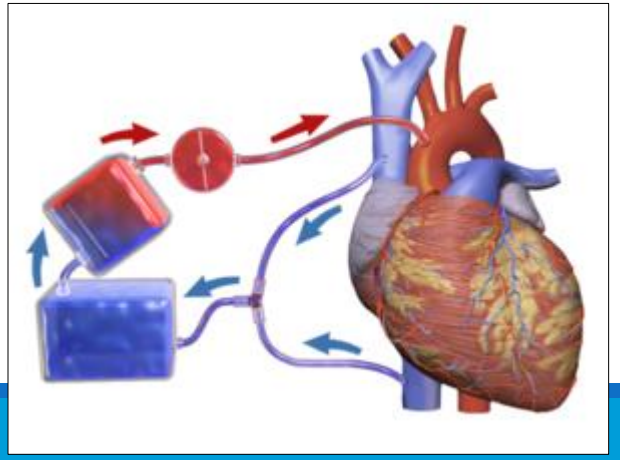


Non-pharmacologic therapy
CABG: **Procedure**

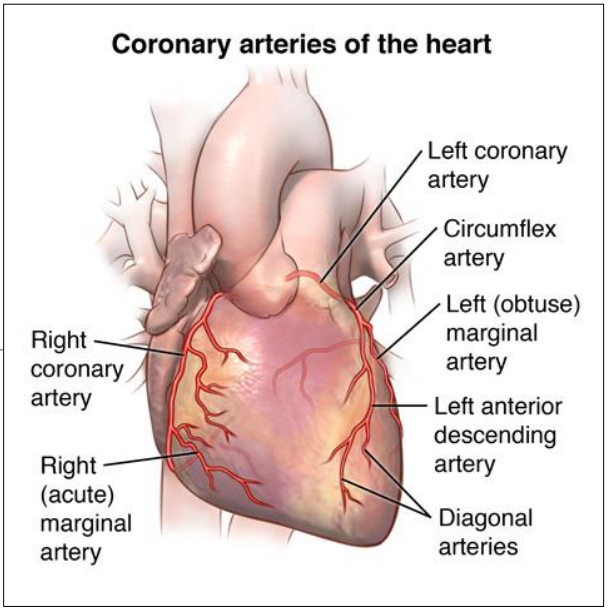
- Sternotomy: Division of sternum to provide direct access to the heart “open-heart surgery!”
- Vascular conduits taken from other body areas to *bypass* the atherosclerotic plaque

- Most common vascular conduits:
  - Saphenous vein grafts (SVG) from the leg: more prone to atherosclerosis
  - Left internal mammary artery (LIMA) from the chest wall: more prone to vasospasm
- Less common vascular conduits:
  - Radial arteries
  - Gastroepiploic arteries

- Patients are often placed on cardiopulmonary bypass (on-pump CABG)
- Heart is then arrested until installing the bypass grafts



Non-pharmacologic therapy
CABG: **Indications**



- Left main CAD:
  - ≥ 50% stenosis
  - *Unprotected* by collateral coronary blood flow or patent bypass grafts
- 2-vessel CAD:
  - ≥ 70% stenosis in the proximal left anterior descending coronary artery + One additional major coronary artery
- Multivessel CAD:
  - ≥ 70% stenosis in three or more major coronary arteries
- Patients who survived sudden cardiac death due to significant (≥ 70% stenosis) CAD in ≥ 1 artery
- Patients who have refractory angina after receiving optimal GDMT for SIHD
  - PCI is often preferred (less invasive)

Non-pharmacologic therapy
CABG: **Complications**

- **Death**
  - Early mortality within 30 days is generally low (1% - 2%)
  - Early mortality is higher in high-risk cases (multiple comorbidities, elderly…)
- **Neurological complications**
  - Stroke, delirium, cognitive deficits…
  - Occur due to hypoxia, emboli, hemorrhage, metabolic abnormality…
  - Higher risk in the elderly, previous stroke/TIA, HTN, ASCVD, atrial fibrillation, and prolonged cardiopulmonary bypass duration
- **MI**
- **Atrial fibrillation** (often transient)
- **Major bleeding**
- **Acute kidney injury** (may require hemodialysis; higher risk with prolonged cardiopulmonary bypass duration)
- **Surgical wound infections**
- **Mediastinitis** (infection of sternum)

Non-pharmacologic therapy
CABG: **Complications (Prevention)**

- Off-pump bypass coronary surgery:
  - Prevents neurologic and renal complications

- Minimally invasive direct coronary artery bypass:
  - A small left anterior thoracotomy in lieu of a Sternotomy
  - Only patients with single-vessel disease (left anterior descending artery or right coronary artery)
  - Similar clinical outcomes; Increased post-operative pain; Quicker recovery time (vs. sternotomy)

Non-pharmacologic therapy
CABG: **Complications (Prevention)**

- Recommendations before CABG:
  - Hold / Do not initiate antiplatelets before surgery to reduce bleeding risk
  - **Patients already on ASA 81 - 325 mg:** Hold at the time of surgery
  - **Patients not already on ASA:** Do not initiate
  - **Patients already on $P2Y_{12}$ inhibitor:** Hold before surgery
    - Prasugrel: Hold for at least 7 days before elective CABG
    - Clopidogrel and Ticagrelor: Hold for at least 5 days before elective CABG
    - Cangrelor (IV): Hold for a few hours before CABG (short half-life)
    - Before urgent CABG: Hold $P2Y_{12}$ inhibitors for at least 24 hours before surgery
  - **Patients not already on $P2Y_{12}$ inhibitor:** Do not initiate
  - May initiate β-blockers or Amiodarone to reduce the risk of postoperative atrial fibrillation

Non-pharmacologic therapy
CABG: **Complications (Prevention)**

- Recommendations after CABG:
  - ASA, high-intensity statins, β-blockers, *continuation* of ACE inhibitors (ACC/AHA Class I recommendations)
  - ASA 81 - 325 mg daily should be resumed/initiated within 6 hours of CABG and continued indefinitely → To reduce the risk of graft closure and acute MI
  - If patients have ASA allergy, Clopidogrel is an alternative
  - If patients were taking DAPT following a previous PCI, resume DAPT after CABG
  - High-intensity statin → To reduce the risk atherosclerosis in the bypass grafts
  - β-Blockers → To reduce the risk of postoperative atrial fibrillation
  - Initiating ACE inhibitors may increase the risk of HoTN and AKI; particularly if administered early after CABG
    - May be considered if compelling indication (e.g. HFrEF, HTN, DM, CKD)
  - Resuming previous ACE inhibitor → May decrease cardiac, cerebral, and renal events

Evaluation of therapeutic outcomes

- Adverse drug reactions
- Progress toward achieving treatment goals (BP, A1c, weight…)
- Monitoring frequency:
  - Q 1 - 2 months until goals are achieved
  - Q 6 - 12 months thereafter
- For monitoring symptom improvement, ask patients about:
  - Number and severity of angina episodes
  - Weekly SL NTG use
  - Exercise capacity or duration of exertion needed to induce angina
  - Ability to engage in daily activities
  - Instruments for symptom assessment (e.g. Seattle Angina Questionnaire)
- Once patients received optimal GDMT, symptoms should improve in 2 - 4 weeks