**College of Pharmacy**

**Fourth year. Clinical Pharmacy**

**Cardiovascular disorders**

**Ischemic Heart Disease**

**Introduction**

1-Ischemic heart disease (IHD) is defined **as lack of oxygen and decreased or no blood flow to the myocardium resulting from coronary artery narrowing or obstruction**.

2-It may present as **acute coronary syndrome** (**ACS**) [which includes unstable angina and non–ST-segment elevation (**NSTE**) or ST-segment elevation (**STE**) myocardial infarction (MI)], **chronic stable exertional angina**, **ischemia without symptoms**, **microvascular angina**, or **ischemia due to coronary artery vasospasm** (**variant or Prinzmetal angina**).

**Pathophysiology**

1-Angina pectoris usually results **from increased myocardial oxygen demand** in the setting of a **fixed decrease in myocardial oxygen supply because of atherosclerotic plaque.**

2-Major determinants of **oxygen demand** are heart rate (HR), myocardial contractility, and intramyocardial wall tension during systole. **A doubling in any of these individual parameters requires a 50% increase in coronary flow to maintain myocardial supply.**

3-Coronary plaques that occupy less than 50%–70% of the vessel luminal diameter rarely produce ischemia or angina. However, **smaller plaques have a lipid-rich core and thin fibrous cap and are more prone to rupture and cause acute thrombosis**.

4-When the luminal diameter of epicardial vessels is reduced by 70% or more, minimal physical exertion may result in a flow deficit with myocardial ischemia and often angina.

5-Some patients have plaque that causes a fixed decrease in supply but also have reduced myocardial oxygen supply transiently **due to vasospasm at the site of the plaque** (referred to as **variable threshold angina**). Ischemic episodes may be **more common in the morning hours** (due to circadian release of vasoconstrictors) and be precipitated by cold exposure and emotional or mental stress.

6-Patients **with variant (Prinzmetal) angina usually do not have a coronary flow-obstructing plaque** but instead have significant reduction in myocardial oxygen supply due to **vasospasm in epicardial vessels**.

**Clinical presentation**

1-Patients typically complain of **chest pain precipitated by exertion** or activities of daily living that is described as squeezing, crushing, heaviness, or chest tightness. It can also be more **vague and described as a numbness or burning in the chest**.

2-The location is often **substernal and may radiate to the right or left shoulder or arm** (left more commonly), **neck**, **back**, or **abdomen**. Ischemic symptoms may be associated with **diaphoresis, nausea, vomiting, and dyspnea**.

3-Chest pain generally **lasts from 5 to 20 minutes** and is usually **relieved by rest or sublingual nitroglycerin (SL NTG).**

4-Some patients (especially **women and older individuals**) present with **atypical chest pain,** characterized by midepigastric discomfort, effort intolerance, dyspnea, and excessive fatigue. **Patients with diabetes mellitus may have decreased pain sensation due to neuropathy**.

5-Patients with **variant (Prinzmetal)** angina are typically **younger** and may present with **chest pain at rest**, often early in the **morning**, and may have transient ST-segment elevation on the ECG.

**Diagnosis**

1-Obtain the **medical history** to identify the quality and severity of chest pain, precipitating factors, location, duration, pain radiation, and response to nitroglycerin or rest.

2-Ischemic chest pain may resemble pain from noncardiac sources, and **diagnosis of anginal pain may be difficult based on history alone.**

3-Assess **nonmodifiable risk factors for coronary artery disease** (CAD): age, sex, and family history of premature atherosclerotic disease in first degree relatives (male onset before age 55 or female before age 65).

4-Identify the presence of **modifiable CAD risk factors**: hypertension, diabetes mellitus, dyslipidemia, and cigarette smoking.

5-**Physical exam findings** are usually nonspecific, but patients having an ischemic episode may present with tachycardia, diaphoresis, shortness of breath, nausea, vomiting, and lightheadedness.

6-Markers of inflammation, such as high-sensitivity **C-reactive protein (hs-CRP), may be elevated.** Cardiac **troponin concentrations are not typically elevated in stable IHD**.

7-**Resting ECG is normal in at least half of patients with angina who are not experiencing acute ischemia.** About 50% of patients develop ischemic ECG changes during an episode of angina, which can be observed on the ECG during an **exercise stress test.**

8-**Coronary angiography** is the most accurate test for confirming CAD but is invasive and requires arterial access. Myocardial **perfusion imaging**, **cardiac magnetic resonance**, and **CT angiography** can also be used to detect CAD.

**Treatment**

Goals of Treatment:

1-A primary goal of therapy is complete (or nearly complete) **elimination of anginal chest pain and return to normal activities**.

2-Long-term goals are to **slow progression of atherosclerosis and prevent complications** such as MI, heart failure, stroke, and death.

**Nonpharmacologic Therapy**

1-**Lifestyle modifications** include daily physical activity, weight management, dietary therapy (reduced intake of saturated fats, trans-fatty acids, and cholesterol), smoking cessation, psychological interventions (eg, screening and treatment for depression if appropriate), limitation of alcohol intake, and avoiding exposure to air pollution.

2-**Surgical revascularization** options for select patients include coronary artery bypass grafting (**CABG**) or percutaneous coronary intervention (**PCI**) with or without stent placement.

**Pharmacologic Therapy**

1-Guideline-directed **medical therapy** (GDMT) **reduces the rates of death and MI similar to revascularization therapy.**

2-Approaches to **risk factor modification** include the following recommendations:

* **Dyslipidemia**: Use moderate- or high-dose **statin** therapy in addition to lifestyle changes. Addition of ezetimibe (first) or a PCSK9 inhibitor (second) is reasonable for patients who do not tolerate statins or do **not attain a 50% decrease in LDL cholesterol (or LDL remains above 70–100 mg/dL).**
* **Blood pressure**: If BP is ≥130/80 mm Hg, institute drug therapy in addition to or after a trial of lifestyle modifications.
* **Diabetes mellitus**: Pharmacotherapy to achieve a target A1C of ≤7% is reasonable for select patients (eg, short duration of diabetes and long life expectancy). An A1C goal of <8% is reasonable for other patients, such as those with micro- or macrovascular complications or coexisting medical conditions.
* **Annual influenza vaccinations** are recommended.

**Antiplatelet Therapy**

1-**Aspirin** reduced platelet activation and aggregation. A small percentage of patients are nonresponsive to aspirin's antiplatelet effects.

2-The ACC/AHA guidelines contain the following recommendations for stable IHD:

* **Aspirin**: 75–162 mg daily should be continued indefinitely in the absence of contraindications.
* **Clopidogrel**: 75 mg daily is an appropriate alternative when aspirin is contraindicated.

3-**Patient responsiveness to clopidogrel is highly variable**, with estimates of nonresponsiveness ranging from 5% to 44% of patients. The most common cause of nonresponsiveness is **nonadherence**, but **genetic polymorphisms** to CYP2C19 may contribute in some patients.

4-Some studies have suggested that patients receiving a **PPI** (most often omeprazole) together with clopidogrel have reduced antiplatelet activity and more ischemic events due to inhibition of cytochrome P450 enzymes involved in converting clopidogrel to its active metabolite. However, a clinical trial **found no increased rate of clinical events in patients given clopidogrel plus omeprazole.**

5-**Dual antiplatelet therapy** (DAPT) with aspirin plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) is beneficial **after PCI** **with coronary stent placement** and after **treatment for ACS**. The combination of aspirin (75–162 mg daily) and clopidogrel 75 mg daily may be reasonable in **certain high-risk patients**.

**Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)**

1-**ACE inhibitors have not been shown to improve symptomatic ischemia or reduce chest pain episodes**.

2-The ACC/AHA guidelines for **stable IHD** recommend the following strategies:

* **Use ACE inhibitors in patients who also have** hypertension, diabetes, heart failure with reduced ejection fraction (HFrEF), or chronic kidney disease, unless contraindicated.
* **ARBs** are recommended for the same populations if patients are **intolerant to ACE inhibitors.**

**β-Adrenergic Blockers**

1-β-Blockers competitively inhibit the effects of neuronally released and circulating catecholamines on β-adrenoceptors. Blockade of β1-receptors in the heart and kidney reduces HR, contractility, and BP, thereby decreasing **oxygen demand**.

2-β**-Blockers are recommended over calcium channel blockers** (CCBs) for initial control of angina episodes in patients with stable IHD.

3-The target is to lower the **resting** **HR to 50–60 beats/min** and the **exercise HR to <100 beats/min.** For patients (eg, **elderly**) who cannot tolerate these ranges, the target HR should be as low as can be tolerated above 50 beats/min.

4-**β-Blockers may be combined** with CCBs or long-acting nitrates when initial treatment with β-blockers alone is unsuccessful.

5-**Only the β-blockers** **carvedilol**, **metoprolol** succinate, and **bisoprolol** should be used in patients with **HFrEF**, starting with low doses and titrating upward slowly.

6-β1-Selective agents are preferred in patients with chronic obstructive pulmonary disease, peripheral arterial disease (PAD), diabetes, dyslipidemia, and sexual dysfunction.

7-Drugs with combined α1- and β-blockade are effective for IHD, but **agents with intrinsic sympathomimetic activity provide little to no reduction in resting HR and are not preferred except perhaps in patients with PAD or dyslipidemia.**

8-**Common adverse effects include** bradycardia, hypotension, heart block, impaired glucose metabolism, altered serum lipids (transiently increased triglycerides, decreased HDL-C, and no change in LDL-C), fatigue, depression, insomnia, and malaise.

9-**β-Blockers are contraindicated in patients with** preexisting bradycardia, hypotension, 2nd- or 3rd-degree atrioventricular (AV) block, uncontrolled asthma, severe PAD, hypotension, HFrEF with unstable fluid status, and diabetes associated with frequent episodes of hypoglycemia.

10-**If β-blocker therapy must be discontinued, doses should be tapered over 2–3 weeks** to prevent abrupt withdrawal, which can significantly increase **oxygen demand** and induce ischemia and even MI because of up-regulation of β-receptors in the myocardium.

**Calcium Channel Blockers**

1-All CCBs reduce **oxygen demand** by reducing wall tension via lowering arterial BP and (to a minor extent) depressing contractility. CCBs also provide some increase in supply by inducing coronary vasodilation and preventing vasospasm.

2-CCBs or long-acting nitrates should be prescribed for relief of symptoms **when β-blockers are contraindicated or cause unacceptable side effects.**

3-**Dihydropyridine CCBs** (eg, nifedipine, amlodipine, isradipine, and felodipine) primarily affect vascular smooth muscle with little effect on the myocardium.

**4-Short-acting agents should not be used because of their greater propensity to cause reflex tachycardia.** Other side effects of these CCBs include hypotension, headache, gingival hyperplasia, and peripheral edema.

5-Although most CCBs are contraindicated in patients with HFrEF, **amlodipine and felodipine are considered safe options in these patients.**

6-**Nondihydropyridine CCBs** (**verapamil** and **diltiazem**) mostly affect the myocardium with minimal effects on vascular smooth muscle.**Common side effects of these CCBs include** bradycardia, hypotension, AV block, and symptoms of LV depression. These agents should be avoided in patients with concomitant HFrEF due to negative inotropic effects.

7-**Verapamil may cause constipation** in ∼8% of patients. **Verapamil and diltiazem inhibit clearance of drugs** that utilize the cytochrome P450 3A4 isoenzyme such as carbamazepine, cyclosporine, lovastatin, simvastatin, and benzodiazepines.

8-**Verapamil, and to a lesser extent diltiazem, also inhibit P-glycoprotein–mediated drug transport**, which can increase concentrations of digoxin and cyclosporine. Verapamil also decreases digoxin clearance.

9-Agents that induce the 3A4 isoenzyme can reduce the effectiveness of all CCBs.

**Nitrates**

1-Nitrates cause vasodilation. **Most vasodilation occurs on the venous side**, leading to reduced preload, myocardial wall tension, and **oxygen demand**.

2-**All patients should have access to sublingual (SL) NTG 0.3 or 0.4 mg tablets or spray** to treat acute angina episodes. Relief typically occurs within 5 minutes of administration.

3-**SL nitrates can also be used to prevent acute episodes if given 2–5 minutes before activities known to produce angina**; protection can last for up to 30 minutes with SL NTG and up to 1 hour with SL isosorbide dinitrate (ISDN).

4-Long-acting nitrates (or CCBs) should be prescribed for relief of symptoms **when β-blockers are contraindicated or cause unacceptable side effects.**

5-**Transdermal patches** and **isosorbide mononitrate (ISMN)** are most commonly prescribed for **long-term prevention of angina episodes**. **ISDN** is also effective, but the **three times daily regimen** requires dosing every 4–5 hours during the day to provide a nitrate-free interval.

6-**Chronic nitrate use should incorporate a 10- to 14-hour nitrate-free interval each day to reduce nitrate tolerance.** Because this approach places the patient at risk for angina episodes, the **nitrate-free interval is usually provided during the nighttime hours** when the patient has a reduced **oxygen demand** while sleeping.

7-The **extended-release ISMN products** that are dosed **twice daily** should **be given 7 hours apart (**eg, 7:00 AM and 2:00 PM). An extended-release, once daily ISMN product is available that provides 12 hours of nitrate exposure followed by a 12-hour nitrate-free interval.

8-**Transdermal NTG patches** are typically prescribed as “on in the AM and off in the PM” but patients should be given specific application and removal times (eg, apply at 8:00 AM

and remove at 8:00 PM).

9-**Nitrates should not be used routinely as monotherapy for stable IHD** because of the **lack of angina coverage during the nitrate-free interval**, and potential for reflex tachycardia.

10-**Concomitant β-blocker or diltiazem therapy** can prevent rebound ischemia during the nitrate-free interval.

11-**Common nitrate side effects include** headache, flushing, nausea, postural hypotension, and syncope. **Headache can be treated with acetaminophen** and usually resolves after about 2 weeks of continued therapy.

12-**Transdermal NTG may cause skin erythema and inflammation**. Initiating therapy with smaller doses and/or rotating the application site can minimize transdermal nitroglycerin side effects.

**Ranolazine**

1-Ranolazine reduces ischemic episodes by selective inhibition of late **sodium current (INa)**, which reduces intracellular sodium concentration and improves myocardial function and perfusion.

2-**It does not impact HR, BP, the inotropic state, or increase coronary blood flow**. Ranolazine is effective as monotherapy for relief of angina symptoms but should only be used **if patients cannot tolerate traditional agents** due to hemodynamic or other adverse effects.

3-Because it does not substantially affect HR and BP, it is recommended as add-on therapy to traditional antianginal agents for **patients who achieve goal HR and BP and still have exertional angina symptoms, patients who cannot achieve these hemodynamic goals due to adverse effects, and patients who reach maximum doses of traditional agents but still have angina symptoms.**

4-**It can be combined with a β-blocker** when initial treatment with β-blockers alone is unsuccessful.

5-**Adverse effects include** constipation, nausea, dizziness, and headache. Ranolazine can **prolong the QTc interval** and should be used with caution in patients receiving concomitant QTc-prolonging agents.

6-Potent **inhibitors of CYP3A4 and P-glycoprotein** or **potent inducers of CYP3A4** and P-glycoprotein are **contraindicated with ranolazine** due to significant increases and decreases in ranolazine drug concentrations, respectively.

7**-Moderate CYP3A4 inhibitors** **can be used with ranolazine**, but the maximum dose should not exceed 500 mg twice daily.

**Treatment of Variable Threshold Angina and Prinzmetal Angina**

1-Patients with **variable threshold angina require pharmacotherapy for vasospasm**. Most patients respond well to **SL NTG for acute attacks.**

2-Both **CCBs (**Nifedipine, verapamil, and diltiazem) **and nitrates are effective for chronic therapy**. **CCBs may be preferred** because they are dosed less frequently.

3-**Patients unresponsive to CCBs alone may have nitrates added.** **β-Blockers are not useful for vasospasm** because they may induce coronary vasoconstriction and prolong ischemia.

**Evaluation of therapeutic outcomes**

1-Assess for symptom improvement by **number of angina episodes, weekly SL NTG use, and increased exercise capacity or duration of exertion needed to induce angina.**

2-**Once patients have been optimized on medical therapy, symptoms should improve over 2–4 weeks and remain stable until the disease progresses**. Patients may require evaluation **every 1–2 months until target endpoints are achieved**; follow-up **every 6–12 months thereafter is appropriate.**

3-If the patient is doing well, no other assessment may be necessary.

4-**Monitor for adverse drug effects such as headache and dizziness** with nitrates; fatigue and lassitude with β-blockers; and peripheral edema, constipation, and dizziness with CCBs.

**Reference**

**Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach,**

**11th Edition. 2021.**