Cardiovascular Pharmacology

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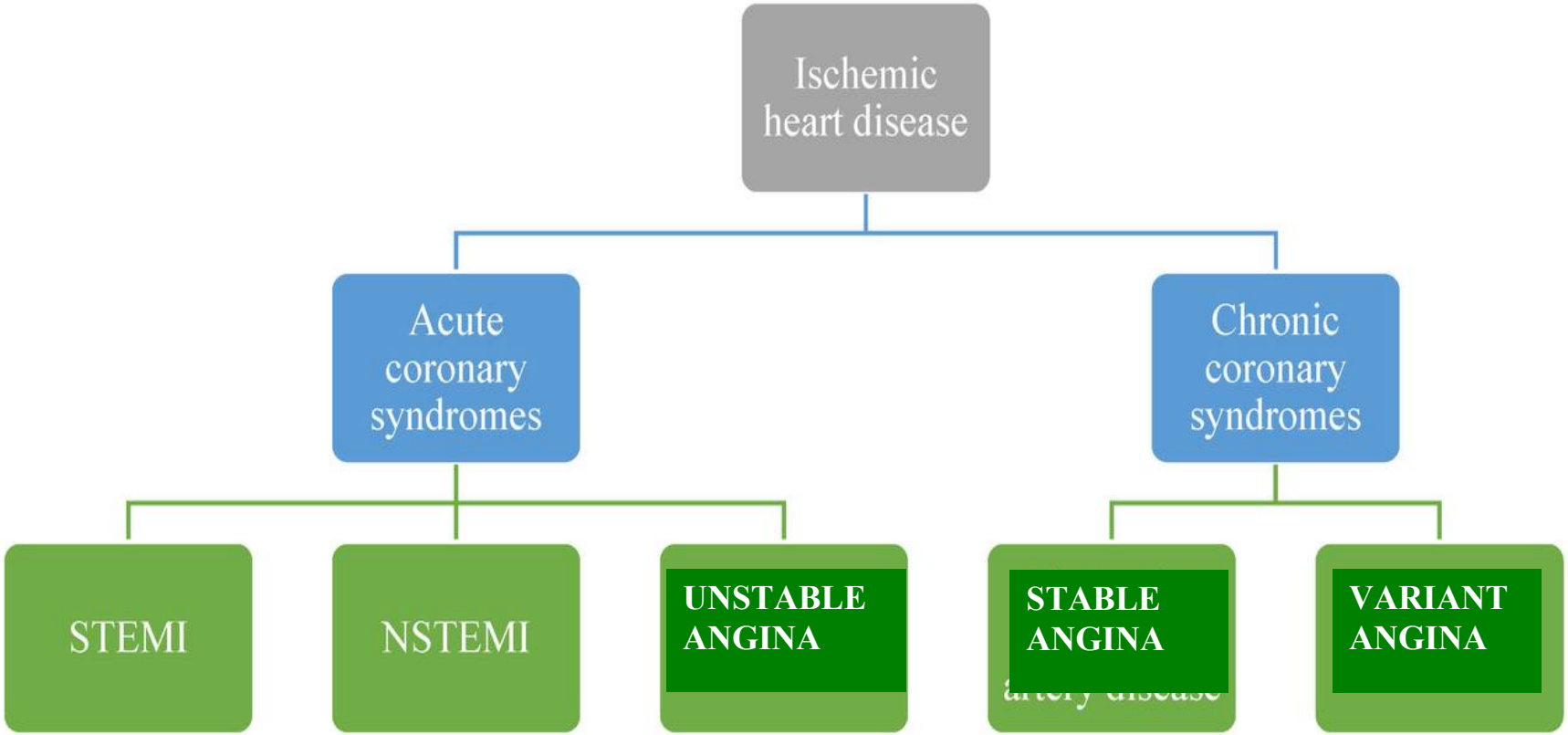
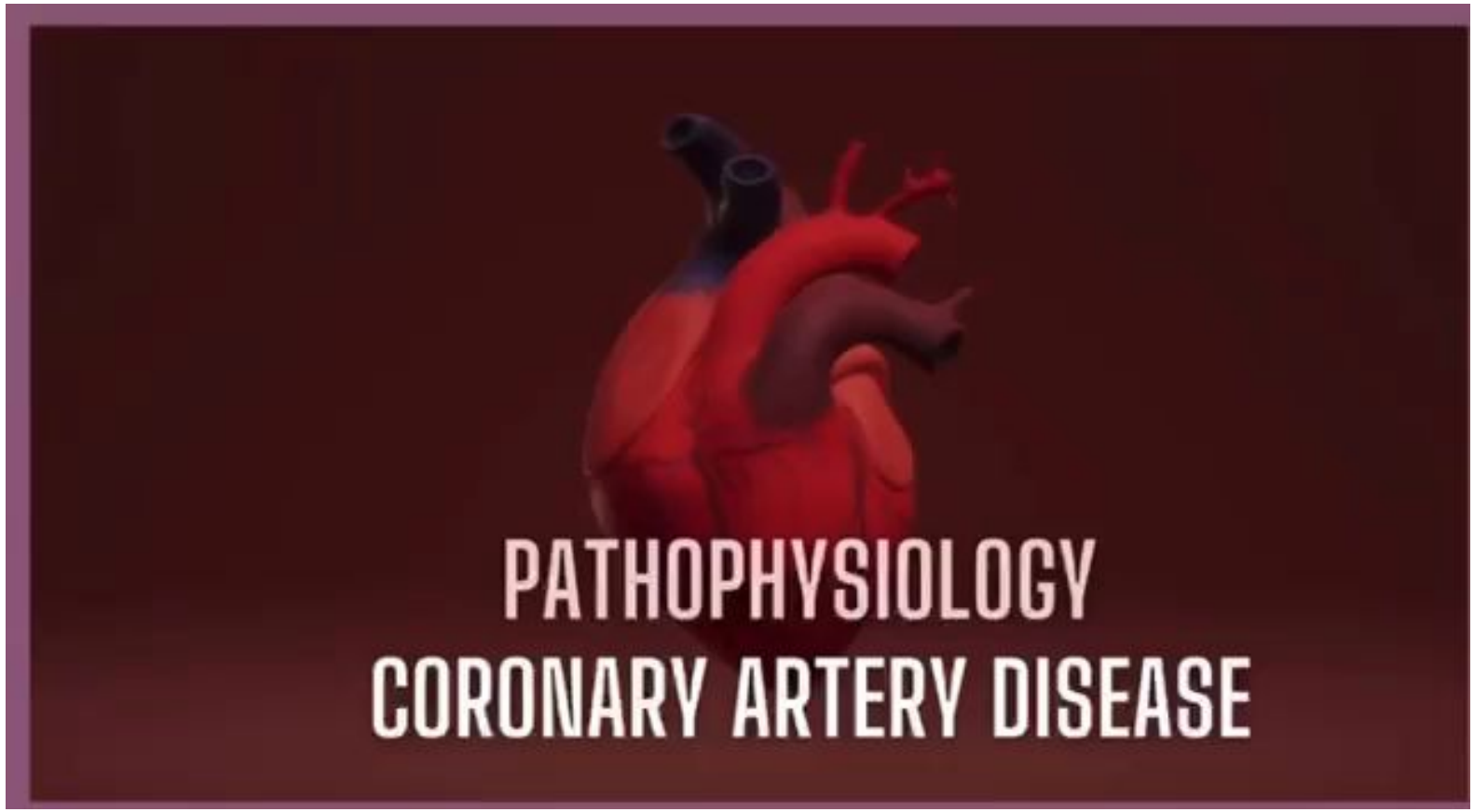
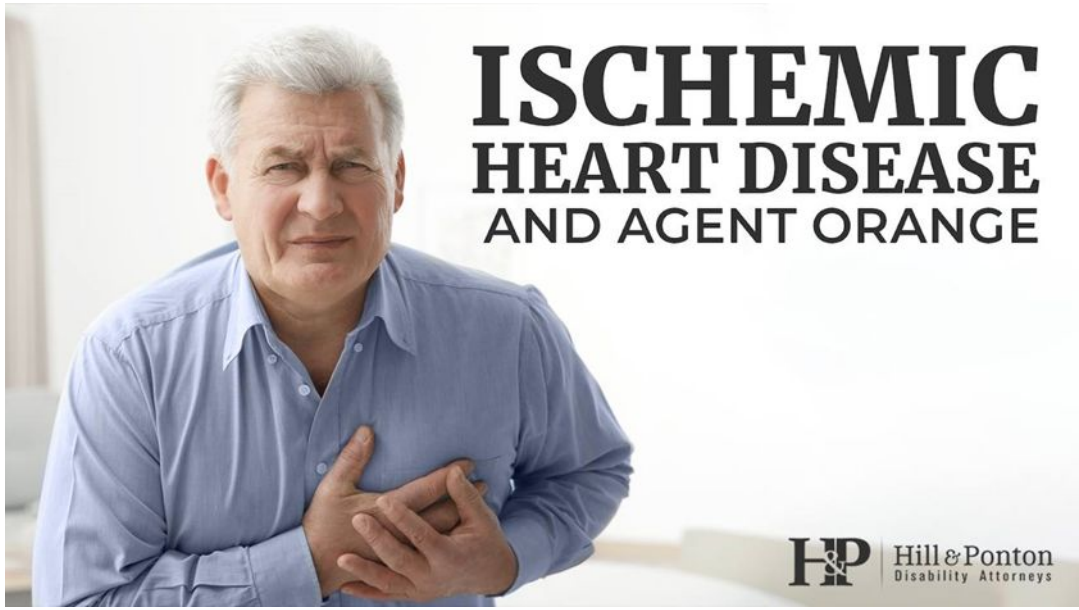
Ischemic Heart Diseases/CAD



Pathophysiology of IHDs



Therapy for Ischemic Heart Diseases



Management of IHD

- Basic assessment and identification of comorbidities (DM, HT, obesity, Smoking..)
- Basic testing (Biochemical tests, ECG, Echo…)
- Establishing a diagnosis (using noninvasive functional imaging or invasive procedures for myocardial ischemia)
- Once the diagnosis is established, consider patients risk stratification and planning for therapeutic decisions (lifestyle changes, pharmacological treatment, need for revascularization)

Treatment of CCS

1- Non-Pharmacological:

- Diet Control (fresh fruit/ vegetables and salt/ fat restriction)
- Weight reduction
- Regular exercise (up to but not beyond the point of chest discomfort), 20 minutes daily three times/week
- Cessation of Smoking

2- Pharmacological (antianginal drugs)

Pharmacological Treatment of CCS

1. Aspirin (low dose 75 mg daily) (or alternative antiplatelet ex clopidogrel 75mg daily)
2. B-blocker (ex bisoprolol 5-15mg daily or slow release metoprolol 50-200mg daily)
3. CCB
4. Nitrate (in acute attack, NG is the choice while in between, the intermediate or long acting)
5. Statins (atorvastation, rousvastation…)

If the pain persist, ACS should be suspected and must refer the patient to the hospital

Antianginal Drugs: Strategy

- The pharmacological strategy is to restore the balance between cardiac work (O2 consumption) and blood supply (O2 delivery).
- So the objective is to improve survival primarily by the prevention of myocardial infarction and death and second to improve the quality of life (and exercise capacity) by relief of symptoms

Antianginal Drugs: Types

- Four types of drugs, used either alone or in combination, are commonly used to manage patients with CCS: organic nitrates, β-blockers, calcium channel blockers,, and the sodium channel–blocking drug/others
- These agents help to restore the balance between cardiac oxygen supply and demand by affecting blood pressure, venous return, heart rate, and contractility.

Organic Nitrate: Classification -1

A- Short Acting:

1. Amyl nitrite (inhalation, break ampoule)
2. Nitroglycerin (Glyceryl Trinitrate) (S/L, Buccal spray, IV)
3. Isosorbide dinitrate (S/L)

B- Intermediate Acting: (Isosorbide dinitrate 'oral, SR')

C- Long Acting : Isosorbide mononitrate (Oral, SR)

D- Nitroglycern Patch (for nocturnal angina)

Organic Nitrate: Mechanism of action

- Nitrates relaxes vascular smooth muscles by their intracellular conversion into *Nitric Oxide (NO)* which in turn activates guanylate cyclase to produce cGMP.
- Elevated cGMP leads to dephosphorylation of myosin light chain (intracellular calcium falls), resulting in vascular smooth muscle relaxation.
- Then nitrate decrease oxygen demand by dilation of the large veins, decrease venous return, cardiac work *(main effect)*. They also improve oxygen delivery by increasing coronary arteries perfusion *(minor effect)*.

Organic Nitrate: Pharmacological Effects

- Nitrates provide an exogenous source of vasodilator nitric oxide (NO).
- *Main effect*: vasodilation of the large veins (capacitance vessels), thereby reduction in the preload and subsequently decrease in the cardiac work and oxygen demand.
- *Minor effect*: nitrate also dilate the coronary vasculature (dilation of the coronary arteries and redistribution of the blood) and thus improve coronary artery perfusion (increase blood supply to the heart muscle).

Organic Nitrate: PKs

- Good absorption (from the site of administration)
- Nitrates differ in their *onset of action and rate of administration*. The onset of action varies from 1 minute for NG to 30 minutes for isosorbide mononitrate.
- Exposed to *first pass metabolism* (90% of oral nitrate lost by first pass metabolism by the liver), an exception is the isosorbid mononitrate (not undergo first pass metabolism).
- Significant first-pass metabolism of NG occurs in the liver. Therefore, it is commonly administered via the sublingual or transdermal route (patch), thereby avoiding the hepatic first-pass effect.
- Oral isosorbide dinitrate undergoes denitration to two mononitrates, both of which possess antianginal activity. .

Organic Nitrate: PKs

Note: Why we use S/L, Buccal, or inhalation nitrate in acute attack?....the answer is to ensure fast onset of action (within 1-2 minutes and to avoid first pass metabolism).

Organic Nitrate: Therapeutic Uses

1. All types of Angina
2. Acute heart failure, Acute Pulmonary oedema and LVF
3. Biliary colic
4. Cyanide poisoning

Organic Nitrate: Contraindications

1. Early MI and Right Ventricular MI
2. Hypotension (less than 90mmHg)
3. Recent use of Sildenafil. Phosphodiestrase type 5 inhibitors such as sildenafil potentiate the action of nitrate, result in dangerous hypotension. So such combination is contraindicated.
4. Severe anemia
5. Closed-angle glaucoma
6. constrictive pericarditis
7. Head trauma and cerebral hemorrhage

Organic Nitrate: Side effects

1. Severe throbbing headache (most common). Headaches frequently limit dose and often respond to aspirin.
2. Syncopy and hypotension (serious). Alcohol or cotherapy with other vasodilators (like sildenafil..) may augment hypotension.
3. Tachycardia (frequent)
4. Facial flashing, dizziness, halitosis (sublingual)
5. Methemoglobinemia
6. Tolerance

Organic Nitrate: Tolerance

1. Continues use of nitrate cause tolerance. Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitised to vasodilation.
2. To avoid tolerance, nitrate free interval used. 12 hours nitrate and 12 hours free of nitrate (may be replaced by B-blocker) usually at night when the patient is inactive, decreased myocardial oxygen demand.
3. As the variant angina worsens early in the morning (due to circadian catecholamine surges), the nitrate free interval in patients with variant angina should occur in the late afternoon.

Organic Nitrate: Serious Drug-Drug interaction

1. Interaction with PDE-5 inhibitors (Sildenafil, Tadalafil, and Vardenafil). Erectile dysfunction is often treated by one of these drugs, which are also systemic vasodilators, and can all cause serious hypotension when combined with nitrates because they inhibit the breakdown of cGMP
2. Triple therapy of angina (Nitrate, B-blockers, CCB), each drug can predispose to excess hypotension

B-Blockers -2

- B-blockers; bisoprolol, metoprolol, atenolol..) are the first choice in stable angina
- The dose should be adjusted to ensure resting HR not more than 60 and exercise HR not more than 100.
- Avoid B-blockers with intrinsic sympathomimetic activity (like pindolol)
- Withdrawal should be gradual over 2-4 weeks (as abrupt withdrawal cause rebound effects may precipitate dangerous arrhythmias, worsening angina or MI (β-blocker withdrawal syndrome).
- Contraindicated in Prinzmetal Angina

B-Blockers: Mechanism of action

- Decrease myocardial O2 consumption (By blocking B1-adrenoceptors, they decrease myocardial contractility and heart rate, COP and Bp)
- Improve blood and O2 supply to ischemia area (lower heart rate, prolong diastolic perfusion time)
- These agents reduce myocardial oxygen demand during exercise and at rest, so they reduce frequency and severity of anginal attack.

B-Blockers

- Why combination of B-blockers and Nitrate is recommended in the treatment of angina
- To avoid tolerance
- To counter the undesirable effects of nitrate (like increase in HR, contractility and decrease in diastolic filling time or phase)

CCBs: Mechanism of action -3

- The antianginal effects of CCBs (Nefidipine, amlodipine, verapamil..) related to their hemodynamic effects which decrease myocardial O2 demand and increase myocardial perfusion
- Calcium influx is increased in ischemia in response to hypoxia leading to increment in muscle tone that can worsen the case and lead to more complications. The CCBs protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds.
- They decrease PVR , afterload and BP,
- They have –ve inotropic and –ve chronotropic effects. Decreased HR is associated with increase in diastolic perfusion time which increases myocardial perfusion.
- In addition they relieve coronary spasm

CCBs: General remarks

- CCBs are alternative (second choice) to B-blockers (in case of B-blocker contraindications like *severe bradycardia, asthma, sick sinus syndrome, second degree AV block, severe heart failure*….) in the treatment of stable angina.
- Add on therapy to b-blockers (BB+CCBs)
- Treatment of Prinzmetal angina (CCB is first choice).
- Verapamil mainly affects the myocardium, whereas amlodipine exerts a greater effect on smooth muscle in the peripheral vasculature. Diltiazem is intermediate in its actions

Treatment of Prinzmetal Angina

- CCBs (Verapamil, Diltiazem and Nefidepine) is the first choice treatment of Prinzmetal angina
- Long acting nitrate (isosorbid mononitrate) is also effective in the treatment of Prinzmetal angina

Adjuvent Newer Antianginal Drugs -4

- Metabolic agents : *Trimetazidine* (pFOX inhibitor) and *Ranolazine* (Na channel blocker)
- Nicorandile (K channel opner)
- Ivabradine (fI current inhibitor)

Trimetazidine (metabolic agent)

- Trimetazidine (pFOX inhibitor) (prevent free fatty acid oxidation)
- Metabolic Switch Action: Acts by inhibiting fatty acid oxidation in the myocardium, thus shifting metabolism to glucose (instead of Free Fatty Acid) which requires less oxygen to metabolize
- No hemodynamic effects

Ranolazine (Na channel blocker)

- Ranolazine (Na channel blocker) has antianginal as well as antiarrhythmic properties
- It slows the sodium current, so reduces intracellular sodium and calcium load, thereby relaxes muscles and improve diastolic function and oxygen supply.
- No hemodynamic effects
- It is extensively metabolized by CYP 3A4 and 2D6, so potential for drug interaction.
- It can prolong QT interval, thus should be avoided with other drugs than can cause QT prolongation

Nicorandil

- Nicorandil (K channel opener)
- It has a double cellular mechanism of action, acting both as a potassium channel activator and having a nitrate-like effect (NO donor).
- Act by dilation of the large coronary arteries
- By activating K channel, it also relaxes cardiac myocytes and decrease oxygen demand.

Ivabradine

- Ivabradine
- An inhibitor of the funny channels (current If) in sinus node pace-making, causes heart rate reduction, it is alternatiove to B-blockers as it avoiding drawbacks of b-blocker therapy such as depressed contractility and bronchoconstriction


Thank You