Cardio Pharmacology

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Booklet Disclaimer

About StudyAid

About StudyAid StudyAid is a student organization at the Jagiellonian University in Krakow. Throughout the academic year we host seminars in the major theoretical subjects: anatomy, physiology, biochemistry, immunology, pathophysiology, supplementing the lectures provided by the university. We are a group of 25 tutors, who are students at JU, each with their own field of specialty. To make our seminars as useful and relevant as possible, we teach in an interactive manner often using drawings and diagrams to help students remember the concepts. In addition to most seminars we create booklets, on which the seminars are based to aid the students in following the presentations. If you have any questions, do not hesitate to contact StudyAid at www.studyaid.no, we are always happy to answer any questions you may have academically related or not.

Objective

The objective of this booklet is to consolidate information about the pertinent subjects for the Cardo Pharmacology unit into a concise and coherent package. We have chosen to focus on the drugs that were presented in the reading list given by the coordinator. Additionally, we have done our best to adhere to the recommended resources and materials when discussing the drugs.

You will find that some of the drugs and information is repeated in different sections. This is done because certain drugs have several applications and are essential for treatment plans of multiple pathologies.

It should be noted that this booklet is intended to be supplementary to other resources. Bearing this in mind, it is inadvisable to use it as a sole resource when studying for the exam.

Based on our experience, BRS, USLME First Aid, and Sketchy Pharm are excellent resources.

On behalf of the StudyAid team, we hope that you find this booklet useful and wish you well on your exam!

Table of Contents

Section 1 – Anti-Anginal Therapy

1.1– Physiology
1.2– Vasodilators
1.3– Other Anti-anginal Drugs
1.4– Approach to Anginal Treatment
1.5– Assorted High Yield Facts

1.1 – Physiology

- Angina pectoris refers to chest pain
- Lack of oxygen in the heart leads to metabolite accumulation which presents as angina.
- The most common cause is coronary artery disease (CAD) which obstructs large vessels.
- Classic angina (angina of effort) occurs due to insufficient blood flow.
- Variant angina (aka Prinzmetal or vasospastic angina) occurs because of intermittent vascular spasms which lead to ischemia and pain.
- Unstable angina (acute coronary syndrome) occurs at rest with increasing intensity and frequency from the previous stable angina.
    - Caused by increased coronary artery resistance or small clots near the atherosclerotic plaques.
- Angina occurs when the heart requires more oxygen than it is supplied with.
    - Treatment can be focused on decreasing O_2 demand or increasing delivery (by increasing blood flow).

1.1.1 – Myocardial oxygen demand

- This is determined by heart rate contractility and wall stress.
    - Wall stress is influenced by wall thickness, ventricular volume, and intraventricular pressure.
    - An increase in these factors leads to an increase in oxygen demand.
    - Arteriolar blood pressure determines the systolic wall stress, venous tone the diastolic.
- Even without additional stress, the heart uses up about 75% of total oxygen available.

1.1.2 – Vasodilation

- Decreasing cGMP and intracellular Ca^{2+} can help.
    - *(see below for specifics)*
- Prevention of the depolarization of vascular smooth muscle (aka stabilization) can be achieved by increased K^+ permeability.
    - K^+ - channel openers (like minoxidil sulfate) can do this.
- Increasing cAMP in vascular smooth muscle cells increases the rate of inactivation of myosin light chain kinase, thereby terminating the interaction between actin and myosin.
    - NOT really used for angina!
    - Accomplished by β_2 agonists and D_1 agonists.

1.2 – Vasodilators

1.2.1 – Organic nitrites and nitrates

I. Mechanism

- cGMP facilitates myosin light chain dephosphorylation, preventing the myosin-actin interaction, thus stopping the contraction and vasodilating instead.
- Nitric oxide activates guanyl cyclase, leading to an increase in cGMP.
- Nitroprusside and organic nitrates supply the nitric oxide.
- Can also lead to increased oxygen delivery.
- Excretion is mainly via the kidneys.
- Have indirect effects due to baroreceptor and hormonal response to decreased BP.
    - This leads to tachycardia, increased cardiac contractility, and increased salt and water retention.
    - Happens more the longer acting the nitrate.
    - This is why tolerance occurs (drug doesn't work as well then).
- Improved perfusion to ischemic tissue
    - Achieved via increased collateral flow *(can by-pass problematic artery)*
- Improved subendocardial perfusion
    - Due to decrease in left ventricular diastolic pressure.

II. Uses (nitrates)

- Organic nitrates are the main drugs used for immediate relief of angina.
- Treat angina of effort
    - Decreased myocardial oxygen requirement
        - Via decrease in ventricular volume, arterial pressure, and ejection time
        - 1st two decrease wall tension.
- Treat variant angina by reversing coronary artery vasospasm.
    - Dilate the epicardial coronary arteries.
- Treat unstable angina
    - Via decrease in oxygen demand and dilation of coronary arteries.
- Pulmonary edema

III. Side effects (nitrates)

- Increased myocardial oxygen requirement *(yes, ironic)*
    - Due to reflex tachycardia and reflex increase in contractility (cardiac force)
        - Treat with β-blockers
- Decreased coronary perfusion
    - Happens when tachycardia leads to a decreased diastolic perfusion time.
- Meningeal vasodilation
- Contraindications

    - Right ventricular infarction
- Exposure to nitrates at work may lead to "Monday's disease", in which patients experience at headache, dizziness, and tachycardia upon re-exposure at work on Monday.
    - They develop tolerance during the week, and then lose it over the weekend.

IV. Drugs

1. Amyl nitrite

- ONLY NITRITE (REST ARE NITRATES)
- Inhalation route (avoids first-pass effect) is used for acute situations.
- Rapid onset and short-acting (a few minutes).
- *Now discontinued due to short duration of action and terrible smell.*

1.2 Uses

- Acute anginal situations
- Erectile dysfunction
    - Vasodilation in penis leads to erection

1.3 Side effects

- Throbbing headaches and temporal artery pulsation.
- Pseudocyanosis, tissue hypoxia, and death at large doses.
    - Nitrite ion reacts with hemoglobin to make methemoglobin, which has a very low affinity for oxygen.
    - Treated with methylene blue or hydroxocobalamin (form of vitamin B_{12}).
- Methemoglobinemia at large doses (nitrites in general)

2. Isosorbide mononitrate

- Generally long-acting
- Active metabolite of isosorbide dinitrate.

2.1 Uses

- Used for prophylaxis (given orally).
- *Makes sense since its long acting and thus allows for easier long-term administration.*
- When used with nadolol, it is very effective in preventing rebleeding

2.2 Contraindications

- Increased intracranial pressure.

3. Isosorbide dinitrate

- Sublingual route (avoids first-pass effect) is used for acute situations.
- May be long (oral, sublingual large dose) or short (sublingual low dose) acting.

2.1 Contraindications

- Increased intracranial pressure.

4. Nitroglycerine

- High lipid solubility causes the rapid absorption.

4.1 Mechanism

- Must be activated with the release of nitric oxide.
  - Requires enzymatic action.
  - Glutathione S-transferase can do so in smooth muscle and other cells.
  - Aldehyde dehydrogenase isoform 2 (ADLH2) and 3 (ALDH3) can also do so
- Relaxes smooth muscles in all vessels.
  - Venous relaxation leads to an increased venous capacitance and decreased ventricular preload.
  - There is a decrease in venous return, heart size and pulmonary vascular pressure.
  - Cardiac output will decrease (unless the patient has heart failure).
- Decreased contractility of the heart
- Decreases platelet aggregation.

- Sublingual route (avoids first-pass effect) is used for acute situations.
  - Oral and transdermal for prophylaxis
  - IV for acute coronary syndrome
- May be long (oral, buccal, transdermal) or short (sublingual) acting.
- When given transdermally, concentrations are high for about a day.
  - Tolerance develops after about 10 hours, so the effect is lost then.

4.2 Uses

- Unstable angina

4.3 Side effects

- Orthostatic hypotension and syncope
  - Due to increased venous capacitance, so less blood goes back to the heart.
- Throbbing headaches and temporal artery pulsation
- Tachycardia

4.4 Contraindications

- Increased intracranial pressure.

1.2.2 – Calcium channel blockers

I. Mechanism

- Reduce intracellular Ca^{2+}.
  - Calcium is important in the myosin light chain kinase formation, and thus in vasoconstriction.
  - They reduce the Ca^{2+} influx into the cardiac muscle, thus reducing the rate and contractility, and thus the O_2 requirements.
    - Also decreased due to decreased vascular resistance (due to dilation)
- Can lead to increased oxygen delivery.
- There are 2 types of CCBs – dihydropyridine (DHP) and non-dihydropyridine (NDHP)
  - Both are used to treat angina
    - DHPs act on (vascular) smooth muscle, NDHPs primarily on cardiac muscle.

II. Uses

- Good for anginal prophylaxis.
- Treat angina
  - Decrease vascular tone, thus decreasing heart load.
- Used for angina treatment if nitrates or β-blockers are contraindicated, have bad side effects, or do not work
- Treat variant angina by reversing coronary artery vasospasm.
- Hypertension
  - Decrease arterial and intravenous pressure.
  - Prophylaxis as well
- Supraventricular tachyarrhythmias

III. Side effects

- Basically excessive action of what they are supposed to do.
  - Cardiac depression: bradycardia, AV block, cardiac arrest, heart failure.
- Gingival hyperplasia
- Minor: flushing, dizziness, nausea, peripheral edema

IV. DHPs

- Dihydropyridines

1. Mechanism

- Act on smooth muscle
  - Decreased calcium current leads to long-lasting vasodilation.
  - Act on all smooth muscle, but primarily on vascular smooth muscle.

2. Uses

- Safer in atrioventricular conduction abnormalities
  - Since they don't really affect the nodes.

3. Side effects

- Heart: Less than those of NDHPs because DHPs act on vessels at lower concentrations.
- Increased risk of side effects in patients with HTN and diabetes.
- Greater decrease of BP than NDHPs
  - May cause excessive hypotension
  - The baroreceptor reflex to this may cause tachycardia
- Peripheral edema, flushing, dizziness
- Additive with other vasodilators

4. Drugs

4.1. Amlodipine

- Aka Norvasc
- DHP

4.1.1 Uses

- Only safe CCB in heart failure (especially if due to nonischemic left ventricular systolic dysfunction)
- Angina and HTN

- Longest half life (30-50 hours)

4.5 Isradipine

- DHP

4.2.1 Uses

- Mostly HTN

4.6 Nicardipine

- DHP

4.3.1 Uses

- Prevents cerebral vasospasm associated with stroke.
- Angina
- HTN

4.3.2 Contraindications

- Unstable angina (because Nicardipine is short-acting)

4.7 Nifedipine

- DHP
- Fastest onset and shortest duration of action

4.4.1 Uses

- Angina
- HTN
- Raynaud's phenomenon

4.4.2 Side effects

- May increase the risk of MI in patients with HTN.

4.4.3 Contraindications

- Unstable angina (because Nifedipine is short-acting)

V. NDHPs

1. Mechanism

- Act on cardiac muscle
- Decreased cardiac current leads to decreased heart contractility and decreased nodal (SA and AV) conduction, thus decreased heart rate.
- Slight Na-channel block.

2. Uses

- Preferred in patients with history of atrial tachycardia, flutter, and fibrillation.
    - This is because they have some antiarrhythmic effects.

3. Side effects

- Cardiac depression: bradycardia, AV block, cardiac arrest, heart failure.
    - Increased risk if co-administered with β-blockers or nitrates.
    - Higher rates than in DHPs
- Constipation and edema are also possible
- Additive with other cardiac depressants and hypotensive drugs.

4. Drugs

4.1 Diltiazem

- NDHP (but kind of between the two)
    - Acts both on cardiac and on vascular smooth muscle Ca-channels.

4.1.1 Uses

- Angina
- HTN
- Raynaud's phenomenon
- Decreases frequency of post MI-angina (if the Q wave is ok)
- Prophylaxis of angina of effort

4.1.2 Contraindications

- Unstable angina (because Diltiazem is short-acting)

4.2 Verapamil

- NDHP

4.2.1 Mechanism

- Inhibits K-channels in vascular smooth muscle as well, leading to limited vasodilation.

4.2.2 Uses

- Stroke mortality/morbidity reduction.
- Angina
- HTN
- Arrhythmia
- Migraine

4.2.3 Side effects

- Constipation
  - *Possible in all CCBs, but common with verapamil.*
- Hyperprolactinemia
- Increases level of digoxin.

1.2.3 – β-blockers

- "olol"

I. Mechanism

- Pretty similar to verapamil
- NOT vasodilatory
- Reduce the Ca^{2+} influx into the cardiac muscle, thus reducing the rate and contractility, and thus the O_2 requirements.
- *Only nebivolol and carvedilol are vasodilators*
- Hemodynamic effects: decrease heart rate, blood pressure, cardiac output, and contractility
  - Decreases myocardial O_2 requirements both at rest and during exercise.
  - Lowered HR allows for more perfusion time, and thus improves it.
  - Increase ejection time
  - May increase end-diastolic volume

II. Uses

- Prophylaxis of angina
- Management of effort angina

    - Decreases myocardial O_2 requirements.
- Better for stable angina than CCBs.*
- Silent (ambulatory) ischemia
- Decreases mortality of patients with recent MIs.
- Prevents stroke (and improves survival if it does happen) in patients with HTN.
- Decrease heart rate, blood pressure, and renin

III. Side effects

- Increased end-diastolic volume and ejection time
    - These increase myocardial O_2 requirement
- Can be balanced by co-administering nitrates
- Rare: fatigue, insomnia, unpleasant dreams, exercise intolerance, worsening of claudication, and erectile dysfunction.

IV. Contraindications

- Asthma and other bronchospastic diseases
    - Especially with non-selective βBs
- Severe bradycardia
- Severe unstable left ventricular heart failure
- AV block
- Bradycardia-tachycardia syndrome
- *Cardiac effects are additive with all other cardiac depressants.*

V. Drugs

1. Atenolol

- Selective for β_1

1.1 Mechanism

- Increases K^+ conductance
- Decreases cAMP

1.2 Uses

- Migraine

2. Metoprolol

- Selective for β_1

2.1 Uses

- Migraine

3. Nadolol

- Equal β_1 and β_2
- Half-life prolonged in renal failure
- Long duration of action

3.1 Uses

- Atrial fibrillation
- Migraine
- Hypertension
- Decreases mortality rate due to bleeding in patients with cirrhosis
- Decreases incidence of bleeding from esophageal varices.
- When used with isosorbide mononitrate, it is very effective in preventing rebleeding.

3.2 Contraindications

- Asthma

4. Propranolol

- Equal β_1 and β_2

4.1 Uses

- Anginal prophylaxis
- Mild to moderate hypertension
- Decreases mortality rate due to bleeding in patients with cirrhosis
- Decreases incidence of bleeding from esophageal varices.
- Stage fright
- Alcohol withdrawal symptoms

4.2 Contraindications

- Asthma

1.3 – Other antianginal drugs

1.3.1 – Ranolazine

I. Mechanism

- Reduces late sodium current (I_{Na}) that normally facilitates Ca entry via the Na-Ca exchanger.
- This leads to a reduced intracellular calcium concentration, thus reducing cardiac contractility and diastolic wall tension.
- Decreases cardiac O_2 demand
- Modifies fatty acid oxidation
    - may improve the efficiency of cardiac O_2 utilization

II. Uses

- Angina that doesn't respond to other therapies
- Prophylaxis of angina (given orally)

III. Side effects

- Constipation
- Dizziness
- Headache
- Nausea
- Prolongation of QT interval
- Concentration and duration of action increased by CYP3A inhibitors.

1.3.2 – Ivabradine

I. Mechanism

- Bradycardic drug
- Fairly selective I_f (inwards sodium funny current, acts as pacemaker) sodium channel blocker.
- Thus prevent hyperpolarization in the sinoatrial node.
- This means that it inhibits the sinoatrial pacemaker.
- Reduces oxygen demand by reducing heart rate.

II. Uses

- Decrease anginal attacks.

III. Side effects

- Lower than that of CCBs and BBs because Ivabradine doesn't affect the smooth muscle in the GI nor the lungs.

1.3.3. – Trimetazidine

I. Mechanism

- Metabolic modulator known as pFOX inhibitor
- Inhibits the fatty acid oxidation in the myocardium.
    - (Ischemic myocardium shifts to fatty acid oxidation for metabolism, which requires more oxygen per each ATP made.)
- Improve the metabolic status of ischemic tissue
    - Achieved via partial inhibition of enzymes required for fatty acid oxidation (LC-3KAT = long-chain 3-ketoacyl thiolase)

1.4 – Approach to Anginal Treatment

- Since coronary artery disease (CAD) is the most common cause for angina, it is important to treat both.
    - This also decreases the risk of myocardial infarction.
- 1st line treatment of CAD depends on underlying diseases and lifestyle.
    - Smoking, hypertension, hyperlipidemia, obesity, depression

- Statins also help reduce the incidence and severity of ischemia in exercise.
- Anginal patients and non-ST segment elevation myocardial infarction require aggressive therapy with stenting, anti-lipids, heparin, and antiplatelets
- Maintenance of chronic stable angina
    - Nitrates (long-acting)
        - Preferred in normal blood pressure
    - CCBs (long-acting)
        - Preferred in HTN (same if slow-release)
    - β-blockers (long-acting)
        - Preferred in HTN (same if slow-release)
    - βB + CCB (DHP)or CCB (DHP) + CCB (NDHP) is better than just one drug alone
        - A combination is both more effective and decreases side effects.
- Vasospastic angina
    - Nitrates & CCBs prevent ischemic episodes by preventing coronary artery spasm
- Unstable angina and acute coronary syndrome
    - Anti-platelet, anti-lipid, and ACEI therapy is also needed
    - Nitroglycerin and βBs can also be used
    - CCBs are indicated to relieve myocardial ischemia

1.5 – Assorted High Yield Facts

- Major common determinant of myocardial oxygen consumption is fiber tension.
    - Blood volume, cardiac output, heart rate, and diastolic blood pressure all contribute to the fiber tension.
- CCBs are the best choice in long term management of chronic stable angina.
- Do not give non-selective β-blockers in asthma.
- Nitroglycerin increases cardiac force
    - It leads to a decrease in blood pressure which then leads to a sympathetic stimulation.
- CCBs and βBs both decrease the amount of angina attacks.
- Nitroglycerin, prazosin, and ganglion blockers all lead to orthostatic hypotension.
    - Nitrates cause throbbing headaches.
    - Ganglion blockers may cause sexual problems.
- Isosorbide dinitrate can be used to treat angina and HTN, and it may lead to severe tachycardia.
- Diltiazam, propranolol, verapamil, and guathenidine will all tend to increase decrease heart rate.
- Drugs that cause HTN or tachycardia (whether directly or through a reflex) can also lead to angina in a patient with coronary obstruction.
    - Examples of such drugs: amphetamine, hydralazine, terbutaline, and isoproterenol.
    - This will not occur if cardiac work is reduced (ex: by nitrates)
- Ni***mo***dipine can be used to treat he***mo***rrhagic stroke)

- Nitrates have opposite effects than CCBs and βBs on heart rate, heart size, ejection time, and force.
- Terbutaline can cause angina.
- Hydralazine (direct vasodilator) can cause angina.
    - Contraindicated in patients with coronary disease unless the heart rate is well controlled.
    - Hydralazine does not affect autonomic receptors directly.
- Active nitrates (glyceryl dinitrate and isosorbide mononitrate) are denitrated in the liver after oral administration.
- Sildenafil and any other vasodilating drugs are contraindicated when taking nitrates.
- CCBs leads to decreased O_2 demand via
    - Decreased vascular resistance (due to dilation)
    - Decreased cardiac rate
    - Decreased cardiac force

Section 2 – Anti-Hypertensives

2.1 - Thesis

2.1.1 - Definition of Hypertension

- Hypertension is a condition in which the pressure within blood vessels is persistently elevated. It is typically asymptomatic but if it is sustained or severe, it may result in a number of complications in the cardiovascular system as well as many other parts of the body.
- The goal of antihypertensive therapy is to reduce blood pressure to acceptable levels while maintaining cardiovascular function and preventing end-organ damage.

2.1.2 - Values

- Normal Blood Pressure: 120/80
- Pre-hypertensive: 120-139/80-90
- Hypertensive: 140-160/100
- Hypertensive Emergency: 180/110

2.2- ACE Inhibitors (Angtiotensin-converting enzyme inhibitors) -pril

2.2.1 - Drugs

- Captopril
- Lisinopril
- Fosinopril
- Perindopril

2.2.2 - Mechanism of Action

- Inhibit ACE: angiotensin I cannot be converted to angiotensin II
- Constricts efferent arterioles, decreasing GFR
    - “ACE: Always Constricts Efferent”
- Renin increases due to decreased renal perfusion
- ACE inhibition prevents inactivation of bradykinin

2.2.2 - Clinical Uses

- Hypertension
- Decreased mortality in heart failure
- Cardioprotective in chronic heart failure
    - Protects against further damage of cardiac tissue
- Decreased glomerular pressure
    - Slows glomerular thickening

2.2.3 - Adverse Effects (Remember "CAPTOPRIL")

- Cough
    - Due to increased bradykinin, a vasodilator
        - "Brady-coughin'"
- Allergic reactions
- Potassium elevation
    - Due to increased aldosterone
- Taste change
- Oedema
- Photosensitivity
- Renal failure
    - Contraindicated in renal artery stenosis
        - Decreased GFR may precipitate renal failure
- Indigestion
- Low blood pressure

- ACE inhibitors are teratogenic and may cause renal malformations

2.3 - ARBs (Angiotensin II Receptor Blockers) -sartan

2.3.1 - Drugs

- Losartan
- Valsartan
- Irbesartan

2.3.2 - Mechanism of Action

- Block binding of angiotensin II to AT1 receptor in lungs

2.3.3 - Clinical Uses

- Alternative to ACE inhibitors
- ARBs do not increase bradykinin and associated coughing

2.3.4 Adverse Effects

- Hyperkalemia
    - Due to decreased aldosterone production
- Decreased GFR
- Hypotension
- Teratogenic

2.4 - Diuretics (Drugs that promote diuresis: increased urination)

2.4.1 Description

- Diuretics reduce blood volume which subsequently reduces blood pressure. There is a relatively minimal compensatory response compared to other antihypertensives.

2.4.2 -Thiazides (Metolazone, Indapamide)

I. Mechanism of Action

- Inhibit NaCl reabsorption in early distal convoluted tubule
- Decreased Ca excretion (Calcium-sparing)

II. Clinical Uses (Remember "CHICO")

- Congestive heart failure
- Hypertension
    - Preferred for mild HTN
- Insipidus (Diabetes)
- Calcium oxalate stones
- Osteoporosis

III. Side Effects (Remember "HyperGLUC")

- Hyper:
    - Glycemia
    - Lipidemia
    - Uricemia
    - Calcemia
- Hyponatremia

2.4.3 - Loops (Furosemide)

I. Mechanism of Action

- Inhibit NaK2Cl cotransporter in thick ascending limb
- Stimulate PDE
    - Vasodilates afferent arteriole
- Increases Ca excretion
    - Calcium-wasting

II. Clinical Use

- Edematous States
    - Heart failure
    - Cirrhosis
    - Nephrotic syndrome
    - Pulmonary edema
- Preferred for moderate and severe hypertension
- Hypercalcemia

III. Side Effects (Remember "GLUE")

- Glucose increase
- Lipid increase
- Uric acid increase
- Electrolyte decrease
- And "HypO"
    - Hyponatremia
    - Hypokalemia
    - Hypomagnesemia
    - Otoxocity

2.4.4 - K-Sparing (Spironolactone, Eplerenone)

I. Mechanism of Action

- Aldosterone receptor blockers in collecting tubule
    - "K-sparing Knocks out aldosterone in Kollecting tubule which is Kool" 4 K's ;)

II. Clinical Use

- Hyperaldosteronism
- Hypokalemia
- Heart failure

III. Side Effects

- Hyperkalemia
    - May precipitate arrhythmias
- (Spironolactone) Endocrine abnormalities
    - Gynecomastia “Spirono-Boob-tone”

2.5 Other Drugs

2.5.1 - Nitroprusside

- Used in hypertensive emergency
    - Short-acting
- Increases cGMP via direct release of NO
- May cause cyanide toxicity

2.5.2 - Aliskiren

I. Mechanism of Action

- Inhibits renin, blocking conversion of angiotensinogen to angiotensin I
    - “AlisKiRen Kills Renin”

II. Clinical Use

- Hypertension

III. Side Effects

- Hyperkalemia
- Decreased GFR
- Hypotension
- Angioedema
- Contraindicated in pregnancy
- Disadvised in patients taking ACE inhibitors or ARBs

2.5.3 – Nitroglycerin

I. Mechanism of Action

- Causes vasodilation by increasing NO in vascular smooth muscle
- Increases cGMP, causing smooth muscle relaxation
    - Preferential dilation of veins
        - Decreases preload

II. Clinical Use

- Angina
- Acute coronary syndrome
- Pulmonary edema

III. Side Effects

- Reflex tachycardia
- Hypotension
- Flushing
- Headache

2.5.4 - Hydralazine

I. Mechanism of Action

- Increases cGMP, causing smooth muscle relaxation
- Preferentially dilates arterioles
    - Reduces Afterload

II. Clinical Use

- Severe hypertension
- Heart failure
- Safe in pregnancy

III. Side Effects

- Reflex tachycardia
- Fluid retention
- Lupus-like syndrome
- Headache
- Angina

2.5.5 - Diazoxide

I. Mechanism of Action

- Potassium channel activator: increases membrane permeability to K ions
    - Causes local relaxation of smooth muscle

II. Clinical Use

- Moderate and severe Hypertension

III. Adverse Effects

- Decrease insulin release
    - Due to potassium induced hyperpolarization

2.5.6 - Nesiritide

- Recombinant form of BNP (B-type Natriuretic Peptide)
- BNP is produced in ventricles and is released when there is increased ventricular pressure

I. Mechanism of Action

- Counteracts Renin-Angiotensin-Aldosterone system
    - Remember that the “N” stands for natriuretic which means urinary sodium excretion

II. Clinical Use

- Used for acute decompensated heart failure

III. Adverse effects

- Hypotension
- Bradycardia
- Renal failure

2.5.7 - Bosentan

I. Mechanism of action

- Blocks endothelin-1 receptors
    - Endothelin normally constricts pulmonary blood vessels
- Decreases pulmonary vascular resistance

II. Clinical Uses

- Pulmonary Arterial Hypertension
- Treatment of digital ulcers

III. Adverse Effects

- Teratogenic
- Hepatotoxicity
    - Subsequent edema
    - Decreased hemoglobin and hematocrit

Section 3 - HEART FAILURE MEDICATIONS

3.1 - Introductory Principles

3.1.1- Terms

-Preload: end diastolic volume that stretches ventricle to it's greatest dimensions.

i.e. Volume of blood the ventricle pushes out

- Afterload: The pressure the heart pushes against during systole

i.e. Aortic/pulmonary artery pressure

- Cardiac output: Volume of blood being pumped by the heart per unit time

- Remodelling: changes in size, shape, structure, and function of heart
- Physiologic: from exercise
- Pathologic: from injury to heart muscle
- Ejection fraction: volumetric fraction of blood ejected during each systole
- Contractility: ability of heart muscle to contract
- Decompensation: heart failure from a previously compensated injury

3.1.2 - Definition of heart failure: Cardiac output insufficient for the body's oxygen demands

- Divided into two types:

I. Systolic failure

- Reduced pumping action
    - Reduced Contractility
    - Reduced ejection fraction

      50% of younger patients
- Reduced contractility and ejection fraction

- Primary defect believed to be in excitation- contraction coupling
    - Also involves many other processes and organs:
        - Baroreceptor reflex
        - Sympathetic nervous system
        - Kidneys
        - Angiotensin II and other peptides
        - Aldosterone
        - apoptosis of cardiac cells

II. Diastolic failure

- Stiffening of heart
    - Reduced filling and cardiac output
    - Proportion of patients with diastolic failure increases with age ncrease with age

3.1.3 - Stages of Heart Failure

I. Stage A

- High risk for other diseases
- No signs or symptoms of heart failure

II. Stage B

- Evidence of structural heart disease
- No symptoms of heart failure

III. Stage C

- Have structural heart disease
- Have symptoms of heart failure
- Symptoms are responsive to ordinary therapy

IV. Stage D

- Treatment resistant heart failure
- Need special interventions
- Resynchronization therapy
- Transplant

3.1.4 - Treatment Overview

- Heart failure is a progressive disease: gradual reduction in cardiac performance
    - Often presence of acute episodes of decompensation
- Two treatment goals:
    - Slow progression
    - Manage acute episodes

-Therapy directed at non cardiac targets are more effective than positive inotropic agents

- Only agents that actually prolong life in Chronic HF:
    - ACE inhibitors
    - Angiotensin receptor blockers
    - B- blockers (some of them)
    - Aldosterone receptor antagonists
    - Combined hydralazine- nitrate therapy
        - (Useful in both systolic and diastolic heart failure)

3.1.5 - Physiology

I. **Contraction results from interaction of activator Calcium (during systole) with actin-troponin-tropomyosin**

II. **Activator Calcium released from SR**
- Amount released depend on amount of Calcium stored and amount of
- Trigger Calcium that enters cell during platau of action potential

III. **Brain natriuretic peptide and Atrial natriuretic peptide**
- Increase sodium excretion in kidneys and GFR
- Released in response to atrial stretching and sympathetic stimulation
- Plasma concentration increases in heart failure
- Inhibits release of Renin and Aldosterone
- Cause vasodilation

IV. **Vasodilation**

- Effective in heart failure:
    - Reduction in preload: venodilation
    - Reduction in afterload: arteriolar dilation
- Some drugs may reduce pathologic remodelling of the heart
    - Hydralazine
    - Isosorbide dinitrate

3.2 – Contractile Drugs

3.2.1 - Levosimendan

- Increase Calcium sensitivity
- May also inhibit phosphodiesterase
- Reduced symptoms of HF

3.2.2 - Ryanodine

- Potent negative inotropic plant alkaloid
- Interferes with release of Ca2+ from SR
- Amount of Ca2+ released from SR
- Function: concentration dependent
    - Initial small rise in cytoplasmatic Ca2+
    - Opening of calcium-gated, ryanodine-sensitive calcium channels (SR)
    - Rapid release of Ca2+ into cytoplasm
- (Amount released proportional to amount stored)
- Small concentration (nanomolar) locks calcium channels in a half- open state
- Bigger concentration (micromolar) closes calcium channels

- Amount of Ca2+ stored in SR
    - SERCA (Sarcoplasmic Endoplasmic Reticulum Ca2+ ATPase)
        - Very effective Ca2+ uptake transporter
            - Maintain very low cytoplasmatic [Ca2+] during diastole
                - Pump Ca2+ into SR
        - Normally inhibited by Phospholamban
            - Protein kinase A phophorylates phopholamban, remove inhibition
                - (Done by B- agonists)
        - Amount of Ca2+ in SR determined by amount available to SERCA and activity of Sympathetic NS
            - This therefore dependent on balance of influx (from membrane L- type Ca2+- channels) and efflux (Sodium-calcium exchanger)

3.3 - Inotropic Drugs

- Positive inotropic agents helpful in acute systolic failure
    - Also reduce symptoms in chronic systolic HF

3.3.1 - Digoxin

I. Pharmacokinetics
- 65-80% absorbed after oral administration
- Widely distributed, including CNS
- 2/3 excreted unchanged in kidneys
- Renal clearance proportional to Creatinine clearance
- Half- life: 36-40 hours

3.3.2 - Digoxin immune Fab

I. Mechanism
- Bind Digoxin, making it unable to bind on acting sites

II. Uses
- Digoxin overdose if one of the following:
    - 1. Haemodynamically unstable arrhythmia
    - 2. End organ damage

III. Contraindications
- Hypokalemia
    - Reduces potassium, and can precipitate fatal cardiac arrhythmias
- Monitor closely for anaphylactic shock

3.2.3 - Dobutamine

I. Mechanism

- Direct acting sympathomimetic
    - B1>B2>>>a
- Activates adenylyl cyclase
- Increase cardiac output with less reflex tachycardia
    - Because it acts less on B2 receptors
    - Relatively greater positive inotropic than chronotropic action
- Increase cardiac output with relatively little vasoconstriction

II. Uses

- IV, adjust dosage for desired effect
    - Onset of effect is within 2 min
- Short- term relief of heart failure symptoms in ventricular dysfunction
    - Most useful in acute decompensated heart failure with hypotension
        - i.e. Cardiogenic shock
- Intermittent infusion may be of benefit in chronic heart failure
- Pharmacologic cardiac stress test

III. Side effects

- Risk of producing angina or arrhythmias in coronary artery disease
- Because there is some tachycardia and increased myocardial oxygen consumption

IV. Contraindications

- Idiopathic hypertrophic subaortic stenosis

3.3.4 - Dopamine

I. Mechanism

- At low doses: dopamine receptors and B1 receptors
    - Positive inotropic and chronotropic effect
- At high doses: a1 receptors
    - Vasoconstriction

II. Uses

- Continuous IV drip
    - Half- life is only 1 min in adults
- Short- term relief of heart failure symptoms in ventricular dysfunction
    - Most useful in acute decompensated heart failure with hypotension
        - i.e. Cardiogenic shock

III. Side effects

- Worsening kidney function
- Arrhythmia and angina

IV. Contraindications

- Pheochromocytoma
- Uncorrected tachycardia

3.3.5 – Milrinone

I. Mechanism

- Inhibit phosphodiesterases
    - Phosphodiesterase inactivates cAMP and cGMP
    - cAMP causes increased activation of protein kinase A
    - Protein kinase A phosphorylates calcium channels, potassium channels, and myofilaments
- Have positive inotropic and chronotropic action
- Vasodilation

II. Uses

- IV
- Acute heart failure
- Severe exacerbation of chronic heart failure
- Severe pulmonary arterial hypertension

III. Side effects

- Nausea and vomiting
- Arrhythmia
- Thrombocytopenia
- Liver enzyme changes

3.4 - Beta-Adrenoceptor Blockers

3.4.1 - Carvedilol

I. Mechanism

- Non selective b- blocker (b1 and b2) and a1 blocker
- Benefit in heart failure
    - Not fully understood, but possible suggestions are:
        - Lessen adverse effects of high concentrations of catecholamines
            - Apoptosis and remodeling
        - Up regulation of B- receptors
        - Decreased heart rate
        - Lessen free radical- initiated lipid peroxidation
        - Inhibit vascular smooth muscle mitogenesis

II. Uses

- Chronic heart failure

III. Side effects

- Dizziness
- Fatigue
- Hypotension
- Bradycardia
- Diarrhea

IV. Contraindications

- Bronchial asthma
- Bronchospastic conditions

V. Other B-blockers used in chronic heart failure

- Metoprolol
- Bisoprolol

3.5 - Other Drugs

3.5.1 - Angiotensin-converting enzyme (ACE) inhibitors (-pril)

- Lisinopril,
- Fosinopril,
- Perindopril

3.5.2 - Angiotensin receptor antagonists (ARB) (-sartan)

-Valsartan
-Losartan
-Irbesartan

3.4.3 - Aldosterone Antagonists

-Spironolactone
-Aldactone
-Eplerenone

3.4.4 - Aliskiren

Renin Antagonist

3.4.5 - Sacubitril

I. Mechanism
   - Inhibits Neprilysin
     - Neprilysin degrades atrial and brain natriuretic peptide

        - ANP and BNP reduce blood volume
    - Neprilysin degrades bradykinin
        - Bradykinin is an inflammatory mediator causing vasodilation

II. Uses

- In combination with Valsartan (angiotensin receptor blocker)
- Heart failure with reduced ventricular ejection fraction

III. Side effects

- Cough
- Hyperkalemia
- Kidney dysfunction
- Hypotension

IV. contraindications

- Pregnancy (because of Valsartan)

3.4.6 - Hydralazine

I. Mechanism

- Causes release of nitric oxide in vascular smooth muscle
- Dilates arterioles, but not veins

II. Uses

- Useful in combination therapy with nitrates
    - Heart failure
    - Severe hypertension

III. Side effects

- Headache
- Nausea
- Anorexia
- Sweating and flushing
- Reflex tachycardia
- Lupus- like syndrome in high doses

3.4.7 - Isosorbide dinitrate

I. Mechanism

- Converted to nitric oxide
    - Activates guanylyl cyclase
        1. increases cGMP
            - Relaxation of smooth muscle cells and vasodilation
- Venodilation

II. Uses

- Angina
- Combination therapy for heart failure

III. Side effects

- Nitrate tolerance
- Postural hypotension
- Tachycardia
- Headache

3.4.8 - Nesiritide

I. Mechanism

- Synthetic form of BNP
    - Look above for effects of BNP and ANP
    - Agonist of natriuretic peptide receptors

II. Uses

- Continuous IV infusion
- Acute heart failure

III. **Side effects**

- Hypotension
- Renal damage and death

3.4.9 - Bosentan

I. Mechanism

- Nonselective endothelin receptor blocker
    - Endothelin family
        2. Potent vasoconstrictor peptides

II. Uses

- Pulmonary arterial hypertension

III. Side effects

- Fatal hepatotoxicity
- Edema
- Headache
- Anemia

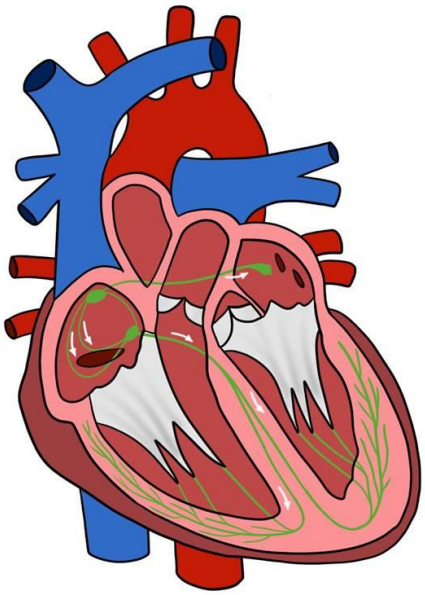
IV. Contraindications

- Pregnancy
-

Section 4 – Antiarrhythmics

4.1 – Background Information

- Arrhythmia: any inappropriate heart rhythm
    - may be unsynchronized, too fast, or too slow
- Heart rate should be 60-100 bpm
- Heart rate originates from the sinoatrial (SA) node in the right atrium
- The current then moves through the atrioventricular (AV) node and then to the ventricles through the His-Purkinje fibers
- Arrhythmias will occur if the aforementioned sequence is disrupted, resulting in a different site of origin, altered rate, or an irregular rhythm or conduction. Essentially anything that disturbs impulse formation and/or impulse conduction.
- Important to treat because the decreased cardiac output and the increased risk of various cardiovascular events.



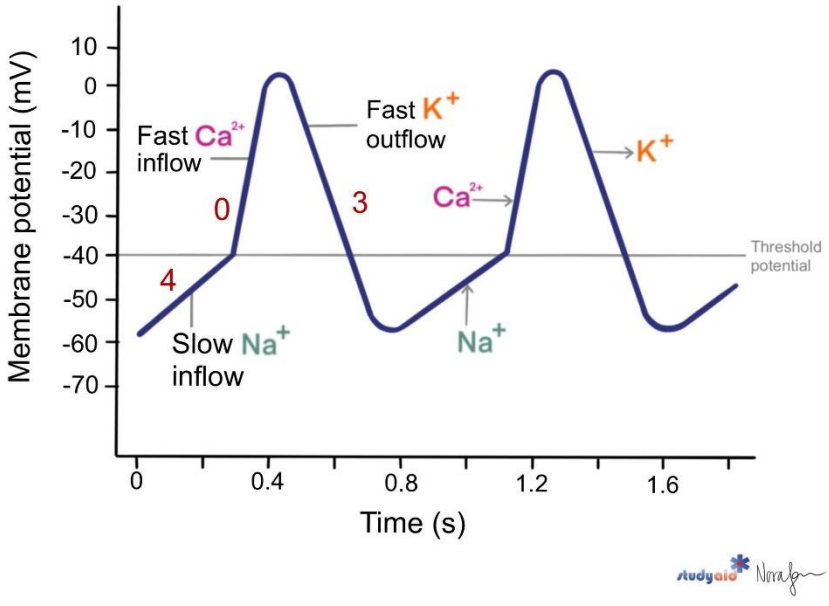
4.1.1 – EKG review

I. Basics

- SA node and ventricular action potentials differ from those of skeletal muscle because they have calcium channels.
- Depolarize = become less negative.
- Hyperpolarize = become more negative.
- Extracellular K concentration and the inward channel functions are main determinants of membrane potential of resting cardiac cell.
    - K effects are especially important in pacemaker cells, especially ectopic ones.
    - Increased extracellular K increases conductance.
    - Hyperkalemia has a reduced action potential, slowed conduction, and decreased pacemaker rate.
    - Hypokalemia has a prolonged action potential and increased pacemaker rate.

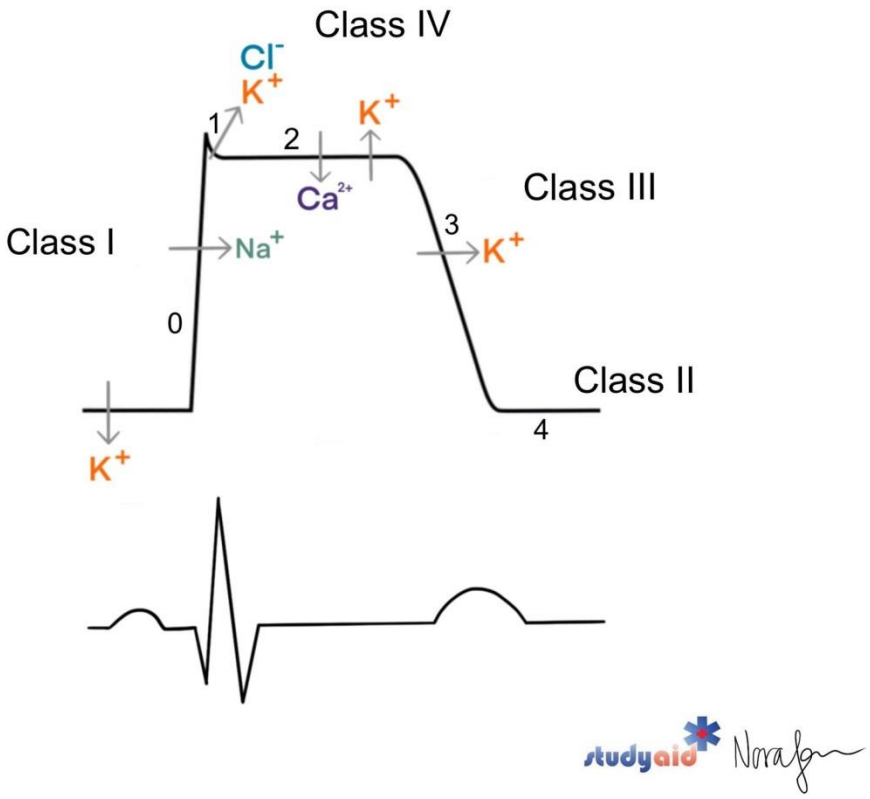
II. SA node

- Pacemaker cells
- Don't really have a resting membrane potential.
- Mainly dependent on slow Ca channels.
- In phase 4 spontaneous depolarization triggers the action potential.
- Phase 0 demonstrates the depolarization of the action potential by Ca.
- Phase 4 shows repolarization via K.



III. Ventricular

- Mainly dependent on fast Na channels.
- Na channels are closed at rest.
- In phase 0 the cell depolarizes with a large influx of Na ions.
- In phase 1 there is a slight repolarization as the Na channels close and K and Cl move out of the cell.
- Phase 2 is a plateau that is maintained by K going out, and Ca coming in.
    - Voltage-gated K channels (Ki) close, but the K efflux continues through ungated channels.
- Phase 3 the cell repolarizes completely as the Ca channels close, but K keeps going out.
- In phase 4, both the gated and ungated K channels are open, and there is an efflux of K.
- The P wave shows phase 4.
    - The P waves shows the SA node action, so atrial depolarization.
- The QRS complex shows phases 0 & 1 and ventricular depolarization (systole).
- The ST segment shows phase 2.
- The T wave is phase 3 and shows ventricular repolarization (diastole).



4.1.2 – Pharmacology

- There are four families or classes of antiarrhythmic drugs
    - Class I: Sodium channel blockers
    - Class II: Beta-adrenergic blockers
    - Class III: Potassium channel blockers
    - Class IV: Calcium channel blockers
- Some of these are state-dependent drugs (aka use-dependent)
    - Prefer to act on cells that are frequently used or inactivated.
    - Occurs mostly in tachycardia (frequent depolarization) or during a long resting potential (lots of inactivated channels).

4.2 – Class I: Sodium Channel Blockers

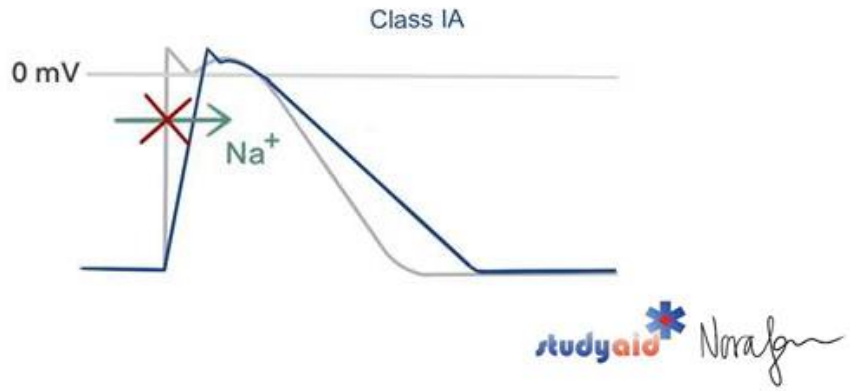
- Slow or block conduction, particularly in depolarized cells.
- Prolong phase 0 (depolarization).
- State-dependent
- There are 3 different subgroups (A,B, and C)
    - Binding strength (effectiveness): C > A > B

2.1 – Class IA: procainamide, disopyramide, quinidine

- Have some local anesthetic actions
- Oldest groups of antiarrhythmic drugs

I. Mechanism

- Moderate Na-channel block (I_{Na}) – primary
- Increase action potential (AP) duration
- The two above increase the effective refractory period (ERP) in ventricles
- Increase the QT interval
- Reduce K repolarizing current (I_{Kr}) during phase 3 – secondary
- Slows conduction velocity and pacemaker rate



II. Uses

- Atrial and ventricular arrhythmias
- Wolff-Parkinson-White syndrome
- Ventricular tachycardia and supraventricular tachycardia
    - Especially ectopic and re-entrant

III. Side effects

- Widen the QRS complex and increase the QT interval
    - This leads to torsade de pointes arrhythmia and syncope
        - *Yes, antiarrhythmics can cause arrhythmia*
- Thrombocytopenia
- Worsened by hyperkalemia

IV. Specific Drugs

1. Procainamide

- Given intravenously, intramuscularly, or orally.
    - Active orally (a lot of drugs need to be activated when given orally)
- Eliminated by kidneys and liver
- Requires frequent dosing (shortest ½ life of 1 – 3-4 hours)

1.1 Mechanism

- N-acetylprocainamide (NAPA) also blocks K channels (thus prolongs AP)
- Acts directly on SA and AV nodes

1.2 Uses

- 2nd/3rd choice in sustained ventricular arrhythmias associated with MI
    - Lidocaine and amiodarone are better

1.3 Side effects

- Hypotension due to decrease vascular resistance
    - Especially if used IV, as rapid infusion, or if with left ventricular dysfunction
- SLE-like syndrome
    - Especially arthralgia and arthritis
    - Almost all patients will have increased antinuclear antibodies, but if they are asymptomatic the medication may be continued
    - Reversible
    - + ANA antibodies
    - Especially after prolonged treatment
    - Mainly joint, skin, and systemic changes
        - NO renal changes
- Rare: nausea, diarrhea, rash, fever, hepatitis, and agranulocytosis
- Treat: sodium lactate.

- Increases sodium current by increasing the ionic gradient.
- Alkalinizes the tissue, reducing drug-receptor binding.

2. Disopyramide

- Most effective
- Administer with a drug that slows AV conduction when treating atrial flutter of fibrillation
- Oral administration
- Decrease dose in renal issues

2.1 Uses

- Mostly used for ventricular arrhythmias

2.2 Side effects

- Significant antimuscarinic effects.
- Heart failure (due to negative inotropy), so rarely used.
- Urinary retention
- Dry mouth
- Blurred vision
- Constipation
- Worsening of glaucoma

2.3 Contraindications

- Heart failure

3.Quinidine

- Absorbed in GI tract and eliminated hepatically.
- Least commonly used anti-arrhythmic drug
- Can also be used to treat malaria
- Derived from bark of cinchona tree.

3.1 Mechanism

- Strongest vascular effects
- Also blocks some K channels
- Prolongs refractoriness and slows conduction

3.2 Side effects

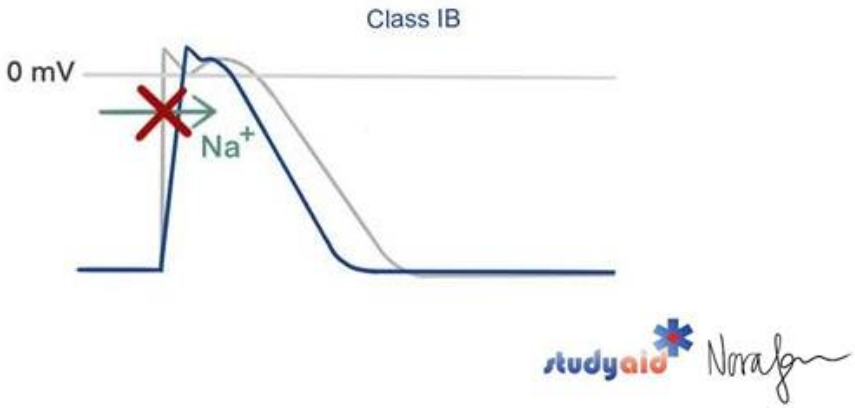
- Very toxic, rarely used in arrhythmias.
- GI effects (diarrhea, nausea, and vomiting) are common
- Cinchonism (headache, tinnitus, and dizziness)
- Immunological reactions (rare)
- QT interval prolongation and torsade de point arrhythmia
- Muscle weakness

- Thrombocytopenia, may progress to purpuric rash.

4.2.2 – Class IIB: lidocaine, mexiletine, phenytoin

I. Mechanism

- Weak blockade of Na-channels (I_{Na})
  - Blocks both activated and inactivated channel with fast kinetics.
- Decreases AP duration (slow its upstroke)
- Shorten repolarization
- Preferentially affect ischemic or depolarized Purkinje fibers or ventricular tissue



II. Uses

- Best post-MI drug
- Acute ventricular arrhythmia (especially post-MI)
- Arrhythmias induced by digoxin

III. Side effects

- CNS stimulation or depression
  - Tremor, nausea, blurred vision
- Cardiovascular depression

IV. Specific Drugs

1.Lidocaine

- IV administration only
- Can also be used as local anesthetic.
- Causes very little changes in EKG (if any)
- Increase dose in MI
  - Generally well-tolerated
- Decrease dose in liver or heart failure

1.1 Use

- Good for arrhythmias associated with MI
- Stop ventricular tachycardia
- Prevent ventricular fibrillation following cardioversion with acute ischemia
    - Should not be done routinely because it increases asystole and thus mortality

1.2 Side effects

- Hypotension (especially if pre-existing heart failure)
- Neurological: paresthesia, poor hearing, convulsions, tremors
    - Treat seizures with diazepam
- Arrhythmia (rare)

2. Mexiletine

- Oral administration
- Basically lidocaine in a different form

2.1 Uses

- Chronic pain (like diabetic neuropathy and nerve injury)
- Ventricular arrhythmias

2.2 Side effects

- Lethargy

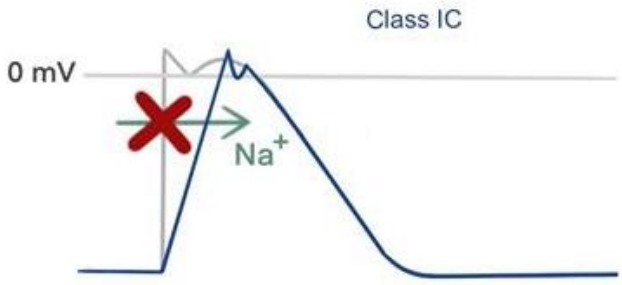
3. Phenytoin

- Primarily used to treat epilepsy

4.2.3 – Class IC: propafenone, flecainide

I. Mechanism

- Strong Na channel blockade (I_{Na})
    - Dissociates from channel with slow kinetics
- Prolongs ERP in AV node and accessory pathways



- Does NOT affect ERP in Purkinje and ventricular tissuesDoes NOT prolong the AP (or only minimally)

II. Uses

- Supraventricular tachycardias (including atrial fibrillation)
    - Suppresses premature ventricular contractions
    - Heart must otherwise be healthy
        - Do NOT use in ischemic conditions (post-MI)
    - Can be using in refractory VT, but not preferred

III. Side effects

- Arrhythmias (pretty commonly)

IV. Contraindications

- post-MI
- Structural and ischemic heart disease
- (will lead to an arrhythmia)

V. Specific Drugs

1. Propafenone

- Has some weak beta-adrenergic activity
- Orally active
- Metabolized in the liver

1.1 Uses

- supraventricular arrhythmias

1.2 Side effects

- Metallic taste and constipation

2. Flecainide

- Blocks K channels as well
- Administered orally
- Eliminated by liver and kidney

2.1 Side effects

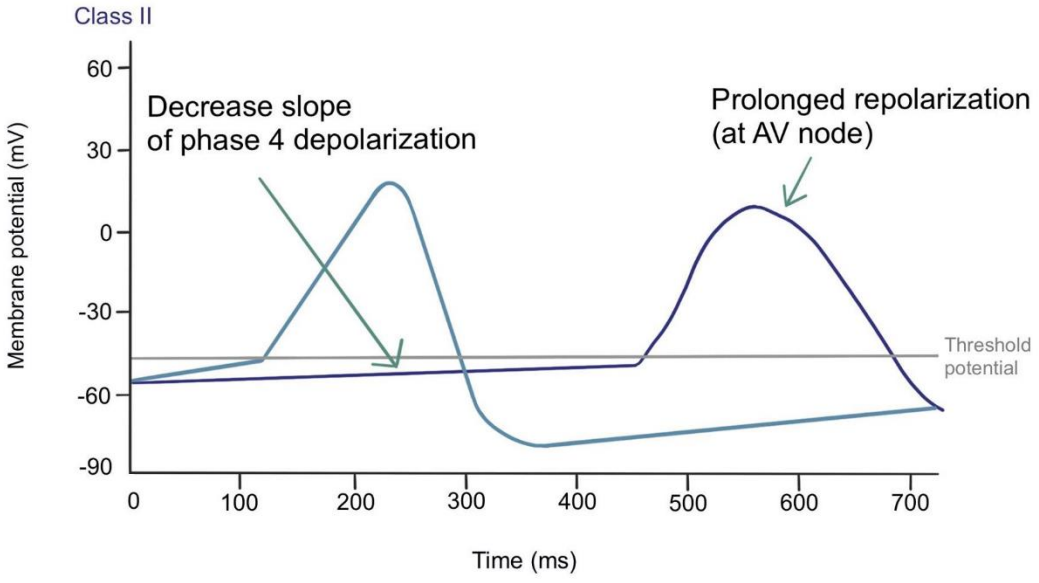
- Arrhythmias

4.3 – Class II: Beta-adrenoceptor Blockers

- Beta-blockers end in "-lol"
    - Ex: esmolol (Brevibloc), acebutolol, metoprolol

4.3.1 Mechanism

- Block the β- receptor
- Decrease the slope of phase 4, leading to the suppression to abnormal pacemakers.
- Decrease the cAMP and Ca^{2+} current to decrease SA and AV nodal activity
    - The AV node is particularly effective, leading to an increase in the PR interval
- Direct membrane effect (Na^{+}-channel block)
- Prolongs AP



4.3.2 Selectivity

I. **Selective for β_1**

- **A**tenalol
- **B**etaxolol
- **E**smolol
- **A**cebutlol
- **M**etoprolol
- **C**eliprolol
- **A**lprenolol
- **N**ebivolol
- ***<u>A</u>-BEAM-CAN***
  - ***<u>A</u> implies 1, hence selective for β_1***

II. equal for β_1 and β_2

- **ca**rteolol
- **pe**nbutolol
- **pi**ndolol
- **na**dolol
- **ti**molol
- **pr**opranolol
- **Cape pina tipr**

III. β_2 selective

- butoxa**mine**
- ***"mine!"*** *indicates you want more, hence* ***2***

IV. mixed ($\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$)

- **lab**etalol
- **carv**edilol
- ***lab-carv****ing competition has people who win, lose, and tie*
- *(all of them participate, but with varying degrees of success)*

4.3.3 Uses

- Rhythm and rate control
  - Supraventricular tachycardia
  - Control ventricular rate in atrial fibrillation and atrial flutter

4.3.4 Side effects

- Cardiovascular effects
    - Bradycardia
    - AV block (leading to more arrhythmias)
    - Heart failure
- CNS effects
    - Sedation
    - Problems sleeping, altered sleeping patterns
- Impotence
- Exacerbation of lung issues (COPD and asthma)
- *Hypoglycemia has similar presentation and thus may be missed in the patients since the symptoms are attributed to adverse drug effects.*
- Non-selective ones may cause unopposed α_1-stimulation in pheochromocytoma or cocaine toxicity.
- Treat overdose with saline, atropine, and glucagon.
- β_2 will also have asthma exacerbation

4.3.5 - Drugs

I. Acebutolol

- Selective for β_1

II. Esmolol

- Alternative name: Brevibloc
- Selective for β_1
- Short acting
    - So it cannot be used chronically
    - Metabolized rapidly when given IV
- Inactive orally (so used only IV)
- Uses
    - During surgeries
    - Acute arrhythmias

III. Metoprolol

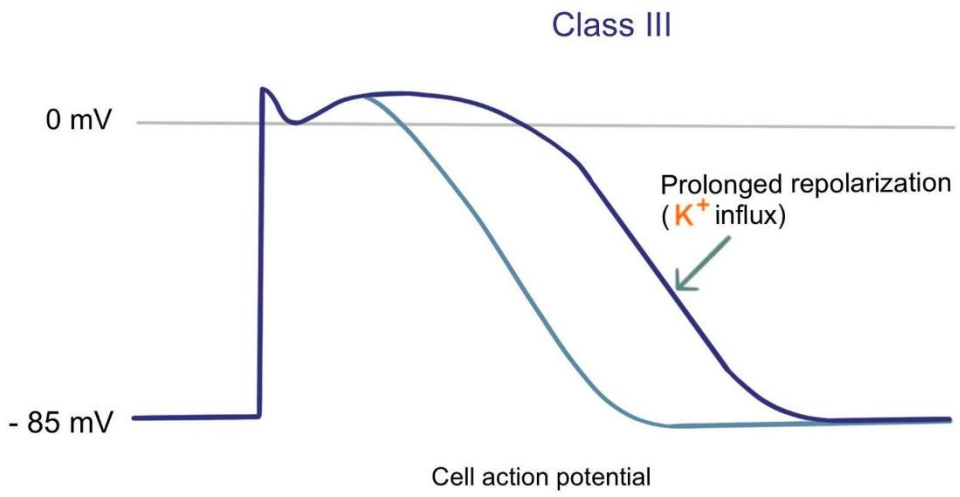
- Selective for β_1
- Side effects
    - Dyslipidemia

Can use non-selective (ex: propranolol) as well to treat arrhythmias, but they tend to have more side effects.

4.4 – Class III: Potassium Channel Blockers

4.4.1 Mechanism

- Prolong the effective refractory period (ERP) by prolonging the action potential (AP)
    - They block the K going out of the cell (block I_{Kr})



4.4.2 Uses

- Supraventricular arrhythmias (atrial fibrillation and atrial flutter)

4.4.3 Side effects

- QT prolongation (torsades de pointes arrhythmia)
    - *This is also part of the mechanism, but excessive prolongation is a side effect since it creates a new arrhythmia*

4.4.4 Specific Drugs

I. Amiodarone

- Alternative name: Cordarone
- Lipophilic
- Long half life (100 days)
    - Longest of all antiarrhythmics
- Has some mechanism similar to classes I-IV
    - *Its not really in one class in particular, but its closest to class III.*

1. Mechanism

- Prolongs action potential duration by blocking I_{Kr}
    - Interferes with outward potassium current

- Also has weak calcium channel blocking $I_{Ca\text{-}L}$ and β-adrenergic effects.
- Also blocks sodium channels (I_{Na})
- Causes peripheral vasodilation, especially when given IV
- Slows heart rate and AV node conduction
- Prolongs QT

2. Uses

- Severe ventricular and supraventricular arrhythmias
- Prevents recurrent ventricular tachycardia

3. Side effects

- Bradycardia and heart block in patients with pre-existing heart disease.
- Accumulates in a variety of tissues, leading to a variety of side effects.
- Pulmonary fibrosis, which may be fatal**
- Liver abnormalities and hypersensitivity
    - Amiodarone is metabolized by the liver
- Gray-blue skin discoloration, especially in areas exposed to sun.
- Halos in peripheral field of vision.
- Hypo- or hyperthyroidism**
    - Due to blockage of conversion of T_4 to T_3 (T_3 is the active form)
    - Amiodarone is 40% iodine by weight
- Constipation
- Torsades de pointes is actually relatively rare
- The function of various organs (especially thyroid, liver, and lungs) must be evaluated periodically.
- Inhibits P450 enzymes, so other drugs metabolized by this (like warfarin and statins) but have altered doses.

II. Dronedarone

1. Mechanism

- Similar to amiodarone, but without to iodine, so there are less adverse effects. (it's a derivative of amiodarone)
- Also functions as a β-blocker.
- Has multichannel action
    - May activate inward current

2. Uses

- Paroxysmal atrial fibrillation
- Conversion of rhythm in atrial fibrillation or flutter (administered IV)

3. Side effects

- Liver toxicity

4. Contraindications

- Acute decompensated or advanced (stage IV) heart failure

III. Ibutilide

- Cleared by liver

1. Mechanism

- Blocks the rapid (I_{Kr}) potassium current.
- Multichannel action.

2. Uses

- Rapid correction of supraventricular tachycardias.
- Decrease in mortality in atrial fibrillation

IV. Dofetilide

1. Mechanism

- Blocks rapid potassium current (I_{Kr}) which increases in hypokalemia
- Very high bioavailability
- Prolongs AP and ERP

2. Uses

- Restore and maintain sinus rhythm in atrial fibrillation

3. Contraindications

- Very large QT (> 450ms (normal < 120))
    - Be especially careful with other QT-prolonging drugs (additive)
- Bradycardia < 50 (normal heart rate: 60-100)
- Hypokalemia (normal potassium: 3,5 – 5,5 mmol/L)

V. Sotalol

1. Mechanism

- β-blocker (class 2)
- Blocks I_{Kr}
- Directly prolongs action potential (class 3)
- Very high bioavailability
- Excreted by kidneys

2. Uses

- Ventricular arrhythmias (especially life-threatening ones)
- Supraventricular and ventricular arrhythmias in kids

3. Side effects

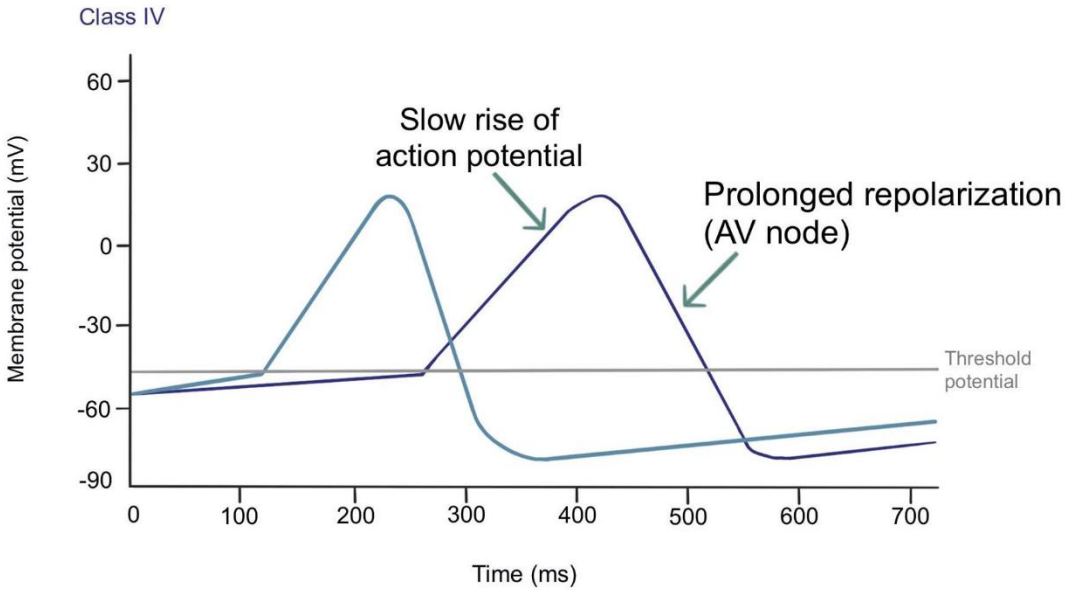
- Excessive β-blockade (so those of β-blockers)

4.5 – Class IV: Calcium Channel Blockers (CCB)

- There are 2 types of CCBs – dihydropyridine (DHP) and non-dihydropyridine (NDHP)
    - only NDHP are used to treat arrhythmias
        - act on L-type calcium channels in vascular smooth muscle
    - DHPs ("-dipine"; ex: nifedipine) may actually cause an arrythmia
        - Act on L-type calcium channels in cardiac muscle.
- SA and AV node activation depends exclusively on calcium channels, so these drugs have a strong impact there.

4.5.1 Mechanism

- Decrease the conduction velocity
- Increase the ERP and PR interval



4.5.2 Uses

- Rate control in atrial fibrillation and flutter
    - Not really return to sinus rhythm though q2
- Prevention of nodal arrhythmias (ex: SVT)

4.5.3 Side effects

- Constipation
- Flushing
- Edema
- Nervousness
- Cardio-vascular effects
    - Heart failure
    - AV block
        - Treat with atropine and β-receptor stimulation
    - Sinus node depression

4.5.4 Specific Drugs

I. Diltiazem

1. Side effects

- Hypotension
- Bradycardia

II. Verapamil

1. Mechanism

- Blocks both activated and inactivated L-type calcium channels

2. Uses

- One of two main drugs used for supraventricular tachycardias.
    - Other is adenosine
- Hypertension and peripheral vasospastic disorders
- Ventricular arrhythmias
    - Can be, but its not very common

3. Side effects

- Peripheral vasodilation

III. Adenosine

1. Mechanism

- Really short ½-life (< 10 seconds).
    - Often used acutely
    - Chronic administration isn't really a thing because you'd have to give the drug constantly
- Activates inward K current leading to hyperpolarization.
- Inhibits outward Ca current leading suppression of Ca-dependent action potentials.
- Directly affects AV node and increase its refractory period.
    - Same with SA node, but to a lesser degree.

2. **Uses**
    - Drug of choice in rapid conversion of paroxysmal supraventricular tachycardia to sinus rhythm.
        - It has a very high efficacy and short half life.
        - Also the drug of choice in diagnosing this.
    - One of two main drugs used for supraventricular tachycardias.
        - Other is verapamil
    - Good for acute nodal tachycardia.

3. **Side effects**
    - Flushing
    - Shortness of breath
    - Chest burning (perhaps due to bronchospasm)
    - Sense of impending doom.
    - Rarely: headache, nausea, hypotension, paresthesia

4. **Drug interactions**
    - Less effective when given with theophylline (used on COPD and asthma) or caffeine since they are adenosine-receptor blockers.
    - Effects increased by dipyridamole (anti-coagulant) since it prevents the uptake of adenosine.

IV. Digoxin
- May also be called digitalis

1. **Mechanism**
    - Increases free Ca concentration near contractile proteins to increase cardiac contractility (+ inotropy) via
        - 1. Inhibiting Na^+/
        - K^+-ATPase, leading to an increase in intracellular Na concentration
        - 2. This reduces the gradient for the Na^+-Ca^{2+} exchanger, leading to a lower amount on Ca^{2+} leaving the cell
        - 3. The increased cytoplasmic calcium in stored in the SR for later use (greater contractions).
    - Increase stroke volume and thus increase cardiac output.
    - At first: prolongs action potential
    - Later: shortens it (especially the plateau phase)
        - Due to increased K^+ conductance, caused by increased intracellular Ca^{2+}
        - Increases PR, decrease QT
    - Decreases sympathetic tone
    - Increases elimination of Na^+ and H_2O

2. **Uses**
    - Can help control ventricular rate in heart failure.
    - Atrial fibrillation
        - Decreases conduction at AV node and depresses SA node (leading to an increase in vagal activity)
    - *A lot of textbooks still have this, but it is actually used very rarely due to its dangerous toxicities and narrow therapeutic index (bad combo – you are likely to not have an affect or to have lots side effects). To avoid this, it requires very good patient cooperation and adherence to drug schedule, so it is often used as a last resort.*

3. **Side effects**
    - Arrhythmias and AV block
    - Vomiting
    - Peaked T waves, induced U waves
    - Blurry yellow vision
    - Treat with
        - Slowly normalize K^+, Mg^{2+}, anti-digoxin Fab fragments, cardiac pacing

4.6 – Approach to Anti-arrhythmic Therapy

- 1. Make sure there are not external causative factors.
    - Electrolyte imbalances, hypoxia, drugs, underlying diseases (like hyperthyroidism or cardiac disease).
- 2. Diagnose the type of arrhythmia.
- 3. Evaluate the heart (check for structural abnormalities)
- 4. Determine if treatment is required.
    - Required if life-threatening arrhythmia or problematic symptoms.
    - Don't want to always do because of side effects.
- Only β-blockers decrease mortality in asymptomatic patients. *(unknown why)*
- When immediate action is required, IV administration is preferred.
- When chronic treatment of prophylaxis, then use long-acting drugs.
- Atrial fibrillation is the most common chronic arrhythmia.
    - Diagnosed by ECG
    - May be caused by hyperthyroidism (treat that instead)
    - Treatment goal is to relieve symptoms and prevent complications which may arise from thromboembolism and tachycardia-induced heart failure.
    - Initial treatment is controlling ventricular rate.
        - CCBs +/- βBs
        - Digoxin good if heart failure already present.
    - Later treatment aims to restore and maintain sinus rhythm
        - Rate control is more important than rhythm control
        - Class 1 antiarrhythmics are good for this purpose
        - Propafenone and flecainide (class 1C) in single dose are preferred for paroxysmal atrial fibrillation.

    - In emergency (atrial fibrillation together with angina or hypotension)
        - DC cardioversion is the best.
        - Followed by class 1 or 3 antiarrhythmic to maintain sinus rhythm.

4.7 – Assorted High Yield Facts

- Lidocaine: best drug to use in management of ventricular tachycardias associated with acute MI
    - lidocaine does not slow conduction and has little effect on atrial function
- Propranolol: drug of choice to treat atrial fibrillation in patient with hyperthyroidism
    - Hyperthyroidism increases β-adrenoreceptors
    - Propranolol (and other β-blockers) can actually decrease symptoms of hyperthyroidism as well as treat the arrhythmia
- Digoxin can be added to quinidine to treat atrial flutter if quinidine alone doesn't do the job.
    - Digoxin and procainamide cannot be combined because amplify each other and thus lead to massive side effects.
    - Its actions can be potentiated by hypokalemia
        - Diuretics such as hydrochlorothiazide may cause this
- Procainamide is safe to use in asthma since it has little to no β-blocking effect.
    - Procainamide does not interact with digoxin either.
- Lidocaine reduces automaticity in ventricles.
- Amiodarone, quinidine, verapamil, and disopyramide can be given orally to for chronic angina therapy.
- CCBs and adenosine can both be used to treat acute nodal tachycardias, but adenosine is less toxic
- All class 1a and class 3 drugs reduce the K current during phase 3 and prolong AP.
    - 1B drugs (ex: lidocaine) actually shorten it.
- Adenosine is the only antiarrhythmic that consistently alters the AV node resting potential. It hyperpolarizes the tissue ad prevents the action potential conduction.
- Class IB drugs block sodium channel decrease AP duration
    - Mexiletine is active orally, lidocaine is not
- Verapamil, adenosine, and β-blockers slow AV conduction.
    - Only verapamil acts primarily on L-type calcium channels.
- Tocainide is an analog of lidocaine
    - Doesn't have 1st pass metabolism

Sections 5 Lipid Lowering Agents

5.1 - Thesis
5.2 - Bile Acid Resins
5.3 - Fibrates
5.4 - HMG-CoA Inhibitors
5.5 - Niacin
5.6 - Ezetimibe

5.1 - Thesis

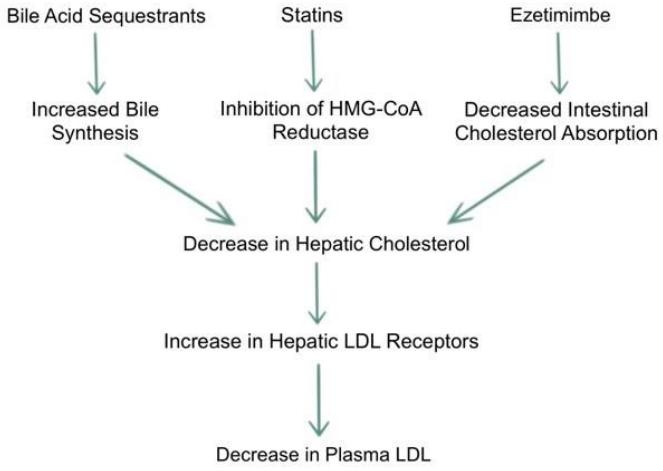
5.1.1 - Definition

- Elevated cholesterol can increase the risk atherosclerosis and subsequent cardiovascular complications. Triglycerides are not as strongly associated with cardiovascular issues, however there is an association with pancreatitis.
- Lipid lowering agents are generally given as a part of a cardioprotective multidrug regimen rather than for specific pathology.

5.1.2 -Types of cholesterol

- Very Low Density Lipoproteins (VLDL)
    - Serves as the body's transport system for lipids
- Low Density Lipoproteins (LDL)
    - Known as "bad" cholesterol
- Transports fat to cells throughout the body
    - High Density Lipoproteins (HDL)
    - Transports lipids to the liver

Generally you want LDL to be "Low" and HDL to be "High"



5.2 -Bile Acids Resins

5.2.1 - Drugs

- Cholestyramine
- Colestipol
- Colesevelam

5.2.2 - Mechanism of Action

- Prevents intestinal reabsorption of bile acids
- Liver must use cholesterol to make additional bile acids

5.2.3 - Clinical Objectives

- Marked LDL reduction
- Slightly elevated HDL and triglyceride

5.2.4 - Adverse Effects

- GI upset
- Decrease drug absorption
- Decreased absorption of fat soluble vitamins

5.3 - Fibrates -fibr-

5.3.1 - Drugs

- Gemfibrozil
- Bezafibrate
- Fenofibrate

5.3.2 -Mechanism of Action

- Upregulates LPL
    - Increases triglyceride clearance
- Activates PPAR-a
    - Induces HDL synthesis

5.3.3 -Clinical Objectives

- Markedly decreased triglycerides

5.3.4 - Adverse Effects

- Myopathy
    - Risk increased with simultaneous statin use
- Cholesterol gallstones
    - Due to inhibited cholesterol 7a-hydroxylase

5.4 - HMG-CoA Reductase Inhibitors -statin

5.4.1 - Drugs

- Lovastatin
- Pravastatin

5.4.2 -Mechanism of Action

- Inhibit conversion of HMG-CoA to mevalonate
    - Mevalonate is a cholesterol precursor
- Decreases mortality in coronary artery disease patients

5.4.3 - Clinical Objectives

- Markedly decreased LDL
- Increased HDL
- Decreased triglycerides

5.4.4 - Adverse Effects

- Hepatotoxicity
- Myopathy
    - Increased risk with simultaneous fibrate use

5.5 - Niacin (Vitamin B3)

5.5.1 - Mechanism of Action

- Inhibits lipolysis in adipose tissue
- Reduced hepatic VLDL synthesis

5.5.2 - Clinical Objectives

- Significantly decreased LDL
- Significantly increased HDL

5.5.3 - Adverse Effects

- Flushed face
- Hyperglycemia
- Hyperuricemia

5.6 - Ezetimibe

5.6.1 - Mechanism of Action

- Prevents cholesterol absorption at small intestine brush border by inhibiting sterol transporter

5.6.2 - Clinical Objectives

- Decreased LDL
- Normal or slightly elevated HDL
- Normal or slightly decreased triglycerides

5.6.3 -Adverse Effects

- Diarrhea
- Elevated liver enzymes

Section 6.1 – Anti-Thrombotics

6.1 - Warfarin

6.2 - Direct Thrombin Inhibitors

6.3 - Thrombolytics

6.4 - Fibrinolytics

6.5 - Anti-Platelet Drugs

6.6 - PDE Inhibitors

6.7 - Other Drugs

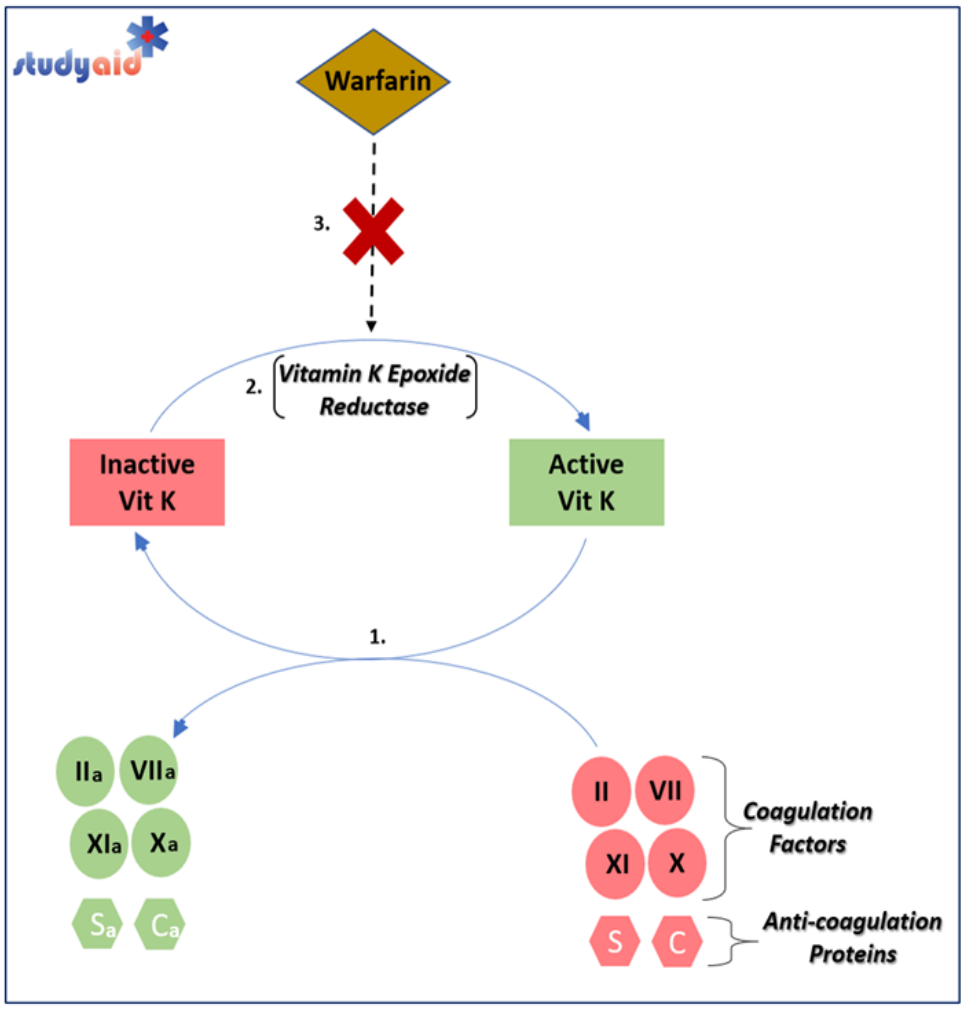


Figure 1:

1. Vitamin K activates coagulation factor II, VII, XI, X and anti-coagulation protein S & C
2. Inactive Vitamine K is re-activated by the enzyme Vitamin K Epoxide Reductase
3. Warfarin inhibits action of Vitamin K Epoxide Reductase, and thereby the activation of the Coagulation Factors and Protein S & C

6.1.1 – Warfarin

I. Mechanism:

- Inhibits γ-carboxylation of Vitamin K epoxide by the enzyme Vitamin K epoxide reductase (the enzyme that turns inactive Vit K (epoxide) into active free Vit K)
- Vitamin K works as an activator of coagulation Factor II, VII, IX and X (also, activator of the **anti**-coagulants protein C and protein S)
- By inhibiting Vit K activation, it also inhibits the extrinsic coagulation cascade

II. Use

- Used as a long-term treatment for patients with a high risk of hypercoagulability (e.g patients with Atrial Fibrillation or at risk of DVT after cardiovascular surgery)
- Has an action delay of 8-12 hours (because it only inhibits new coagulation Factors) (the existing active coagulation factors are still active, must wait for their replacements)
- Recommended dosage: 5-10mg (in extreme scenarios up to 0.75mg/kg)

III. Measurements

- Prothrombin Time (PT)
  - Evaluates clotting velocity of the extrinsic pathway
  - Should be prolonged until it suggests a prothrombin activity of only 25% (prothrombin activity less than 20% indicates warfarin overdosage)
  - Mainly decided by Factor VII, because it has the shortest half-life of 6 hours (is therefore the first Factor affected by warfarin and first influencer of PT)

- Internationalized Normalized Ratio (INR)
  - Also evaluates extrinsic pathway activity, but uses more factors than PT and also accounts for PT results in its evaluation
  - Should preferably be 2-3 in a patient taking warfarin (upscaled up to 3.5 in patients in a hypercoagulable state)

IV. Side effects

i. Short **hyper**coagulable state (cause it inhibits **anti**-coagulant protein C & S first)

V. Administration & Metabolism

- To prevent hypercoagulability, the first week of warfarin administration is overlayered with co-administration of LMWH (to inhibit the already active coagulation factors)
- Warfarin is metabolized by Cytochrome P450 in the liver (36 hour half-life)
- Warfarin half life may increase/decrease if taken with drugs that affect Cyt P450 activity (e.g pyrazolones, Barbiturate and Rifampin)

VI. Contraindications

- Certain disorders like hepatic disease and hyperthyroidism may also alter warfarin activity (increase coagulation turnover → larger warfarin dose is necessary)

VII. Reversibility (of its action)

- Stop Warfarin administration (in mild cases, that is enough)
- Oral or parenteral Vitamin K_1 (phytonadione)
- Fresh-Frozen Plasma (FFP) with coagulation factors
- Prothrombin-complex concentrates (e.g Bebulin or Proplex T)
- Recombinant Factor VII_a (active version Factor VII)

6.1.2 – Heparin

I. Use

- Acute Myocardial Infarction (acute MI)
- Pulmonary Embolism (PE)
- Deep Vein Thrombosis (DVT)

II. Mechanism

- Binds to antithrombin III → accelerates it 1000-fold → inhibition of active clotting factors II, IX and X (inhibits the intrinsic pathway)
- Fibrin clot formation is done by active Factor II, but because Factor II is activated by Factor X which itself is activated by Factor IX, inhibiting any of the three factors will decrease clot formation

III. Measurements

- Partial Thromboplastin Time (PTT): Measures the activity of the intrinsic pathway (helps to assess Heparin function and we aim for 2-3 times the baseline values)
- Heparin activity may also be assessed by protamine titration and anti-Xa units (although PTT is the main test of choice)

IV. Administration

- Starts with a bolus injection of 80-100 units/kg
- Followed by continuous infusion of 15-22units/kg/h to maintain anti-X_a activity (should be measured every 6 hour)
  - for low-dose prophylaxis, give 5000 units subcutaneously every 15-22 hours (never give it intramuscular, high risk of **hematoma** formation)

V. Reversibility

- Heparins' action can be reversed by administering Protamine Sulfate (a positive binding molecule that binds the negatively charged Heparin molecule)
- For every 100 units of Heparin, 1mg of Protamine Sulfate is given

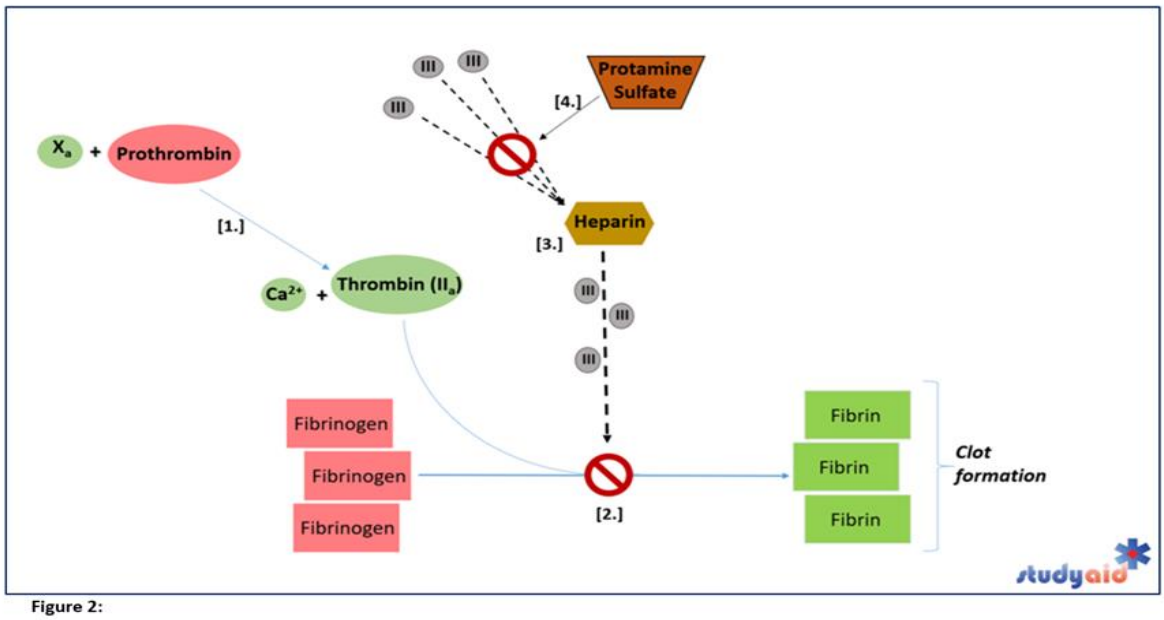


Figure 2:

1. Prothrombin Reacts with Factor Xa to create active Thrombin (Factor IIa)
2. In a Calcium-rich environment, Thrombin binds Fibrinogen to create active Fibrin, able to form a clot
3. Heparin increases the ability of Antithrombin (Factor III) to bind active Thrombin (IIa), and thereby preventing Fibrin-clot formation
4. Protamine sulfate inhibits Heparin from reacting with Antithrombin (III) and may be used as a reversing agent

VI. Side Effects

- Bleeding (look out for intracranial hemorrhage)
- Osteoporosis
- Hypoaldosteronism (affects the adrenal glands to secrete less)
- Hyperkalemia (due to hypoaldosteronism (less K^+ wasting)

VII. Heparin Induced Thrombocytopenia (HIT)

- Hypercoagulable state occurring in 1-4% of patients taking Heparin for >7 days
- Occurs when the body makes antibodies against platelet factor 4 → thrombocytopenia
- The hyper coagulability occurs because thrombocytopenia itself can cause a paradoxical response of increased platelet aggregation
- First signs are often pale and swollen legs (DVT)

VIII. Contraindicated

- HIT
- Hemophilia or other bleeding disorder
- Intracranial hemorrhage
- Infections like endocarditis or TB
- Ulcers or visceral carcinomas
- Hepatic or renal disorders
- Patients recently undergone surgery of the brain, spinal cord or eye
- Recently had lumbar puncture

IX. Additional Info

- Due to its large size, the unfractioned Heparin molecule does not cross the placenta and is therefore safe to use by pregnant women
- Is metabolized by the kidneys and its action may be affected when given with drugs affecting the renal system (not used for patients with renal insufficiency)

6.1.3 – LMWH

Referred to as "Low-Molecular Weight Heparin"

I. Drugs:

I. Enoxaparin

- Given subcutaneously at a dosage of 30mg twice/day or 40mg once/day
- At most may be given at dosage of 1mg/kg every 12 hours

II. Dalteparin

- Prophylactic dose of 5000 units/day subcutaneously
- Therapeutic dose of 200 units/kg for venous disease and 120 units every 12 hours for acute coronary syndrome

III. Tinzaparin

II. Mechanism

- Like Heparin also binds antithrombin III (but mostly affects Factor X_a)
- Proven to have equal efficacy as Heparin, with even greater bioavailability and requires less frequent dosing (plus the risk of developing HIT is smaller)
- Due to their greater bioavailability, their half-life is longer than Heparin
- Due to the molecule being smaller and without charge, Protamine Sulfate is less effective in reversing LMWH as it is with unfractionated Heparin
- (e.g 1mg Protamine sulfate can only remove 1mg enoxaparin)

III. Monitor

- PTT may be used to monitor LMWH, but is much less reliable than it is with Heparin
- Anti-X_a activity is often the method of choice for monitoring LMWH activity

(although because LMWH cause less side effects, they are often not monitored)

IV. Contraindicated

- Renal insufficiency (metabolized by the kidneys)
- Body weight >150kg
- Bleeding disorders
- Recent surgery (risk of intracranial hemorrhage)

V. Side Effects

- Although much less likely, LMWH may also cause hyperkalemia induced by hypoaldosteronism

6.1.4 – Fondaparinux

I. Mechanism

- Binds to antithrombin III → increased binding of Factor Xa (higher specificity for Factor Xa than LMWH or Heparin)
- Half life of 15 hours allowing for 1/day subcutaneous dosing

II. Monitor

- Although not necessary, can be monitored using PTT or anti-Xa factor testing

III. Additional Info

- Has the lowest risk of causing HIT
- Protamine Sulfate is not as effective at reversing its action

6.1.5 – Direct Factor Xa Inhibitors

I. Mechanism

- Inhibit factor Xa in the final common pathway of clotting

II. Administration

- Are given orally and do not require monitoring
- Rapid onset of action and half lives of approximately 10 hours (longer in elderly patients and those with renal impairment)

III. Drugs

i. **Rivaroxaban**

- Use: preventing thromboembolism following hip or knee surgery

ii. **Apixaban**

- Use: stroke prevention in patients with atrial fibrillation
- Still under clinical development (yet often mentioned on exams)

iii. **Edoxaban**

- Use:
  - Preventing thromboembolism following hip or knee surgery
  - Preventing stroke following non-central systemic embolism
  - May be given after 5-10 days following initial anticoagulation therapy of patients at risk of further developing DVT or PE

IV. Metabolism

- Both drugs are excreted by the kidneys and therefore not suitable for patients with renal insufficiency or that are taking drugs affecting the renal system

(in such patients, the hepatically metabolized warfarin is preferred)

6.2 – Direct Thrombin (II) Inhibitors

6.2.1 – Bivalirudin

I. Administration

- Rapid onset and offset of action and given parenterally
- Short half-life with clearance being 20% renal and 80% metabolic

(preferred treatment in patients with hepatic insufficiency)

II. Mechanism

- Directly bind and inhibit Thrombin (factor II), inhibiting its action
- Their rapid onset and offset of anticoagulation gives us the ability to avoid overlapping them with other medications (cause we can organize their use and action much easier)

III. Indication

- Percutaneous Coronary Angioplasty

IV. Use

- Often used for patients that are at risk of developing HIT
- Additionally, also inhibits platelet activation
- Have the advantage in that they have predictable effect and bioavailability

(allow for fixed dosing without necessity of monitoring)

6.2.2 – Argatroban

I. Mechanism

- Has a short half-life and is given intravenously
- Directly bind and inhibit Thrombin (factor II), inhibiting its action
- Their rapid onset and offset of anticoagulation gives us the ability to avoid overlapping them with other medications (cause we can organize their use and action much easier)

II. Use

- Often used for patients that are at risk of developing HIT
- Have the advantage in that they have predictable effect and bioavailability

(allow for fixed dosing without necessity of monitoring)

III. Side Effects

- Increased risk of bleeding (especially GI bleeding, then we use Warfarin)

IV. Indicated

- Patients at risk of developing HIT when taking Heparin

V. Monitored

- Partial Prothrombin Time

VI. Metabolism

- Hepatically (advantage for patients with renal insufficiency)

6.2.3 – Dabigatran

I. Mechanism:

- 3-7% oral bioavailability and half-life of 12-17 hours
- Directly bind and inhibit Thrombin (factor II), inhibiting its action
- Their rapid onset and offset of anticoagulation gives us the ability to avoid overlapping them with other medications (cause we can organize their use and action much easier)

II. Use

- The first and most frequently used thrombin inhibitor
- Mainly applied for patients at:
  - Risk of stroke
  - Risk of Systemic Embolism in patients with atrial fibrillation
  - Risk of Venous Thromboembolism in patients undergone knee or hip surgery
- Have the advantage in that they have predictable effect and bioavailability (allow for fixed dosing without necessity of monitoring)

III. Side Effects

- Increased risk of bleeding (especially GI bleeding, then we use Warfarin)

IV. Metabolism

- Renal (do not give to patients with renal insufficiency)

6.3 – Thrombolytics

6.3.1 – Streptokinase

I. Mechanism & Use

- A protein synthesized by streptococci that catalyzes TPA activity □ more plasmin
- Because fibrinolysis by catalyzing plasminogen conversion (by the enzyme Tissue Plasminogen Activator (TPA) into active plasmin (plasmin breaks down fibrin clots)
- We need these drugs because infusion of active plasmin has no effect on fibrinolysis (gets quickly bound by inhibitor molecules in the plasma)

II. Monitored

- Prothrombin Time
- Partial Thromboplastin Time
- Plasma D-dimer level

III. Indications

- PE with hemodynamic instability
- Severe DVT (as in vena caval syndrome)
- Ascending thrombophlebitis (with leg edema)
- Ischemic stroke (should be administered within the first 3-4.5 hours)
- Acute STEMI (if Percutaneous Coronary Intervention is not possible)

IV. Administration

- Should be administered within 3-4.5 hours of an ischemic stroke
- Mainly given IV, although may be given intraarterially in some cases (e.g in patients iwith peripheral vascular disease)

V. Contraindications

- Hypertension
- Recent head trauma
- Recent intracranial surgery
- At risk of developing an allergic reaction (streptokinase)

VI. Allergy

- Patients with anti-strep antibodies may develop fever and an allergic reaction or therapeutic resistance

VII. Side Effects

- Risk of intracranial hemorrhage in ischemic stroke patients that have received over 1.5 million units

6.3.2 – Other Thrombolytics

I. Alteplase

- An analog of the TPA enzyme
- Dosage of 60mg/h the first hour, then 20mg/h for the next 2 hours

II. **Tenectaplase**

- An analog of the TPA enzyme (slightly more clot-specific)
- Given as a bolus IV 0.5mg/kg

III. **Reteplase**

- An analog of the TPA enzyme
- Dosage: Two IV bolus injections of 10 units separated by 30 minutes

6.4 – Fibrinolytics

6.4.1 – Aminocaproic Acid

I. **Mechanism**

- A synthetic inhibitor of fibrinolysis
- Competitive inhibitor of plasminogen

II. **Uses & Administration**

- Used to reverse the effect of fibrinolytic agents
  (e.g when they cause intracranial hemorrhage)
- Given orally, rapidly absorbed and then matabolised by the kidneys
  (be aware drug interactions or renal insufficiency)

6.4.2 – Tranexamic Acid

I. Mechanism

- An analog of Aminocaproic Acid (also inhibitor of plasminogen)
- Dosage: given orally, first 15mg/kg loading dose, then 30mg/kg every 6 hours

II. **Clinical Use**

- Therapy in hemophilia patients
- Uncontrolled bleeding due to fibrinolysis
- Prophylaxis against rebleeding from intracranial aneurysms
- Against postsurgical GI- or prostate-bleeding

III. Side Effects

- IV thrombosis
- Hypotension
- Myopathy
- Mild variety of GI pathologies

IV. Contraindications

- DIC
- Genitourinary upper tract bleeding

6.5– Anti-Platelet

6.5.1 – Reaction During Bleeding

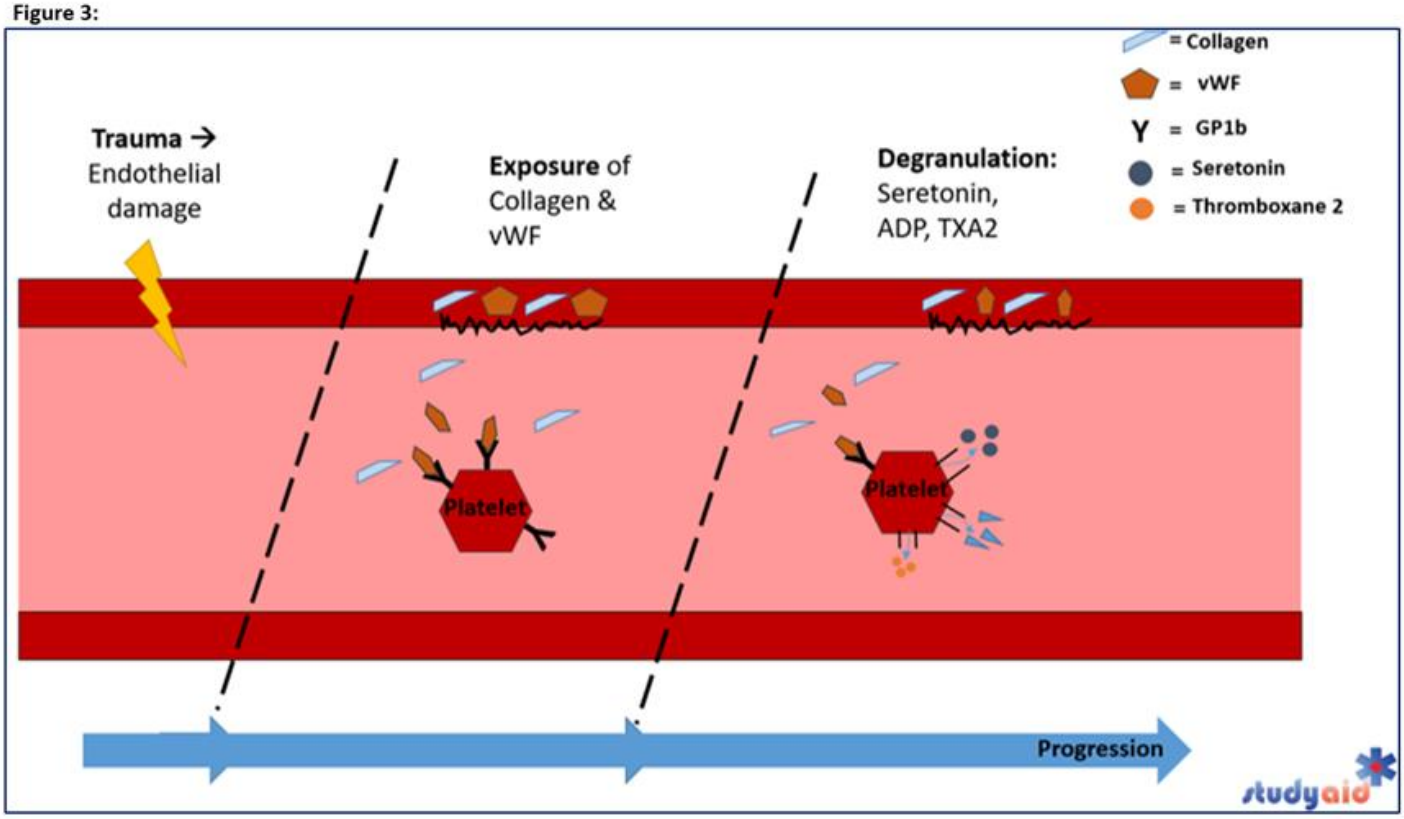
I. Endothelial damage → exposure of collagen and von Willebrand Factor (vWF)

II. GP1b platelet receptors bind to the exposed vWF → platelet activation

III. Platelet degranulation (ADP, 5-HT3 and TXA_2)

- ADP binds to P2-Y12 reeptors of other platelets → further platelet aggregation
- 5-HT3 (serotonin): causes further aggregation and vasoconstriction
- TXA_2: synthesized from Arachidonic Acid by COX-1 and causes vasoconstriction and further platelet activation

Figure 3:



6.5.2 – Aspirin

I. Mechanism

- **Irreversibly** acetylates COX-1 to inhibit its action of making TXA_2 → decreased platelet aggregation & decreased vasoconstrictive stimuli
- It is non-selective and therefor might also inhibit COX-2 (enzyme that make inflammatory prostaglandins)
- Differs from NSAID's in that their inhibitory effect is **reversible**, thereby temporary

II. Contraindications

- Patients with aspirin pseudo-allergy to Aspirin (use **Clopidogrel** instead) (seen in asthma and nasal polyposis)
- The allergy-like symptoms are due to the fact that the enzyme Lipoxygenase (LOX) also uses AA and makes Leukotrienes (more AA → more Leukotrienes → anaphylaxis)

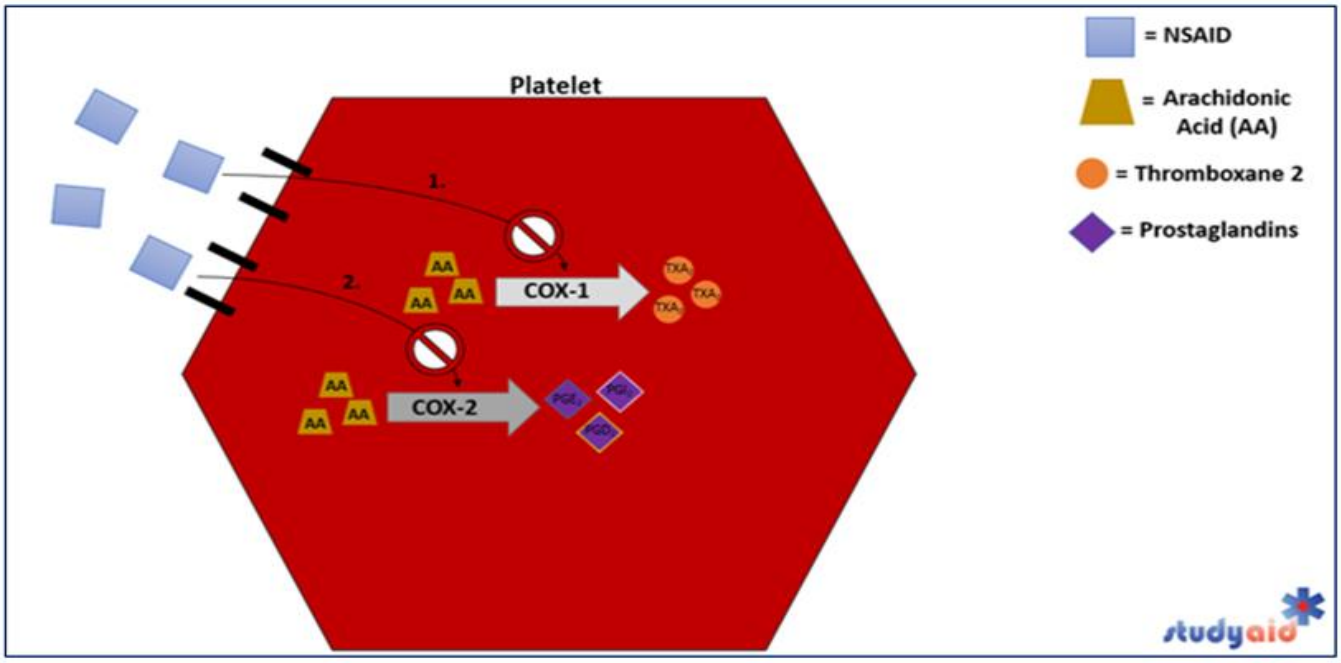


Figure 4:

1. NSAIDs like **Aspirin** are able to diffuse through the platelet membrane and inhibit the enzyme Cyclooxygenase-1 (COX-1) from turning Arachidonic Acid (AA) into Thromboxane 2 (TXA2)

2. Most NSAIDs (Aspirin as well) also inhibit the enzyme Cyclooxygenase 2 (COX-2) from turning Arachidonic Acid (AA) into inflammatory prostaglandins

6.5.3 – GP2Y12-Blockers

I. Mechanism

- Reduce platelet aggregation by competing with ADP in binding to the platelet receptor GP2Y12 (irreversible)
- Unlike aspirin, they do not affect COX-1 or COX-2

II. Use

- Mainly used to prevent thrombosis after placement of a coronary stent
- Also used for prevention of ischemic stroke in patients with Atherosclerosis and Cerebrovascular disease

III. Indications

- Unstable angina
- NSTEMI (combined with aspirin)
- STEMI
- Prophylaxis against stroke, MI, or peripheral artery disease

IV. Drugs

i. **Clopidogrel**
   - Provides 7-10 days of antiplatelet effect (even after we stop administration)
   - Some patients might show resistance to the drug
   - (Still develop stroke or thrombosis after undergoing drug therapy)
   - Metabolized Hepatically by P450

ii. **Prasugrel**
   - Similar action as Clopidogrel, but requires a smaller dose and given with aspirin
   - Dosage: oral 10mg/day
   - Have paradoxic side effect in that certain doses may cause a bleeding risk (therefor contraindicated in TIA and stroke patients)
   - Some patients might show resistance to the drug (still develop stroke or thrombosis after undergoing drug therapy)
   - Metabolized renally (be aware of patients with renal insufficiency)

iii. **Ticagrelor**
   - Same action as mentioned above
   - Also given with aspirin
   - Dosage: oral, start with 180mg loading dose, then 75-150mg/day
   - Metabolized hepatically by P450 (be aware of hepatic failure)

iv. **Elinogrel**
   - The only **reversible** GP2Y12 inhibitor
   - "Quick" onset and offset (12 hour activity)
   - Metabolized renally (be aware of renal insufficiency)

v. **Cangrelor**
   - The only GP2Y12 inhibitor that is given IV
   - Often given as an additional drug with Clopidogrel for better results
   - Side effect: respiratory autoimmunity → dyspnea

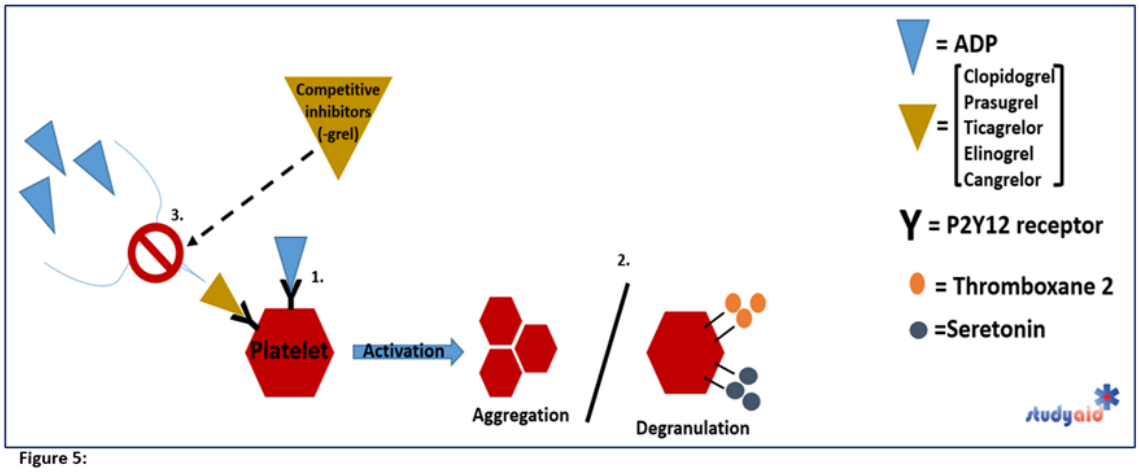


Figure 5:

1. ADP binds to P2Y12 receptors on the platelets, causing an activation response
2. When activated, the platelets start to aggregate as well as degranulate, releasing Thromboxane 2 (TXA2) and Seretonin (5-HT3)
3. Competitive P2Y12 inhibitors prevent ADP from binding to the receptors and thereby preventing platelet activation

6.5.4 – IIb/IIIa-receptor Blockers

I. Mechanism

- This receptor can bind to fibrinogen (mainly), vitronectin or vWF
  (when stimulated, it activates the "final common pathway" of platelet activation)
- The drugs mentioned under are competitive inhibitors of the IIb/IIIa-receptor
- Glanzmann's thrombasthenia: patients lacking this receptor (high risk of bleeding)

II. Use

- Used during percutaneous coronary intervention
- Palliatively for Acute Coronary Syndrome

III. Drugs

i. **Abciximab**
ii. **Eptifibatide**
iii. **Tirofiban**

IV. Administration

- Parenteral

6.6– Phosphodiesterase (PDE) Inhibitors

6.6.1 – Dipyridamole

I. Mechanism & Use

- Inhibits breakdown of platelet cAMP by PDE → block the platelet aggregation response (also inhibits ADP reuptake by the platelets)
- Has and additional role as a vasodilator

II. Combination

- Often combined aspirin as prophylaxis of cerebrovascular ischemia/disease
- May also be combined with Warfarin for prevention of thromboemboli in patients with prosthetic heart valves

6.6.2 – Cilostazol

I. Mechanism & Use

- Also inhibits platelet aggregation by blocking PDE and causing cAMP increase
- Works also as a coronary artery dilator
- Used primarily as treatment of intermittent claudation

II. Side effects

- Coronary Steal: (dilating all other coronary arteries than the injured one → ischemia of the affected area)

6.7– Other Drugs

6.7.1 – Iloprost

I. Mechanism

- Prostacyclin (PGI_2) analog that is mainly used as a vasodilator of systemic and pulmonary vascular beds (mainly for Pulmonary Arterial Hypertension)
- It inhibits platelet aggregation, but the mechanism is unknown (speculation of it inhibiting GP2Y12 receptors)

6.7.1 – Epoprostenol

I. Mechanism & Action

- Also an analog of Prostacyclin (PGI_2) used for Pulmonary Arterial Hypertension
- Stimulates Adenylyl Cyclase to increase cAMP production → decreased platelet aggregation (also counteracts platelet response to TXA_2)

6.7.2 – Treprostinil

I. Mechanism

- Prostacyclin (PGI_2) analog that also decreases platelet aggregation (unknown mechanism)

6.7.3 – Vorapaxar

I. Mechanism

- Blocks the PAR-1 receptor on platelets from binding to thrombin (which when stimulated causes G-coupled platelet activation)

II. Use

- Given as prophylaxis of myocardial infarction and peripheral arterial disease

6.7.4 – Terutroban

I. Mechanism

- Selective TXA_2-receptor antagonist (inhibiting aggregation and vasoconstriction)