CARDIAC PHARMACOLOGY
Drugs Affecting Hemostasis

N.B.: Thyroid hormones increase the catabolism of endogenous compounds (including clotting factors) → effects of coagulability are enhanced.

1. Antiplatelet drugs; aspirin, clopidogrel, abciximab
2. Anticoagulants; heparin, enoxaparin, warfarin
3. Fibrinolytic (Thrombolytic); streptokinase, alteplase
4. Drugs for bleeding disorders; Vit K, desmopressin, aminocaproic acid
Antiplatelet drugs: Aspirin, Clopidogrel, Abciximab

Aspirin:
- MOA **Irreversible** inactivation of Cox 1 (lasts for the life of the platelet, i.e. 4-10 days)
- High dose aspirin does not have antiplatelet effect.

Clopidogrel:
- Irreversible blockade of Gi-coupled platelet ADP receptor→ inhibits the binding of fibrinogen to platelet surface
- Adverse effect: bleeding

Uses of Aspirin and Clopidogrel:
- Unstable angina
- MI (prophylaxis and treatment)
- Arterial Thromboembolism/stroke prophylaxis

Abciximab:
- Non-competitive blocking of the platelet glycoprotein IIb/IIIa receptor complex (final common pathway)→ prevents binding of adhesive ligands
- Uses: UNSTABLE ANGINA
Anticoagulant drugs: Heparin, Enoxaparin, Warfarin

**Heparin:**
- Large, sulfated, **acidic**, and negatively charged
- Types: HMWH and LMWH
- Heparin accelerates the action of (ATIII) antithrombin III, a protease inhibitor → clotting factors are inactivated rapidly
- Administered IV or SC (Bioavailability=0)
- Drug **STAYS** in the vascular compartment (Vd=4L)
- Drug is monitored by the (**aPTT**) activated partial thromboplastin time
- Adverse effects: bleeding, hematuria, epistaxis, **heparin induced thrombocytopenia (HIT)**
- **Heparin induced bleeding can be reversed by an IV infusion of protamine sulfate** (+vely charged)

**Warfarin (Coumarin):**
- Vitamin K is an essential cofactor for the synthesis of coagulation factors (e.g. prothrombin)
- Warfarin is a **vitamin K antagonist** (blocks the reductive conversion of Vit K epoxide back to the reduced form) → acts on the liver and prevents the formation of **novel** clotting factors
- Onset of action → 8-12 hours
- Drug effects can be reversed by Vitamin K administration → takes 24 hours
- Metabolized in liver, Bioavailability is >95%
- Drug is monitored by the (**PT**) Prothrombin time
• **CONTRAINDICATED IN PREGNANCY**; fetal toxicity and teratogenic (1st trimester)

Certain drugs inhibit the metabolism of warfarin and cause **potentiation** of anticoagulation (Increased PT) →
- Cimetidine, acute alcohol intoxication, Disulfiram, Metronidazole, broad spectrum antibiotics (impaired Vit K synthesis by flora)

Certain drugs stimulate the metabolism of warfarin and cause **attenuation** of anticoagulation (Decreased PT) →
- Vitamin K, Barbiturates, Rifampin

**Indications of anticoagulants:**
- DVT (Heparin initially → later warfarin)
- Arterial Thromboembolism (prophylactic/treatment)
- Atrial Fibrillation (long-term heparin)
- prosthetic valve (long-term **warfarin**)
- prosthetic valve during pregnancy (**heparin**)
- Acute MI, DIC (heparin)
- **Extracorporeal machines** (heparin; acts in vivo & invitro)

**Contraindications of anticoagulants:**
- Active bleeding
- Disease that increases the risk of hemorrhage (Aplastic anemia, leukemia, peptic ulcer, active pulmonary TB)
- Pregnancy (warfarin)
Fibrinolytic drugs

Streptokinase (non-enzymatic), Alteplase (human tPA)

- All act by converting plasminogen to active plasmin
- Administered IV (oral bioavailability is 0)
- Adverse effects: Cerebral bleeding due to lysis of fibrin at sites of vascular injury

Contraindications:
- Active bleeding/hemorrhagic disorders
- Previous CVA
- Hypertension
- Aortic dissection
- Acute pancreatitis
- Pericarditis (if drug is given → cardiac tamponade)

Indications:
- Acute MI
- DVT
- Arterial Thromboembolism (Pulmonary)

Drugs for bleeding disorders
- Vitamin K
- Desmopressin increases factor VIII activity and is used to treat hemophilia and von Willebrand disease.
- **Aminocaproic acid** competitively inhibits the binding of plasma to fibrin. (NO EFFECTS ON COAGULATION). Used to treat acute bleeding due to hemophilia, Fibrinolytic therapy, etc.
Antihyperlipidemic Drugs

1. HMG-CoA inhibitors; **Lovastatin, Atorvastatin**
2. Bile acid binding resin; **Cholestyramine**
3. VLDL secretion inhibitors; **Niacin**
4. Fibric acid derivative; **Gemfibrozil**
5. Inhibitor of intestinal sterol absorption; **Ezetimibe**

Two major sequelae of hyperlipidemias

Plaques in vessel wall $\rightarrow$ Atherosclerosis

Increased risk of gall stones $\rightarrow$ Acute pancreatitis

HMG CoA Reductase Inhibitors (Statins)
**Lovastatin, Atorvastatin**

\[ \text{HMGCoA} \rightarrow \text{Mevalonic acid (normal reaction)} \]

- Inhibit the rate limiting step (HMG CoA reductase) of cholesterol biosynthesis $\rightarrow$ liver compensates and up regulates the LDL receptors $\rightarrow$ decreases LDL from blood $\rightarrow$ decreases hepatic VLDL production
- **Up to 55% reduction in LDL**
- **Up to 35% reduction of triglycerides**
- **Small increase (10%) of HDL**
- **First pass metabolism (bioavailability does not matter)**

Adverse effects:
- Hepatotoxicity (discontinue drug if aminotransferase activity is 3X normal)
- myopathy with rhabdomyolysis $\rightarrow$ myoglobinuria $\rightarrow$ renal obstruction (increased risk if also using fibric acid)
derivatives, niacin or drugs that inhibit P450 [Always monitor these patients by measuring CPK levels]

Contraindications:
- Hepatic disease, jaundice and cholestasis
- Renal insufficiency (myoglobin increased??)
- HIGHEST PREGNANCY RISK CATEGORY (CLASS X) → teratogenic
- Children and teenage

Indications:
- Hyperlipidemias & atherosclerosis
- Primary prevention of IHD
- Stroke prevention

**Bile acid-binding Resins**

**Cholestyramine**
- MOA: Resins bind negatively charges bile acids (*by exchanging chloride ions*) and salts in the ileum→ form an insoluble complex→ prevent there reabsorption→ Bile excretion is increased up to ten fold (leads to up regulation of hepatic LDL receptors)→ excretion of bile-resin complex in the feces
- Causes constipation
- *Only drug that can actually increase triglyceride levels*
- Up to 35% reduction in LDL
- Adverse effects: Constipation, steatorrhea, hyperchloremic acidosis, decreased absorption of other drugs

Contraindications:
• Cholelithiasis & biliary obstruction (secretion of bile already impaired)
• Severe hypertriglyceridemia (may increase it further)

**Indications:** (rarely used alone; use with statins)

- **Hyperlipidemias with isolated increases in LDL**
- Itching due to cholestasis
- Diarrhea with excess fecal bile acids
- Pseudomembranous colitis

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**Niacin (Nicotinic Acid, Vitamin B₃)**

- MOA: inhibition of VLDL production by the hepatocyte
- Up to 25% reduction of LDL
- **Up to 40% reduction of VLDL**
- **Up to 50% reduction of triglycerides**
- **Up to 30% increase in HDL**
- Reduction of fibrinogen levels
- Stimulation of prostaglandin production and histamine release
- Inhibits tubular secretion of uric acid
- Decreased glucose tolerance

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**Adverse effects:**

- Intense cutaneous flush [>90%]
- HEPATOTOXICITY→ dose dependant (STOP if ALT > than 3X)
- Hyperuricemia [>20%], Hyperglycemia
- Rhabdomyolysis (increased risk when given with statins)
- Peptic ulcer worsens→ due to histamine release
Contraindications: PUD, DM, Gout, Liver disease, bleeding, coagulopathy and surgery

Indications: Hyperlipidemias

**Fibric Acid Derivatives**  
*Gemfibrozil*

- MOA: Increased synthesis of lipoprotein lipase → chylomicrons and VLDL are hydrolyzed in the plasma → triglycerides are delivered to the adipocytes → decreased delivery of triglycerides to the liver → inhibition of VLDL production in liver
- **Up to 60% reduction of triglycerides**
- Up to 30% reduction of VLDL
- Up to 10% increase in HDL
- Bound in plasma, renally excreted (glucuronide conjugates)
- Adverse effects: Rhabdomyolysis (increased risk when given with statins), GI disturbance, gall stones

Contraindications: Gall bladder disease, hepatic disease & biliary cirrhosis

Indications:

- **Type III hyperlipoproteinemia (DOC)**
- **Hypertriglyceridemia**
- Best drug for pt. with elevated triglycerides and VLDL, and in those that are at risk of developing pancreatitis

**Inhibitors of Intestinal Sterol Absorption**  
*Ezetimibe*

- Inhibits the intestinal absorption of cholesterol
- Up to 20% reduction of LDL
- Orally administered, metabolism by glucoronidation
- Used for hyperlipidemias, *often with a statin*
# Antihypertensive Drugs

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- **Hypertensive crisis**: diastolic blood pressure > 120 mm Hg
  1. hypertensive emergency (with end-organ damage)
  2. hypertensive urgency (without end-organ damage)
- **Accelerated hypertension**: diastolic blood pressure > 130 mm Hg without end organ damage
- **Malignant hypertension**: accelerated hypertension with end-organ damage

- **Diuretics and ACE inhibitors** are the DOC in all stages of heart failure.
- Aortic dissection → treat with **Nitroprusside and Beta-blockers**
- Chronic diabetic glomerulopathy → DOC are **ACE inhibitors**
Diuretics
Hydrochlorothiazide, Indapamide, Furosemide, Spironolactone

- Initial hypotensive effects of diuretics is associated with a reduction of blood volume and cardiac output but after 6-8 weeks blood volume normalizes but PERIPHERAL VASCULAR RESISTANCE DECREASES (hence used as an antihypertensive)
- Gradual loss of Na⁺ → fall in ICF smooth muscle Na⁺ → fall in ICF muscle Ca²⁺ → vascular tone decreased
- Most effective drugs used to reduce B.P. in patients with normal renal function
  - Thiazide diuretics → good for females with osteoporosis
  - Effects: TPR reduced (later)

Centrally Acting Sympatholytic Drugs
Clonidine, Methyldopa

- Clonidine → alpha-2 receptor agonist located in Nucleus of Tractus Solitarius (+Alpha 2 → decrease cAMP → inhibition)
- Methyldopa → adrenergic neurons convert it into methyNE which acts just like clonidine
- These drugs cause decreased firing of the reticulospinal → decrease in central adrenergic tone
- **Clonidine is used in Smoking cessation programs**
- Effects: TPR decreased
- **Methy dopa is preferably used in pregnancy.** (M for mom)
- Both are 2nd choice drugs
- Toxicity:
  1. Sedation and drowsiness (20%)
  2. clonidine withdrawal can cause hypertensive crisis (receptors upregulated)
3. xerostomia and asialism

4. sexual dysfunction

Alpha-1 Blockers
Prazosin

- MOA: selective alpha-1 receptor blocker
- Effects:
  1. HR (unchanged or increased due to reflex tachycardia)
  2. venous tone and TPR decreased
  3. postural hypotension (prominent)
- 2nd choice in mild-moderate hypertension (often used in combination)
- used to treat BPH

Beta Blockers
Propranolol, Labetalol

- MOA: decrease in cardiac output (beta-1 block) and inhibition of renin release (beta-1 block of JG cells)
- Propranolol (and other beta blockers); decrease HR, decrease CO, TPR (early increase, later decrease)
- Labetolol (alpha-1,beta) (and other alpha-beta blockers); venous tone and TPR decreased, postural hypotension is evident.
- Highly effective drugs used in:
  1. young age
  2. hyperkinetic hypertension (i.e. with increase in CO, HR and NE/Epi)
  3. supraventricular arrhythmias
  4. exertional angina
  5. post MI
  6. hypertensive emergency
Vasodilators

Hydralazine, Minoxidil, Diazoxide, Fenoldopam → arterioles
Nitroprusside → arterioles and veins

Hydralazine:
- arteriolar vasodilator
- not used often due to tolerance
- adverse effects: Lupus-like syndrome (lupoid) can occur with high doses (also with procainamide), can cause myocardial ischemia (don’t use in IHD, CVA)
- used as a 2nd choice

Nitroprusside:
- MOA: Drug is metabolized by smooth muscle cells to NO → activation of cGMP → vasodilation
- Effects: CO decreased, HR increased, venous tone and TPR significantly reduced, renal blood flow is decreased
- RBC metabolize drug → release cyanide → metabolized to thiocyanate
- Adverse effects:
  1. accumulation of cyanide: metabolic acidosis, arrhythmias → death (prophylaxis: sodium thiosulphate, treatment: amyl nitrite)
  2. accumulation of thiocyanate: confusion, hyperreflexia, psychosis, convulsions
- Uses:
  1. Hypertensive emergencies
  2. Acute dissecting aortic aneurysm
  3. Heart failure
  4. Induce hypotension in surgery
Minoxidil:
- MOA: opens K+ channels in smooth muscles → membrane stabilizes → contraction less likely
- TPR decreased
- HR, CO and renal blood flow is increased
- 3rd or 4th choice drug → many side effects (H2O/Na+ retention, edema, reflex tachycardia, hypertrichosis)

Diazoxide:
- MOA: dilation of the arterioles (opens K+ channels in smooth muscles → membrane stabilizes → contraction less likely)
- Uses: Hypertensive emergencies and eclampsia
- Contraindicated in DIABETES
- Adverse effect: hyperglycemia (50%)

Dopamine (D1) Receptor Agonists
**Fenoldopam**
- MOA: stimulate D1 receptors → vasodilates the renal and mesenteric beds → decreases blood pressure
- Contraindications: Glaucoma, angina, portal hypertension
- Uses: Hypertensive emergencies

Calcium Channel Blockers
**Nifedipine, Verapamil, Diltiazem**
- All lower BP by blocking the calcium influx
- HR: increased by dihydropyridines, unchanged or decreased by verapamil and diltiazem
- TPR is reduced
- Adverse effect: Constipation
• 1\textsuperscript{st} choice drug in mild-moderate hypertension
• can be used in hypertensive emergency

\textbf{ACE-Inhibitors}
\textit{Captopril, Enalaprilat}

• inhibits ACE (peptidyl dipeptidase) and \textit{prevents A-I} \rightarrow \textit{A-II}
  and also \textit{prevents the inactivation of bradykinin}
• venous tone and TPR is decreased
• \textbf{Prodrug} must become activated in the liver, renally excreted
• \textbf{Adverse effects (not many)}
  1. first dose syncope and postural hypotension
  2. \textit{dry and disturbing cough (due to bradykinin)}
  3. URINARY SYSTEM: Renal insufficiency (if pt. with bilateral renal artery stenosis)
  4. \textcolor{red}{dysgeusia (loss of taste)}
  5. hyperkalemia

\textbf{Contraindications:}
  1. \textbf{PREGNANCY (Risk Factor D)}
  2. Bilateral renal artery stenosis
  3. severe aortic stenosis
  4. renal insufficiency
  5. hyperkalemic states
  6. CAD
  7. \textcolor{red}{Past history of angioedema.}

\textbf{Uses:}
  1. \textbf{1\textsuperscript{st} choice antihypertensive}
  2. hypertensive emergencies (enalaprilat)
  3. MI
4. CHF
5. hyperaldosteronism
6. **DOC for chronic diabetic glomerulopathy**

**Angiotensin II Receptor Antagonist**

**Losartan**

- **MOA:** blocks AT$_1$ receptors
- produces **vasodilation** and **blocks aldosterone secretion**
  (leads to increased water and salt excretion)

**Contraindications:**

1. PREGNANCY (Risk Factor D)
2. Bilateral renal artery stenosis
3. severe aortic stenosis

**Uses:** Hypertension
DRUGS CONTRAINDICATED IN PREGNANCY:

- WARFARIN
- ALL STATINS (LOVASTATIN, ATORVASTATIN)
- ACE INHIBITORS (CAPTOPRIL, ENALAPRILAT)
- AMIODARONE

HYPERTENSIVE EMERGENCY TREATMENT:

- NITROPRUSSIDE
- DIAZOXIDE
- LABETALOL
- ENALAPRILAT

EFFICACY OF TREATMENT:

HIGH ➔
NITROPRUSSIDE, DIAZOXIDE, LABETALOL, MINOXIDIL, FENOLDOPAM

INTERMEDIATE ➔ EVERYTHING ELSE

LOW ➔ DIURETICS
Antiarrhythmic Drugs

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<td>Flecainide-Ic</td>
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The duration of phase 2 and slope of phase 3 mainly influence the effective refractory period (refractoriness).

ECG & Membrane Potential of Ventricular Cell

- Phase 0: Fast Na⁺ influx
- Phase 1: Transient efflux of K⁺
- Phase 2: Influx of Ca²⁺ and Na⁺
- Phase 3: Efflux of K⁺ > influx of Ca²⁺ and Na⁺
- Phase 4: Na⁺ - K⁺ - pump

Steep phase 0 means rapid depolarisation.
Most antiarrhythmic drugs have high affinity for activated or inactivated channels but very low affinity for resting channels.

**Quinidine (Class Ia)**

- Oral bioavailability ~80%
- 80% metabolized in liver, 20% renally excreted

**MOA:**
1. Blockade of activated Na+ channels → slows the rapid upstroke of phase 0 → decreases conduction velocity
2. Blockade of activated K+ channels → decreases the slope of phase 4 → increases refractoriness
3. Antimuscarinic effect: acts on S.A and A.V. node → paradoxical tachycardia
4. Alpha blocking activity → vasodilator

**ECG effects:** PR (I or D), QRS duration (I) QT (I)

**Adverse effects:**
- Cardiovascular: arrhythmias, Polymorphic ventricular tachycardia (torsade de pointes) (Drugs that increase the QT interval can cause PVT), digitalis toxicity
- CNS: symptoms of cinchonism; blurred vision, tinnitus, headache, delirium and psychosis.
- GI: diarrhea

**QUINIDINE OVERDOSE IS TREATED BY SODIUM LACTATE**
(Because increases Na+ current & decreases drug-receptor binding by alkalinizing the tissue)

**Uses:**
**Arrhythmias:** Atrial flutter & fibrillation, Paroxysmal supraventricular tachycardia, Paroxysmal ventricular tachycardia, arrhythmias associated with WPW syndrome
**Procainamide (Class Ia)**

**MOA:** similar to Quinidine (class Ia)
- Oral bioavailability ~75%
- 25% hepatic transformation to NAPA → class III effect
- 75% renally excreted

**PROCAINAMIDE OVERDOSE IS TREATED BY SODIUM LACTATE**
(Because increases Na+ current & decreases drug-receptor binding by alkalinizing the tissue)

**Adverse effects:**
- Cardiovascular: arrhythmias, Polymorphic ventricular tachycardia (torsade de pointes) (Drugs that increase the QT interval can cause PVT), digitalis toxicity, hypotension
- CNS: dizziness, depression, hallucinations
- LUPOID SYNDROME (~30%)

**Uses:**
**Arrhythmias:** Paroxysmal supraventricular tachycardia, Paroxysmal ventricular tachycardia, arrhythmias associated with WPW syndrome

**Lidocaine (Class Ib)**
(Other Class Ib agents; Mexiletine, Phenytoin)

**DOC for emergency treatment of cardiac arrhythmias**

**Group Ib agents** rapidly dissociate and associate from Na+ channels → shorten phase 3 repolarization → **decrease the duration of the action potential** (normal cells)

**MOA:**
Blocks Na+ channels **(inactivated > activated)** (In damaged/ischemic cells → lots of Na+ channels are inactivated)
- **Lidocaine suppresses arrhythmias caused by abnormal automaticity and also prevents ventricular reentry**
  - Administered only IV (low oral bioavailability)
  - (in normal cells) decreased refractoriness, (depolarized cells) increased refractoriness

**Adverse effects:** *(LEAST CARDIOTOXIC DRUG)*
- CNS: dizziness, nausea, anxiety (therapeutic doses)
- CNS: nystagmus, blurred vision, slurred speech, ataxia, tremors, (high dose)

**Uses:**
1. **DOC emergency treatment of ventricular arrhythmias** (in ICU, post MI, post cardioversion or during open heart surgery)
2. **Digitalis-induced arrhythmias**
   [Ineffective in treating arrhythmias caused by WPW syndrome]

Mexiletine & Phenytoin are other class Ib drugs. **LIDOCAINE/PHENYTOIN CAN BE USED IN DIGITALIS-INDUCED ARRHYTHMIAS**

**Flecainide (Class Ic)**
MOA: blockade of Na+ channels→ suppresses the Phase 0 upstroke
- **Less used because it is very arrhythmogenic**

Used for life threatening supraventricular arrhythmias, when other drugs are poorly tolerated or ineffective
Beta-Blockers as Antiarrhythmics (Class II)
Metoprolol, Propranolol, Esmolol

MOA:
- block beta receptors
- decreased conduction (AV node)
- increased refractoriness

Uses:
1. **DOC for arrhythmias due to hyperthyroidism or pheochromocytoma**
2. AV nodal reentrant tachycardia, Atrial flutter or fibrillation

**Amiodarone** (Class I, II, III & IV)

- 100% metabolized in the liver
- **Half life ~25 days**
- Contains *iodine* and is related structurally to thyroxine

MOA:
1. Blockade of K+ channels
2. Blockade of inactivated Na+ channels (only)
3. Prolongation of the *action potential* duration and the *refractory period*
4. marked decrease in refactororiness
5. strong decrease in automaticity

ECG effects: PR interval (I, slightly), QRS (I), **QT interval (I, markedly)**

Effects:
Cardiovascular: **Vasodilation of coronary vascular bed** (due to alpha blocking and calcium channel blocking activity)
Adverse effects:
- hypotension
- constipation
- CNS: headache, insomnia, tremors, dizziness, ataxia
- Respiratory: Pneumonitis & Pulmonary fibrosis
- Hypothyroidism

Contraindications and Precautions:
- Congenital long QT syndrome
- Torsade de pointe
- Cardiogenic shock
- Pulmonary disease
- Iodine hypersensitivity
- PREGNANCY (Thyroid risk for the fetus)

**Indications:** Serious supraventricular or ventricular arrhythmias

**Ibutilide & Sotalol are other class III drugs.**

**Sotalol:**
- Non-selective beta blocker and also blocks K+ channels

**Ibutilide:**
- Blocks K+ channels also activates an inward Na+ current→ prolongation of action potential duration
Calcium channel blockers (Class IV)  
(Verapamil, Diltiazem)

- MOA: blockade of activated and inactivated calcium channels
- Decreased conduction in slow fibers, increased refractoriness
- PR interval increased, **QT interval (not changed)**
- More effective in treating atrial than ventricular dysrhythmia
- **Uses**: supraventricular tachycardia, atrial flutter and fibrillation
- **Contraindication**: Arrhythmias with the presence of WPW/long QT

**Adenosine**

- Activation of Ach-sensitive K+ channels $\rightarrow$ hyperpolarization of the SA and AV nodes $\rightarrow$ inhibition of cAMP-induced Ca++ influx
- **DOC FOR PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA**

**Magnesium**

Uses:
1. episodes of torsade de pointes
2. digitalis-induced arrhythmias

**Digitalis Glycosides**

**Cardiac parasympathetomimetic action**

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**Non-Genetic Causes of Prolonged QT interval:**

1. Diseases: hypothyroidism, hypokalemia, hypomagnesia
2. **Drugs: Class Ia/III antiarrhythmics**, TCAs, quinolones, Macrolide antibiotics, Neuroleptics