PHARMACOKINETICS AND PHARMACODYNAMICS: CARDIOVASCULAR APPLICATIONS

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I INTRODUCTION AND CORE DEFINITIONS

- **Pharmacokinetics (PK — "What the Body Does to the Drug"):** Quantitative characterization of the time course of drug **Absorption, Distribution, Metabolism (Biotransformation), and Excretion (ADME)**, governed by four primary mathematical parameters: **Bioavailability (F)**, **Volume of Distribution (Vd)**, **Clearance (CL)**, and **Elimination Half-Life (t1/2 = [0.693 x Vd] / CL)**.
- **Pharmacodynamics (PD — "What the Drug Does to the Body"):** The biochemical, cellular, and physiological effects of a drug at its molecular target (cardiac ion channels, G-protein-coupled receptors, enzymes, or transport pumps), characterized by **receptor affinity, potency (EC50), maximal efficacy (Emax), therapeutic index, and hysteresis**.

II PHARMACOKINETIC (PK) PRINCIPLES APPLIED TO CARDIOVASCULAR DRUGS

- **Absorption and Oral Bioavailability (F) — Loop Diuretics in Heart Failure:**
  - **Clinical Application: Oral Furosemide** has highly erratic and variable bioavailability (**10 to 90 percent**, mean ~50 percent), which is further impaired in acute decompensated right heart failure due to **splanchnic venous congestion and intestinal mucosal edema** (prolonging time to peak concentration without food). In contrast, **Torsemide** and **Bumetanide** possess predictable, rapid, high oral bioavailability (**80 to 90 percent**), making them superior for oral maintenance in congestive heart failure.
  - **Volume of Distribution (Vd = Dose / Plasma Concentration C0) and Loading Doses:**
  - **Amiodarone (Massive Vd): Amiodarone** is extremely lipophilic with a colossal apparent **Volume of Distribution (~60 L/kg, or 4,000 to 5,000 Liters in a 70-kg adult)** and an elimination half-life of **40 to 55 days** (up to 100 days for its active metabolite desethylamiodarone). Because it sequesters rapidly into deep peripheral compartments (adipose tissue, liver, lung, skeletal muscle), achieving therapeutic myocardial concentrations requires a **large cumulative loading dose of 8 to 10 grams** (e.g., 400 mg TID for 1–2 weeks, then 400 mg OD) before stepping down to 100 to 200 mg daily.
  - **Digoxin in Skeletal Muscle vs. Renal Failure: Digoxin** also has a large Vd (**5 to 7 L/kg**) because it binds extensively to **Na+/K+-ATPase in skeletal muscle**; in **elderly, sarcopenic, or severe CKD patients**, Vd is reduced by 30 to 50 percent, necessitating a **lower loading dose** (as well as a lower maintenance dose due to reduced renal clearance).
  - **Hepatic Biotransformation (First-Pass Metabolism, Prodrugs, and Active Metabolites):**
  - **High First-Pass Extraction:** Oral **Propranolol, Metoprolol, Verapamil, and Nitroglycerin** undergo extensive hepatic first-pass metabolism, which is why intravenous doses of Propranolol (1 to 5 mg) or Verapamil (5 to 10 mg) are an order of magnitude smaller than oral doses (40 to 160 mg).
  - **Prodrugs Requiring Bioactivation: Clopidogrel** (activated via **CYP2C19**; impaired in about half of Indians, who carry **2/*3* LoF alleles),** Prasugrel** (rapid esterase + single CYP step, unaffected by CYP2C19 polymorphisms), **Enalapril/Ramipril/Perindopril** (esterase hydrolysis to "-prilat"; only **Lisinopril** and **Captopril** are active parent ACE inhibitors), **Candesartan cilexetil** (prodrug), and **Losartan** (converted to its more potent active metabolite EXP-3174).
  - **Active Metabolites with Dissociated Kinetics: Procainamide** (Na+ channel blocker, Class IA) is acetylated via hepatic *NAT2* into **N-Acetylprocainamide (NAPA)**, an active metabolite that lacks Na+ channel activity and acts purely as a **Class III K+ channel (IKr) blocker**; in renal failure, NAPA accumulates and precipitates **Torsades de Pointes**.
  - **Renal vs. Hepatic Clearance (CL) — The DOAC Spectrum:**
  - **Renal Clearance Hierarchy Among DOACs: Dabigatran (~80 percent renal clearance)** > **Edoxaban (~50 percent renal)** > **Rivaroxaban (~33 percent unchanged renal)** > **Apixaban (~27 percent renal)**. Consequently, **Dabigatran is strictly contraindicated when CrCl is less than 30 mL/min**, whereas **Apixaban** has the lowest renal dependence and safest bleeding profile in advanced CKD.
  - **Ultra-Short Context-Sensitive Half-Life: Esmolol** (hydrolyzed by **red blood cell cytosol esterases**, t1/2 = **9 minutes**), **Clevidipine** (plasma esterases, t1/2 = **1 minute**), and **Adenosine** (endothelial/erythrocyte uptake and adenosine deaminase, t1/2 < **10 seconds**) allow rapid titratability unaffected by hepatic or renal failure.

Cardiovascular Drug	Key Pharmacokinetic (PK) Feature	Key Pharmacodynamic (PD) Feature	High-Yield Clinical Implication
Clopidogrel	Inactive **Prodrug**; 85% inactivated by CES1; 15% requires 2-step **CYP2C19** oxidation	**Irreversible** covalent binding to platelet **P2Y12** receptor for lifespan of platelet (7–10 d)	Slow onset (2–6 h); high resistance in *CYP2C192/3*; hold **5 days** before CABG
Ticagrelor	**Direct-acting** parent drug (+ active CYP3A4 metabolite AR-C124910XX)	**Reversible**, allosteric non-competitive **P2Y12** antagonist (+ ENT1 adenosine reuptake block)	Rapid onset (30 min); unaffected by *CYP2C19*; causes **adenosine-mediated dyspnea/ventricular pauses**; hold **3 days** before surgery
Amiodarone	Huge **Vd (~60 L/kg)**; **t1/2 = 40–55 days**; inhibits CYP2C9, CYP2D6, CYP3A4, and **P-gp**	Multichannel blocker (**Class III IKr/IKs + Class I INa + Class II beta + Class IV ICa-L**)	Requires **8–10 g loading dose**; low TdP risk despite QTc prolongation (reduces transmural dispersion)
Digoxin	Large skeletal muscle Vd; cleared unchanged by renal GFR + **P-gp** tubular secretion (t1/2 = 36–48 h)	Inhibits **Na+/K+-ATPase** -> raises intracellular Na+ -> reverses **NCX** -> raises SR Ca2+ + vagotonic effect	**Narrow therapeutic index (0.5–0.9 ng/mL in HF)**; **hypokalemia** allosterically increases Na+/K+-ATPase binding -> toxicity at normal levels
Loop Diuretics (Furosemide)	95%+ albumin bound; secreted into proximal tubule via **OAT1/OAT3**	Inhibits luminal **NKCC2** cotransporter in thick ascending limb of Loop of Henle	**Steep Sigmoidal ("Threshold & Ceiling") Dose-Response Curve**: doubling dose is required in HF/CKD to reach tubular threshold

III PHARMACODYNAMIC (PD) PRINCIPLES IN CARDIOLOGY

- **Potency vs. Maximal Efficacy & The Loop Diuretic "Threshold" Curve:**
  - **Potency vs. Efficacy: Bumetanide (1 mg) = Torsemide (20 mg) = Furosemide (40 mg oral / 20 mg IV)** differ in **potency** (milligram dose required), but all three loop diuretics share identical **maximal natriuretic efficacy (Emax: excreting up to 20 to 25 percent of filtered sodium)**—which is far superior to the maximal efficacy of **Thiazide diuretics** (Emax: 5 percent of filtered sodium).
  - **Steep Sigmoidal Dose-Response ("Threshold Effect"):** Loop diuretics act from the **luminal** side of the nephron and exhibit a steep logarithmic dose-response curve; in heart failure or CKD, reduced renal blood flow and organic acid competition shift this curve to the right—meaning **giving sub-threshold doses (e.g., 20 mg twice daily) produces zero diuresis**, whereas **doubling the single bolus dose** to exceed the tubular threshold achieves brisk natriuresis.
  - **Use-Dependence vs. Reverse Use-Dependence of Antiarrhythmic Ion Channel Blockers:**
  - **Use-Dependence (Fast Heart Rates): Class IC (Flecainide, Propafenone)** and **Class IA** sodium channel blockers bind preferentially to open/inactivated Na+ channels and dissociate slowly (**Flecainide** has the slowest unbinding kinetics); consequently, **QRS widening and proarrhythmia increase markedly during tachycardia (exercise or rapid atrial flutter)**.
  - **Reverse Use-Dependence (Slow Heart Rates): Class III IKr blockers (Sotalol, Dofetilide, Ibutilide)** prolong action potential duration and the **QT interval most markedly at slow heart rates (bradycardia or post-conversion pauses)**—which is why **Torsades de Pointes** classically initiates after a **"short-long-short" pause sequence**.
  - **Narrow Therapeutic Index and Electrolyte PD Modification (Digoxin):** In the **DIG Trial** post-hoc analysis, serum digoxin concentrations of **0.5 to 0.9 ng/mL** reduced HF hospitalizations, whereas levels **1.2 ng/mL or greater** increased mortality. Because **Extracellular Potassium (K+)** competes with Digoxin for the same binding site on the alpha-subunit of the sarcolemmal **Na+/K+-ATPase pump**, **hypokalemia** dramatically increases Digoxin binding and precipitates fatal toxicity (**bidirectional VT, paroxysmal atrial tachycardia with 2:1 AV block**) even when serum digoxin concentration is within the "normal" laboratory range.
  - **Receptor Desensitization, Down-Regulation, and Pharmacodynamic Tolerance:**
  - **Nitrate Tolerance:** Continuous 24-hour exposure to organic **Nitrates** depletes vascular sulfhydryl groups, inhibits **mitochondrial aldehyde dehydrogenase (ALDH-2)**, and generates superoxide (peroxynitrite) that uncouples eNOS, causing rapid **tachyphylaxis within 24 to 48 hours**; prevented by providing a mandatory **10-to-14-hour daily nitrate-free interval**.
  - **Beta-1 Receptor Up-Regulation in HFrEF:** Chronic sympathetic catecholamine bombardment in HFrEF activates **G-protein-coupled receptor kinase-2 (GRK2 / beta-ARK1)** and beta-arrestin, causing **selective down-regulation (by 50 to 60 percent) and uncoupling of myocardial Beta-1 receptors**; chronic **Beta-Blocker therapy** causes an initial transient negative inotropic dip followed over **3 to 6 months** by **Beta-1 receptor resensitization/up-regulation** and improved ejection fraction.

KEY REFERENCES

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