PHARMACOGENOMICS IN CARDIOLOGY: CURRENT STATUS & HIGH-YIELD GENES

Prepared by **Dr. Sidhartha Mullapudi**, DrNB (Cardiology), MD (General Medicine)
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I OVERVIEW AND GUIDELINE INTEGRATION (CPIC / ESC / ACC-AHA)

- **Core Principle:** Cardiovascular pharmacogenomics (PGx) examines how germline genetic variations alter drug-metabolizing enzymes (**CYP2C19, CYP2C9, CYP2D6**), influx/efflux membrane transporters (**SLCO1B1 / OATP1B1, ABCB1 / P-gp**), and pharmacodynamic targets (**VKORC1, RYR2/SCN5A**)—predicting therapeutic failure or life-threatening toxicity before drug administration.
- **Clinical Pharmacogenetics Implementation Consortium (CPIC) Actionability:** Four cardiovascular drug-gene pairs hold high-level CPIC or Dutch Pharmacogenetics Working Group (DPWG) guideline actionability: **Clopidogrel–*CYP2C19***, **Statins–*SLCO1B1 / ABCG2 / CYP2C9***, **Warfarin–*CYP2C9 / VKORC1 / CYP4F2***, and **Beta-Blockers / Antiarrhythmics–*CYP2D6***.

II CLOPIDOGREL AND THE CYP2C19 GENE (THE HIGHEST-YIELD CATH LAB INTERACTION)

- **Pharmacokinetic Mechanism: Clopidogrel** is an orally administered **inactive thienopyridine prodrug**. Approximately 85 percent of absorbed clopidogrel is hydrolyzed by hepatic carboxylesterase-1 (CES1) into an inactive carboxylic acid derivative; the remaining **15 percent undergoes mandatory two-step hepatic bioactivation predominantly via Cytochrome P450 2C19 (CYP2C19)** into the active thiol metabolite that irreversibly blocks the platelet **P2Y12** receptor.
- **Genetic Variants and Metabolizer Phenotypes:**
  - **Loss-of-Function (LoF) Alleles (*CYP2C19*2** [c.681G>A splicing defect] and *CYP2C19*3** [c.636G>A premature stop codon]):** Carrying **one LoF allele** (e.g., **1/*2*,** 1/*3*, or **2/*17*) defines an** Intermediate Metabolizer**; carrying** two LoF alleles** (e.g., **2/*2*,** 2/*3*, or **3/*3*) defines a** Poor Metabolizer**.
  - **Gain-of-Function Allele (*CYP2C19*17*): **Increases gene transcription (**Rapid [**1/*17*] or Ultrarapid [**17/*17*] Metabolizer**).
  - **Clinical Consequence (High On-Treatment Platelet Reactivity):** Intermediate and Poor Metabolizers Treated with standard Clopidogrel after PCI generate significantly lower active metabolite levels, resulting in inadequate platelet inhibition and a **2- to 3-fold increased risk of Stent Thrombosis, recurrent Myocardial Infarction, and ischemic stroke** (FDA Boxed Warning).
  - **Landmark Randomized Trials and CPIC 2022 / ESC Guideline Solution:**
  - **POPular Genetics Trial (*NEJM* 2019, STEMI undergoing Primary PCI):** Demonstrated that a **CYP2C19 genotype-guided de-escalation strategy** (giving Clopidogrel to *CYP2C19* normal metabolizers while giving **Ticagrelor or Prasugrel** to **2/*3* LoF carriers) was** non-inferior for net clinical adverse events and ischemic MACE** while **significantly reducing PLATO major or minor bleeding (9.8 percent vs. 12.5 percent; HR 0.78)** compared to universal Ticagrelor/Prasugrel.
  - **TAILOR-PCI Trial (*JAMA* 2020, ACS and Stable PCI):** In *CYP2C19* LoF carriers, genotype-guided escalation to Ticagrelor reduced 1-year composite ischemic events from 5.9 percent to 4.0 percent (HR 0.66; p = 0.056; missing the ambitious prespecified 50 percent RRR primary target at 12 months, but with a post hoc analysis showing a **79 percent reduction in ischemic events during the first 90 days post-PCI**).
  - **CPIC Mandate:** In patients with ACS or undergoing PCI who carry one or two *CYP2C19* LoF alleles (**2* or** 3*), **avoid Clopidogrel and prescribe Prasugrel or Ticagrelor** (neither of which requires CYP2C19 bioactivation).

III STATINS AND THE SLCO1B1 (OATP1B1) GENE (STATIN-ASSOCIATED MYOPATHY)

- **Pharmacokinetic Mechanism:** The ***SLCO1B1* gene** on chromosome 12p12 encodes the hepatic sinusoidal uptake transporter **Organic Anion Transporting Polypeptide 1B1 (OATP1B1)**, which transports hydrophilic and lipophilic statins from portal blood into hepatocytes.
- **The *SLCO1B1*5* (rs4149056, c.521T>C, p.Val174Ala) Variant:** Reduces OATP1B1 transporter function, impairing hepatic statin uptake and causing **marked systemic plasma accumulation of statin acid** (increasing **Simvastatin acid AUC by 221 percent** in homozygotes, with smaller increases for Atorvastatin, Pitavastatin, Rosuvastatin, and Pravastatin, and minimal effect on Fluvastatin).
- **Landmark Evidence (SEARCH Collaborative Group, *NEJM* 2008):** Identified that each copy of the *SLCO1B1* C allele increased the risk of myopathy on Simvastatin 80 mg by **4.5-fold per allele (and 16.9-fold in CC homozygotes)**.
- **CPIC 2022 Guideline Solution:** In patients with Decreased or Poor **SLCO1B1** transporter function, **avoid Simvastatin** (and limit high doses of Atorvastatin/Pitavastatin), switching instead to **Rosuvastatin (at lower starting doses, unless *ABCG2* variant is also present), Pravastatin, or Fluvastatin**, or adding non-statin therapies (**Ezetimibe, Bempedoic Acid, PCSK9 inhibitors**).

Drug Class	Primary Gene(s) & Protein	High-Risk Allele(s)	Clinical Consequence	CPIC / Guideline Actionable Solution
Clopidogrel	***CYP2C19*** (Hepatic bioactivation enzyme)	***2*, 3** (Loss-of-Function; carried by **about half of Indians**)	**Impaired prodrug activation -> Stent Thrombosis / MI**	Switch to **Ticagrelor** or **Prasugrel** (**POPular Genetics / TAILOR-PCI**)
Statins (Simvastatin > Atorvastatin)	***SLCO1B1*** (Hepatic **OATP1B1** uptake transporter)	***5* / 15** (c.521T>C; rs4149056)	**High systemic statin plasma levels -> Myopathy / Rhabdomyolysis (SEARCH)**	Avoid Simvastatin; use **Rosuvastatin, Pravastatin, or Fluvastatin** (or non-statins)
Warfarin	***CYP2C9*** (S-warfarin clearance) & ***VKORC1*** (target enzyme)	*CYP2C9* ***2*, 3** (updates **5, *6*, 8, *11*); *VKORC1*** -1639G>A**	**Delayed clearance + heightened sensitivity -> Supra-therapeutic INR & ICH (GIFT Trial)**	Use pharmacogenetic dosing algorithm (IWPC/Gage) to **reduce dose**, or **prefer a DOAC**
Beta-Blockers (Metoprolol)	***CYP2D6*** (Hepatic metabolism)	Homozygous gene deletions / non-functional alleles (PMs)	**3-to-5-fold plasma Metoprolol surge -> Severe Bradycardia / AV Block**	Reduce Metoprolol dose by 50–75% or switch to **Bisoprolol, Atenolol, or Nebivolol/Carvedilol**

IV WARFARIN AND THE CYP2C9, VKORC1, AND CYP4F2 GENES

- **Dual Pharmacokinetic and Pharmacodynamic Genetic Control:** Genetic variants together explain **40 to 50 percent of the inter-individual variability** in stable Warfarin dose requirements:

- ***CYP2C9* (Pharmacokinetic Clearance):** Metabolizes the biologically potent **S-enantiomer of Warfarin**. Loss-of-function variants (***CYP2C92** and** 3*** in European/South Asian populations; **5, *6,* 8, *11* in African ancestry) reduce S-warfarin clearance by 40 to 90 percent, causing prolonged half-life and high risk of over-anticoagulation and major bleeding.
- ***VKORC1* (Pharmacodynamic Target):** Encodes **Vitamin K Epoxide Reductase Complex Subunit 1**, the target enzyme inhibited by Warfarin. The promoter polymorphism ***VKORC1* -1639G>A** reduces hepatic *VKORC1* mRNA expression, making AA homozygotes **highly sensitive to Warfarin** (requiring ~50 percent lower maintenance doses).
- ***CYP4F2* ****(*3 allele, p.Val433Met): **Reduces hepatic vitamin K1 catabolism, increasing hepatic vitamin K stores and requiring a slightly** higher** Warfarin dose (+0.5 to 1 mg/day).
- **Clinical Trial Evidence (EU-PACT, COAG, and GIFT Trials) and Modern DOAC Practice:** While the **GIFT Trial** (*JAMA* 2017) proved that genotype-guided Warfarin initiation reduced the composite of major bleeding, INR >=4, venous thromboembolism, or death compared to clinical dosing, in contemporary clinical practice **DOACs (Apixaban, Rivaroxaban, Dabigatran, Edoxaban) are preferred (Class I)** in non-valvular AF and VTE, reserving Warfarin for mechanical prosthetic valves, rheumatic mitral stenosis, and antiphospholipid syndrome.

V BETA-BLOCKERS / ANTIARRHYTHMICS AND THE CYP2D6 AND NAT2 GENES

- **Metoprolol, Propafenone, and Flecainide (*CYP2D6*): Metoprolol** is the most **CYP2D6-dependent** beta-blocker (70 to 80 percent metabolized by CYP2D6; Carvedilol is metabolized by both CYP2D6 and CYP2C9). In **CYP2D6 Poor Metabolizers** (5 to 10 percent of Caucasians, 2 to 5 percent of Indians), standard Metoprolol doses produce a **3- to 5-fold increase in plasma concentrations**, causing profound sinus bradycardia, AV block, and hypotension; **Propafenone** also accumulates in CYP2D6 Poor Metabolizers, increasing its beta-blocking, proarrhythmic, and CNS adverse effects. **DPWG Guidance:** Reduce the Metoprolol dose or switch to a beta-blocker cleared independently of CYP2D6, such as **Bisoprolol** (balanced 50% renal / 50% CYP3A4), **Atenolol**, or **Nadolol**.
- **Hydralazine and Procainamide (*NAT2* Slow Acetylators):** Patients with slow **N-acetyltransferase 2 (*NAT2*)** genotypes experience higher parent drug levels and a markedly increased risk of **drug-induced systemic lupus erythematosus (anti-histone antibodies)**.

VI PRACTICAL CONSIDERATIONS IN THE INDIAN CLINICAL CONTEXT

- **High Prevalence of *CYP2C19* Loss-of-Function Alleles in Indians:** Population pharmacogenomic studies across India demonstrate that **about half of Indians (CYP2C19*2 allele frequency 30 to 40 percent) carry at least one* CYP2C19*2 (or** 3*) loss-of-function allele **(and 10 to 15 percent are homozygous*** 2/2* Poor Metabolizers)—significantly higher than the 25 to 30 percent prevalence in European populations. Consequently, **Ticagrelor or Prasugrel is preferred upfront (Class I)** over Clopidogrel in Indian ACS patients undergoing PCI, and point-of-care *CYP2C19* genotyping (or platelet function testing) is strongly advised before de-escalating to Clopidogrel in complex Left Main or bifurcation PCI.

KEY REFERENCES

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