PGx of Cardiovascular drugs

ANTIPLATELETS

CLOPIDOGREL

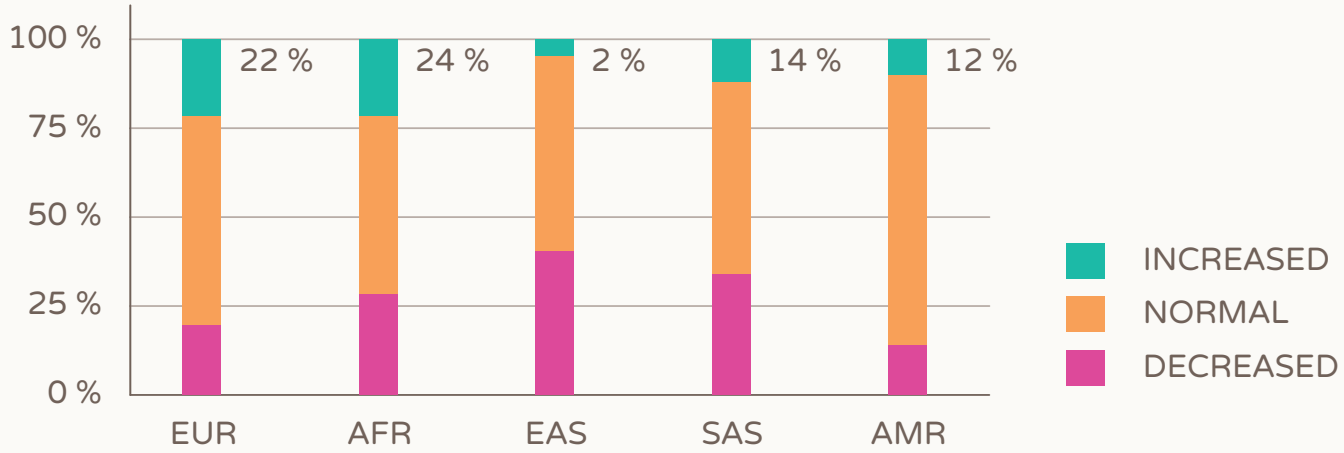
Clopidogrel and low-dose aspirin have become the mainstay oral antiplatelet regimen to prevent recurrent ischaemic events after acute coronary syndromes or stent placement.

Metabolism of clopidogrel

Clopidogrel, a pro-drug, requires biotransformation by Cytochrome P-450 (CYP) enzymes, mainly ***CYP2C19*** to the active irreversible inhibitor of the receptor involved in platelet aggregation. 15% of clopidogrel is metabolized in a 2-step process by ***CYP2C19*** to the active product while 85% is metabolized to an inactive product.

CYP2C19 is a polymorphic enzyme and the global activity map (Figure 1) highlights that 10-40% of population have reduced function of the enzyme while 2-24% percent have increased function.

Variability of CYP2C19 activity in major populations



EUR: Europeans, AFR: Africans, EAS: East Asians, SAS: South Asians, AMR: Admixed Americans

Adapted from: Y Zhou et al., *Clin Pharmacol Ther* (2017) 102:688-700

TRITON–TIMI 38 Clinical Trials

Clopidogrel-treated subjects with reduced-***CYP2C19*** function had:

- **53% relative increase in risk of death** from cardiovascular causes, MI, stroke,
- **Increase in risk of stent thrombosis** by a factor of 3, as compared with non-carriers[1].

Meta-analysis of clinical trials

Some meta-analysis assessing impacts of ***CYP2C19*** variation on risk of adverse clinical events conclude that the association is proven[2] while others conclude the opposite[3].

A review of 11 overlapping discordant meta-analyses inferred that conclusions differed due to between-study heterogeneity and bias being handled differently[4].

Overall, meta-analyses have consistently shown a larger effect of ***CYP2C19*** loss-of-function variations on Stent Thrombosis (ST) as compared with effect on clinical end point. ST is associated with higher risk of experiencing myocardial infarction (MI) and death, components of the composite clinical end point[4].

Recommendations by regulatory bodies and professional societies

The US FDA recommends alternative treatment to clopidogrel in patients identified as ***CYP2C19*** Poor Metabolizers. The CPIC and DPWG Guideline for clopidogrel recommend an alternative antiplatelet therapy (e.g., prasugrel, ticagrelor) for ***CYP2C19*** Poor or Intermediate Metabolizers, if no contraindications.

1. Mega JL et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med.* 2009;360(4):354-62
2. Mega JL et al. Reduced-function ***CYP2C19*** genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for ***PCI***: a meta-analysis. *JAMA* 2010;304(16):1821-30
3. Bauer T et al. Impact of ***CYP2C19*** variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. *BMJ* 2011;343:d4588.
4. Osnabrugge RL et al. A systematic review and critical assessment of 11 discordant meta-analyses on reduced-function ***CYP2C19*** genotype and risk of adverse clinical outcomes in clopidogrel users. *Genet Med.* 2015;17(1):3-1

Clinical implementation of PGx-guided antiplatelet therapy

Multicenter investigation assessed outcomes following clinical implementation of ***CYP2C19***-guided antiplatelet therapy after Percutaneous Coronary Intervention (PCI). Institutions recommended alternative antiplatelet therapy, either prasugrel or ticagrelor in 60% of patients with a loss-of-function ***CYP2C19*** variation[5].

Major adverse cardiovascular events like MI, stroke, or death, within 12 months of PCI was significantly higher in patients with a loss-of-function *CYP2C19* variation prescribed clopidogrel versus alternative therapy.

WARFARIN:

Warfarin, the most commonly prescribed anticoagulant, has a narrow therapeutic index. Excessive anticoagulant effect can result in hemorrhage whereas sub-therapeutic dosage can result in thrombotic complications.

Metabolism of warfarin

Warfarin is extensively metabolized by ***CYP2C9***, a polymorphic enzyme. The ***VKORC1*** gene codes for enzyme responsible for the vitamin K-dependent activation of clotting factors. Variations in ***CYP2C9*** and ***VKORC1*** gene explain 40-60% of the known variability in warfarin dose requirements.

ENGAGE AF-TIMI 48 clinical trial

This randomised, double-blinded trial confirmed the role of ***VKORC1*** and ***CYP2C9*** in warfarin response[6] and that 39% of the studied population needed dose adjustments. 36% of the studied population was ‘sensitive responders’ with a 2.4-4 mg warfarin dosage requirement while 3% were ‘highly sensitive responders’ with a 1-2 mg warfarin dosage requirement.

5. Cavallari LH et al. Multisite Investigation of Outcomes With Implementation of ***CYP2C19*** Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv.* 2018;11(2):181-191
6. Mega JL et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* 2015;385(9984):2280-7

Meta-analysis of PGx-guided and conventional dosing

A meta-analysis concluded:

Genotype-guided dosing significantly shortened the time to maintenance dose and significantly reduced the risk of adverse events but did not improve the time within the therapeutic range compared to conventional dosing[7].

Sensitivity of PGx test

Inadequate sensitivity of the PGx test undermined the US-based Clarification of Oral Anti-coagulation through Genetics (COAG) trial for warfarin dosing[8]. The PGx test included variations common in Caucasians, excluding variants important in African Americans leading to significant dosing error in this population with some specific variation carriers being significantly overdosed, sometimes by 2 mg/day or more[9]. Inclusion of ***CYP2C9*** variations with reduced activity that commonly occur in African-Americans (*5, *6, *8, *11), as well as analysis of the ***CYP4F2*** gene, improved the prediction of warfarin maintenance dose in the subsequent GIFT trials in the US[10].

7. Shi C et al. Pharmacogenetics-Based versus Conventional Dosing of Warfarin: A Meta-Analysis of Randomized Controlled Trials. *PLoS One* 2015;10(12):e0144511
8. Kimmel SE et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med.* 2013;369(24):2283-93.
9. Drozda K et al. Poor Warfarin Dose Prediction with Pharmacogenetic Algorithms that Exclude Genotypes Important for African Americans. *Pharmacogenet Genomics.* 2015; 25:73–81
10. Limdi NA et al. Race influences warfarin dose changes associated with genetic factors. *Blood* 2015;126(4):539-45

STATINS

Variations in ***SLCO1B1***, that codes for the transporter mediating hepatic uptake of statins, result in altered transport of statins. Clinical studies show that statin blood concentrations are higher in people with a specific variation in the ***SLCO1B1*** gene, increasing risk of statin-induced myopathy. The mechanisms by which statins cause myopathy remains unknown but appears to be related to statin concentrations in the blood.

SIMVASTATIN AND MYOPATHY

A study tracked the cumulative percentage of patients with myopathy during a six-year period since starting 80 mg dose of Simvastatin. Patients homozygous for a specific variation in the ***SLCO1B1*** gene had an 18% cumulative risk, with myopathy occurring primarily during the first year[11].

Recommendations

The CPIC guidelines states: *'If patients with a specific variation in the **SLCO1B1** gene (C variation at rs4149056) do not achieve optimal LDL cholesterol-lowering efficacy with a lower dose (e.g. 20 mg) of simvastatin, alternate statins such as atorvastatin, rosuvastatin, or pitavastatin should be considered.'*

PCSK9 inhibitors

Patients homozygous for the 'C' variation (rs4149056) in the ***SLCO1B1*** gene may not be able to tolerate even low doses of statins and require alternative treatment such as ***PCSK9*** inhibitors.

11. SEARCH Collaborative Group, ***SLCO1B1*** variants and statin-induced myopathy - a genomewide study. *N Engl J Med.* 2008;359(8):789-9

BETA-BLOCKERS

METOPROLOL

Metoprolol is mainly metabolized by ***CYP2D6*** and plasma concentration of metoprolol can range from sub-therapeutic in the ***CYP2D6*** Ultrarapid Metabolizer to supra-therapeutic and potentially toxic in ***CYP2D6*** Poor Metabolizer.

A meta-analysis of ***CYP2D6*** metabolizer phenotype and metoprolol pharmacokinetics demonstrated significant differences in: peak plasma concentration, AUC and elimination half-life between Ultrarapid and Poor ***CYP2D6*** Metabolizers[12].

Other beta-blockers with PGx information

Dosing guidelines are available from DPWG for ***CYP2D6*** Poor Metabolizers prescribed flecainide, while the drug label for carvedilol lists side effects for ***CYP2D6*** Poor Metabolizers.

IN CONCLUSION

Inclusion of PGx in medication management can enhance prescribing decisions and is becoming the standard of care for drugs with PGx guidelines.
For more information on Pillcheck, a PGx test optimized for the multi-ethnic Canadian population, please refer to www.pillcheck.ca website.

12. Blake CM et al. Meta-analysis of ***CYP2D6*** metabolizer phenotype and metoprolol pharmacokinetics. *Clin Pharmacol Ther.* 2013; 94(3): 394–399