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Pharmacodynamic comparison of prasugrel versus ticagrelor in patients with CYP2C19 loss-of-function genotype:

a validation study in patients with stable coronary artery disease

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Abstract

Therapeutic inhibition of platelet activation is essential for the management of ischemic cardiovascular disease. The use of platelet adenosine diphosphate (ADP) $P2Y_{12}$ receptor antagonists (clopidogrel, prasugrel, and ticagrelor) in addition to aspirin are associated with a decrease in cardiovascular events in high-risk coronary artery disease (CAD) patients. Clopidogrel is the most broadly utilized $P2Y_{12}$ receptor antagonist. However, among clopidogrel treated patients, there is broad variability in antiplatelet drug response which is known carry prognostic implications. Polymorphisms of the cytochrome P450 (CYP) 2C19 enzyme has been consistently shown to modulate clopidogrel response. Accordingly, the Food and Drug Administration (FDA) has issued a warning on the potential for reduced efficacy of clopidogrel among carriers of loss-of-function alleles (LOF) for CYP2C19 and suggest considering alternative antiplatelet therapies for these individuals.

The pharmacodynamic (PD) effects of prasugrel and ticagrelor are not affected by CYP2C19 genetic polymorphisms. However, to date there are no head-to-head PD comparisons between these agents among patients with different CYP2C19 genetic polymorphisms which is currently under investigation in CAD patients undergoing PCI at UF Health-Jacksonville (UFJ 2014-12, NCT 02065479). In order to rule out play of chance findings, pharmacogenetic investigations require external validation cohorts to support the study findings. Therefore, the present study is designed to serve as an external validation cohort conducted in patients with established CAD not undergoing PCI testing the non-inferiority in platelet reactivity of prasugrel versus ticagrelor among CYP2C19 LOF allele carriers.

Background and Significance

Therapeutic inhibition of platelet activation is essential for the management of ischemic cardiovascular disease [1,2]. In particular, the use of platelet adenosine diphosphate (ADP) $P2Y_{12}$ receptor antagonists (clopidogrel, prasugrel, and ticagrelor) in addition to aspirin are associated with a decrease in cardiovascular events in high-risk coronary artery disease (CAD) patients [3-5]. Clopidogrel is a second-generation thienopyridine and inhibits ADP-induced platelet activation [1]. Clopidogrel is an inactive form of pro-drug requiring a 2-step oxidation process by the hepatic cytochrome P450 (CYP) system to be in its active form. Clopidogrel is the most broadly utilized $P2Y_{12}$ receptor antagonist, including in patients with acute coronary syndromes (ACS) and/or undergoing percutaneous coronary interventions (PCI) [6-8]. However, among clopidogrel treated patients, there is broad variability in antiplatelet drug response and patients with poor clopidogrel response are at increased risk of thrombotic complications [9-11]. Inter-individual variability in clopidogrel response is a multi-factorial process, including clinical, cellular, and genetic factors [9-11]. Among the latter, polymorphisms of the CYP2C19 enzyme has been consistently shown to modulate clopidogrel response [12-17].

Various studies have demonstrated that carriers (heterozygotes and homozygotes) of loss-of-function (LOF) alleles have reduced clopidogrel metabolism leading to lower levels of its active metabolite and reduced platelet inhibition [12-17]. The most common LOF alleles include the CYP2C19*2 and CYP2C19*3 alleles which are found in approximately 15-40% of patients with a prevalence which may vary according to ethnicity (about 15 % in Caucasians and Africans, and range between 30% and 40% in Asians) [18-20]. Importantly, carriers of any LOF allele have an increased rate of cardiovascular adverse events, particularly in the setting of PCI

[12]. These observations have led the Food and Drug Administration (FDA) to issue a warning on the potential for reduced efficacy of clopidogrel among CYP2C19 LOF carriers and suggest considering alternative antiplatelet therapies for these individuals [21].

The new-generation ADP $P2Y_{12}$ receptor blockers, prasugrel and ticagrelor, have more potent, prompt, and predictable antiplatelet effects compared with clopidogrel, which translate into greater reduction of cardiovascular events in ACS patients albeit at the expense of a higher risk of bleeding [4,5]. Importantly, the pharmacodynamic (PD) effects of both drugs have not shown to be affected by CYP2C19 genetic polymorphisms [22-25]. Moreover, post-hoc analyses of two large, international trials have not shown any clinical interaction between CYP2C19 LOF polymorphisms and ticagrelor or prasugrel [26,27]. Although, PD investigations have shown equipoise between prasugrel and ticagrelor [28], to date there are no head-to-head PD comparisons between these agents among patients with CYP2C19 LOF alleles.

Tailoring antiplatelet therapy according to results of genetic testing has been limited in real world clinical practice of patients by having readily accessible results of individual's genetic makeup. Recently, a new rapid genotyping assay for the CYP2C19 LOF polymorphisms, SpartanRX (Spartan Bioscience, Ottawa, Canada), has been developed [29,30]. This technology is currently being testing in a prospective, randomized fashion the comparative PD effects of prasugrel vs. ticagrelor in CAD patients with CYP2C19 LOF alleles undergoing PCI at UF Health-Jacksonville (UFJ 2014-12, NCT 02065479). In order to rule out play of chance findings, pharmacogenetic investigations require external validation cohorts to support the study findings [13,31-33]. Therefore, in line with these recommendations, the present study is designed to serve as an external validation cohort to UFJ 2014-12 which is testing the non-inferiority in platelet

reactivity of prasugrel versus ticagrelor among CYP2C19 LOF allele carriers. This validation cohort will be composed of patients with established CAD not undergoing PCI.

Specific aim and study hypothesis

The primary aim of the present study is to compare the PD effects of prasugrel and ticagrelor in patients with established CAD (not in the setting of PCI) and CYP2C19 LOF alleles. This study will serve as an external validation cohort to UFJ 2014-12 which is currently ongoing and assessing the same objective in the context of patients undergoing PCI. In particular, this will allow for an external validation cohort composed of CAD patients without the confounding factors related to the PCI procedure itself, including peri-procedural intravenous antithrombotic therapy as well the prothrombotic milieu generated by the coronary intervention. The study hypothesis is the non-inferiority in platelet reactivity at 24 hours of prasugrel versus ticagrelor among CYP2C19 LOF allele carriers.

Research Design and Methods

Study Population

CYP2C19 genotyping is currently being performed in patients undergoing cardiac catheterization as part of an implementation program at UF Health Jacksonville. This program has allowed for the results of CYP2C19 genotyping to be available in our electronic medical records (i.e., EPIC) providing the opportunity to clinicians to consider this information to aid their decision making on the choice of antiplatelet therapy to be used. Therefore, patients meeting study entry criteria will be identified from EPIC. These patients will be contacted by

phone (see attached script for description of the phone call). Patients will also be identified during their routine clinic visits. Specific study inclusion and exclusion criteria are provided below.

• ***Inclusion criteria:***

1. Patients with CAD [defined as the presence of at least a 50% stenosis in a major epicardial vessel or major branch, or any prior coronary revascularization (PCI or coronary bypass graft surgery)] on treatment with either aspirin (81mg/day) or aspirin and clopidogrel (75m/day) for at least 30 days as per standard of care
2. Age 18-75 years
3. Participated in UFJ 2016-14 study with genetic buccal swab test and have at least one CYP 2C19 LOF allele (CYP2C19*2 and CYP2C19*3)

• ***Exclusion criteria:***

1. Known allergies to prasugrel or ticagrelor
2. Age >75 years
3. Weight <60kg
4. Considered at high risk for bleeding
5. Currently active bleeding
6. History of ischemic or hemorrhagic stroke or transient ischemic attack, or intracranial hemorrhage
7. Known severe hepatic dysfunction
8. On treatment with oral anticoagulant therapy (Vitamin K antagonists, dabigatran, apixaban, rivaroxaban)
9. Platelet count $<80x10^6$/mL
10. Hemoglobin <10 g/dL.
11. Creatinine Clearance <30 mL/minute
12. Patients with sick sinus syndrome (SSS) or high degree AV block without pacemaker protection.

13. Current treatment with drugs interfering with CYP3A4 metabolism (to avoid interaction with ticagrelor): CYP3A Inhibitors (ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, and telithromycin) and CYP3A Inducers (rifampin, phenytoin, carbamazepine, and phenobarbital)
14. Pregnant or breastfeeding females*

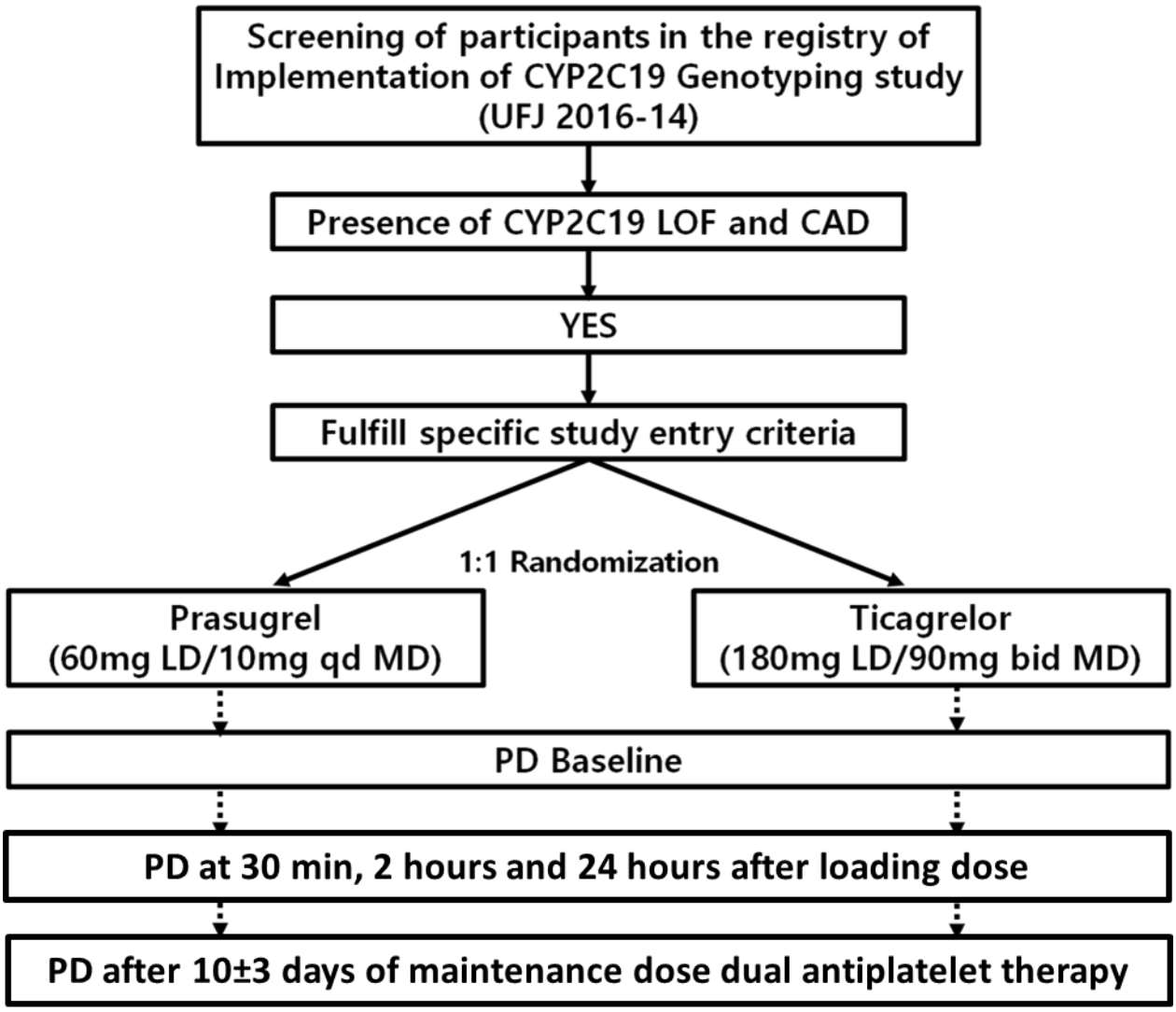
*Women of childbearing age must use reliable birth control (i.e. oral contraceptives) while participating in the study.

Lab results performed within the past 90 days will be considered valid for screening purposes. Individuals who do not have lab results during this time frame will require screening labs to verify that study entry criteria are met.

Research design

Patients must fulfill specific study entry criteria described above. Carriers of *2 or *3 LOF allele [homozygotes (*2/*2, *3/*3 or *2/*3) or heterozygotes (*1/*2, *1/*3, *2/*17, *3/*17)] will be eligible for randomization. Patients will be randomly (1:1) assigned to receive FDA approved doses of either prasugrel (60 mg loading dose - 10 mg/day maintenance dose) or ticagrelor (180 mg loading dose - 90 mg b.i.d maintenance dose). Maintenance dose will be maintained for 10±3 days. Prasugrel and ticagrelor will be provided to study participants. Patients will maintain aspirin during the conduct the study. Patients on clopidogrel will discontinue the drug 24 hours prior to randomization; patients will remain off clopidogrel for the duration of the study. Afterwards, patients will continue with the antiplatelet therapy recommended by the treating cardiologist. A follow-up call will be made 10±3 days after

conclusion of the study to confirm that patients have resumed their standard of care antiplatelet medication and to rule out any adverse effects. The study design is represented in the figure below.



Blood sampling

In patients meeting study entry criteria, blood sampling will be performed at 5 time points: a) baseline (prior to loading dose administration of antiplatelet therapy); b) 30 minutes after loading dose administration; c) 2 hours after loading dose administration; d) 24 hours after loading dose administration (before the morning dose of either prasugrel or ticagrelor, in order to measure trough levels of platelet inhibition); e) after 10±3 days of maintenance dose antiplatelet therapy (blood will be drawn before the morning dose of either prasugrel or ticagrelor).

Platelet Function Assay:

VerifyNow Point-of-care Testing: The VerifyNow System is a turbidometric based optical detection system which measures platelet induced aggregation as an increase in light transmittance (Accumetrics, San Diego, CA) and will be utilized according to manufacturer's instructions [34,35]. The assay is based on microbead agglutination and uses specific reagents for the pathways of interest. The instrument measures this change in optical signal and reports results in $P2Y_{12}$ Reaction Units (PRU). High on-treatment platelet reactivity (HPR) is defined by PRU >208 [36].

Study Endpoints and Determination of Sample Size:

The primary endpoint is the non-inferiority in platelet reactivity, measured as PRU, at 24 hours of prasugrel versus ticagrelor among LOF allele carriers. Under the assumption of 0 difference at 24 hours in mean PRU between ticagrelor and prasugrel and a common standard deviation of 50 PRU, a sample size of 22 patients per group allows for the 95% CI to stay within

± 45 PRU with a 90% power and alpha = 0.05. Considering the two arms of treatment and a possible drop out of 10-15%, we will randomize a total 50 patients to ensure that complete data will be available for analysis. Secondary endpoints include: differences in PRU between prasugrel and ticagrelor at 30 minutes, 2 hours, and 10±3 days, and rates of HPR at all study time points.

Statistical Analysis:

The PD population will include all patients with PD data and without a major protocol deviation thought to significantly affect PD profiles. All patients who received at least 1 dose of study drug will be included in the safety population. Erroneously treated patients (e.g., those randomized to 1 treatment, but actually given the other) will be accounted for on the basis of actual treatment received. All continuous variables will be expressed as mean values ± standard deviations. Categorical variables will be expressed as frequencies and percentages. The SPSS software (ver. 21.0 for Window; SPSS, Chicago, IL) will be used for all analyses. An independent Student's *t*-test or Wilcoxon rank-sum test will be used to compare continuous variables between groups. Comparisons between categorical variables will be performed using McNemar test or binomial exact test. Missing data will not be imputed. A p values less than 0.05 were considered statistically significant.

Possible Discomforts and Risk

The most important adverse effect associated with the use of prasugrel is bleeding [5]. The risk of non-surgical bleeding is 2.4%. The most common side effects of prasugrel were

blurred vision, dizziness, headache, nervousness. The most important adverse effect associated with the use of ticagrelor is also bleeding [4]. The risk of non-surgical bleeding is 2.8%. Also, the most common clinically side effects of ticagrelor were dyspnea (13.8%), headache (6.5%), cough (4.9%), dizziness (4.5%), and nausea (4.3%), principally. However, these rates are those reported after 1 year of treatment with events that accrue over time, while this study is limited to only 10±3 days of treatment thus reducing the risk of these events. All clinical events, if they were to occur, including myocardial infarctions both fatal and non-fatal, strokes, peripheral vascular disease, bypass surgery (coronary or peripheral vascular), repeated hospitalizations, and bleeding will be recorded. Clinical events will be evaluated by a local committee, comprised of 2 faculty members (2 cardiologists), not directly involved in the research. In the event of a report of a serious adverse event (major bleeding – defined as life-threatening: fatal, symptomatic intracranial hemorrhage, leading to a drop in hemoglobin of at least 5 g/dL, significant hypotension requiring intravenous inotropes, requiring surgical intervention, or requiring transfusion of 4 or more units of blood; non–life-threatening: substantially disabling, intraocular bleeding leading to vision loss, or requiring at least 2 units of blood; thrombocytopenia <50,000), the local committee will meet and antiplatelet treatment will be withdrawn.

Definition of Adverse Events

An adverse event is any unintended or undesirable experience that occurs during the course of the clinical investigation whether or not it is considered to be therapy related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the initiation of study treatment. Adverse events will be followed until resolution

while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study therapy will be followed until resolution or until the patient starts a new treatment regimen.

Serious Adverse Events (SAE): An adverse event occurring while on study and considered related (reasonable possibility that the study treatment caused the adverse experience) to the study treatment that results in any of the following outcomes:

- Death
- A life-threatening adverse experience.
- A persistent or significant disability, incapacity, or is a congenital anomaly, or birth defect.
- Requires inpatient hospitalization, or prolongation of existing hospitalization.

The definition of serious adverse event also includes 'important medical event'. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and/or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Possible benefits

The present investigation is aimed to evaluate the PD differences between ticagrelor and prasugrel in patients with stable CAD and CYP2C19 LOF alleles. Although, this study is not designed to evaluate differences in clinical outcomes, the results obtained from this study may prompt further large scale clinical investigation.

Potential Financial Risks

None

Potential Financial Benefits

None

Conflict of Interest

Dr. Angiolillo is a consultant for Eli-Lilly/Daiichi-Sanyo, the makers of prasugrel (Effient), and Astra Zeneca, the makers of ticagrelor (Brilinta).

REFERENCES

1. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. *Nature reviews. Cardiology*, 12(1), 30-47 (2015).
2. Franchi F, Rollini F, Angiolillo DJ. Antithrombotic therapy for patients with STEMI undergoing primary PCI. *Nature reviews. Cardiology*, (2017).
3. Yusuf S, Zhao F, Mehta SR *et al.* Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *The New England journal of medicine*, 345(7), 494-502 (2001).
4. Wallentin L, Becker RC, Budaj A *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine*, 361(11), 1045-1057 (2009).
5. Wiviott SD, Braunwald E, McCabe CH *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine*, 357(20), 2001-2015 (2007).
6. Levine GN, Bates ER, Blankenship JC *et al.* 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*, 124(23), e574-651 (2011).
7. Anderson JL, Adams CD, Antman EM *et al.* 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, 61(23), e179-347 (2013).
8. Levine GN, Bates ER, Bittl JA *et al.* 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation*, 134(10), e123-155 (2016).
9. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E *et al.* Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *Journal of the American College of Cardiology*, 49(14), 1505-1516 (2007).
10. Stone GW, Witzenbichler B, Weisz G *et al.* Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet*, 382(9892), 614-623 (2013).
11. Tantry US, Bonello L, Aradi D *et al.* Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *Journal of the American College of Cardiology*, 62(24), 2261-2273 (2013).
12. Mega JL, Simon T, Collet JP *et al.* Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *Jama*, 304(16), 1821-1830 (2010).
13. Shuldiner AR, O'Connell JR, Bliden KP *et al.* Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *Jama*, 302(8), 849-857 (2009).

14. Collet JP, Hulot JS, Pena A *et al.* Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet*, 373(9660), 309-317 (2009).
15. Simon T, Verstuyft C, Mary-Krause M *et al.* Genetic determinants of response to clopidogrel and cardiovascular events. *The New England journal of medicine*, 360(4), 363-375 (2009).
16. Mega JL, Close SL, Wiviott SD *et al.* Cytochrome p-450 polymorphisms and response to clopidogrel. *The New England journal of medicine*, 360(4), 354-362 (2009).
17. Simon T, Bhatt DL, Bergougnan L *et al.* Genetic polymorphisms and the impact of a higher clopidogrel dose regimen on active metabolite exposure and antiplatelet response in healthy subjects. *Clinical pharmacology and therapeutics*, 90(2), 287-295 (2011).
18. Scott SA, Sangkuhl K, Stein CM *et al.* Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clinical pharmacology and therapeutics*, 94(3), 317-323 (2013).
19. Man M, Farmen M, Dumaual C *et al.* Genetic variation in metabolizing enzyme and transporter genes: comprehensive assessment in 3 major East Asian subpopulations with comparison to Caucasians and Africans. *Journal of clinical pharmacology*, 50(8), 929-940 (2010).
20. Holmes DR, Jr., Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Journal of the American College of Cardiology*, 56(4), 321-341 (2010).
21. Society for Cardiovascular A, Interventions, Society of Thoracic S *et al.* ACCF/AHA Clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. *Circulation*, 122(5), 537-557 (2010).
22. Tantry US, Bliden KP, Wei C *et al.* First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel: the ONSET/OFFSET and RESPOND genotype studies. *Circulation. Cardiovascular genetics*, 3(6), 556-566 (2010).
23. Alexopoulos D, Dimitropoulos G, Davlouros P *et al.* Prasugrel overcomes high on-clopidogrel platelet reactivity post-stenting more effectively than high-dose (150-mg) clopidogrel: the importance of CYP2C19*2 genotyping. *JACC. Cardiovascular interventions*, 4(4), 403-410 (2011).
24. Kelly RP, Close SL, Farid NA *et al.* Pharmacokinetics and pharmacodynamics following maintenance doses of prasugrel and clopidogrel in Chinese carriers of CYP2C19 variants. *Br J Clin Pharmacol*, 73(1), 93-105 (2012).
25. Brandt JT, Close SL, Iturria SJ *et al.* Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *Journal of thrombosis and haemostasis : JTH*, 5(12), 2429-2436 (2007).
26. Mega JL, Close SL, Wiviott SD *et al.* Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet*, 376(9749), 1312-1319 (2010).
27. Wallentin L, James S, Storey RF *et al.* Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet*, 376(9749), 1320-1328 (2010).
28. Rollini F, Franchi F, Cho JR *et al.* A head-to-head pharmacodynamic comparison of prasugrel vs. ticagrelor after switching from clopidogrel in patients with coronary artery disease: results of a prospective randomized study. *European heart journal*, 37(35), 2722-2730 (2016).

29. Roberts JD, Wells GA, Le May MR *et al.* Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet*, 379(9827), 1705-1711 (2012).
30. So DY, Wells GA, McPherson R *et al.* A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with ST-elevation myocardial infarction: the RAPID STEMI study. *Pharmacogenomics J*, 16(1), 71-78 (2016).
31. Angiolillo DJ, Bernardo E, Zanoni M *et al.* Impact of insulin receptor substrate-1 genotypes on platelet reactivity and cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. *Journal of the American College of Cardiology*, 58(1), 30-39 (2011).
32. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E *et al.* Contribution of gene sequence variations of the hepatic cytochrome P450 3A4 enzyme to variability in individual responsiveness to clopidogrel. *Arterioscler Thromb Vasc Biol*, 26(8), 1895-1900 (2006).
33. International Warfarin Pharmacogenetics C, Klein TE, Altman RB *et al.* Estimation of the warfarin dose with clinical and pharmacogenetic data. *The New England journal of medicine*, 360(8), 753-764 (2009).
34. Price MJ, Berger PB, Teirstein PS *et al.* Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *Jama*, 305(11), 1097-1105 (2011).
35. Collet JP, Cuisset T, Range G *et al.* Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *The New England journal of medicine*, 367(22), 2100-2109 (2012).
36. Bonello L, Tantry US, Marcucci R *et al.* Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *Journal of the American College of Cardiology*, 56(12), 919-933 (2010).