Clinical and genetic predictors of anti-platelet therapy selection in coronary artery disease patients undergoing percutaneous coronary intervention

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INTRODUCTION

- Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the standard of care in patients undergoing percutaneous coronary intervention (PCI) with stent placement
- The most widely prescribed P2Y12 inhibitor, clopidogrel, is a prodrug, that requires hepatic bioactivation to its active metabolite via CYP2C19
- Approximately one-third of patients in the U.S. carry loss-of-function (LOF) *CYP2C19* alleles, classified as intermediate or poor metabolizers (IM/PM), and may be at increased risk of major adverse cardiovascular events (MACE) when when compared to those without LOF alleles, classified as ultra-rapid or extensive metabolizers (UM/EM)
- There is no consensus on whether CYP2C19 genotyping should be routinely incorporated into practice
- In July 1012, UNC implemented an algorithm that considers clinical and CYP2C19 genetic information to guide P2Y12 inhibitor selection in high risk patients undergoing PCI

OBJECTIVES

- Evaluate use of the CYP2C19 genotype-guided algorithm in clinical practice
- Identify the key factors significantly associated with P2Y12 inhibitor selection in patients undergoing PCI

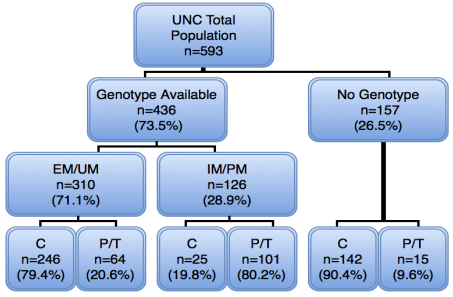
METHODS & ANALYSIS

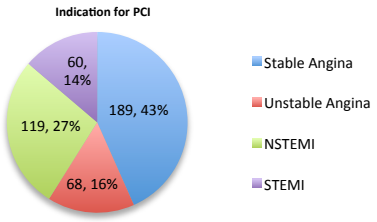
Study design: Retrospective cohort study
Study site: University of North Carolina Hospitals
Subjects: Patients undergoing PCI at UNC between 07/01/2012 and 06/30/2013 that underwent coronary artery stent placement and CYP2C19 genotyping were included (n=436)
Data: Demographic and clinical information were extracted through their EPIC electronic health records (EHR)
Genotyping: *CYP2C19* genotyping (**2, *3,* and **17* alleles) was performed by the McLendon Molecular Genetics Laboratory at UNC Hospitals (turnaround: 24-48 hours) and categorized based on genotype:

- Ultrarapid (UM): **17/*17*
- Rapid (RM): **1/*17*
- Extensive (EM): **1/*1*
- Intermediate (IM): **1/*2, *1/*3, *2/*17, *3/*17*
- Poor (PM): **2/*2, *2/*3, *3/*3*

Analysis: Descriptive statistics and CYP2C19 genotype were compared across final maintenance drug selection (clopidogrel vs prasugrel/ticagrelor) using Student's t-test, χ^2 test, and Fisher's exact test as appropriate with SAS-JMP Version 12.0 (Cary, NC). Associations and odds ratios were calculated at the 95% confidence interval using logistic regression models. *P* values <0.05 were deemed significant.

PATIENT POPULATION (N = 436)





Demographics	
Age	62 ± 12
Male	282 (65%)
African American	84 (93%)
Comorbidities	
Obese (BMI ≥30)	172 (39%)
Current/recent smoker	128 (29%)
Hypertension	347 (80%)
Diabetes	164 (38%)
CAD History	
Previous MI	95 (22%)
Prior revascularization	207 (47%)
Clopidogrel on admission	84 (19%)
Prasugrel/ticagrelor on admission	15 (3%)

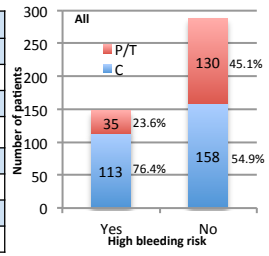
Predictors of bleeding	
High risk for bleeding[1]	148 (34%)
Prasugrel contraindication	103 (24%)
Age ≥75 years	73 (17%)
Weight <60 kg	33 (7%)
Previous TIA or CVA	26 (6%)
Previous significant bleed	34 (8%)
Current ESRD	19 (4%)
Anticoagulant at discharge	23 (5%)

[1] High risk for bleeding defined as : age ≥75, weight <60kg, previous CVA/TIA, previous bleed, current ESRD OR anticoagulant prescribed at discharge

PREDICTORS OF P2Y12 INHIBITOR SELECTION

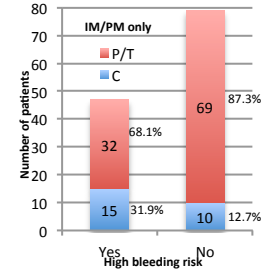
Predictors of prasugrel/ticagrelor selection – all genotyped patients (n=436)

Predictors of drug selection	Clopidogrel (n=271)	Prasugrel/Ticagrelor (n=165)	Odds ratio (95% CI)
LOF carrier	25 (9.2%)	101 (61.2%)	15.5 (9.40-26.50)
Acute MI	97 (35.8%)	82 (50.0%)	1.77 (1.20-2.63)
Clopidogrel on admission	68 (25.1%)	16 (9.7%)	0.32 (0.17-0.56)
Age ≥75	56 (20.7%)	17 (10.3%)	0.44 (0.24-0.77)
Weight <60 kg	28 (10.3%)	5 (3.0%)	0.27 (0.09-0.66)
Previous TIA or CVA	22 (8.1%)	4 (2.4%)	0.28 (0.08-0.75)
Current ESRD	16 (5.9%)	3 (1.8%)	0.30 (0.07-0.90)



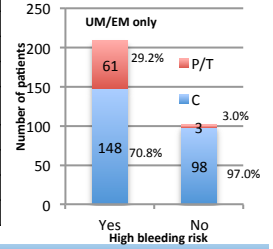
Predictors of prasugrel/ticagrelor selection – IM/PM only

Predictors of drug selection	Clopidogrel n=25	Prasugrel/Ticagrelor n=101	Odds ratio (95% CI)
LOF carrier	25 (19.8%)	101 (80.2%)	N/A
Acute MI	9 (36.0%)	47 (46.5%)	1.55 (0.64-3.96)
Clopidogrel on admission	7 (28.0%)	12 (11.9%)	0.35 (0.12-1.04)
Age ≥75	5 (20.0%)	16 (15.8%)	0.75 (0.26-2.52)
Weight <60 kg	2 (8.0%)	5 (5.0%)	0.60 (0.12-4.36)
Previous TIA or CVA	4 (16.0%)	3 (3.0%)	0.16 (0.03-0.78)
Current ESRD	2 (8.0%)	3 (3.0%)	0.35 (0.06-2.79)



Predictors of prasugrel/ticagrelor selection – EM/UM only (n=310)

Predictors of drug selection	Clopidogrel (n=246)	Prasugrel/Ticagrelor (n=64)	Odds ratio (95% CI)
LOF carrier	0 (0.0%)	0 (0.0%)	N/A
Acute MI	88 (35.8%)	35 (54.7%)	2.17 (1.24-3.80)
Clopidogrel on admission	61 (24.8%)	4 (6.3%)	0.20 (0.06-0.52)
Age ≥75	51 (20.7%)	1 (1.6%)	0.06 (0.00-0.29)
Weight <60 kg	26 (10.6%)	0 (0.0%)	<0.01
Previous TIA or CVA	18 (7.3%)	1 (1.6%)	0.20 (0.01-1.00)
Current ESRD	14 (5.7%)	0 (0.0%)	<0.01



CONCLUSIONS & LIMITATIONS

- Our study suggests the potential utility of genotype-guided selection of P2Y12 therapy among high-risk patients in a clinical setting:
  - Genotype-guided selection of P2Y12 inhibitor is feasible in clinical practice
  - Maintenance P2Y12 selection was influenced by both clinical factors and *CYP2C19* genotype.
  - CYP2C19 genotype is the strongest predictor of P2Y12 inhibitor selection following PCI
  - Acute myocardial infarction, prior clopidogrel use, and clinical predictors of high bleeding risk are also independently associated with drug selection
- Observational studies evaluating the relationship between CYP2C19 genotype, and P2Y12 inhibitor use, and clinical outcomes will need to account for clinical factors that influence anti-platelet agent selection

None of the investigators involved in this study have any financial or non-financial relationships to disclose