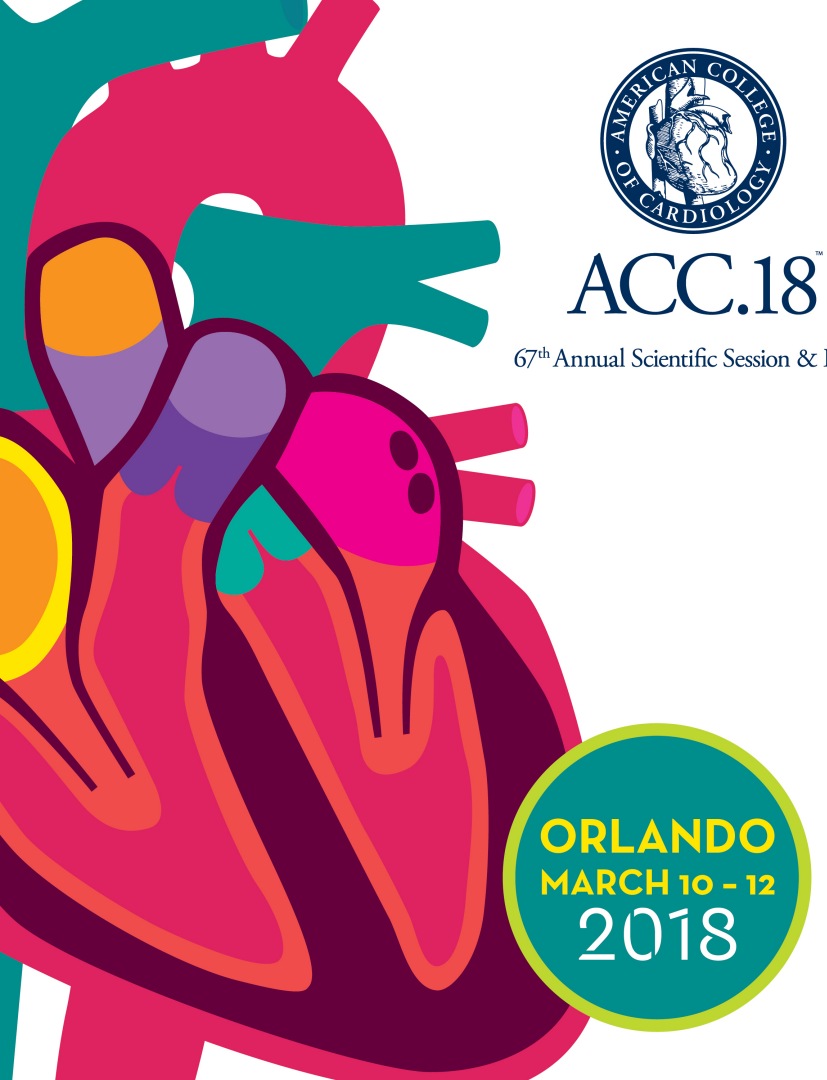

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A PRAGMATIC RANDOMIZED TRIAL OF *CYP2C19* GENOTYPING IMPLEMENTATION FOLLOWING PERCUTANEOUS CORONARY INTERVENTION (PCI)

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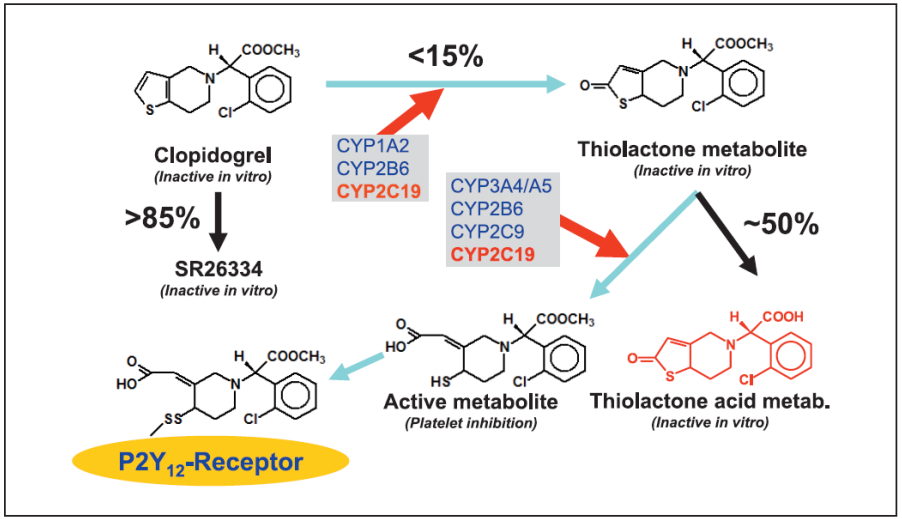
CYP2C19 polymorphisms and clopidogrel response

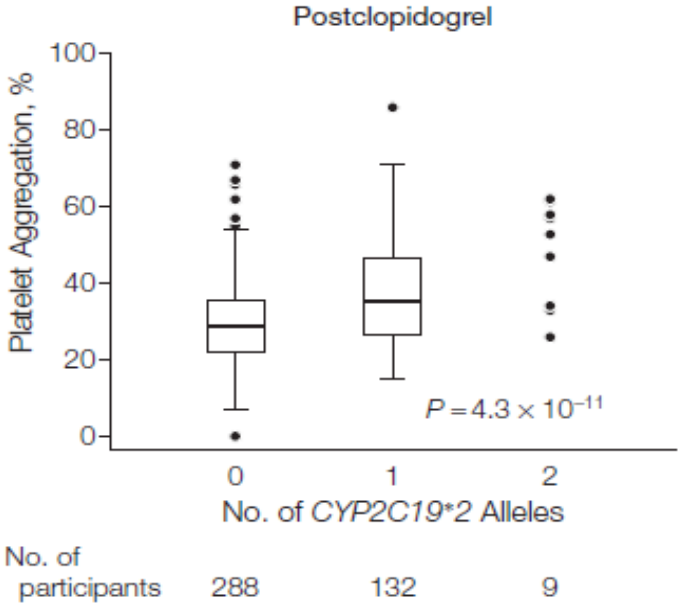


	CYP2C19*2 **Minor allele Frequency**
Europeans	0.15
African	0.15
East Asian	0.29
South Asian	0.35

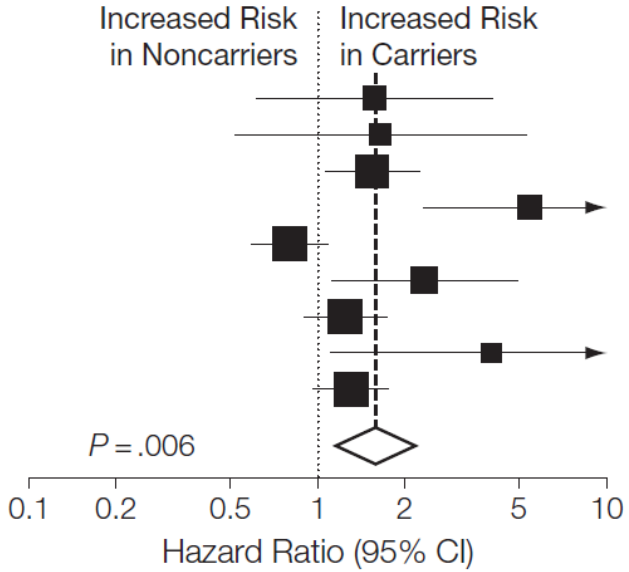
Trenk D et al. Thromb Haemost 2013

Scott et al. Clin Pharm Ther 2013

CYP2C19 polymorphisms and clopidogrel response



Shuldiner AR et al. JAMA 2009



Mega JL et al. JAMA 2010

Conflicting recommendations exist for *CYP2C19* testing

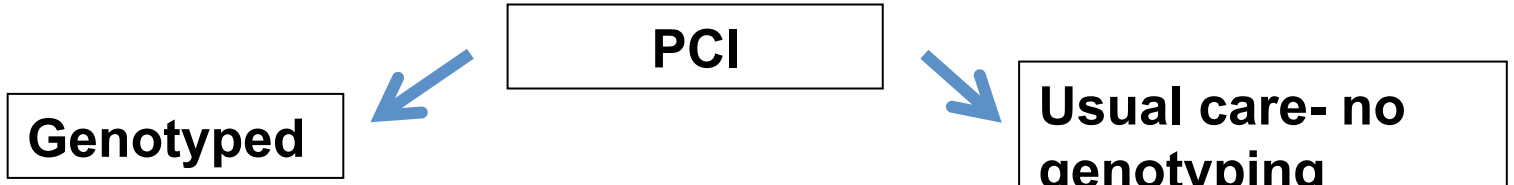
- **Clinical Pharmacogenetics guidelines recommend prasugrel or ticagrelor in *CYP2C19* LOF carriers. [1]**
- **FDA placed a "black box" warning on the clopidogrel label in 2010 recommending alternative agents among carriers of 2 LOF alleles. [2]**
- **ACC/AHA guidelines do not recommend routine *CYP2C19* genetic testing. [3]**

[1] Scott SA et al. Clinical Pharmacology and Therapeutics 2013
[2] https://www.fda.gov/Drugs/DrugSafety/default.htm
[3] Levine GN et al. Circulation 2016

Assessment of prospective *CYP2C19* genotype guided Dosing of AntiPlatelet Therapy in Percutaneous Coronary Intervention (ADAPT)

- **Rationale**
  - **It is unknown how physicians will utilize the *CYP2C19* test results in a real world setting**
- **Objective**
  - **To provide evidence regarding the implementation and effectiveness of *CYP2C19* testing**
- **Hypothesis**
  - **Pharmacogenetic test results will influence prescribing of antiplatelet medications post PCI**

The ADAPT study: *A Pragmatic Randomized Clinical Trial*



Primary endpoint
Proportion of participants receiving prasugrel/ticagrelor

Secondary endpoints

1. Agreement with the genotype guided antiplatelet recommendations
2. Clinical Outcomes: Major Adverse Cardiac Events and Major Bleeding

Study Intervention

- Genotyped Group
  - **Buccal swab for genotyping on the SpartanRx rapid turnaround device (*CYP2C19* *2, *3, *17)**
  - **Genotyped guided recommendations provided verbally**
    - ***CYP2C19* *2 or *3 carriers→ prasugrel or ticagrelor**
    - ***CYP2C19* *1 or *17 carriers → clopidogrel**
  - **Antiplatelet choice remained at the discretion of the treating interventional cardiologist**
- Usual Care
  - **Saliva collected for post study genetic analysis**

Inclusion/Exclusion Criteria

- Inclusion
  - Age ≥ 18 and ≤ 80 years
  - PCI with stent implantation
- Exclusion
  - Need for imminent surgery
  - History of intracranial hemorrhage, stroke
  - Active bleeding
  - Need for long-term anticoagulation
  - Study staff unavailable to conduct randomization or genotyping

Sample size determination

- Rate of pre-study prasugrel/ticagrelor use (~20%)
- Anticipated increase in prasugrel/ticagrelor prescribing based on frequency of *CYP2C19* LOF alleles (~30-35%)
- A sample size of 138 per group would provide 80% power at an alpha=0.05 to detect a 15% difference in prasugrel/ticagrelor prescribing between the groups
- Sample size was increased to 250 per group to allow for subgroup comparisons

Participant Demographics

	Genotyped N=249	Usual Care N=255	P-value
Sex, n(%) Male	 181 (73%)	 190 (74%)	 0.76
Race, n (%) White Black	 194 (78%) 48 (19%)	 197 (77%) 51 (20%)	 0.99
Age	63.0 ± 9.7	62.9 ± 10.2	0.90
ACS	124 (50%)	129 (50%)	0.93

Participant History

	Genotyped N=249	Usual Care N=255	P-value
Medical History, n(%)			
Hypertension	190 (76)	199 (78)	0.67
Cholesterol	112 (45)	113 (44)	0.80
PCI	83 (33)	83 (33)	0.63
Diabetes	89 (35)	79 (31)	0.26
MI	63 (25)	67 (26)	0.84
CABG	32 (13)	36 (14)	0.70
P2Y12 prior, n (%)			
Clopidogrel	80 (32)	85 (33)	0.65
Prasugrel	12 (5)	9 (4)	
Ticagrelor	2 (1)	6 (2)	
None	154 (62)	154 (60)	

Procedure Characteristics

	Genotyped N=249	Usual Care N=255	p-value
Length of stay, mean (SD), days	2.9 ± 3.7	3.1 ± 4.0	0.66
Drug eluting stents, n(%)	237 (95)	236 (93)	0.27
Number of stents, mean (SD)	1.3 ± 0.6	1.4 ± 0.6	0.73

CYP2C19 Genotypes for Intervention Group

Genotyping results available 1.4 ± 0.4 hours post swab

Genotype	Frequency
*1/*1	34%
*1/*17	31%
*17/*17	5%
***1/*2**	**20%**
***2/*17**	**5%**
***2/*2**	**3%**
Inconclusive	4%

28%

Primary Outcome: Antiplatelet Drugs Prescribed

	Genotyped N=249	Usual Care N=255	P-value
Clopidogrel	174 (70%)	201 (79%)	0.03
Prasugrel or Ticagrelor	**75 (30%)**	**54 (21%)**	

Fisher's exact test

Prasugrel/ ticagrelor use greater in the LOF carriers

	Genotyped		Usual Care
	No-LOF N=174	LOF carriers n=68	N=255
Clopidogrel	136 (78%)	32 (47%)	201 (79%)
Prasugrel or Ticagrelor	38 (22%)	36 (53%)	54 (21%)

P<0.001

P<0.001

$$\text{Agreement rate} = \frac{\text{LOF prasugrel/ticagrelor + non-LOF clopidogrel}}{\text{total number genotyped}}$$

Agreement with genotype guided recommendations

CYP2C19 diplotype	Phenotype	Clop	Pras/ Ticag	Non-agreement reasons
*1/*2 *2/*17 *2/*2	Intermediate or poor metabolizer (n=68)	**32 (47%)**	36 (53%)	9- Stable CAD 6- Cost 3- Contraindications 3- MD preference
*1/*1 *1/*17 *17/*17	Normal or rapid metabolizer (n=174)	136 (78%)	**38 (22%)**	6- Disease characteristics 6- Patient already on therapy 5- ACS 5- Recurrent events

Agreement rate 71%

Non-agreement rate 29%

Prior antiplatelet therapy predicted antiplatelet drug choice independent of genotype

Prior P2Y12	OR remaining on same	95%CI	P-value
Clopidogrel	2.04	1.22, 3.45	0.007
Prasugrel/ ticagrelor	99.3	13.2, 744	<0.0001

Genotype did not influence prescribing among patient already on prasugrel or ticagrelor

Prior P2Y12	Genotype agreement rate
Clopidogrel (n=80)	76%
Prasugrel/ticagrelor (n=14)	21%
None (n=147)	73%
P-value	<0.0001

Clinical outcomes

	Genotyped (n=249)	Usual Care (n=255)	P-value
Follow-up time (months)	17.2 (7.5)	16.1 (8.2)	0.14
MACE	34 (13.7)	26 (10.2)	0.27
BARC 3 or 5 bleed	6 (2.4)	8 (3.1)	1.0

MACE= myocardial infarction, stroke, death from cardiovascular cause, stent thrombosis, urgent revascularization

BARC= Bleeding Academic Research Consortium

Summary

- *CYP2C19* test results significantly influenced antiplatelet prescribing
- Genotype guided recommendations were followed 71% of the time
- Prior antiplatelet therapy significantly influenced the choice of antiplatelet drugs

Conclusions

- Antiplatelet prescribing was not universally in agreement with genotype suggested recommendations
- Physicians consider both clinical and genetic factors when prescribing antiplatelet agents following PCI

Post-hoc analysis

	Non-LOF (n=326)	LOF-clop (n=90)	LOF-pras/ticag (n=52)
MACE	33 (10.1)	14 (15.6)	9 (17.3)
Major bleed	6 (1.8)	4 (4.4)	1(1.9)
Non cardiac death	5 (1.5)	1 (1.1)	0 (0)
Composite	42 (12.9)	19 (21.1)	10 (19.2)

HR 1.84
95% CI 1.06 to 3.20
(p=0.03)

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