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Clopidogrel Pharmacogenetics
Can We Impact Clinical Practice?

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Disclosure

Relevant financial relationship(s) with industry

None

Off-label usage

Ticagrelor

Objectives

- Clopidogrel-*CYP2C19* as a drug-gene pair
- Review *CYP2C19* genetic variation
- *CYP2C19* genetic variation and its impact on clopidogrel PK, PD and clinical outcomes
- Why haven't we had an impact on clinical practice?
- TAILOR-PCI
  - Design
  - Pilot Study
  - Impact

Importance

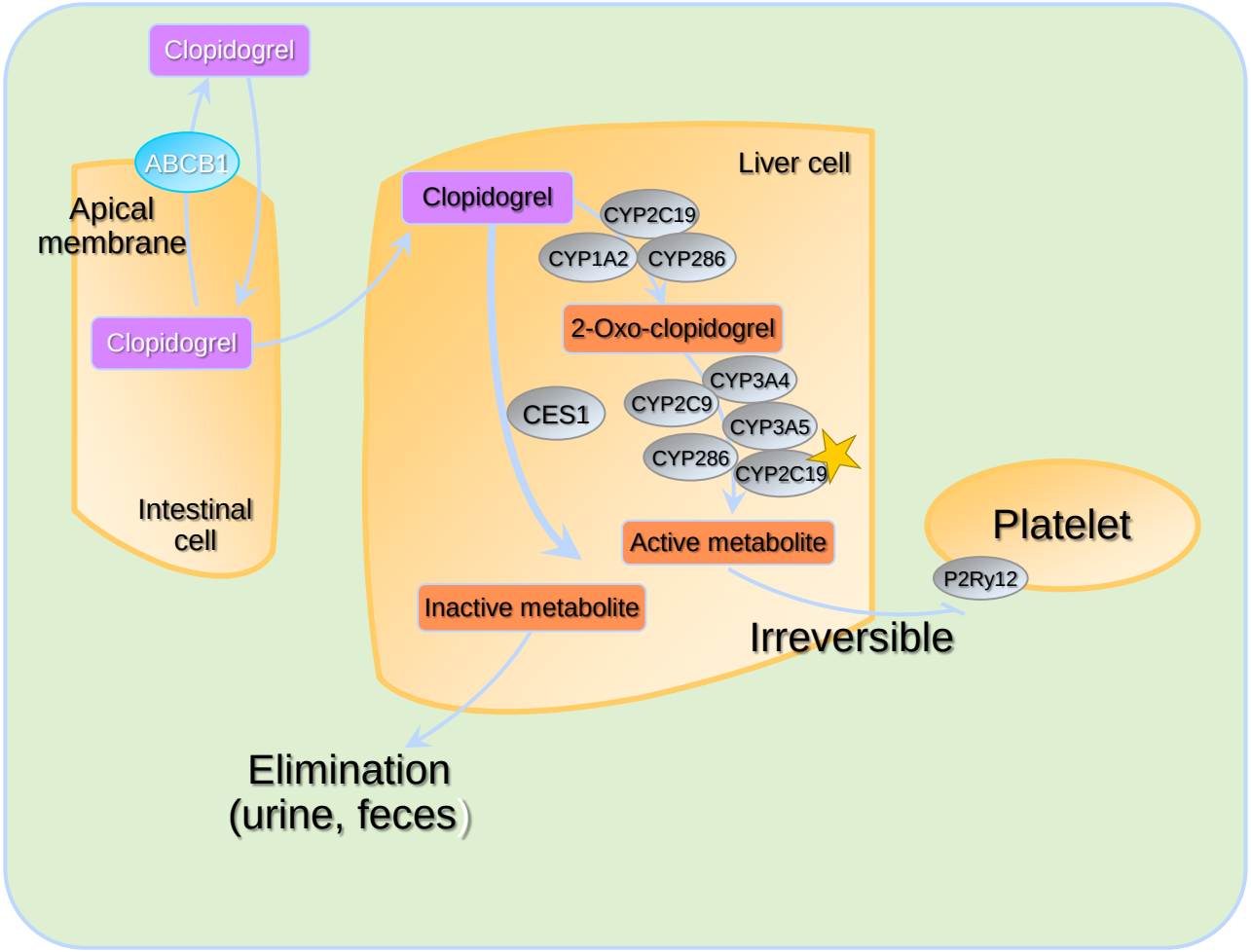
One of the “most important unresolved issues in interventional cardiology”

JACC 2013

Clopidogrel

- CAD affects 7.6 million people in the U.S.
- 2.5 to 3 million clopidogrel prescriptions are written per month
- 2010 sales were $6.1 billion
- Thienopyridine $P2Y_{12}$ADP receptor antagonist
- FDA indications
  - Myocardial infarction
  - Thrombotic CVA
  - Peripheral arterial disease
  - Percutaneous coronary intervention

Clopidogrel metabolism



PharmGKB

Genetic variation in *CYP2C19*

CYP2C19 polymorphisms

Allele	African	American	East Asian	European
*1[3]	0.68	0.69	0.6	0.63
***2**	**0.15**	**0.12**	**0.29**	**0.15**
***3**	**0.0052**	**0.00028**	**0.089**	**0.0042**
*4	0.00093	0.0024	0.00049	0.0025
*5	ND	0.00	0.00062	0.000073
*6	0.00	0.00	0.00	0.00017
*7	ND	ND	ND	0.00
*8	0.00	0.0012	0.00	0.0035
***17**	**0.16**	**0.18**	**0.027**	**0.21**

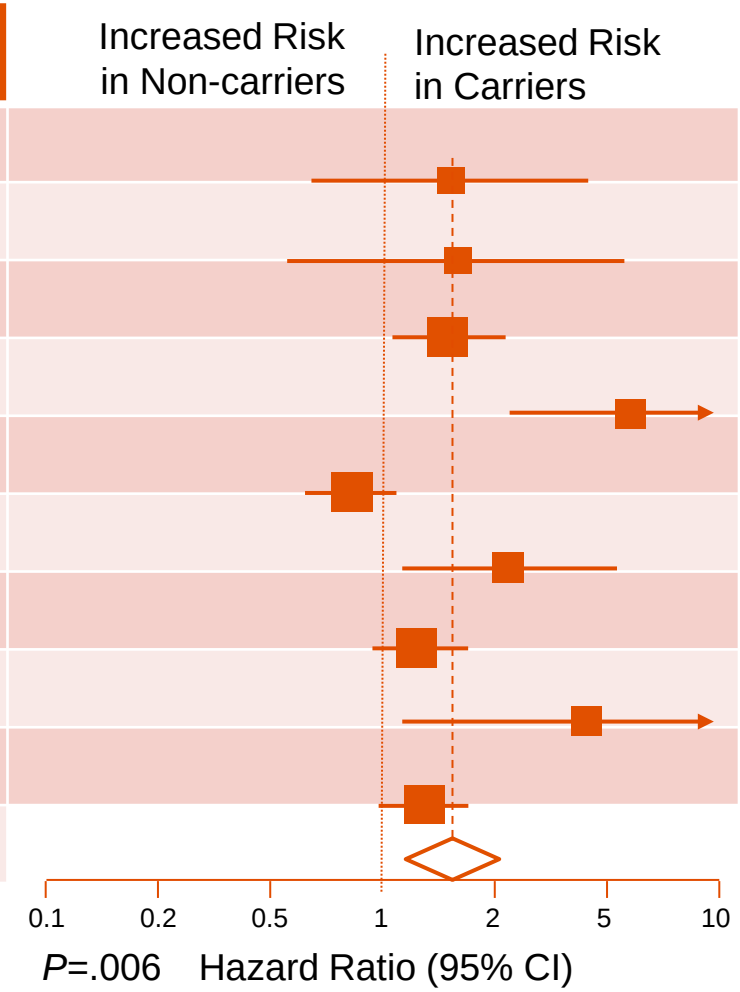
Clin. Pharmacol. Ther. 2011

Does genetic variation in *CYP2C19* affect clopidogrel outcomes?

Meta analysis

CV death, MI, or stroke – *CYP2C19* genotype

	No. of Events/ No. individuals at Risk		
	1 or 2	None	Hazard ratio (95% CI)
Clarity-TIMI 28	8/77	10/150	1.56 (0.61-3.94)
EXCELSIOR	5/243	7/554	1.63 (0.52-5.14)
TRITON-TIMI 38	46/395	83/1064	1.53 (1.07-2.19)
AFIJI	15/73	11/186	5.38 (2.32-12.47)
FAST-MI	63/635	193/1573	0.79 (0.59-1.06)
RECLOSE	15/247	14/525	2.32 (1.12-4.81)
ISAR	55/680	119/1805	1.23 (0.89-1.70)
CLEAR-PLATELETS	6/68	4/160	3.95 (1.11-14.02)
Intermountain	68/344	141/906	1.29 (0.97-1.72)
Totals	**281/2762**	**582/6923**	**1.57 (1.13-2.16)**



JAMA 2010

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CYP2C19 Clinical Outcomes
A meta-analysis

- 91% of patients had PCI performed
- 55% of patients had ACS
- Common genetic variation is associated with **1 in 3 patients** developing ischemic events when treated with standard clopidogrel therapy for PCI

JAMA 2010

Clopidogrel: Black-box warning

PLAVIX® (clopidogrel bisulfate) tablets
Initial U.S. Approval: 1997

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

March 12, 2010

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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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

Writing Committee Members, David R. Holmes, Jr, Gregory J. Dehmer, Sanjay Kaul, Dana Leifer, Patrick T. O'Gara and C. Michael Stein

Circulation 2010;122;537-557; originally published online Jun 28, 2010;

In addition, there are other genetic polymorphisms such as ABCB1 that may also contribute to variation in the response of individual patients to clopidogrel.

Information about the predictive value of pharmacogenomic testing is very limited, but is the focus of multiple ongoing studies. The design of such studies in terms of specific tests and patient populations (eg, acute care versus chronic care settings) will have major implications for the role of testing. A related issue is whether the risk from a given individual's genomic profile changes over time, depending on the specific clinical scenario (eg, ACS versus stable angina pectoris, PCI versus medical therapy, small vessel versus large artery, atherosclerotic ischemic stroke, or carotid stenting versus medical therapy), is relevant. This question has yet to be resolved.

4. The answer to the specific question of the role of genotyping in everyday practice remains unknown at the present time. Although the boxed warning does not mandate testing, proponents would argue that there are common genetic

wide variety of situations. New agents such as prasugrel and ticagrelor, which are not affected by CYP2C19 genetic variants, have been found to be more effective than standard-dose clopidogrel. This relates to the PK characteristics of these newer agents. In very high-risk clinical circumstances (eg, prior stent thrombosis) such agents may be considered alternatives to standard ACCF/AHA and AHA Stroke Council Guideline therapy. This is particularly important in any patient suspected of treatment failure to standard-dose clopidogrel. Other treatment strategies are also being tested, including increased clopidogrel dosing or the addition of a third drug such as cilostazol to aspirin and clopidogrel. In the setting of stroke or transient ischemic neurologic symptoms, the combination of aspirin and extended release dipyridamole and aspirin monotherapy are alternatives recommended by the AHA Stroke Council guidelines for secondary prevention of stroke.[66]

6.2. Recommendations for Practice

The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients.

CYP2C19*2 or *3 (poor metabolizers), or be extended to other variants including the gain-of-function CYP2C19*17 variant (hyper-rapid or ultrarapid metabolizers). As part of this argument, opponents note that the predictive performance of CYP2C19 variant is low, ranging from 12% to 20%, and raise the question of what to do when variant genotype information is identified in patients with no clinical events. Finally, they would note that there are no point-of-care genotyping tests, which severely limits the usefulness of these data in the acute care setting. Currently, there are studies underway or in the planning stages that will address these issues to varying degrees. Despite the gaps in current knowledge, both clinicians and patients need to be aware of genetic polymorphisms that may modulate clopidogrel responsiveness and cause MACE. It is important to emphasize again that in the most recent labeling for clopidogrel, the FDA only informs physicians and patients that genetic testing is available; it neither mandates, requires, nor recommends genetic testing, thereby allowing for flexibility in clinical decisions.

5. Given the concerns about the mortality and morbidity that may be attributable to an inadequate response to antiplatelet therapy, there are a number of alternative approaches to standard guideline-based care with clopidogrel. New agents and new strategies have been used clinically and tested in a

phisms on clinical outcome remains to be determined (eg, the importance of CYP2C19*2 versus *3 or *4 for a specific patient), and the frequency of genetic variability differs among ethnic groups. This has particular relevance related to the frequency of homozygotes, which occurs in approximately 2% of the population, versus heterozygotes, which occurs in approximately 30% of the population, both of whom may have increased risk.

4. Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies. The selection of the specific test, as well as the issue of reimbursement, are both important additional considerations.

5. The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients. In addition, the clinical course of the majority of patients treated with clopidogrel without either genetic testing or functional testing is excellent. Clinical judgment is required to assess clinical risk and variability in patients considered to be at increased risk. Genetic testing to determine if a patient is predisposed to poor clopidogrel metabolism ("poor metabolizers") may be considered before starting clopidogrel

Circulation 2010

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THE WALL STREET JOURNAL.
WSJ.com

HEART BEAT | March 22, 2010

When Pla

By RON WINSLOW

Many doctors are s
Food and Drug Adm

Some patients' genetic ma
Plavix's effectiveness.

HEALTH INDUSTRY | December 28, 2011

Study Challenges FDA on Plavix

Article | Comments (5)

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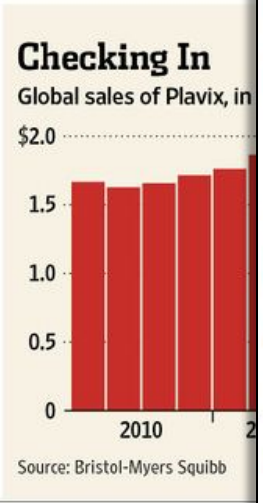
By SHIRLEY S. WANG

A new study casts doubt
taking the popular anti-clo
and Drug Administration
year based on the test, a
physicians.



THE WALL STREET JOURNAL.
WSJ.com

HEART BEAT | June 1, 2012, 3:56 p.m. ET

Heart Patients May Face a New Drug Dilemma

By RON WINSLOW

The newly low cost of Plavix, one of the biggest-selling drugs, is intensifying debate among cardiologists over how to make sure patients get optimal benefit from any blood-thinning medication.

A generic version of Plavix became available this month so there is an incentive to switch patients to it.

But, nearly a third of patients prescribed a blood thinner to prevent heart attack or stroke have a genetic variation that limits

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

6.1.2. Clopidogrel Genetic Testing: Recommendations

CLASS III: NO BENEFIT

1. The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended (829). *(Level of Evidence: C)*

CLASS III: NO BENEFIT

1. The routine clinical use of platelet function testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended (829). *(Level of Evidence: C)*

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Maintenance doses and duration of therapy

DES placed: Continue therapy for 1 y with:

• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day*	I	B

BMS† placed: Continue therapy for 1 y with:

• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day*	I	B

The black box warning has not gone away
The **gap in clinical evidence** remains

Does altering therapy based on
***CYP2C19* status** affect clinical outcomes?

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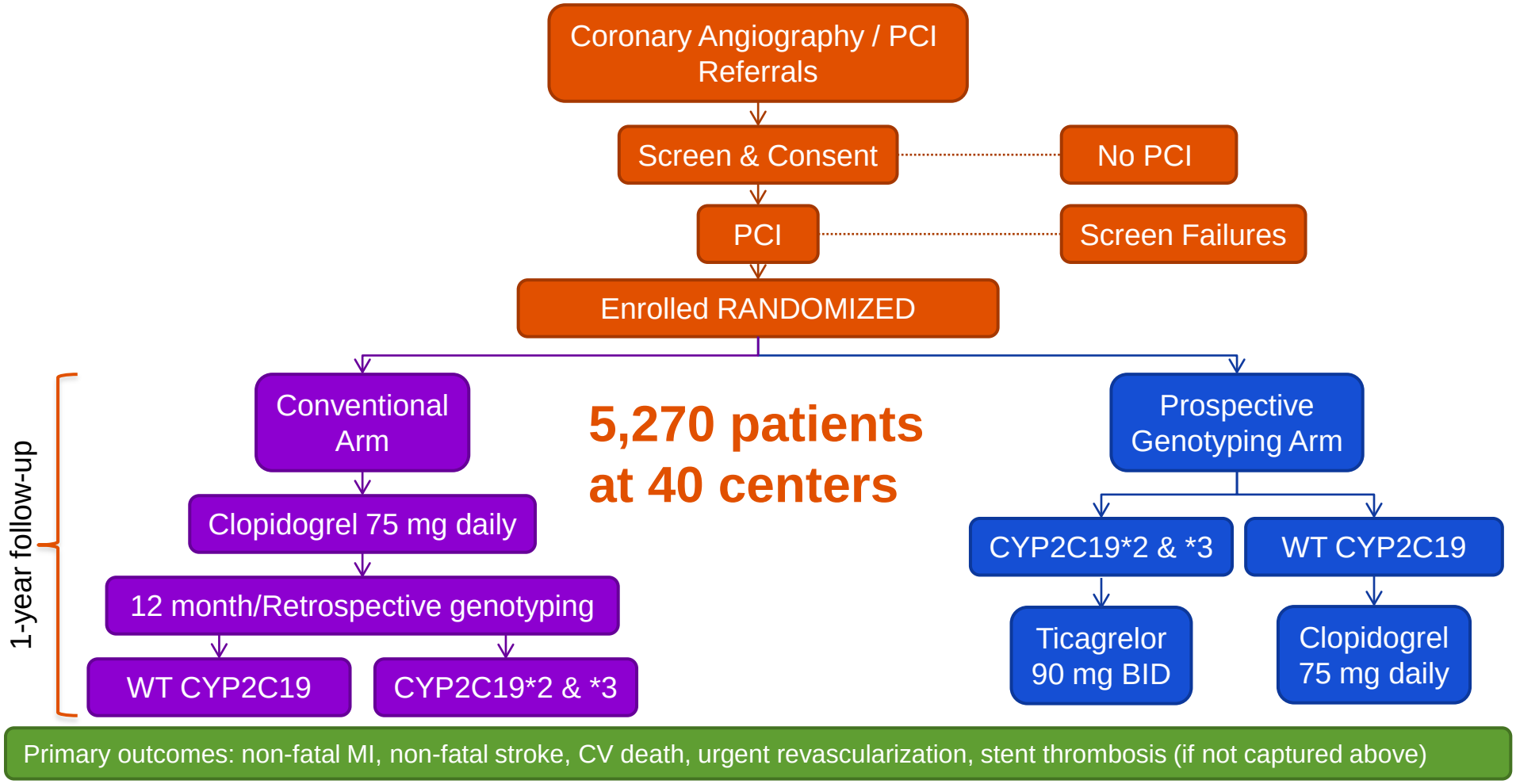
TAILOR-PCI

TAILORED **A**NTIPLATELET **I**NITIATION TO **L**ESSEN **O**UTCOMES DUE TO DECREASED CLOPIDOGREL **R**ESPONSE AFTER **P**ERCUTANEOUS **C**ORONARY **I**NTERVENTION

TAILOR-PCI study design



Study design

- Randomized clinical trial to evaluate the importance of modifying anti-platelet therapy based on *CYP2C19* genotype and its impact on clinical outcomes
- Estimated 1 year event rate for the LOF allele subjects of the intervention group is 8% and 12% for the control group
- Sample size calculated based on 2-sided log-rank test, power of 0.8, α of 0.05, HR 0.65 and LOF allele prevalence of 30% in North America and 50% in Korea
- Patients with ACS only are being recruited from the Canadian and Korean sites. US sites are recruiting ACS and stable patients.

TAILOR PCI versus POPular Genetics

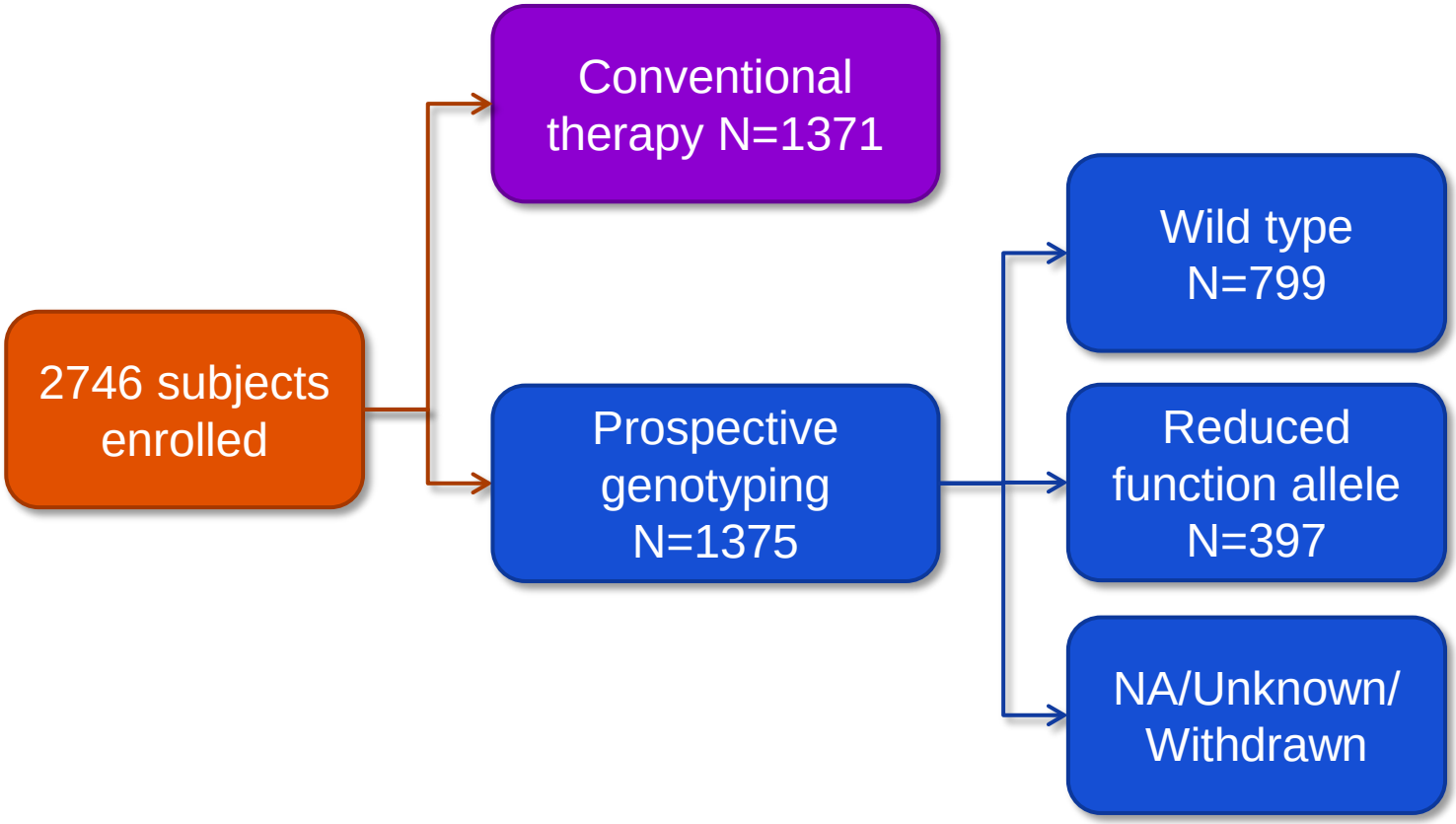
	TAILOR-PCI	POPular
Trial design	RCT – Superiority genetic Rx over conventional Rx i.e. clopidogrel	RCT – Non-inferiority of genetic Rx compared to ticagrelor/ prasugrel
Study population	Post-PCI – ACS, AMI, stable CAD	Post-PCI – STEMI (20-30% of ACS patients)
Sample size	5,270	2,700
End points	CV death, stroke, MI, ST, urgent revascularization	Death, stroke, MI, ST, urgent revascularization, bleeding
Event rate	8% in genetic arm versus12% in clopidogrel arm	16.9% in genetic arm versus 18.8% in ticagrelor/ prasugrel
Follow-up	Telephone calls	Questionnaires
Genotyping	Point of care - Spartan	Multiple different platforms

TAILOR-PCI milestones

- US, Canadian and Korean partnership
- Randomized 2746 patients with 29 centers (3/05/16)
- Innovative trial design to address FDA regulatory issues and feasibility
- Novel “point of care” genotyping platform:

  -Spartan point of care testing
- No Pharma support

Pilot study – data



Pilot study – baseline characteristics

Summary of Patients Enrolled in TAILOR-PCI Pilot	
Age, median (min, max)	**62 (26, 95)**
Sex, n (%)	
Male	2098 (76%)
BMI, median (min, max)	**27.8 (10.2, 67.3)**
Ethnicity, n (%)	
Caucasian	1710 (66%)
Asian	743 (29%)
Black	43 (2%)
Other/Unknown	97 (4%)
Hospital presentation, n (%)	
Stable, asymptomatic	532 (19%)
STEMI, acute coronary syndromes	2214 (81%)
Cardiac history	
History of MI (excluding index event), n (%)	389 (15%)
History of PCI, n (%)	634 (24%)
History of CABG, n (%)	195 (8%)
Comorbidities	
Diabetes, n (%)	684 (26%)
Current smoker, n (%)	604 (23%)
Peripheral Artery Disease, n (%)	61 (2%)
Stroke / TIA, n (%)	71 (3%)
Currently on dialysis, n (%)	1 (0%)
Cardiac anatomy and function	
MVD, n (%)	990 (39%)
LMCA >=70% stenosis, n (%)	81 (3%)
High/C lesion complexity, n (%)	514 (20%)

NIH Grant Approved

May 2016

TAILOR-PCI

- High impact on a highly prevalent disease
- Addresses an unresolved practice issue by using research methodology
- Immediate applicability of genotyping to clinical practice worldwide
- Pharmacoeconomic analysis
- Potential application to other disease states
- Creates a biobank for studies like GWAS
- Creates an infrastructure for other pragmatic cost effective multicenter studies

Summary

- Pharmacogenetic application of *CYP2C19* to clopidogrel, one of the most commonly prescribed drugs in the U.S., remains unresolved
- FDA cautions use of clopidogrel in *CYP2C19* poor metabolizers
- ACC/AHA/ESC recommend against routine genotyping in the absence of a prospective clinical trial
- TAILOR-PCI designed and conducted to address this gap

Thank you!

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