REASSESSMENT OF ANTI-PLATELET THERAPY USING AN INDIVIDUALIZED STRATEGY BASED ON GENETIC EVALUATION – THE RAPID GENE STUDY

TCT 2011

Derek So MD FRCPC FACC
On behalf of the RAPID GENE Investigators
ClinicalTrials.gov (NCT01184300)

UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE UNIVERSITE D' OTTAWA

Rapid Gene

RAPID GENE – Study Organization

Investigators:

Derek YF So (PI), Jason D Roberts (Co-PI),

George A Wells, Michel R Le May, Chris A Glover, Alexander J Dick, Michael P Froeschl, Jean-Francois Marquis, Edward R O'Brien, Sandro C Goncalves, Irena M Druce, Alexandre F Stewart, Michael H Gollob, Marino Labinaz

Sponsor:

Spartan Biosciences, Inc

Regulatory Boards:

Health Canada

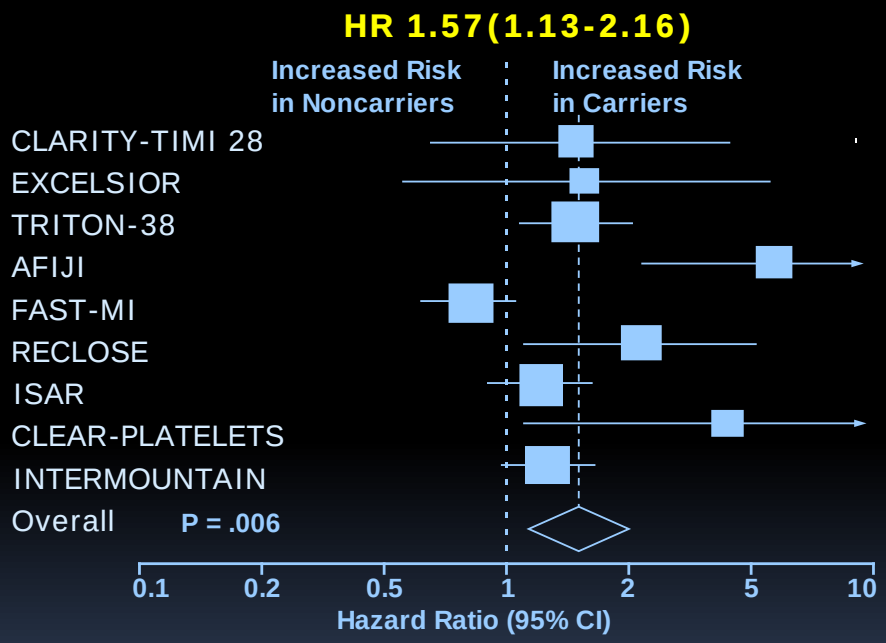
Ottawa Hospital Point-of-care Committee

Special Thanks:

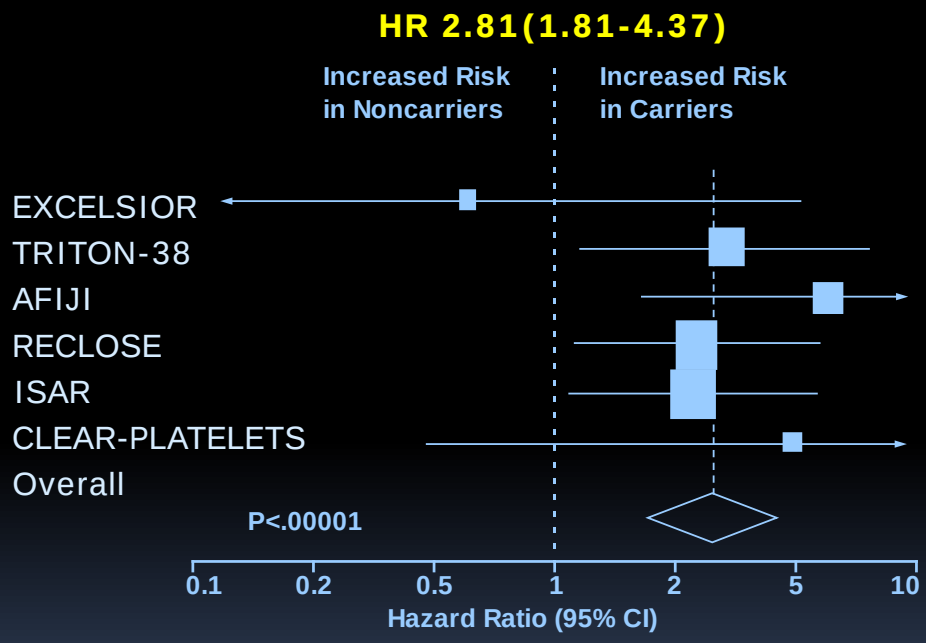
Cheryl Charlebois, Lyne Stuewe, Colleen Chilton, Luan Tran, Jordan Bernick

Accumulated Evidence on *CYP2C19* loss-of-function alleles

Evidence based on 9 studies with 9685 patients suggest an association of *CYP2C19* loss-of-function alleles to MACE and stent thrombosis



CV Death, MI, Stroke



Stent Thrombosis

Mega et al. JAMA 2010. 304(16):1821-30

Use of Pharmacogenetics Data in Patients after PCI

- Major obstacles preclude present application of genetics:
  - Costs
  - Lack of local expertise for genetic testing
  - Inability to provide timely information

- Accordingly, a prospective evaluation of personalized approach to anti-platelet therapy after PCI based on genetic data had not been possible

The RAPID Program: Spartan RX CYP2C19

- Buccal Swab performed by nurses (no prior training in genetics) – ½ hour course on machine
- 1 step insertion into machine
- 60 minutes to identify:
  - CYP2C19*2 carrier status
  - Heterozygous vs. Homozygous

RAPID GENE - Primary Objective and Hypothesis

- To evaluate the first point-of-care genetic test in medicine for its accuracy and potential clinical utility

- We hypothesized that a strategy of rapid genotyping followed by selective administration of prasugrel to *CYP2C19*2* carriers will decrease high on-treatment platelet reactivity compared to standard therapy

RAPID GENE – Study Schema

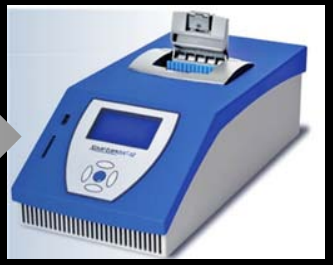
Patients for PCI (non ST-ACS or stable CAD)
All pre-treated minimum 600mg Clopidogrel≤ 24hr

Baseline platelet function testing with VerifyNow P2Y12Assay
Randomized 1:1

Rapid Genotyping (RG)

Standard Therapy (ST)

Point-of-care *genotyping (Spartan RX-CYP2C19) – buccal swab: 1hr.*



CYP2C19*2 **Carriers**

CYP2C19*2 **Non-Carriers**

Prasugrel 10 mg OD

Clopidogrel 75 mg OD

Clopidogrel 75 mg OD

Platelet function testing with VerifyNow P2Y12 Assay at 1 week
Retrospective genetic testing for patients in Standard Therapy Arm

Inclusion and Exclusion Criteria

Inclusion

- Age 18 – 75 receiving PCI for non-ST elevation acute coronary syndrome or stable coronary disease

Exclusion

- Initial treatment with anti-platelet other than aspirin and clopidogrel
- Requirement for warfarin or dabigatran
- History of stroke or TIA
- Platelet count of < 100 000/uL
- Known bleeding diathesis
- Hematocrit of < 30% or >52%
- Severe liver dysfunction
- Creatinine clearance of <30mL/min
- Pregnancy

Primary Outcome

- Proportion of *CYP2C19*2* carriers with a P2Y12 Reactivity Units value (PRU) > 234 (high on-treatment platelet reactivity)[1] in the rapid genotyping arm compared with *CYP2C19*2* carriers in the standard therapy arm after one week of dual anti-platelet therapy.

1.Price et al. Eur Heart J. 2008;29(8):992-1000

Secondary Outcomes

- Mean PRU and percentage platelet inhibition among *CYP2C19*2* carriers
- Platelet function measures between randomized groups
- Concordance of point-of-care genetic testing with direct DNA sequencing
- Composite of cardiovascular death, non-fatal myocardial infarction, re-hospitalization and stent thrombosis (ARC definite and probable)
- Safety outcomes of TIMI major and minor bleeding

Power Analysis: Sample Size Estimates

- Assumptions:
  - 60% non-responder rate among *CYP2C19*2* carriers
  - 75% relative risk reduction with alteration from clopidogrel to prasugrel.

- At a power of 90%, 23 *CYP2C19*2* carriers per group would be required. Assuming a 25% prevalence of *CYP2C19*2* carriers among a population of Western European descent and an 8% loss to follow-up rate, 200 patients were projected for enrollment.

Patient Enrollment

Patients undergoing PCI for non ST-ACS or stable CAD (200)

Excluded patients
After Procedure:
- 2 did not undergo PCI
- 2 withdrawn from study by treating physician
- 1 had coronary dissection and underwent urgent CABG

Rapid Genotyping (102)

Standard Therapy (98)

***CYP2C19*2* Carriers (23)**

Non-Carriers (74)

Clopidogrel 75 mg OD

Prasugrel 10 mg OD

Clopidogrel 75 mg OD

Excluded patients
- 1 refused to return for Day 7 blood work
- 1 loss to follow-up

Platelet Function Testing at 1 week

Excluded patients
- 4 refused to return for Day 7 blood work
- 2 inconclusive readings on platelet function measurements

Point-of-Care Genotyping

***CYP2C19*2* Carriers (23)**

Non-Carriers (68)

***CYP2C19*2* Carriers (23)**

Non-Carriers (73)

UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE UNIVERSITE D' OTTAWA

Rapid Gene

Baseline Characteristics (1)

	Rapid Genotyping (N=91)	Standard Therapy (N=96)
Age – yr	59.5±9.3	60.8±8.7
Female Sex – no. (%)	19 (20.9)	22 (22.9)
Ethnicity – no. Caucasian (%)	85 (93.4)	92 (95.8)
Previous Myocardial Infarction – no. (%)	17 (18.7)	13 (13.5)
Body Mass Index– kgm^{-2}	29.5±4.7	28.3±4.9
Acute Coronary Syndrome – no. (%)	33 (36.3)	37 (38.5)
Cardiac Risk Factors		
Hypertension – no. (%)	56 (61.5)	63 (65.6)
Diabetes Mellitus – no. (%)	23 (25.3)	19 (19.8)
Hypercholesterolemia– no. (%)	77 (84.6)	75 (78.1)
Current smoking – no. (%)	23 (25.3)	35 (36.5)
Past smoking – no. (%)	28 (30.8)	16 (16.7)

Baseline Characteristics (2)

	Rapid Genotyping (N=91)	Standard Therapy (N=96)
Baseline Medications		
Prior Aspirin Use – no. (%)	84 (93.3)	88 (91.7)
Statin – no. (%)	81 (89.0)	83 (87.4)
Ace-Inhibitor– no. (%)	41 (45.1)	43 (45.7)
Beta-Blocker – no. (%)	70 (76.9)	69 (71.9)
Proton Pump Inhibitor – no. (%)	19 (20.9)	18 (18.8)
Angiographic		
Left Main Artery	2 (2.2)	0 (0)
Left Anterior Descending Artery	42 (46.2)	42 (43.8)
Circumflex Artery	32 (35.2)	33 (34.4)
Right Coronary Artery	32 (35.2)	37 (38.5)
Saphenous Vein Graft	4 (4.4)	2 (2.1)
Drug eluting stent	71(78.0)	73 (76.0)

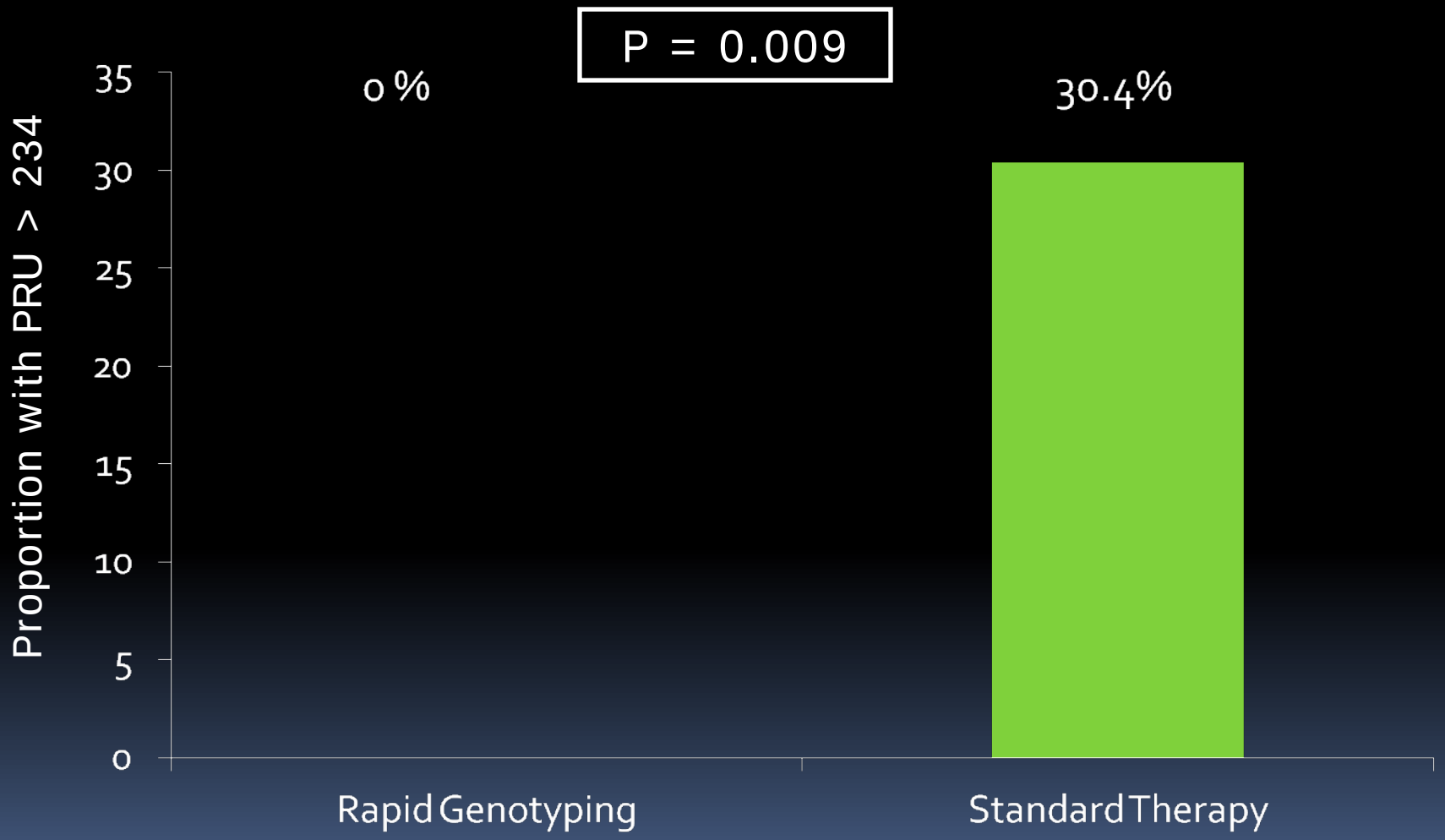
Genotyping Data:

	Rapid Genotyping (N=91)	Standard Therapy (N=96)
Carriers of *CYP2C19*2* allele no.(%)	23(25.3)	23(24.0)
Heterozygous *CYP2C19*2* no.(%)	19(20.9)	20(20.8)
Homozygous *CYP2C19*2* no.(%)	4(4.4)	3(3.1)

Performance Characteristics of Point-of-care Testing vs. Direct DNA Sequencing

- **Sensitivity – 100%**
- **Specificity – 99.4%**
- **Conclusive Rate – 93.6%**

Primary Endpoint: Proportion of *CYP2C19*2* Carriers with High On-treatment Platelet Reactivity (PRU>234)



Secondary Outcomes: Platelet Function Measures in *CYP2C19*2* carriers

	Rapid Genotyping (N=23)	Standard Therapy (N=23)	p-value
Baseline PRU	198.7 80.7	198.7 91.9	1.00
PRU at Day 7	75.6 57.3	207.3 55.8	<0.001
% Platelet Inhibition at Day 7	73.3 20.3	27.0 13.4	<0.001
Change in PRU from Baseline to Day 7	123.09 77.2	-8.48 74.0	<0.001

Secondary Outcomes: Clinical

- There were no major adverse cardiovascular events in either group at 7 and 30 days
- TIMI major or minor bleeding occurred in 5/91 (5.5%) of the rapid genotyping patients and 2/96 (2.1%) of standard therapy patients, p=0.27
- TIMI major bleeding occurred in 2.2% and 1.0% of rapid genotyping and standard therapy patients, respectively, p=0.61
  - 1 of 2 patients in rapid genotyping group with TIMI major bleed was on clopidogrel

RAPID GENE - Summary

- Point-of-care genetic testing following PCI performed at the bedside by clinical nurses permits accurate identification of *CYP2C19*2* carriers
- Point-of-care genetic testing is clinically feasible and facilitates rapid personalization of anti-platelet therapy.
- Administration of prasugrel to *CYP2C19*2* carriers decreased the rate of high on-treatment platelet reactivity relative to standard therapy with clopidogrel.

RAPID GENE

This represents the validation and proof-of-concept of the first point-of-care genetic test in clinical medicine. Results will lead to larger scale studies evaluating the role of pharmacogenomics after PCI