Point-of-Care Genetic Testing for Tailored Anti-Platelet Therapy

Ready for Prime Time?

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New Cardiovascular Horizons

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No Disclosures


**Dual Anti-Platelet Therapy**

- **DAPT**: Standard of care in ACS and PCI/Stent

- Challenge of balancing reduction in ischemic events vs. bleeding risk

- **Ticagrelor**  
  More potent, rapid onset, rapid offset  
  Less inter patient variability, Dyspnea  
  Cost

- **Prasugrel**  
  More potent, rapid onset, ACS/PCI  
  Increased risk of bleeding, Black Box Warnings  
  Inter Patient variability, Cost

- **Clopidogrel**  
  Potent, unpredictable, inter-patient variability  
  Lower bleeding risk, Generics / lower costs
Clopidogrel: Inter-patient Variability

• Prodrug: requires transformation to active metabolite

• Hepatic CYP 2C19 enzyme pathway

• Well described genetic variations in 2C19 gene (*2/*3) resulting in poor conversion of the prodrug to active metabolite (Loss of Function Alleles)

• LoF Allele Carriers: Lower active metabolite levels
  Less platelet inhibition, less efficacy

• LoF *2/*3 Carrier Frequency: 30% in ACS patients
Adverse clinical Outcomes in ACS Patients Who Poorly Metabolize Clopidogrel

Primary Efficacy Outcome:
rate of death from cardiovascular causes, myocardial infarction, or stroke.

FDA BLACK BOX WARNING
How do we individualize Antiplatelet therapies

Are there measurable parameters?

- Clinical judgement: high risk anatomical factors, history of past stent thrombosis, diabetics, bleeding risk etc

- Phenotypic testing: Platelet Reactivity testing

- Genotypic testing: LOF CYP 2C19
Phenotypic Testing: Platelet Reactivity Testing

- Measures the reactivity of patient’s platelets while on a drug to determine if the drug is effective - “clinical surrogate”

- Meta-Analysis: supported the existence of a significant association between clopidogrel non-responders i.e. high platelet reactivity on clopidogrel and adverse cardiovascular outcomes; Sofi:2010; Aradi:2010; Snoep:2007; Combescurcure:2010; Yamaguchi:2012

- Point-of-care testing: VerifyNow Assay, Plateletworks

- No universal gold standards

- RCT comparing adjusted anti-platelet strategy: Gravitas, Trilogy ACS, ARTIC, TRIGGER PCI

- No independent association between low platelet reactivity and clinical outcomes
GRAVITAS

- Evaluated the effect of high dose clopidogrel vs. standard dose clopidogrel in patients with HTPR after PCI

- VerifyNow

- Mainly elective PCI, few high risk ACS patients

- Reduction in PRU but no significant reduction in MACE in High dose 2.3% vs. Standard dose 2.3% clopidogrel

Price, JAMA, 2011, 305:1097-1105
TRILOGY ACS Platlet Function Substudy

• Compared more intense antiplatelet with Prasugrel vs. Clopidogrel in ACS patients managed medical

• No significant differences between Prasugrel and Clopidogrel in MACE at 30 months

• Prasugrel associated with lower platelet reactivity vs. Clopidogrel

• No significant independent association between platelet reactivity and MACE or ischemic outcomes

Gurbel, JAMA, 2012; 308: 1785-1794
ARTIC Trial

• Elective PCI patient population - DES implantation n = 2,440

• Strategy of systematic platelet function testing with anti-platlet therapy adjustment vs. conventional anti-platlet therapy without testing/adjustment

• No significant improvement in MACE rates with platelet reactivity testing and therapy adjustment (34%) vs. conventional anti-platlet therapy (31%) therapy

Collet, NEJM, 2012; 367; 2100-2109
TRIGGER PCI

– Randomized patients with HTPR on Clopidogrel after non urgent PCI to either Prasugrel or standard Clopidogrel therapy

– Study was stopped prematurely due to lower than expected event rates
Platelet Reactivity Testing: Lessons Learned

- Not all ACS patient populations are the same
- Platelet reactivity may correlate with risk but may not be a modifiable risk factor
- **Routine** platelet reactivity testing not recommended......but may be a viable strategy in selected patients with higher risk
Genetic Testing Strategy: 2C19 Genotype

• DNA testing - Cheek swab, send to a central lab

• Presence of LoF Alleles: CYP 2C19 *2, *3

• Higher dose of Clopidogrel or alternative drug

• Cumbersome strategy in ACS patients, results 4 to 14 days

• Limited RCT data
Spartan RX CYP2C19

Point-of-Care Testing

- FDA 510(k) clearance

- Tests for CYP 2C19 *2, *3 Loss of Function genetics

- Simple cheek swab

- Sample to results in one hour

- Accurate: high sensitivity high specificity

- Low cost
RAPID GENE

- Proof of concept study, 187 patients, Elective PCI
- Rapid genotyping screen for CYP2C19 *2, Adjusted therapy
- Lower Platelet reactivity in genotype guided therapy group

RAPID STEMI

- Evaluate pharmacogenomic strategy in STEMI patients
- Rapid genotyping screen for CYP2C19 *2, Adjusted therapy
- Lower platelet reactivity in genotype guided therapy group

Point-of-Care Genetic Testing was logistically feasible using the Spartan Rx Assay
GIANT Trial

- Evaluated clinical impact of 2C19 genetic profiling with adjusted anti-platelet therapy strategy in 1,445 patients vs. conventional therapy (in patients with STEMI/PCI)

- 319 patients with LoF genetics identified (Poor metabolizers)

- LoF carrier group: - 85% adjusted therapy: MACE 3.30%

  - 15% no adjusted therapy: MACE 15.6%

  Control group: MACE 3.04%

12.3% reduction in MACE at one year with genetically tailored Anti-Platelet strategy
• Elective PCI population  n =2,440

• Strategy of systematic platelet function testing with antiplatelet therapy adjustment vs. conventional antiplatelet therapy without testing adjustment

• DNA samples on 1,440 patients
  Slow metabolizers :  2C19 LOF alleles  MACE 32.7%
  Rapid Metabolizers:  GOF alleles            MACE 32.2%

• Conclusion 1 : Monitoring and treatment adjustment did not improve outcomes

• Conclusion 2 : Monitoring and adjusting treatment in the “higher” risk group reduced MACE rates to that of the “lower” risk group
TAILOR PCI

Tailored Antiplatelet Initiations to Lessen Outcomes Due to Decreased Clopidogrel Response after PCI

• Multisite randomized trial comparing POC genotype adjusted antiplatelet strategy in 2C19 LoF carriers vs standard therapy (6000 PCI pts)

• Prospective Genotype Arm: Genetic Testing for 2C19 LoF, Spartan RX
  Carriers of LoF: Adjusted strategy: Ticagrelor 90mg BID
  Non-carriers: Standard Therapy: Clopidogrel 75mg Daily

• Conventional Therapy Arm: No genetic testing initially, standard Clopidogrel, then genotyping will be performed at one year

• Primary Endpoints: MACE rates in LoF 2C19 carriers in the Conventional arm vs. LoF carriers in the Prospective genotype testing arm with adjusted therapy at one year
Conclusion

• Point-of-Care genetic testing for 2C19 LoF alleles is feasible, quick, accurate (RAPID GENE, RAPID STEMI)

• Limited evidence that genetic testing and tailored anti-platelet strategy reduces MACE rates post PCI (GIANT Trial), Possible ARTIC GENE

• Is Genetic guided antiplatelet therapy ready for prime time ??? Probably not routinely…yet…Possibly on an individualized basis
  Await the results of TAILOR PCI Trial
Thank You
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