Platelet Testing Who Should Have It

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Dual antiplatelet therapy (DAPT) with Aspirin and P2Y12 receptor antagonists: Standard of care in Acute Coronary Syndrome and PCI/Stent. Challenge of balancing reduction in ischemic events vs. bleeding risk.

Challenge has become balancing decrease MACE and bleeding as well as variability in drug/platelet activity.

There are three P2Y12 agents currently available:

- Clopidogrel
- Prasagrel
- Ticagrelor
* Ticagrelor

  More potent, rapid onset, rapid offset Less inter patient variability, Dyspnea, Costly

* Prasugrel

  More potent, rapid onset, ACS/PCI
  Increased risk of bleeding, Black Box Warnings Inter Patient variability, Costly

* Clopidogrel

  Potent, unpredictable, inter-patient variability Lower bleeding risk, Generics / lower cost
Clopidogrel Interpatient 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 outcomes in individuals that poorly metabolize Clopidopgrel

Primary Efficacy Outcome:
rate of death from cardiovascular causes, myocardial infarction, or stroke.
How do we individualize platelet therapy? 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: LOFCYP2C19
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 ie high platelet reactivity on clopidogrel and adverse cardiovascular outcomes; Sofi:2010; Aradi:2010; Snoep:2007; Combescure: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

* Evaluted 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
TRILOGY
PRASUGREL VS CLOPIDOGREL

* 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
ARTIC

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

* Strategy of systematic platelet function testing with anti-platelet therapy adjustment vs. conventional

* anti-platelet therapy without testing/adjustment

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

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
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
Conclusions

* 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

* Genetic guided antiplatelet therapy is ready for routine use and should be limited to high risk patients.

* Await the results of TAILOR PCI Trial
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