Platelet Function Testing and Antiplatelet Therapy

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CAN PLATELET FUNCTION TESTING HELP IN SELECTING OPTIMAL ANTIPLATELET THERAPY TO MAXIMIZE THE ANTI-THROMBOTIC BENEFIT AND MINIMIZE BLEEDING RISK?

"Take them until further testing shows they really aren't effective."
Cardiovascular disease

- Since 1900, cardiovascular disease has been the **No. 1 killer in the developed world**

![Diagram of blood clot blocking blood flow](image1)

- **Blood clot blocks blood flow**
- **Unstable plaque ruptures**

![Diagram of heart attack and stroke](image2)

- **Stroke**
- **Heart attack**

![Pie chart of leading causes of death](image3)

- **Respiratory disease**: 13%
- **Injuries and poisoning**: 5%
- **Other cancers**: 20%
- **Lung cancer**: 7%
- **Colo-necal cancer**: 3%
- **Diabetes**: 11%
- **Other CVD**: 8%
- **Coronary heart disease**: 18%
- **Stroke**: 7%

Coronary heart disease statistics. *British Heart Foundation 2010*
Antiplatelet therapy

- Antiplatelet therapy is effective in preventing thrombotic complications
- Families of drugs with proven clinical efficacy

- COX-1 inhibitors e.g. aspirin
- ADP receptor inhibitors e.g. clopidogrel, prasugrel, ticagrelor
- GpIIb/IIIa antagonists e.g. abciximab, eptifibatide, tirofiban

Monotherapy - secondary prevention of MI/Stroke

Combination therapy: ADP receptor antagonists/aspirin - ACS patients undergoing percutaneous coronary interventions (PCI) and AF
Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor

More efficacy α more bleeding

• The beneficial antithrombotic effects of antiplatelet drugs cannot be dissociated from increased risk of bleeding
A delicate balance

Bleeding

Thrombosis
Antiplatelet Therapy and Atherothrombosis

• Some patients continue to have thrombotic events despite being given optimal antiplatelet therapy

• Antiplatelet drugs are prescribed at standard doses based upon outcomes of clinical trials without any laboratory monitoring

• In the last decade, many observational studies have shown great variability in the response to standard doses of antiplatelet drugs e.g. clopidogrel

• Treatment failure as opposed to “resistance” or “poor response” (encompasses the failure of a drug to inhibit its biological target or failure to inhibit thrombosis)

• Most platelet function studies are performed in patients already taking antiplatelet drugs - can therefore be used to define either “high or low on-treatment platelet reactivity”
How to test platelet function?

• Many tests are available to assess platelet function

Restricted to laboratory use  

Designed to be point-of-care
Ideal Platelet Function Test - Does it exist?

• Physiological
• Rapid
• Point of Care
• Native Blood or maintain calcium levels
• Measure Pleiotropic Platelet Function including Thrombin effects, Pro-coagulant activity and Fibrinolysis
• Detect hypo and hyper-reactivity
• Detect pharmaco-dynamic variation on patients on standard dosing of antiplatelet drugs
• Cost effective
Platelet Function Tests for Measuring Response to Aspirin or P2Y\textsubscript{12} inhibition

**Thromboxane as the end point (Aspirin)**

- Serum thromboxane B\textsubscript{2}
- Urinary 11-dehydro thromboxane B\textsubscript{2}

**P2Y\textsubscript{12}-specific**

- VASP (vasodilator stimulated phosphoprotein) phosphorylation (flow cytometry)

**Arachidonic acid or ADP as the stimulus**

- Platelet aggregometry (turbidimetric)
- Whole blood aggregometry (impedance) e.g. Multiplate
- VerifyNow ASA or P2Y\textsubscript{12}
- Plateletworks
- Platelet surface activated GP IIb/IIIa, platelet surface P-selectin, leucocyte–platelet aggregates (flow cytometry)
- TEG PlateletMapping System
- Impact cone and plate(let) analyser

**Global Tests**

- PFA-100 (CEPI or P2Y Innovance)

Modified from Michelson. *Eur Heart J* 2006;8:G53.
Aspirin resistance: position paper of the Working Group on Aspirin Resistance

T. J. Kunicki, ++ F. M. Pulcinelli, ++ C. Cereletti §§ and A. K. Rao, ** on behalf of the Platelet Physiology Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis ***

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Conclusions

The correct treatment, if any, of aspirin ‘resistance’ is unknown. No published studies address the clinical effectiveness of altering therapy based on a laboratory finding of aspirin ‘resistance’. Therefore, other than in research trials, it is not currently appropriate to test for aspirin ‘resistance’ in patients or to change therapy based on such tests. A clinically meaningful definition of aspirin ‘resistance’ needs to be developed, based on data linking aspirin-dependent laboratory tests to clinical outcomes in patients.
Could the efficacy of aspirin be different in diabetes?

- Hyperglycaemia & hyperinsulinaemia have been associated with
  - Increased platelet reactivity
  - Enhanced platelet turnover, evidenced by increased immature platelet fraction

Is another dose and/or change in frequency of aspirin dosing required?
Aspirin dose and platelet function in type 2 diabetes study (the ‘ASP’ study)
Study design (1)

- Randomized, double blind assignment to:
  - 100 mg aspirin once a day (morning)
  - 200 mg aspirin once a day (morning)
  - 100 mg aspirin twice a day (morning and evening)
  - Doses given for 2 weeks and placebo where required

- In between each treatment period, there was a 2 week washout
24 Study Participants

**Major inclusion criteria**
- Type 2 diabetes
- <55 years old
- Stable antihyperglycaemic therapy for last 3 months
- HbA$_{1c}$ ≤64 mmol/mol (≤8%)

**Major exclusion criteria**
- Existing indication for ASA e.g. prior CVD
- ASA or other anti-platelet drug use within the last 30 days
- Insulin treatment
- Triglycerides ≥2 mmol/L
- Excess bleeding risk
  - Uncontrolled hypertension
  - Known GI disorder
  - Known bleeding disorder
  - Planned surgery within the next 3 months
# Study design (2)

**Sequence**

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<th>Period 1</th>
<th>Washout</th>
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1 day 14 days 14 days 14 days 14 days 28 days

**Visit Type:**

- **Screening labs**
- **Platelet function**
- **Platelet function**
- **Platelet function**
- **Platelet function**

- **=100mg active ASA**
- **=100mg placebo ASA**
Endpoints

• Primary
  – Change from baseline in platelet reactivity as measured by the VerifyNow ASA point of care test

• Secondary
  – Change from baseline in a battery of other “established” platelet function tests
VerifyNow™ ASA at baseline and following each of three aspirin regimens.

P values for possible differences between regimens are taken from generalized linear mixed effect models with random subject effects, with adjustment for possible period and sequence interactions.

\( p = 0.043 \)

\( p = 0.20 \)

\( p = 0.44 \)
Arachidonic Acid induced WBA – Multiplate at baseline and the 3 aspirin dose regimens

- Baseline
- Aspirin 100 mg once daily
- Aspirin 200 mg once daily
- Aspirin 100 mg twice daily

p < 0.0001
p = 0.0043
P = 0.19
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<tr>
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<th>Baseline</th>
<th>(A) Aspirin 100mg once-daily</th>
<th>(B) Aspirin 200mg once-daily</th>
<th>(C) Aspirin 100mg twice-daily</th>
<th>A vs B</th>
<th>p value A vs C</th>
<th>B vs C</th>
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<td><strong>Pharmacologic effects</strong></td>
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<td>Urinary dehydro-thromboxane B2 (pg/mg urinary creatinine)</td>
<td>4463±2411</td>
<td>1076±601 (p&lt;0.0001)</td>
<td>1037±641 (p&lt;0.0001)</td>
<td>906±664 (p&lt;0.0001)</td>
<td>0.47</td>
<td>0.048</td>
<td>0.21</td>
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<td>Serum thromboxane B2 (ng/ml)</td>
<td>130.5±76.5</td>
<td>7.2±11.9 (p&lt;0.0001)</td>
<td>5.3±7.9 (p&lt;0.0001)</td>
<td>2.3±1.3 (p&lt;0.0001)</td>
<td>0.39</td>
<td>0.055</td>
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<td><strong>Immature Platelets</strong></td>
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<td>IPF (%)</td>
<td>2.8 (1.7, 3.6)</td>
<td>2.8 (2.0, 3.2) (p=0.51)</td>
<td>2.8 (2.2, 3.3) (p=0.87)</td>
<td>2.7 (2.0, 3.2) (p=0.61)</td>
<td>0.69</td>
<td>0.93</td>
<td>0.76</td>
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<tr>
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<td>Baseline</td>
<td>(A) Aspirin 100mg once-daily</td>
<td>(B) Aspirin 200mg once-daily</td>
<td>(C) Aspirin 100mg twice-daily</td>
<td>A vs B</td>
<td>p value A vs C</td>
<td>B vs C</td>
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<td><strong>COX-1 independent tests</strong></td>
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<td>Multiplate™ (AUC)</td>
<td>50±15</td>
<td>52±20</td>
<td>52±20</td>
<td>52±16</td>
<td>0.61</td>
<td>0.82</td>
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<td>with ADP</td>
<td></td>
<td>p=0.41</td>
<td>p=0.79</td>
<td>p=0.56</td>
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<td>LTA (%)</td>
<td>70±9</td>
<td>47±13</td>
<td>43±16</td>
<td>43±16</td>
<td>0.99</td>
<td>0.49</td>
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<tr>
<td>with ADP</td>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
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<tr>
<td>PFA-100 (secs)</td>
<td>133±42</td>
<td>231±74</td>
<td>250±73</td>
<td>264±60</td>
<td>0.071</td>
<td><strong>0.031</strong></td>
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<tr>
<td>Coll/Epi</td>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
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<tr>
<td>PFA-100 (secs)</td>
<td>104±21</td>
<td>117±59</td>
<td>109±45</td>
<td>118±61</td>
<td>0.60</td>
<td>0.86</td>
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<td>Coll/ADP</td>
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<td>p=0.40</td>
<td>p=0.14</td>
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</table>
Conclusions

Aspirin at all doses inhibited platelet function below thresholds for “high platelet reactivity” in COX-1 dependent tests and PFA-100 CEPI and LTA-ADP

- VerifyNow-ASA, Urinary Thromboxane, & PFA-100 CEPI
  Showed a greater reduction in platelet reactivity with ASA 100 mg twice daily to ASA 100 mg once daily

- Multiplate using AA showed a greater reduction in platelet reactivity between
  ASA 100 mg twice daily or 200 mg once daily to ASA 100 mg once daily

- No influence of aspirin dose on other COX-1 independent tests

- Immature platelet fraction (absolute or %) did not influence dose response on any platelet function test
Remaining questions

• Do the numerically larger reductions in platelet reactivity equate to a clinical benefit?

• What is the bleeding risk for twice daily low dose aspirin?

• Current recommendations use a range of doses for primary prevention, but none discuss twice daily low dose ASA. Should they?

• Large scale cardiovascular outcomes trials are needed to assess safety and efficacy of twice daily low dose ASA.
Research: Treatment

Randomized controlled trial comparing impact on platelet reactivity of twice-daily with once-daily aspirin in people with Type 2 diabetes

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Abstract

Aims Reduced aspirin efficacy has been demonstrated in people with Type 2 diabetes. Because increased platelet reactivity and/or turnover are postulated mechanisms, we examined whether higher and/or more frequent aspirin dosing might reduce platelet reactivity more effectively.

Methods Participants with Type 2 diabetes (n = 24) but without known cardiovascular disease were randomized in a three-way crossover design to 2-week treatment periods with aspirin 100 mg once daily, 200 mg once daily or 100 mg twice daily. The primary outcome was platelet reactivity, assessed using the VerifyNow™ ASA method. Relationships between platelet reactivity and aspirin dosing were examined using generalized linear mixed models with random subject effects.

Results Platelet reactivity decreased from baseline with all doses of aspirin. Modelled platelet reactivity was more effectively reduced with aspirin 100 mg twice daily vs. 100 mg once daily, but not vs. 200 mg once daily. Aspirin 200 mg once daily did not differ from 100 mg once daily. Aspirin 100 mg twice daily was also more effective than once daily as measured by collagen/epinephrine-stimulated platelet aggregation and urinary thromboxane levels, with a similar trend measured by serum thromboxane levels. No episodes of bleeding occurred.

Conclusions In Type 2 diabetes, aspirin 100 mg twice daily reduced platelet reactivity more effectively than 100 mg once daily, and numerically more than 200 mg once daily. Clinical outcome trials evaluating primary cardiovascular disease prevention with aspirin in Type 2 diabetes may need to consider using a more frequent dosing schedule.

Prognostic value of platelet reactivity
(17 studies of 20,839 patients)
Standardized Platelet Function (VerifyNow, Multiplate and VASP)

Trade-off between thrombosis and bleeding

Therapeutic window for P2Y12 inhibitors

Does Personalized anti-platelet therapy really work?

• Large clinical trials have failed to provide evidence that modification of antiplatelet therapy based on platelet function improves clinical outcomes, e.g. GRAVITAS, TRIGGER-PCI, ARCTIC, ANTARCTIC

• Current guidelines discourage the utility of platelet testing in all comers but suggest a role in high risk patients (e.g. stent thrombosis), testing drug compliance or in patients with a high risk of bleeding

• Are the Design of the Trials wrong? Have we actually disproven that platelet testing has no benefit?

• Are current platelet tests "fit" for this purpose?
Personalised Anti-Platelet Therapy Large Clinical Trial Design Issues?

• Only included Stable non-urgent cases
• Used platelet monitoring to only intensify or escalate therapy
• Patients with high thrombotic risk (STEMI) excluded
• Platelet reactivity is highest in the early phase of ACS and then declines
• Magnitude of association between Platelet Reactivity and MACE is linked to the level of cardiovascular risk (Reny et al, 2016)
• The role for platelet function may only be in reducing risk in high risk individuals?
• Many trials used only 1 test - e.g. VerifyNow P2Y12
• Could platelet tests be used for reducing therapy instead?

TROPICAL-ACS trial (Sibbing et al, 2017)
Vascular risk levels affect the predictive value of platelet reactivity for the occurrence of MACE in patients on clopidogrel
Systematic review and meta-analysis of individual patient data

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1,995 identified references
1,937 excluded references (duplicates between databases, animal, no clinical endpoint, non-prospective, no ADP aggregation)
68 full-text articles assessed for eligibility
9 duplicate data
29 excluded studies (non-prospective, no clinical endpoint, no ADP aggregation, non-english)
20 qualifying studies
7 excluded studies (5 not responding to request, 2 refused; not providing data for a total of 957 patients)
13 included studies totaling 6,478 patients

Figure 1: Flow chart of the meta-analysis.

Figure 4: Six-month risk of MACE according to platelet reactivity in the different risk groups. The dashed line represents the overall risk, ignoring platelet reactivity and the black line shows the risk according to the platelet reactivity assessed with 20 μM ADP LIA, in patients with no risk factors (A), one risk factor (B) and two or more risk factors (C).
Tropical ACS Study (Sibbing et al, Lancet 2017)

- Safety and Efficacy of early de-escalation from prasugrel to clopidogrel

- 2610 patients with ACS undergoing PCI randomly assigned to prasugrel for 12 months (controls -1306) or de-escalation from 1 week of prasugrel then 1 week of clopidogrel and then PFT guided therapy (guided group, 1304)

- Primary endpoint (bleeding and thrombosis) was met - 7.3% in guided group and 9.0% in de-escalation group

- Supports the non-inferiority hypothesis of a guided de-escalation strategy

- Take home message: Guided de-escalation strategy might represent an alternative approach to standard therapy with prasugrel
Limitations of Platelet Function Testing

• Lack of consensus regarding the optimal cut-offs for HTPR or which test should be used

• Low standardisation of some methods e.g. LTA

• Influence of pre-analytical variables - anticoagulant, time delays, agonist used and concentrations

• Different tests cannot be directly compared?

• Re-stimulated usually by single agonists = Platelets don’t function this way in vivo - multiple stimulation

• Cannot measure pleiotropic effects of any drug e.g. Ticagrelor

• Thrombin/Procoagulant/Fibrinolytic pathways generally ignored except in TEG based assays

• Few cross validation studies (e.g. POPULAR and PEGASUS-PCI)
New Approaches to Platelet Function Tests

- 96 well plate aggregometry with PRP - dose response curves using lyophilised agonists. e.g. optimul assay

- 96 well plate aggregometry with whole blood - dose response curves with agonists and measure loss of single platelets using the platelet/RBC ratio to count platelets

- Platelet Solutions - POC activation with agonists and fixation - send to reference laboratory for Flow cytometry (long term stability)

- Multiparameter testing of platelet thrombus formation (De Witt et al, 2014)
T-TAS®
Total Thrombus-formation Analysis System

- Automated microchip flow chamber system for the quantitative analysis of thrombus formation under variable flow conditions
- It monitors pressure increase in the capillary channels

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<th>AR-chip</th>
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<td>collagen</td>
<td>collagen + tissue factor</td>
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<td>Sample type</td>
<td>Hirudin</td>
<td>Citrate (+Ca2/CTI)</td>
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<tr>
<td>Thrombus type</td>
<td>Platelet thrombus formation</td>
<td>Fibrin rich white thrombus formation</td>
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<tr>
<td>Thrombus components</td>
<td>Activated platelets</td>
<td>Fibrin, activated platelets, fibrin bound thrombin</td>
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Evaluation of antithrombotic drugs under flow conditions

- Blood from healthy individuals spiked with
  - Ticagrelor 10µM (P2Y12 receptor antagonist)
  - Rivaroxaban 1µM (anti Xa inhibitor)
Laboratory Monitoring of P2Y\textsubscript{12} Inhibitors: a position Statement of the Platelet Physiology Scientific and Standardization Committee.

Running title: Monitoring of P2Y\textsubscript{12} Inhibitors

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Figure 1. Process for obtaining expert consensus recommendations on the laboratory monitoring of P2Y\textsubscript{12} inhibitors.
ISTH SSC position statement (In preparation 2017)

- PFT cannot at present be recommended to guide P2Y12 inhibitor choice or select patients that may benefit from prolonged treatment

- May help in an early de-escalation of prasugrel to clopidogrel in patients not considered to be suitable for long term prasugrel therapy

- In balancing the risk of thrombosis during a delay to surgery and risk of surgical bleeding it may be reasonable to consider the results of P2Y12 inhibitor monitoring to determine timing of surgery - new trials required

- Current evidence does not support PFT guided antiplatelet therapy, limitations of studies, differences in costs between generic clopidogrel and newer P2Y12 drugs and the enhanced bleeding of the latter still motivate research

- Critical issues - study design (sample size and controls), choice of high risk populations, selection of most appropriate tests and timing of switching therapy (within days rather than weeks), defined clinical efficacy outcomes etc

- More research required on new methods
Acknowledgements

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Yihong Sun
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