A Propensity-Matched Nested Case-Control Study of Acute Coronary Syndrome Patients Genotyped for CYP2C19

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Conflict of interest: Patents, genetic algorithm, know-how, methods of genetic testing
Introduction

- Ticagrelor is widely considered superior to clopidogrel however a pharmacogenetic substudy of PLATO indicated that the majority of this difference is due to genetic nonresponders to clopidogrel.
- We evaluated the outcomes following genotyping for CYP2C19 in a propensity matched ACS cohort treated with either clopidogrel or ticagrelor.

Ticagrelor vs Clopidogrel: PLATO PGx

• Newer agents are only beneficial in nonresponders to old Rx (CYP2C19 LOF)

Methods
• 4,995 WDHB ACS patients were identified by ICD10 coding over a period of 5 years (2012-2016).
• Ticagrelor was subsidised by Pharmac in July 2013.
• Patients were genotyped for CYP2C19 *2, *3 and *17 alleles using either the Nanosphere Verigene analyser or Sequenom Massarray, and treatment tailored accordingly.
• Logistic regression and nearest neighbour propensity matching was employed in a 1:3:3 (genotyped:ticagrelor:clopidogrel) fashion to balance patient characteristics.
Genotyping Methods

1. Nanosphere Verigene Analyser $100/assay
2. MALDI-TOF MS $85/assay
3. GeneTitan $70/genome array
4. BDMax RT-PCR $30/assay

Future

Handheld sequencing

Minion

MinION Mkl: portable, real time biological analyses
Results

• 146 patients were genotyped and compared with 438 matched patients taking either clopidogrel, or ticagrelor.
• 93 (64%) genotyped patients were treated with clopidogrel.
• Post July 2013 71% responders versus 54% without genotype information were prescribed clopidogrel ($\chi^2$ 7, 95% CI 4 to 28, p<0.009).

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel N=438</th>
<th>Genotyped N=146</th>
<th>Ticagrelor N=438</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>Male (%)</td>
<td>0.68</td>
<td>0.67</td>
<td>0.64</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>0.61</td>
<td>0.61</td>
<td>0.62</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>0.21</td>
<td>0.22</td>
<td>0.21</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>0.13</td>
<td>0.12</td>
<td>0.09</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>0.59</td>
<td>0.58</td>
<td>0.58</td>
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<tr>
<td>Prior atherosclerosis (%)</td>
<td>0.58</td>
<td>0.60</td>
<td>0.63</td>
</tr>
<tr>
<td>Renal impairment (%)</td>
<td>0.04</td>
<td>0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>PCI (%)</td>
<td>0.35</td>
<td>0.36</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Groups well balanced by Propensity Matching
Prescribing behaviour

Mortality at 1 year

HR 0.4, 95% CI: 0.18 to 0.99, p=0.0002
Readmission with ACS

Readmission with ACS in Genotyped-Clopidogrel Rx group

H = *2/wt or *2/*2
W = wt/wt

6 patients *2/*2, or *3/*3:
- 4/6 Ticagrelor or Prasugrel
- 2 Clopidogrel
  - 1 readmitted ACS within 2 weeks
  - 1 multiple stent occlusions, ICM resulting in cardiac Tx
Results

- Personalised treatment was noninferior to ticagrelor HR 0.9, 95% CI: 0.4 to 2.1 and superior to clopidogrel HR 0.4, 95% CI: 0.18 to 0.99, p=0.0002, with respect to all-cause mortality.

- Readmissions with ACS were higher in nonresponders treated with clopidogrel (HR 2.7, 95% CI 1.4 to 5.5, P = 0.001) but equivalent between responders treated with clopidogrel versus ticagrelor HR 0.9 95% CI 0.5 to 1.5, P = 0.6).
Cardiology interests....are they balanced?

• Stent thrombosis – focus on technical/procedural
• ST is under-recognised
• Virchow’s triad

PCI - $10-21,000

Cardiology in NZ faces and “Existential Crisis”
 – Prevention vs Ambulance at the bottom of the cliff

Conclusion

• Personalised antiplatelet management was noninferior to ticagrelor with respect to all-cause mortality and ACS readmissions.
• It also led to more appropriate use of both clopidogrel and ticagrelor with resultant cost savings.

• CV Genomics needs more support from NZ Cardiologists
  – Talk about it, ask questions, order appropriate tests
Acknowledgements

- Students: Kate Kilpatrick
- Orion PDH – Kelly Atkinson, Kevin Ross
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- Clinical Laboratory WDHB – Kevin Smith, Lee-Ann Weiss, Matt
- Liggins Institute – Phillip Shepherd

Readmissions genotyped CLO responders vs ticagrelor

HR 0.9 95% CI 0.5 to 1.5, P = 0.6