Pharmacist-led CYP2C19 genotyping in patients on clopidogrel therapy following percutaneous coronary intervention

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Background  
CYP2C19, a cytochrome P450 enzyme encoded by a highly polymorphic gene, is involved in the metabolism of clinically important drugs such as clopidogrel. The 2013 Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP2C19 genotype and clopidogrel therapy1, classify CYP2C19 genotypes into 4 groups according to metaboliser status in relation to clopidogrel: ‘Extensive metabolisers’, carrying only normal function alleles (EMs *1/*1), ‘ultra-rapid metabolisers’, carrying at least one gain-of-function (GoF) allele (UMs *1/*17, *17/*17), ‘intermediate metabolisers’, carrying one loss-of-function (LoF) allele (*1/*2, *17/*17), and ‘poor metabolisers’, carrying two LoF alleles (PMs *2/*2).

Objective  
To implement a laboratory-based, pharmacist-led process to genotype patients who were prescribed clopidogrel therapy post-percutaneous coronary intervention (PCI) for the CYP2C19 LoF (*2) and GoF (*17) variant alleles.

Method  
• University Research Ethics Committee approval was granted.  
• After obtaining informed written consent from each of 252 patients undergoing PCI, 5 mL of peripheral blood were collected into a purple-top EDTA tube and stored between 2-8°C. Patients were recruited by non-probability sampling.  
• Genomic DNA purification was undertaken using the QIAamp DNA Mini Kit with the fully automated QiaCube (Qiagen) and frozen at -20°C. CYP2C19 SNP genotyping for variant alleles *2 (rs4244285) and *17 (rs12248560) was undertaken using TaqMan® Universal Master Mix and TaqMan® SNP drug metabolism assays (Life Technologies) on the 7500 Real-Time PCR system (Applied Biosystems).  
• CYP2C19 SNP distribution and total allele frequencies were calculated.

Setting  
Mater Dei Hospital (Cardiac Catheterisation Suite, Cardiology Department and Molecular Diagnostics Unit, Pathology Department)

Results  
Patient demographics (N = 252)  
Mean age of the patients was 65 years (range 29-89 years), 74.6% were male and 99.2% were Caucasian.

CYP2C19 SNP genotype and allele frequency distribution  
• The majority of patients (74.2%) were non-carriers of the CYP2C19 LoF *2 allele (51.2% EMs and 23.0% UMs).  
• 25.8% of patients were carriers of one *2 allele (IMs) and no patients were carriers of two *2 alleles (PMs) (Table 1).  
• Total frequencies of allele *2 and *17 were 13% and 15% respectively.

Table 1: CYP2C19 SNP genotype distribution (N=252)  
<table>
<thead>
<tr>
<th>CYP2C19 genotype (metaboliser status)</th>
<th>Number of patients</th>
<th>Percentage ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1 (EMs)</td>
<td>129</td>
<td>51.2 ± 6.2</td>
</tr>
<tr>
<td>*1/*17 (UMs)</td>
<td>56</td>
<td>22.2 ± 5.1</td>
</tr>
<tr>
<td>*17/*17 (UMs)</td>
<td>2</td>
<td>0.8 ± 1.1</td>
</tr>
<tr>
<td>*1/*2 (IMs)</td>
<td>49</td>
<td>19.4 ± 4.9*</td>
</tr>
<tr>
<td>*2/*17 (IMs)</td>
<td>16</td>
<td>6.4 ± 3.0*</td>
</tr>
</tbody>
</table>

Conclusions and implications to practice  
These findings may have important clinical implications for clopidogrel use in Malta since according to the CPIC genotype-guided therapeutic recommendations2, carriers of one or two LoF *2 alleles (26%) should be switched to an alternative antiplatelet agent, provided there is no contra-indication. For non-carriers of the *2 allele, the guidelines recommend standard dosing of clopidogrel. Pharmacist-guided optimisation of antiplatelet therapy, directed by CYP2C19 SNP genotyping, may limit occurrence of adverse cardiac events, stent thrombosis and stent restenosis post-PCI.

Reference  

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