Improving Stent Outcomes with Pharmacological Manipulation – 2C19 and Plavix

K.KASIRAJAN, MD

Disclosure
President and Founder Titan Molecular Laboratories and ImmunityDx

What has Changed

• No dramatic change in stent technology
• Outcomes are not getting better
• Most significant strides in medicine have come from drug delivery and vaccines.

Aspirin + Clopidogrel

• Peripheral endovascular interventions are highly depended on dual antiplatelet therapy for long-term patency

Black Box Warning - Clopidogrel: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

• Effectiveness of Plavix depends on activation ... by ... CYP2C19 (liver enzyme)
• Tests are available to identify ... CYP2C19 genotype
• Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s042lbl.pdf

Metabolic Status

Thrombus
Bleeding
GIANT

Aspirin+plavix

Normal
Non-responders
Non-responders

End Point (one-year)

Normal (n=1118)
Poor Metabolizers Treatment adjusted (n=272)
Poor Metabolizers Treatment not adjusted (n=55)

Death/MI/stent thrombosis
3.04 %
3.3 %
15.6 %

One-Year rates (%)

2C19 (Plavix)

PM 23/167 (13.77%)
URM 32/279 (11.47%)

2C19 status

Group I (CV+PVD)
(N=588)
Group II (CV only)
(N=3397)
Group III (PVD only)
(N=525)
P-value

PM 16 (2.7%) 81 (2.4%) 17 (3.2%) 0.321
IM 127 (21.6%) 736 (21.7%) 114 (21.7%)
NIM 54 (9.2%) 221 (6.5%) 39 (7.4%)
NM 226 (38.4%) 1262 (37.2%) 197 (37.5%)
RM 138 (23.5%) 949 (27.9%) 139 (26.5%)
URM 27 (4.6%) 148 (4.4%) 19 (3.6%)

IDART Registry (NCT01970709)

- 58,896 patients (56% female) with CV risk factors
- 6127 on clopidogrel for coronary stents.
- 167 (2.73%) Poor Metabolizers (ineffective)
- 279 (4.55%) ultrarapid metabolizers

- Change rate at 60±10 day after test results published

- 2C19 PM 23/167 (13.77%)
- 2C19 URM 32/279 (11.47%)

CREST

<table>
<thead>
<tr>
<th>Event</th>
<th>CEA</th>
<th>CAS</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Death/stroke/MI</td>
<td>6.8%</td>
<td>7.2%</td>
<td>0.51</td>
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<tr>
<td>30-day</td>
<td>4.5%</td>
<td>5.2%</td>
<td>0.38</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.3%</td>
<td>4.1%</td>
<td>0.01</td>
</tr>
<tr>
<td>MI</td>
<td>2.3%</td>
<td>1.1%</td>
<td>0.03</td>
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<tr>
<td>Major Stroke</td>
<td>0.7%</td>
<td>0.9%</td>
<td>0.52</td>
</tr>
<tr>
<td>CN injury</td>
<td>4.8%</td>
<td>0.3%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
• CREST

PM of Clopidogrel developed delayed platelet debris in stents ≈24 hours that resulted in 80% of the CAS related strokes!

Conclusion

• Endovascular Studies need to heed clopidogrel “black box” warnings
• Stents are highly dependent on adequate dual antiplatelet therapy.
• CAS will demonstrate non-inferiority to CEA if 2C19 PM are excluded!

START HEEDING MEDICATION BLACK BOX WARNINGS