Are Drug (Clopidogrel) “Black Box” Warnings Important?

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**Disclosure**
CMO for Molecular Labs in the past (NMTC, RenRx, Ally)!
Currently Unemployed!

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**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

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**One-Year rates (%)**

<table>
<thead>
<tr>
<th>End Point (one-year)</th>
<th>Normal (n=1118)</th>
<th>Poor Metabolizers Treatment adjusted (n=272)</th>
<th>Poor metabolizers Treatment not adjusted (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/stent thrombosis</td>
<td>3.04 %</td>
<td>3.3 %</td>
<td>15.6 %</td>
</tr>
</tbody>
</table>
DART 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%)

How do we fix this non-compliance?

- Physician education (2C19, black box)
- Pay for performance by Insurance, Hospitals,
- Pharmacist as team members
- RCT
- EndoVascular Specialists.......

CREST

<table>
<thead>
<tr>
<th></th>
<th>CEA</th>
<th>CAS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/stroke/MI</td>
<td>6.8%</td>
<td>7.2%</td>
<td>0.51</td>
</tr>
<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>
</tr>
<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>

IM 1289(20%)
NIM 466(7%)
NM 2610 (39%)
PM 199(3%)
RM 1821(27%)
URM 279(4%)

P-value
(N=588) (N=3397) (N=525)
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%)

PM of Clopidogrel had platelet debris form 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!

"Insanity is doing the same thing over & over again & expecting different results." - Albert Einstein