WOEST TRIAL - NO ASPIRIN IN STENTED PATIENTS REQUIRING ANTICOAGULATION

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Conflicts of Interest

- I have been a paid consultant and speaker for AstraZeneca, makers of Ticagrelor (Brilinta)
Some patients referred for PCI have atrial fibrillation or a mechanical valve, for which they are receiving chronic anticoagulation.

Typically, dual antiplatelet therapy (DAPT - with aspirin and a P2Y12 antagonist) is prescribed to prevent stent thrombosis.

The combination of chronic anticoagulation and DAPT is associated with a high risk (4–16% annually) for fatal and nonfatal bleeding.

To date we don’t really know the optimal treatment after coronary stenting in these patients.
WOEST Trial: What is the Optimal antiplatElet and anticoagulation therapy in patients with oral anticoagulation and coronary StenTing

• Investigators randomly assigned 573 adults receiving Warfarin anticoagulation and undergoing PCI to:
  • (a) clopidogrel alone (double therapy) or
  • (b) clopidogrel plus aspirin (triple therapy)

• 1/3rd of the study population received bare-metal stents, and 2/3rd received drug-eluting stents.

• After 1 year of follow-up, the investigators found that double therapy (clopidogrel without aspirin) was associated with a dramatic reduction in bleeding complications and no increase in the rate of thrombotic events when compared with triple therapy.

The Lancet, Early Online Publication, 13 February 2013; doi:10.1016/S0140-6736(12)61777-1 Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. WJM Dewilde, T Oirbans, FWA Verheugt, JC Kelder, BJGL De Smet, JP Herrman, T Adriaenssens, M Vrolix, AACM Heestermans, MM Vis, JGP Tijsen, AW van 't Hof, JM ten Berg, for the WOEST study investigators
**WOEST Trial:** What is the Optimal antiplatelet and anticoagulation therapy in patients with oral anticoagulation and TIMI classification?

<table>
<thead>
<tr>
<th>Type of bleeding reduced</th>
<th>Dual therapy (%)</th>
<th>Triple therapy (%)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bleeding events</td>
<td>19.5</td>
<td>44.9</td>
<td>0.36 (0.26-0.50)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TIMI minimal</td>
<td>6.5</td>
<td>16.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI minor</td>
<td>11.2</td>
<td>27.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI major</td>
<td>3.3</td>
<td>5.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
WOEST Trial: **What is the Optimal antiplatelet and anticoagulation therapy in patients with oral anticoagulation and coronary Stenting**

**Location of TIMI bleeding: Worst bleeding per patient**

<table>
<thead>
<tr>
<th>Location of bleeding</th>
<th>Dual therapy (n)</th>
<th>Triple therapy (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Access site</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>GI</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Skin</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>48</td>
</tr>
</tbody>
</table>

There was no difference in intracranial bleeding, with three cases in each group. The trial was powered for superiority in bleeding, but it was not powered for non-inferiority in efficacy.
**WOEST Trial: What is the Optimal antiplatelet and anticoagulation therapy in patients with oral anticoagulation and coronary Stenting**

**WOEST: Composite efficacy end point**

<table>
<thead>
<tr>
<th>End point</th>
<th>Dual therapy (%)</th>
<th>Triple therapy (%)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite efficacy end point</td>
<td>11.3</td>
<td>17.7</td>
<td>0.60 (0.38-0.94)</td>
<td>0.025</td>
</tr>
<tr>
<td>MI</td>
<td>3.3</td>
<td>4.7</td>
<td></td>
<td>0.382</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>7.3</td>
<td>6.8</td>
<td></td>
<td>0.876</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>1.1</td>
<td>2.9</td>
<td></td>
<td>0.128</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.5</td>
<td>3.2</td>
<td></td>
<td>0.165</td>
</tr>
</tbody>
</table>

Clinical ischemic events were a secondary end point, and results suggested these were not increased by dropping aspirin. Indeed, most end points showed lower numerical rates in the dual-therapy arm, and total mortality was actually significantly reduced.
WOEST Trial: What is the Optimal antiplatElet and anticoagulation therapy in patients with oral anticoagulation and coronary StenTing

- To avoid a bleed by omitting aspirin with Warfarin and Clopidogrel, the number need to treat is just four (NNT = 4).
  - Mostly minimal and minor bleeding reduced
  - These events are not minor from a clinical standpoint.
  - A reduction in minor bleeding is still very important (i.e. If you cut yourself shaving and you can't stop the bleeding, that can be a big deal).

- While the major bleeding reduction was not significant, the NNT to avoid a major bleed was only 40

- The numerical reductions in stent thrombosis and stroke without aspirin were somewhat surprising and could either be a chance finding or could mean that bleeding is more important than antithrombotic effects for outcomes.
WOEST Trial: What is the Optimal antiplatelet and anticoagulation therapy in patients with oral anticoagulation and coronary Stenting

- In short, the results of the WOEST trial show that aspirin is not needed after coronary stenting in chronically anticoagulated patients treated with clopidogrel.

- Although the trial was underpowered to detect a difference in the occurrence of stent thrombosis, no suggestion of increased thrombosis in the patients treated with only double therapy was noted.
Extrapolating from WOEST: STEMI/PCI patients with Atrial Fibrillation

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Section 8.5 - Anticoagulation

- Class I

- 1. Anticoagulant therapy with a VKA should be provided to patients with STEMI and atrial fibrillation with CHADS2# score greater than or equal to 2, mechanical heart valves, venous thromboembolism, or hypercoagulable disorder. (Level of Evidence: C)

- 2. The duration of triple-antithrombotic therapy with a VKA, aspirin, and a P2Y12 receptor inhibitor should be minimized to the extent possible to limit the risk of bleeding. After this initial treatment period, consider therapy with a vitamin K antagonist plus a single antiplatelet agent. (Level of Evidence: C)
Extrapolating from WOEST: STEMI/PCI patients with Atrial Fibrillation (cont.)

Class IIa

1. Anticoagulant therapy with a vitamin K antagonist is reasonable for patients with STEMI and asymptomatic LV mural thrombi. (Level of Evidence: C)

Class IIa

1. Anticoagulant therapy may be considered for patients with STEMI and anterior apical akinesis or dyskinesis. (Level of Evidence: C)
Extrapolating from WOEST: Newer Anticoagulants?

Major results of phase 3 trials of new anticoagulants vs warfarin in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug/trial</th>
<th>Stroke/thromboembolism</th>
<th>Hemorrhagic stroke</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa (Dabigatran) /RE-LY</td>
<td>34% reduction</td>
<td>74% reduction</td>
<td>Similar</td>
</tr>
<tr>
<td>Xarelto (Rivaroxaban) /ROCKET-AF</td>
<td>Noninferior to warfarin</td>
<td>40% reduction</td>
<td>Similar</td>
</tr>
<tr>
<td>Eliquis (Apixaban) /ARISTOTLE</td>
<td>20% reduction</td>
<td>50% reduction</td>
<td>30% reduction</td>
</tr>
</tbody>
</table>
Extrapolating from WOEST: Newer Anticoagulants?

- Pradaxa (Dabigatran): Direct Thrombin Inhibitor
  - 8% of the patients in RE-LY were on clopidogrel; the use of clopidogrel at study entry was not a contraindication.

- Eliquis (Apixiban): Factor Xa Inhibitor
  - APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or DAPT, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

- Xarelto (Rivaroxaban): Factor Xa Inhibitor
  - The lower of the two doses Xarelto (2.5mg BID) tested in the ATLAS ACS 2 TIMI 51 trial reduced overall and cardiovascular mortality vs placebo, despite an increased risk of bleeding and intracranial hemorrhage. All patients took low-dose (75-100 mg) aspirin and 93% were also on clopidogrel.
Moving Forward

- Newer Antiplatelet Therapies are more Potent Agents
  - Ticagrelor
  - Prasugrel
- Which combination will be best?
  - Warfarin/Clopidogrel seems the new standard….today
- Needs Further Study:
  - Warfarin/Ticagrelor or Warfarin/Prasugrel?
  - Factor Xa Inhibitor/P2Y12 Receptor Antagonist of choice
  - Direct Thrombin Inhibitor/P2Y12 Receptor Antagonist of choice
Moving Forward

- If nothing else, with new agents and options....it’s a fun time to be in this area of medicine!!

- Much Thanks

- Questions?

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