L'aspirina è diventata obsoleta nell'era dei nuovi inibitori P2Y12?

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Scientific Advances and Cardiovascular Mortality

Randomised Trial of Intravenous Streptokinase, Oral Aspirin, Both, or Neither among 17187 Cases of Suspected Acute Myocardial Infarction: ISIS-2

Placebo infusion: 1029 vascular deaths (12.0%)
Placebo tablets: 1016 vascular deaths (11.8%)
Placebo infusion and tablets: 568 vascular deaths (13.2%)
Streptokinase: 791 vascular deaths (9.2%)
Aspirin: 804 vascular deaths (9.4%)
Streptokinase and Aspirin: 343 vascular deaths (8.0%)

ISIS-2 Collaborative Group, Lancet 1988; II:349-360
Aspirin in Secondary Prevention


16 secondary prevention trials

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>880 (4.70)</td>
<td>115 (2.59)</td>
<td>995 (4.30)</td>
</tr>
<tr>
<td></td>
<td>1057 (5.79)</td>
<td>157 (3.36)</td>
<td>1214 (5.30)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>95 (0.51)</td>
<td>45 (1.04)</td>
<td>140 (0.67)</td>
</tr>
<tr>
<td></td>
<td>123 (0.67)</td>
<td></td>
<td>0.72 (0.51-1.03)</td>
</tr>
<tr>
<td>Total</td>
<td>149 (0.77)</td>
<td></td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.00001</td>
</tr>
<tr>
<td>Serious vascular event</td>
<td>18 (0.88)</td>
<td>250 (5.88)</td>
<td>1505 (6.69)</td>
</tr>
<tr>
<td></td>
<td>1487 (8.45)</td>
<td></td>
<td>0.78 (0.61-0.99)</td>
</tr>
<tr>
<td>Total</td>
<td>1675 (7.55)</td>
<td></td>
<td>p=0.04</td>
</tr>
</tbody>
</table>

*99% CI or <–< 95% CI*

Limited Data on Aspirin After PCI With Stent Implantation!

16 Secondary Prevention Trials – 43,000 Patient-Years
Risk of Bleeding With Aspirin

**Extracranial Bleeding**

<table>
<thead>
<tr>
<th>PRIMARY PREVENTION</th>
<th>HR (95% CI)</th>
<th>P-Heter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.54</td>
<td>(1.30-1.82)</td>
<td>0.20</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SECONDARY PREVENTION</th>
<th>HR (95% CI)</th>
<th>P-Heter</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.69</td>
<td>(1.25-5.76)</td>
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</table>

**Hemorrhagic Stroke**

<table>
<thead>
<tr>
<th>PRIMARY PREVENTION</th>
<th>HR (95% CI)</th>
<th>P-Heter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.32</td>
<td>(1.00-1.75)</td>
<td>0.40</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SECONDARY PREVENTION</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.67</td>
<td>(0.97-2.90)</td>
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</table>
Clinical Issues With Aspirin

- Treatment Failure ("Aspirin Resistance")
  - Aspirin preparation (ie, enteric coated formulations)
  - Drug-drug interactions (ie, NSAIDs)
  - COX-1 related pathways
  - Medication noncompliance
  - Premature discontinuation

- Irreversible platelet inhibition

- Bleeding risk

- Gastrotoxicity
Bimodal response to aspirin loading and effects on tissue perfusion in STEMI

Fefer et al. Platelets 2013; 24: 435-440
Why has the role of aspirin as an inevitable component of antiplatelet therapy never been seriously challenged?

- Aspirin is established in clinical practice as the default antiplatelet therapy in cardiovascular disease.

- Aspirin alone has not been found sufficient to reduce ischaemic events in several clinical settings. As a result, the concept of dual antiplatelet therapy has become established.

- Studies of newer and stronger P2Y12 receptor inhib. have all been conducted in the presence of aspirin
  
  - Unethical for aspirin not to be included
  
  - In some clinical settings such as in patients receiving coronary stents previous studies suggested that antiplatelet monotherapy without aspirin was ineffective
What is the net clinical effect of aspirin in patients receiving newer and more potent P2Y12 receptor antagonists?
Effects of aspirin and P2Y12 receptor antagonists on platelet pathways

Berger JS Am J Cardiol 2013;112:737-745
ASA-Related Effects via Inhibition of Endothelium-Released PGI$_2$

The Asprin Paradox

Blood vessel (cross section)

Net effect of ASA-induced reduction in PGI$_2$
- Increased vascular tone (resistance)
- Increased platelet reactivity
In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation.
Antiplatelet effects of aspirin vary with level of P2Y12 receptor blockade supplied by ticagrelor

Aspirin in dogs increases vascular resistance with limited additional anti-platelet effect when combined with potent P2Y12 inhibition

Björkman JA et al. Thrombosis Research 131;2013: 313–319
Is there an opportunity to reconsider the unchallenged role of aspirin in this clinical context?

- Aspirin key role as an inhibitor of arachidonic acid-stimulated clotting may by mimicked by P2Y12 inhib.

- The anti-platelet benefit of aspirin and P2Y12 antagonists may not be additive, as inhibition of P2Y12 can also effectively inhibit the TXA2 pathway of platelet activation in the absence of aspirin

- An aspirin-mediated reduction in PGI2 production might oppose the effect achieved by aspirin-mediated inhibition of platelet TXA2 formation
Does aspirin increase clinical risk in the presence of potent P2Y12 receptor antagonists?

Warner TD et al. Heart 2010;96:1693e1694
MATCH study

7,599 pts with recent stroke or TIA. All on clopidogrel. Randomization to receive ASA or Placebo on top.

Vascular death, stroke, MI, rehosp for ACS

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Aspirin and clopidogrel</th>
<th>Placebo and clopidogrel</th>
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<tr>
<td>Aspirin and clopidogrel</td>
<td>3797 3576 3440 3321 3229 3130 2441</td>
<td></td>
</tr>
<tr>
<td>Placebo and clopidogrel</td>
<td>3802 3576 3439 3326 3200 3119 2446</td>
<td></td>
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Intracranial bleeding

<table>
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<tr>
<th>Patients at risk</th>
<th>Aspirin and clopidogrel</th>
<th>Placebo and clopidogrel</th>
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</thead>
<tbody>
<tr>
<td>Aspirin and clopidogrel</td>
<td>3724 3691 3643 3601 3552 3508 2756</td>
<td></td>
</tr>
<tr>
<td>Placebo and clopidogrel</td>
<td>3781 3576 3686 3638 3582 3544 2823</td>
<td></td>
</tr>
</tbody>
</table>

Lancet 2004; 364: 331–37
Rates of the composite end point by open-label median maintenance aspirin dose in patients enrolled in the PLATO trial

Mahaffey KW et al. Circulation 2011;124:544e554
Aspirin dose and ticagrelor benefit in PLATO: fact or fiction?

Source: www.fda.gov/downloads
The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting

Paradigm Shift in Interventional Pharmacology: Is it time to drop aspirin?

Paradigm Shift: Is it time to drop aspirin?

Ongoing Clinical Trials

1. GLOBAL LEADERS
   - Ticagrelor monotherapy in PCI with bioabsorbable stents (n=16,000)

2. ABSORB-OAC
   - Clopidogrel/Ticagrelor monotherapy in PCI with BVS

3. COMPASS
   - Rivaroxiban monotherapy for 2° prevention post-MI & PAD (n=19,500)

4. PIONEER
   - Rivaroxiban + clopidogrel post-PCI with AFib (n=2,100)

5. RE-DUAL PCI
   - Dabigatran + clopidogrel/ticagrelor post-PCI with Afib (n=8520)

6. TRIPLE A Study
   - Apixaban monotherapy +/- aspirin
GLOBAL LEADERS Study Design

A new strategy: DAPT+SAT vs DAPT

≈16,000 patients with BES

R

1 mo aspirin+ticagrelor
23 mo ticagrelor

12 mo DAPT
12 mo aspirin

24 months of follow up after randomization
Primary Endpoint: Composite of all-cause mortality or non-fatal new Q-wave myocardial infarction

NCT01813435
Patient with long-term OAC (CHA_2DS_2-VASc > 1) undergoing PCI

- ABSORB-BVS is implanted

- Elective patients: OAC + Clopidogrel 3 months
  ACS: OAC + Ticagrelol 3 months

- OCT 3 months after the BVS implantation

* OCT will guide antithrombotic regimen beyond 3 months;
  → OAC monotherapy versus OAC + clopidogrel/ticagrelol (6 or 12 months)
XARELTO® (rivaroxaban) Use in Patients With AF Undergoing PCI: PIONEER AF-PCI

- 2100 patients with NVAF
- No prior stroke/TIA
- PCI with stent placement

Randomize

≤72 hours after sheath removal

1,6, or 12 months

- Primary endpoint: TIMI major, minor, and bleeding requiring medical attention
- Secondary endpoint: CV death, MI, stroke, and stent thrombosis

XARELTO® 15 mg qd*
 Clopidogrel 75 mg qd†

XARELTO® 2.5 mg bid
 Clopidogrel 75 mg qd†
 Aspirin 75-100 mg qd‡

XARELTO® 15 mg QD
 Aspirin 75-100 mg qd

VKA (target INR 2.0-3.0)
 Clopidogrel 75 mg qd†
 Aspirin 75-100 mg qd

End of treatment at 12 months

*XARELTO® dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative P2Y₁₂ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d).
Data on File. Janssen Pharmaceuticals, Inc.
Apixaban in AF/ACS: The TRIPLE A Trial Design

Patients with AF (CHADS ≥1) and ACS, PCI or both. Planned P2Y12 x ≥6 months

Randomise

- Apixaban 5.0 mg bid
- Apixaban 2.5 mg bid
- VKA INR 2–3

Randomise

- Aspirin ≤100 mg qd
- Aspirin Placebo

Primary: ISTH Major or CRNM Bleeding at 6 months
Secondary: Death, MI, stroke, stent thrombosis at 6 months
With the arrival of the potent P2Y12 antagonists, ticagrelor and prasugrel, the need for cotreatment with aspirin in acute coronary syndromes must be re-examined.

So far, no information exists on the effect of the more potent P2Y12 antagonists as monotherapy.

Landmark randomized studies investigating these issues are ongoing.
"An aspirin a day will help prevent a heart attack if you have it for lunch instead of a cheeseburger."