Aspirin Therapy in Primary Cardiovascular Disease
Prevention Only for Those at High Cardiovascular Risk, the Dose Under Trials

Raffaele De Caterina
December 11, 2015 – 16:15-16:35, 20 min. + 35 min. disc.
Co-author ESC Guidelines on Atrial Fibrillation 2010-2012

Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI

Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck. Lilly

None related to this topic
The spectrum of cardiovascular risk

Risk of a major cardiovascular event: death, myocardial infarction, stroke (n. of events/100 subjects/year)

- Normal subjects (any age) = <2
- High-risk primary prevention = 2-4
- Post-MI (chronic phase), post-stroke, and stable CAD = >4
- ACS = >10
EFFICACY and EFFICIENCY of aspirin at different levels of CV risk in secondary and primary prevention

<table>
<thead>
<tr>
<th>Condition</th>
<th>CV risk level</th>
<th>No. events % pts/year</th>
<th>Relative RR</th>
<th>Absolute RR (No. Events)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS (high risk)</td>
<td>15</td>
<td>- 30%</td>
<td>4.5</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Stable angina (medium risk)</td>
<td>4</td>
<td>- 30%</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention (low risk)</td>
<td>1</td>
<td>-30% (?)</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nota: However, as primary prevention could be extended to whole populations, the small absolute reduction could translate into exceedingly high numbers.

*De Caterina, Coccheri et al, G Ital Card 2012*
4 recent meta-analyses of trials of primary CV prevention with aspirin

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non fatal MI</strong></td>
<td>0.84 n</td>
<td>0.81*</td>
<td>0.83*</td>
<td>0.80*</td>
</tr>
<tr>
<td><strong>Stroke (all)</strong></td>
<td>0.94 n</td>
<td>0.92 n</td>
<td>0.93 n</td>
<td>0.94 n</td>
</tr>
<tr>
<td><strong>Composite endpoint°</strong></td>
<td><strong>0.90</strong>*</td>
<td><strong>0.86</strong>*</td>
<td><strong>0.88</strong>*</td>
<td><strong>0.90</strong>*</td>
</tr>
<tr>
<td><strong>Vascular mortality</strong></td>
<td>0.99 n</td>
<td>0.96 n</td>
<td>0.96 n</td>
<td>0.99 n</td>
</tr>
<tr>
<td><strong>Total mortality</strong></td>
<td>0.94 n</td>
<td>0.94 n</td>
<td>0.94 n</td>
<td>0.94 n</td>
</tr>
</tbody>
</table>

°Composite endpoint= nf MI + nf Stroke + Vasc Death; *= significant; n=non-significant

**Comment**

Across the 4 meta-analyses, there is total concordance on the composite endpoint (always significant). Negative concordance for vascular and total mortality (claimed significant by Raju). Accord in non-fatal AMI (significant in 3 out of 4).
**NET BENEFIT OF ASPIRIN IN PRIMARY PREVENTION?**

*In fact*

- *In 1000 persons treated for 5 years there were:*
  - About 3 ischemic events avoided
  - About 3 major bleeds caused

  **poor net benefit**

From Berger JS, Am Heart J, 2011
### Benefit and harms (absolute risk figures per 100,000 patient-years of follow-up) in primary prevention with aspirin

<table>
<thead>
<tr>
<th>Benefits (events averted)</th>
<th>Number and (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total mortality</strong></td>
<td>33-46 (250)</td>
</tr>
<tr>
<td><strong>Major CV events</strong></td>
<td>60-84 (138)</td>
</tr>
<tr>
<td><strong>CHD events</strong></td>
<td>47-64 (182)</td>
</tr>
<tr>
<td><strong>Cancer mortality</strong></td>
<td>17-85 (n.c.)</td>
</tr>
<tr>
<td><strong>Colorectal cancer mortality</strong></td>
<td>34-36 (285)</td>
</tr>
</tbody>
</table>

*Source: Sutcliffe P et al. Health Techn Ass 2013*
NEWS 2013-2014
ON PRIMARY PREVENTION OF CV EVENTS

• The use of aspirin seems no longer justifiable in primary prevention in patients with or without diabetes

• Low dose aspirin can cause upper gastro-intestinal bleeding (UGIB): RR 1.90 in primary vs RR 1.40 in secondary prevention: however because of higher baseline risk incidence of UGIB is higher in secondary (NNH 391) than in primary prevention (NNH 601)
  Lin KJ et al. Circulation CQO 2014

Thus, an important shift in advice, as only 5 years before the statement was that «a baby aspirin should be used in every male American >50 years of age»
AND IN PEOPLE WITH DIABETES?

A meta-analysis

• 20 studies including 17,522 pts of which 13 of secondary prevention and 7 of primary prevention

• Aspirin use in secondary prevention associated with lower mortality RR= 0.82; p = 0.03

• Aspirin use in primary prevention : RR = 1.01; n.s.

• Results highly heterogeneous among trials

Simpson SH et al. J Gen Int Med 2011
And in asymptomatic PAD patients?

POPADAD (with diabetes) and AAA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>0.93-0.95 (ns)</td>
</tr>
<tr>
<td>Non fatal AMI</td>
<td>0-91-0.98 (ns)</td>
</tr>
<tr>
<td>Non fatal stroke</td>
<td>0.71-0.87 (ns)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.95-1.23 (ns)</td>
</tr>
<tr>
<td>Composite vascular events</td>
<td>0.98-1.00 (ns)</td>
</tr>
</tbody>
</table>

Safety concerns: Inconclusive results

*There was HIGH STRENGTH OF EVIDENCE for all efficacy endpoints*

Leading to statements like this:

- «… doctors should select on an individual basis after careful discussion with the patient…»
  or
- «aspirin cannot be recommended in primary prevention due to its increased risk of major bleeding” *

*2012 European Society of Cardiology (ESC) Guidelines on Cardiovascular Disease Prevention in Clinical Practice
But if cardiovascular risk is a spectrum, how can we dichotomize recommendations?

Risk of a major cardiovascular event: death, myocardial infarction, stroke (n. of events/100 subjects/year)

- Normal subjects (any age) = <2
- High-risk primary prevention = 2-4
- Post-MI (chronic phase), post-stroke, and stable CAD = >4
- ACS = >10

YES! NO!
“Natura non facit saltus.”
(Nature does not make jumps)
Gottfried Leibniz

REVIEW TOPIC OF THE WEEK

Aspirin Therapy in Primary Cardiovascular Disease Prevention
A Position Paper of the European Society of Cardiology Working Group on Thrombosis

Sigrun Halvorsen, MD,* Felicita Andreotti, MD, PhD,† Jurriën M. ten Berg, MD,‡ Marco Cattaneo, MD,§ Sergio Coccheri, MD,|| Roberto Marchioli, MD,¶ João Morais, MD,# Freek W. A. Verheugt, MD,** Raffaele De Caterina, MD, PhD††
Major CV events
Y = -0.015 + 0.152 X
P = 0.017; R² = 0.532

Major Bleeding*
Y = 0.013 + 0.060 X
P = 0.112; R² = 0.285

Major GI Bleeding*
Y = 0.024 + 0.032 X
P = 0.211; R² = 0.213

Halvorsen S, ...De Caterina R, JACC 2015
Low-dose aspirin and cancer mortality - a new element in decision-making

• A meta-analysis of 23 randomized trials of low dose aspirin, primary or secondary prevention, any duration

• All trials reported that non-vascular mortality was reduced by aspirin: RR 0.88 (0.81-0.96)

• 11 trials reported that cancer mortality was even more reduced: RR 0.77 (0.63-0.95)

• Effects became statistically significant after 4y follow up

Effect of aspirin on cancer incidence and mortality

From an analysis of 51 randomized trials

• In six trials of primary CV prevention low dose aspirin reduced cancer incidence from 3y onwards in men and women (OR 0.76/0.77, p significant)

• With increasing follow up effect on CVE and bleeding declined leaving alone the reduced risk of cancers

• The absolute reduction in cancer incidence was 3.13 cases per 1000 pts/year from 3y onwards

Rothwell PM et al. Lancet 2012
Aspirin prevention of cancer

- Strength of evidence of long-term prophylactic effect of low-dose aspirin towards cancer is higher for:
  - Long duration (> 5 y)
  - Colorectal versus other types of cancer
  - Daily administration and compliance

- However, results are based on trials of several types: and especially on groups nested in studies “post hoc” rather than “ad hoc”

- And still some groups deny primary prevention of cancer by aspirin (Hollestein LM et al. Int J Cancer 2014)
Ongoing randomized trials of low-dose aspirin for primary CVD prevention

**TABLE 2 Ongoing Randomized Trials of Low-Dose Aspirin for Primary Prevention**

<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Regimen(s)</th>
<th>Treatment Duration</th>
<th>N</th>
<th>Eligibility</th>
<th>Primary Endpoint</th>
<th>End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCEPT-D (23)</td>
<td>Aspirin 100 mg versus open control; simvastatin for all</td>
<td>5 yrs</td>
<td>5,170</td>
<td>Diabetes, no CVD</td>
<td>CV death, nonfatal stroke, nonfatal MI, other CV hospitalization</td>
<td>2015</td>
</tr>
<tr>
<td>ARRIVE (25)</td>
<td>Aspirin 100 mg versus placebo</td>
<td>5 yrs</td>
<td>~12,000</td>
<td>10-20% estimated 10-yr risk of CHD</td>
<td>MI, stroke, CV death, unstable angina, TIA</td>
<td>2016</td>
</tr>
<tr>
<td>ASPREE (24)</td>
<td>Aspirin 100 mg versus placebo</td>
<td>5 yrs</td>
<td>~19,000</td>
<td>Elderly, no diabetes or CVD</td>
<td>Death, dementia or significant disability</td>
<td>2017</td>
</tr>
<tr>
<td>ASCEND (22)</td>
<td>Aspirin 100 mg versus placebo (ω3FA vs. placebo)</td>
<td>7.5 yrs</td>
<td>~15,000</td>
<td>Diabetes, no CVD</td>
<td>MI, stroke or TIA, or CV death</td>
<td>2018</td>
</tr>
</tbody>
</table>

ACCEPT-D = Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trials in Diabetes; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = ASPirin in Reducing Events in the Elderly; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; FA = fatty acids; MI = myocardial infarction; TIA = transient ischemic attack.

Paterno C, JACC 2015;66:74-85
# Ongoing Randomised Trials of Aspirin vs Placebo: High-Risk Cancer Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen(s)</th>
<th>Treatment duration</th>
<th>N</th>
<th>Eligibility</th>
<th>Primary endpoint</th>
<th>Estimated total of all cancers</th>
<th>End date</th>
</tr>
</thead>
<tbody>
<tr>
<td>AspECT</td>
<td>A300 vs P</td>
<td>8 y</td>
<td>2500</td>
<td>Barrett’s oesophagus</td>
<td>Death/adenocarcinoma or high-grade metaplasia</td>
<td>~120</td>
<td>2017</td>
</tr>
<tr>
<td>seAFOod</td>
<td>A300 vs P</td>
<td>1 y</td>
<td>904</td>
<td>Multiple adenomas at BCSP</td>
<td>≥1 adenoma at 1 year screen</td>
<td>&lt;10</td>
<td>NA</td>
</tr>
<tr>
<td>ASCOLT</td>
<td>A200 vs P</td>
<td>3y</td>
<td>2660</td>
<td>Dukes C or high-risk Dukes B cancer</td>
<td>3 year disease-free survival</td>
<td>900</td>
<td>NA</td>
</tr>
<tr>
<td>ADD-Aspirin</td>
<td>A100 vs A300 vs P</td>
<td>5y</td>
<td>~9,920</td>
<td>CRC, breast, gastro-oesophageal, prostate ca</td>
<td>Disease-free survival (death for gastro-oesophageal)</td>
<td>3400</td>
<td>2025</td>
</tr>
</tbody>
</table>

**Abbreviations:** BCSP = Bowel Cancer Screening Programme; CRC = colorectal cancer

Patrono, JACC 2015;66:74-85
CONCLUSIONS AND PROPOSED RECOMMENDATIONS

• Aspirin use in primary prevention of MCE should be guided by an assessment of the global cardiovascular risk. Risk of colorectal cancer may support long term duration of treatment.

• Aspirin is expected to be beneficial at the level of risk of MCE > 2/100 person-years, in absence of an increased risk of bleeding

Source: Halvorsen S…De Caterina R. JACC, 2014

Collaborative group:
S. Halvorsen (Oslo); F. Andreotti (Rome); J.M. Ten Berg (Nieuwegein); M. Cattaneo (Milan); S. Coccheri (Bologna); R. Marchioli (Chieti); J. Morais (Leiria); F.W.A. Verheugt (Amsterdam); R. De Caterina (Chieti).
Low-dose aspirin in primary CVD prevention

Step 1: Assess 10 year risk of major CV events

- <10%
- 10-20%
- >20%

Step 2: history of bleeding without reversible causes, concurrent use of other medications that increase bleeding risk

- Yes
- No

Consider family history of GI (especially colon) cancer / patient values and preferences

- Yes
- No

Low-dose aspirin

Stop
Caution
Go!

Halvorsen S, …De Caterina R, JACC 2015
• We are aware of the lack of data in the high-risk primary prevention category
• But lack of evidence is NOT evidence against
• Decisions in the meantime will have to be taken
• And logic should here help

At the end, we don’t put hands on fire, despite having no RCT to support this
Aspirin Therapy in Primary Cardiovascular Disease Prevention

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Sigrun Halvorsen, MD,* Felicita Andreotti, MD, PhD,† Jurriën M. ten Berg, MD,‡ Marco Cattaneo, MD,§ Sergio Coccheri, MD,|| Roberto Marchioli, MD,¶ João Morais, MD,# Freek W. A. Verheugt, MD,** Raffaele De Caterina, MD, PhD††
DOCUMENTO DI CONSENSO

La terapia con aspirina nella prevenzione cardiovascolare primaria. Documento di consenso intersocietario italiano

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³Università degli Studi di Bologna
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Thank you!