Low-Dose Aspirin, Atherothrombosis and Cancer

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• European Commission, FP6 and FP7 Programmes
• Bayer, Servier
Acetylation of Platelet COX-1, Inhibition of TXA₂ Production and Reduction of Vascular Events by Aspirin are Saturable at Low Doses

Mechanism of Action

Clinical Pharmacology of Platelet COX-1

ATT Collaboration Meta-Analysis of Aspirin Trials in High-Risk Patients

Comparison | Aspirin | Control | Reduction
---|---|---|---
Asp 75-150 | 11.0% | 15.2% | 32%±6
Asp 160-325 | 11.5% | 14.8% | 26%±3
Asp 500-1500 | 14.5% | 17.2% | 19%±3
Any aspirin | 12.9% | 16.1% | 23%±2 (2P<0.00001)

J Clin Invest 1982;69:1366-72

BMJ 2002;324:71-86
## Serious Vascular Events in Primary Prevention Trials

<table>
<thead>
<tr>
<th>End-point</th>
<th>Events (% per annum)</th>
<th>Ratio of annual event rates (&amp; CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated aspirin</td>
<td>Adjusted control</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>596 (0.18%/y)</td>
<td>756 (0.23%/y)</td>
</tr>
<tr>
<td>CHD death</td>
<td>372 (0.11%/y)</td>
<td>393 (0.12%/y)</td>
</tr>
<tr>
<td>(a) Any major coronary event</td>
<td>934 (0.28%/y)</td>
<td>1115 (0.34%/y)</td>
</tr>
<tr>
<td>(b) Any Stroke</td>
<td>655 (0.20%/y)</td>
<td>682 (0.21%/y)</td>
</tr>
<tr>
<td>(c) Vascular death</td>
<td>619 (0.19%/y)</td>
<td>637 (0.19%/y)</td>
</tr>
<tr>
<td>(a/b/c) any serious vascular event</td>
<td>1671 (0.51%/y)</td>
<td>1883 (0.57%/y)</td>
</tr>
</tbody>
</table>

- **99% or 95% confidence intervals**
- **Aspirin better**
- **Aspirin worse**

**ATT Collaboration, Lancet 2009;373:1849-60**
Balancing the Benefits and Bleeding Risks of Aspirin, as a Function of CHD Risk

ATT Collaboration, Lancet 2009; 373:1849-60
Balancing the Benefits and Bleeding Risks of Aspirin, as a Function of CHD Risk

5-year CHD risk >10%

A = Aspirin
C = Control

$\Delta = +10$ per 1,000 in 5 yr

Aspirin ALONE

A C
14.0% 16.0%

Non-fatal MI, stroke or vascular death

Aspirin ADDED to other drugs that halve risk

A C
7.0% 8.0%

Non-fatal GI bleed

ATT Collaboration, Lancet 2009; 373:1849-60
American College of Chest Physicians 2012 Guidelines

For persons aged 50 years or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).

Vandvik et al, CHEST 2012; 141(Suppl):e637S–e668S
Aspirin cannot be recommended in primary prevention due to its increased risk of major bleeding (Grade IIIIB).

Perk et al, Eur Heart J 2012; May 3 Epub ahead of print
“Hence, the currently available trial results do not seem to justify general guidelines advocating the routine use of aspirin in all asymptomatic individuals above a moderate level of coronary risk, unless additional long-term benefits of antiplatelet therapy become established”.

Patrono et al, Eur Heart J 2011; 32:2922-32
Arachidonic Acid

Aspirin

NSAIDs

COX-1

COX-2

PGH₂

Prostaglandin synthases

PGD₂, PGF₂α, PGI₂, TXA₂

PGE₂


PPARδ

β-Catenin

EGF-R

PI₃K/AKT

transcriptional activity

Cyclin D₁

Bcl-2

VEGF

Biologic activities

Growth

Migration & invasion

Anti-apoptosis

Angiogenesis

Modified from Markowitz. NEJM 2007;356:2195-8
RCTs of Aspirin or COX-2 Inhibitors in Patients with Previous Polyps or Colorectal Cancer

- **4 RCTs of aspirin**

- **3 RCTs of COX-2 inhibitors**
  - Baron JA et al. Gastroenterology 2006; 131:1674-82
Relative Risk of Any Colorectal Adenoma at Follow-up Endoscopic Examination

<table>
<thead>
<tr>
<th>Drug/dose</th>
<th>RR (95% CI)</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib 400 mg bid</td>
<td></td>
<td>APC, 2006</td>
</tr>
<tr>
<td>Celecoxib 200 mg bid</td>
<td></td>
<td>APC, 2006</td>
</tr>
<tr>
<td>Rofecoxib 25 mg</td>
<td></td>
<td>APPROVe, 2006</td>
</tr>
<tr>
<td>Aspirin 325 mg</td>
<td></td>
<td>Sandler et al, 2003</td>
</tr>
<tr>
<td>Aspirin 325 mg</td>
<td></td>
<td>Baron et al, 2003</td>
</tr>
<tr>
<td>Aspirin 81 mg</td>
<td></td>
<td>Baron et al, 2003</td>
</tr>
</tbody>
</table>

Patrono & Rocca, ATVB 2008;28:25S-32S
Activated Platelets at Sites of Intestinal Mucosal Injury

Pro-angiogenic

\[ \text{TXA}_2 \]
\[ \text{PDGF} \]
\[ \text{TGF}\beta \]

Endothelial cells

\[ \uparrow \text{COX-2} \]

\[ \downarrow \text{Angiogenesis} \]

Low-dose Aspirin

Pro-inflammatory

\[ \text{PGE}_2 \]
\[ \text{IL-1}\beta \]

Stromal cells

\[ \uparrow \text{COX-2} \]

\[ \downarrow \text{Apoptosis} \uparrow \text{Cellular proliferation} \]

Aspirin and Colorectal Cancer

• If aspirin does indeed prevent the early development of an adenomatous lesion, one would require a long-term follow-up of aspirin-treated patients in order to detect a beneficial effect on the risk of colorectal cancer (CRC) and CRC-related death.
Long-Term Effect of Aspirin on Colorectal Cancer Incidence and Mortality: 20-Year Follow-Up of Five Randomised Trials.

Rothwell PM et al. Lancet 2010;376:1741-50
Pooled Analysis of the Effect of Low-Dose (75-300mg) Aspirin (thick line) versus Control (thin line) on Subsequent Incidence and Mortality Due to Colorectal Cancer in TPT, SALT and UK-TIA

A: 4030 3618 3095 2552 779
C: 4043 3645 3149 2545 806

Rothwell PM et al, Lancet 2010; 376:1741-50
Aspirin and Colorectal Cancer

- If the chemopreventive effect of aspirin is related - directly or indirectly - to its antiplatelet action, then one would expect saturability of cancer prevention at low doses (ie 75-100 mg) given once daily.
Death Due to Colorectal Cancer on Long-Term Follow-Up After Randomization in Trials of Aspirin vs Control

<table>
<thead>
<tr>
<th>Deaths due to Cancer</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td><strong>Control</strong></td>
<td></td>
</tr>
<tr>
<td>500-1200mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>British Doctors Study (500mg)</td>
<td>59/3429</td>
<td>40/1710</td>
</tr>
<tr>
<td>UK-TIA (1200mg)</td>
<td>11/821</td>
<td>16/817</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>70/4250</td>
<td>56/2527</td>
</tr>
<tr>
<td>75 - 300mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK-TIA (300mg)</td>
<td>8/811</td>
<td>16/817</td>
</tr>
<tr>
<td>TPT (75mg)</td>
<td>34/2545</td>
<td>55/2540</td>
</tr>
<tr>
<td>SALT (75mg)</td>
<td>7/676</td>
<td>10/684</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>49/4032</td>
<td>81/4041</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>119/8282</td>
<td>137/6568</td>
</tr>
</tbody>
</table>

Heterogeneity: p=0.84

Rothwell PM et al, Lancet 2010; 376:1741-50
Aspirin and Colorectal Cancer

• One would not expect short-term effects of aspirin on cancer incidence and mortality, unless the drug also interferes with cancer metastasis.
Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials

Peter M Rothwell, Jacqueline F Price, F Gerald R Fowkes, Alberto Zanchetti, Maria Carla Roncaglioni, Gianni Tognoni, Robert Lee, JIll F F Belch, Michelle Wilson, Ziyah Mehta, Tom W Meade

Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials

Peter M Rothwell, Michelle Wilson, Jacqueline F Price, Jill F F Belch, Tom W Meade, Ziyah Mehta

Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials

Annemijn M Algra, Peter M Rothwell
Cancer Incidence During Six Randomised Trials of Daily Low-Dose Aspirin in Primary Prevention of Vascular Events

<table>
<thead>
<tr>
<th>Trial Follow-up</th>
<th>Events/Subjects</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2.9 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAA</td>
<td>50/1675</td>
<td>1.02</td>
<td>0.68-1.52</td>
</tr>
<tr>
<td>TPT</td>
<td>72/2545</td>
<td>0.92</td>
<td>0.66-1.27</td>
</tr>
<tr>
<td>POPADAD</td>
<td>23/638</td>
<td>1.00</td>
<td>0.56-1.80</td>
</tr>
<tr>
<td>JPAD</td>
<td>12/1262</td>
<td>1.01</td>
<td>0.45-2.26</td>
</tr>
<tr>
<td>HOT</td>
<td>219/9399</td>
<td>0.97</td>
<td>0.81-1.17</td>
</tr>
<tr>
<td>PPP</td>
<td>69/2226</td>
<td>1.29</td>
<td>0.90-1.84</td>
</tr>
<tr>
<td>TOTAL</td>
<td>445/17745</td>
<td>1.01</td>
<td>0.88-1.15</td>
</tr>
</tbody>
</table>

| ≥3 years        |                 |            |              |
| AAA             | 116/1593        | 0.79       | 0.61-1.02    |
| TPT             | 84/2431         | 0.74       | 0.56-0.99    |
| POPADAD         | 22/532          | 0.58       | 0.34-1.00    |
| JPAD            | 3/1095          | 0.44       | 0.11-1.69    |
| HOT             | 75/9063         | 0.87       | 0.64-1.18    |
| PPP             | 24/1689         | 0.71       | 0.42-1.21    |
| TOTAL           | 324/16463       | 0.76       | 0.66-0.88    |

Rothwell et al, Lancet 21 March 2012
Five-Year Risk of Vascular Events and Major Bleeding Based on Primary Prevention Trials of Aspirin vs Placebo, and Hypothetical 10% Reduction in Cancer Incidence by Age and Sex

Females, age 50-59 years

<table>
<thead>
<tr>
<th></th>
<th>5-year risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>A 0.3% C 0.2%</td>
</tr>
<tr>
<td>CVD</td>
<td>A 0.9% C 1.1%</td>
</tr>
<tr>
<td>Cancer</td>
<td>A 2.8% C 3.1%</td>
</tr>
</tbody>
</table>

Females, age 65-74 years

<table>
<thead>
<tr>
<th></th>
<th>5-year risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>A 0.9% C 0.5%</td>
</tr>
<tr>
<td>CVD</td>
<td>A 3.9% C 4.5%</td>
</tr>
<tr>
<td>Cancer</td>
<td>A 5.8% C 6.5%</td>
</tr>
</tbody>
</table>

Five-Year Risk of Vascular Events and Major Bleeding Based on Primary Prevention Trials of Aspirin vs Placebo, and Hypothetical 10% Reduction in Cancer Incidence by Age and Sex

Males, age 50-59 years

- Non-fatal bleeding events
- Vascular death
- Non-fatal MI/stroke
- All cancers

<table>
<thead>
<tr>
<th></th>
<th>Bleeding</th>
<th>CVD</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.5%</td>
<td>3.4%</td>
<td>3.1%</td>
</tr>
<tr>
<td>C</td>
<td>0.3%</td>
<td>3.9%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Males, age 65-74 years

<table>
<thead>
<tr>
<th></th>
<th>Bleeding</th>
<th>CVD</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.2%</td>
<td>8.0%</td>
<td>9.9%</td>
</tr>
<tr>
<td>C</td>
<td>0.7%</td>
<td>9.2%</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

The Human Activated Platelet

- Neurodegeneration?
- Inflammation
- Amyloid β-peptide
- Prostanoids
- Vascular Occlusion
- Myocardial Infarction
- Ischemic Stroke
- Inflammatory cytokines & oxygen radicals
- Amyloid precursor peptide
- Colo-rectal carcinogenesis
- Growth Factors
- COX-2 Induction

Patrono, in Michelson Ed. *Platelets* 2013
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