ASCEND: Is it the End of Aspirin for Primary Prevention in Diabetes?

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Disclosure Statement

No actual or potential conflicts of interest to disclose.
Lecture Objective

By the end of the presentation, learners will be able to:

• Discuss the recent literature evaluating the use of aspirin in primary prevention of cardiovascular events in patients with diabetes
Aspirin (acetylsalicylic acid)

Irreversibly blocks cyclooxygenase 1 and 2

- Low-dose aspirin (typically 75-162 mg) results in inhibition of TXA₂ and prostacyclin synthesis
  - Inhibits platelet aggregation, vasoconstriction and proliferation of vascular smooth-muscle cells
  - Increased risk of GI bleed with long-term use

TXA2: thromboxane A2; GI: gastrointestinal

Background

T2DM associated with ↑ CV risk
• Approximately 2 – 4x risk of coronary heart disease, ischemic stroke, and mortality¹

Aspirin and CV Disease
• Low-dose aspirin use well established and strongly recommended for secondary prevention of CV and cerebrovascular events
• Low-dose aspirin use for primary prevention remains controversial²-⁴
  o Clinical practice guidelines remain inconsistent


T2DM: type 2 diabetes mellitus; CV: cardiovascular
A Study of Cardiovascular Events in Diabetes (ASCEND)

Study Objective
To assess the efficacy and safety of aspirin compared to placebo in people who have diabetes without any history of CV disease

Study Design
Multicenter, randomized, two-by-two factorial, double-blind, placebo controlled trial
- Enteric coated aspirin 100 mg vs placebo
- Omega-3 fatty acid 1 g capsule vs placebo

Enrollment period: June 2005 – July 2011
Setting: United Kingdom

* Results reported separately
Study Population

Inclusion Criteria

• Men and women > 40 years of age
• Diagnosis of type 1 or 2 diabetes
• Absence of baseline CV disease

Exclusion Criteria

• Clear indication for aspirin
• Presence of clinically significant conditions limiting adherence to trial regimen for at least 5 years
• Contraindication to aspirin

- MI
- Angina
- Revascularization procedure
- Stroke
- Transient ischemic attack

- High risk of bleed
- Active hepatic disease
- Use of warfarin or other anticoagulants
- History of aspirin allergy

MI: myocardial infarction; TIA: Transient ischemic attack
Outcomes

Primary Efficacy Outcome

First SVE, defined as composite of nonfatal MI, stroke, TIA, or vascular death

Primary Safety Outcome

First major bleed, defined as composite of intracranial hemorrhage, sight-threatening bleed in eye, GI bleed, or any other bleed

Secondary Outcome

GI related cancers

SVE: serious vascular event
Patient Enrollment and Follow-up

Identification
Diabetes registries, trial databases, and general practices in United Kingdom

Questionnaire
Indicated if they were willing and eligible to participate*

Run-In Phase
8-10 week period to assess adherence

Eligibility
Returned survey confirming willingness to continue and remain adherent to trial regimen

Randomization
• 1:1 aspirin vs placebo
• n = 15,480

Follow-up
• Delivery of interventions and questionnaires every 6 months
• Mean follow-up 7.4 years

* Family doctor informed of potential participation. Requested to submit blood/urine samples and vitals.
## Baseline Characteristics (n= 15,480)

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n=7740)</th>
<th>Placebo (n=7740)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.2±9.2</td>
<td>63.3±9.2</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>62.6%</td>
<td>62.5%</td>
</tr>
<tr>
<td>White race (%)</td>
<td>96.5%</td>
<td>96.5%</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.8±6.2</td>
<td>30.6±6</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>94.1%</td>
<td>94.1%</td>
</tr>
<tr>
<td>Duration of diabetes (years), median [IQR]</td>
<td>7 [3-13]</td>
<td>7 [3-13]</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>61.6%</td>
<td>61.6%</td>
</tr>
<tr>
<td>Statin Use (%)</td>
<td>75.6%</td>
<td>74.9%</td>
</tr>
<tr>
<td>High Vascular Risk* (%)</td>
<td>17.0%</td>
<td>17.4%</td>
</tr>
</tbody>
</table>

Reported as mean ± SD unless otherwise specified
* Calculated ≥ 10% 5 year risk of SVE without aspirin or omega-3 fatty acid

### Run-in phase data

- **A1c (%) n = 9813**
  - <7.5%  •  6824 (69%)

- **eGFR (ml/min/1.73m²) n = 9815**
  - ≥90  •  4523 (46%)

- **UACR (mg/mmol) n = 9774**
  - ≥ 30  •  160 (2%)

eGFR: estimated glomerular filtration rate; UACR: urinary albumin/creatinine ratio
# Outcomes

## Primary Efficacy Outcome

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n=7740)</th>
<th>Placebo (n=7740)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First SVE</td>
<td>658 (8.5%)</td>
<td>743 (9.6%)</td>
<td>0.88 (0.79-0.97)</td>
<td>p = 0.01</td>
</tr>
</tbody>
</table>

## Primary Safety Outcome

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n=7740)</th>
<th>Placebo (n=7740)</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First major bleed</td>
<td>314 (4.1%)</td>
<td>245 (3.2%)</td>
<td>1.29 (1.09-1.52)</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>Intracranial</td>
<td>55 (0.7%)</td>
<td>45 (0.6%)</td>
<td>1.22 (0.82-1.81)</td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>57 (0.7%)</td>
<td>64 (0.8%)</td>
<td>0.89 (0.62-1.27)</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>137 (1.8%)</td>
<td>101 (1.3%)</td>
<td>1.36 (1.05-1.75)</td>
<td></td>
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</tbody>
</table>

## Secondary Outcome

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n=7740)</th>
<th>Placebo (n=7740)</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal tract cancer</td>
<td>157 (2.0)</td>
<td>158 (2.0)</td>
<td>0.99 (0.80-1.24)</td>
<td>p = 0.88</td>
</tr>
<tr>
<td>Hepatobiliary and pancreatic cancers</td>
<td>87 (1.1)</td>
<td>82 (1.1)</td>
<td>1.06 (0.78-1.43)</td>
<td></td>
</tr>
</tbody>
</table>
Authors’ Conclusion

• Aspirin significantly reduced risk of SVE and also significantly increased the risk of major bleeding
  o 91 NNT vs 112 NNH
• No group in which the benefits clearly outweighed risks
• Aspirin did not reduce the risk of GI related cancers
  o Longer follow-up warranted

NNT: number needed to treat; NNH: number needed to harm
Study Critique

**Strengths**
- Long follow-up
- Large trial
- Randomized, blinded design
- Improved assessment of aspirin

**Limitations**
- Intention-to-treat analysis underestimation
- 100 mg dosing
- Relationship between PPI use and GI bleed
- Lack of statistical power to assess cancer risk
- Generalizability of study participants
## Recommendations for Clinical Practice

|---------------------------------------------|---------------------------------------------|----------------------------------------------------------|
| **Consider** low-dose aspirin if no ↑ risk of bleed in patients with type 1 or type 2 diabetes aged ≥ 50 years with at least 1 additional risk factor:  
- Hypertension  
- Hyperlipidemia  
- Smoking  
- Albuminuria  
- Family history of premature CV events  
 (LOE C) | Aspirin (75–162 mg/day) may be considered primary prevention in those with diabetes at increased CV risk, after a discussion with patient on benefits vs increased bleeding risk.”  
 (LOE C) | Aspirin (75-100 mg/day) might be considered for primary prevention of ASCVD among select adults 40-70 years of age at higher ASCVD risk but not at increased bleeding risk.  
 (COR IIb; LOE A) |

COR: class of recommendation; LOE: level of evidence
Questions?

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