ASCEND

Randomized placebo-controlled trial of aspirin 100 mg daily in 15,480 patients with diabetes and no baseline cardiovascular disease

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on behalf of the ASCEND Study Collaborative Group

Funded by British Heart Foundation, UK Medical Research Council
and support from Abbott, Bayer, Mylan and Solvay
Designed, conducted and analysed independently of the funders
University of Oxford is the trial sponsor

Declaration of interest

- Research contracts (Medicines Company, Bayer, Mylan, formerly Merck)

Conclusions

- Aspirin did **not** reduce the risk of gastrointestinal or any other cancer with no apparent effect emerging with longer follow-up
- Aspirin significantly reduced the risk of serious vascular events by 12% but significantly increased the risk of major bleeding by 29%
- The absolute benefits from avoiding serious vascular events were largely counterbalanced by the increased risk of bleeding
- There was no group in which the benefits clearly outweighed the risks

Background

Aspirin and cardiovascular disease

- Aspirin use is well established in secondary prevention of cardiovascular disease
- Diabetes is associated with increased risk of heart attacks and strokes but it is unclear whether aspirin should be routinely prescribed to prevent a first cardiovascular event

Aspirin and cancer

- Cautious about aspirin use:

Post-hoc analysis of selected randomized trials of aspirin suggest reductions in the risk of cancer, particularly gastrointestinal cancers.

ESC guidance 2016

"…antiplatelet therapy for primary prevention may be considered in high risk patients with DM on an individual basis".

EUROASPIRE III 2010

28% with diabetes (asymptomatic) taking aspirin (Kotseva et al 2010)

ASCEND trial design

Eligibility: Age ≥ 40 years, any DIABETES and **no** baseline cardiovascular disease

Participants: 15,480 UK patients, average 63 yrs, 63% men

Factorial randomization: Aspirin 100 mg daily vs placebo

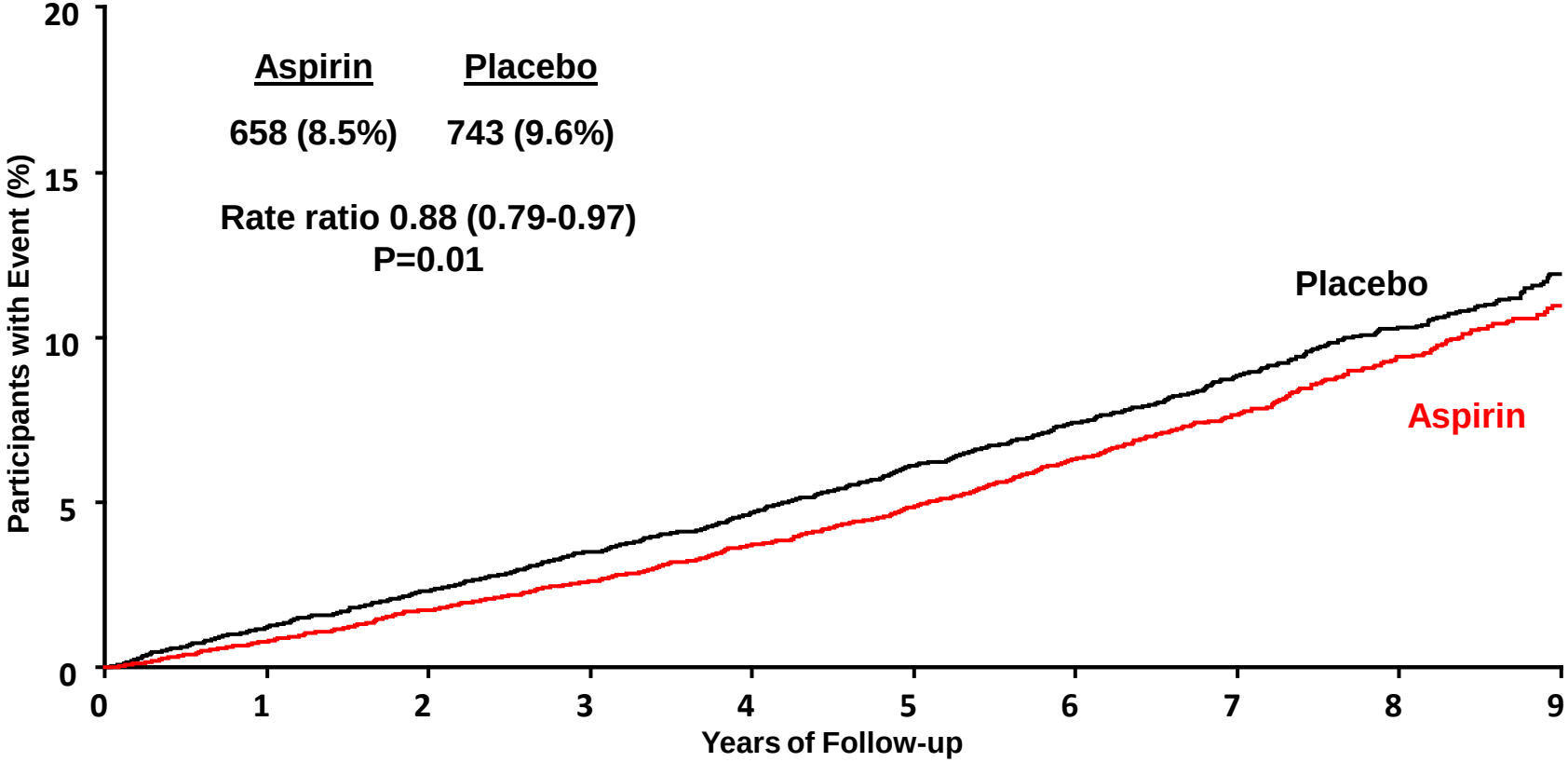
(& to omega-3 fatty acid supplements vs placebo)

Follow-up: Mean 7.4 years, >99% complete for morbidity and mortality

Primary outcomes: Serious Vascular Events and Major Bleeding

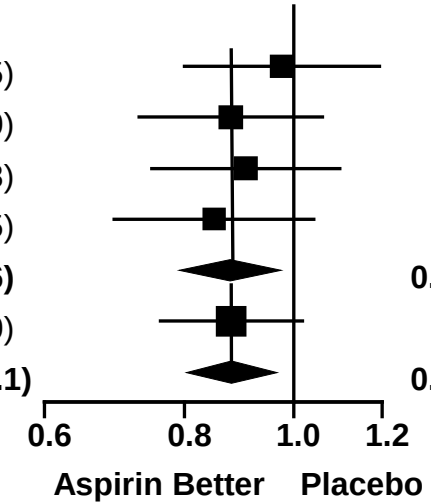
Adherence: Average difference in anti-platelet use between groups 69%

Effect of aspirin on Serious Vascular Events



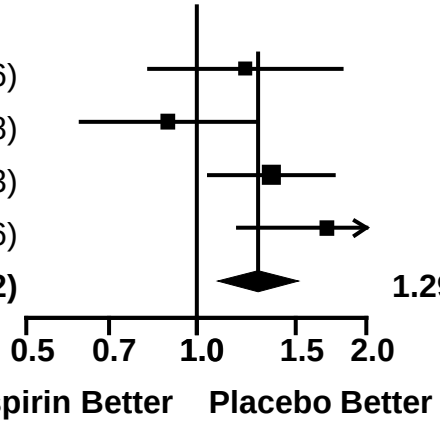
Components of the primary efficacy outcome plus revascularization

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)
	no. of participants with events (%)		
Vascular outcomes			
Non-fatal myocardial infarction	191 (2.5)	195 (2.5)	
Non-fatal presumed ischaemic stroke	202 (2.6)	229 (3.0)	
Vascular death excl. intracranial haemorrhage	197 (2.5)	217 (2.8)	
Transient ischaemic attack (TIA)	168 (2.2)	197 (2.5)	
Any serious vascular event	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97) P = 0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97) P = 0.01**



Effect of aspirin on major bleed

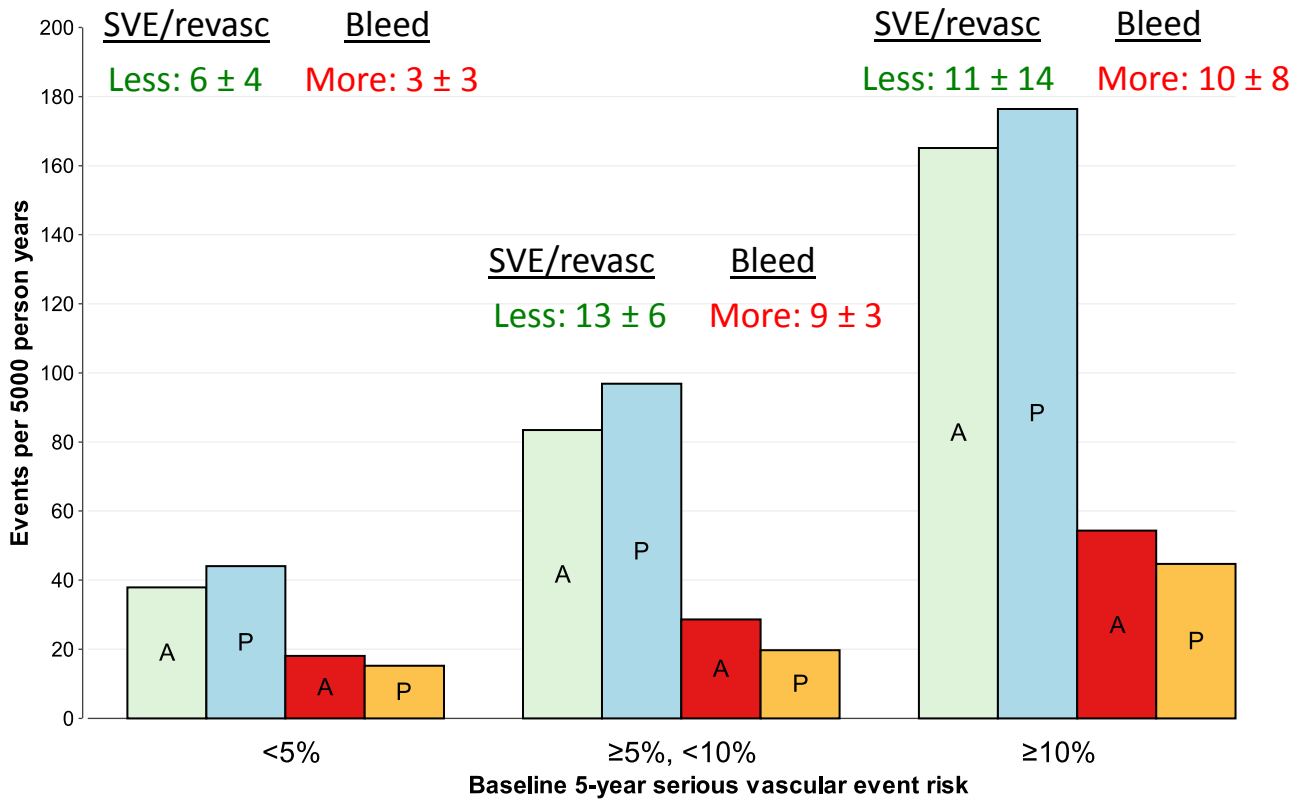
Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	Absolute Difference (%)
	no. of participants with events (%)			
Major bleed				
Intracranial hemorrhage	55 (0.7)	45 (0.6)		0.1
Sight threatening eye bleed	57 (0.7)	64 (0.8)		-0.1
Serious gastrointestinal hemorrhage	137 (1.8)	101 (1.3)		0.5
Other major bleed	74 (1.0)	43 (0.6)		0.4
Any major bleed	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)** P = 0.003	**0.9**



Observed effects per 5000 person years of aspirin by vascular risk

SVE or revascularization
- assigned placebo (P)

± = Standard Error



Importance

- Diabetes is common and most patients do not have cardiovascular disease
- Whether to treat with aspirin to prevent first event is uncertain
- ASCEND participants were well managed: most on statins and blood pressure treatments with good glucose control.
- For these diabetic patients there was no added benefit of aspirin
- Aspirin did not reduce the risk of cancer

Extra slides

Baseline demographics (N=15,480)

Characteristic	Aspirin	Placebo
Age, years	63	63
Male	63%	63%
Type 2 diabetes	94%	94%
Diabetes duration, median years	7	7
Hypertension	62%	62%
Statin use	76%	75%
Body Mass Index, kg/m^2	31	31
Glycated haemoglobin, mmol/mol	55 (7.2%)	55 (7.2%)

Key outcomes

Primary efficacy outcome: Serious Vascular Event (SVE)

Non-fatal myocardial infarction,
Non-haemorrhagic stroke or transient ischaemic attack, or
Cardiovascular death, excluding any intracranial haemorrhage

Primary safety outcome: Major bleed

Intra-cranial haemorrhage,
Sight-threatening eye bleed,
Serious gastrointestinal bleed, or
Other serious bleed

Key secondary outcomes:

i) SVE or any revascularization (pre-specified for subgroup analyses)
ii) Gastrointestinal tract cancer

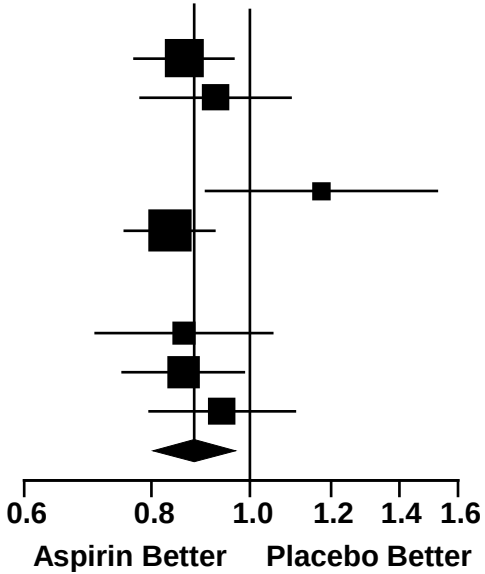
Effect of aspirin on cancer

	Aspirin	Placebo	Rate Ratio
Gastrointestinal tract	157 (2.0%)	158 (2.0%)	0.99 (0.80-1.24)
Other gastrointestinal*	87 (1.1%)	82 (1.1%)	1.06 (0.78-1.43)
Respiratory	101 (1.3%)	103 (1.3%)	0.98 (0.74-1.29)
Genitourinary	332 (4.3%)	294 (3.8%)	1.13 (0.97-1.32)
Haematological	88 (1.1%)	86 (1.1%)	1.02 (0.76-1.38)
Breast	97 (1.3%)	96 (1.2%)	1.01 (0.76-1.34)
Melanoma skin	50 (0.6%)	59 (0.8%)	0.85 (0.58-1.23)
Any cancer	**897 (11.6%)**	**887 (11.5%)**	**1.01 (0.92-1.11)**

* Hepatobiliary and pancreas

Effects of aspirin assignment on SVE or revascularization in different types of participant

Baseline Characteristic	Aspirin (N=7740) no. of participants with events (%)	Placebo (N=7740) no. of participants with events (%)	Rate Ratio (95% CI)
Sex			
Men	573 (11.8)	658 (13.6)	0.86 (0.77–0.96)
Women	260 (9.0)	278 (9.6)	0.92 (0.78–1.09)
Weight at randomization (kg)			
<70	118 (13.1)	108 (11.4)	1.17 (0.90–1.52)
≥70	694 (10.4)	812 (12.3)	0.83 (0.75–0.92)
5-year vascular risk			
<5%	179 (5.7)	208 (6.6)	0.86 (0.71–1.05)
≥5% <10%	384 (11.7)	431 (13.2)	0.86 (0.75–0.99)
≥10%	270 (20.5)	297 (22.0)	0.94 (0.80–1.11)
All	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*