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

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Designed, conducted and analysed independently of the funders
University of Oxford is the trial sponsor

Background

Aspirin and cardiovascular disease

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

Aspirin and cancer

- Post-hoc analyses of selected randomized trials of aspirin suggest reductions in the risk of cancer, particularly gastrointestinal cancers, with effects apparent after about 3 years

ASCEND trial design

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

Participants: 15,480 UK patients

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

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

ASCEND Study Collaborative Group. Am Heart J 2018;198:135-144

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:

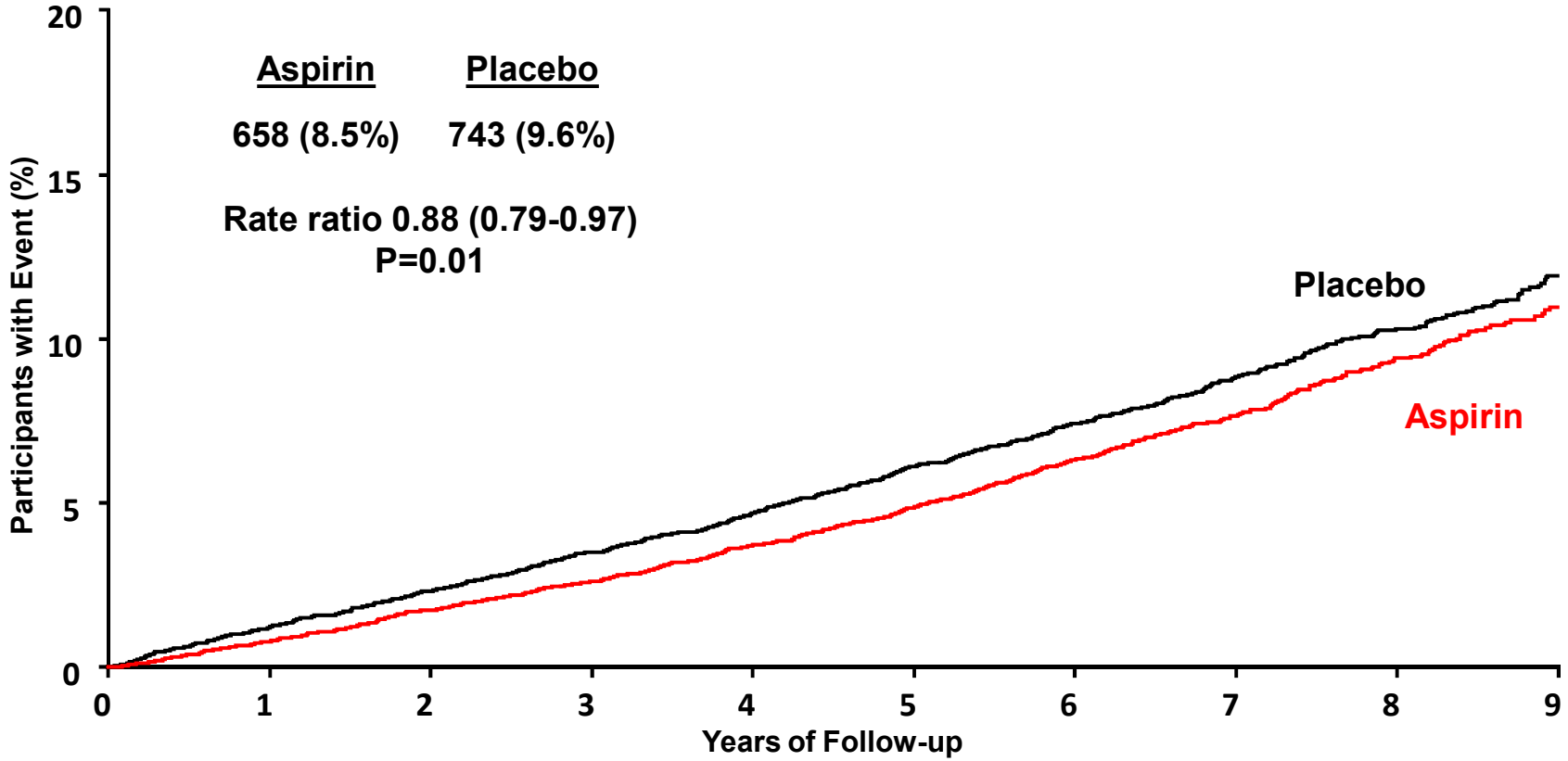
i) SVE or any revascularization (pre-specified for subgroup analyses)
ii) Gastrointestinal tract cancer

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)**

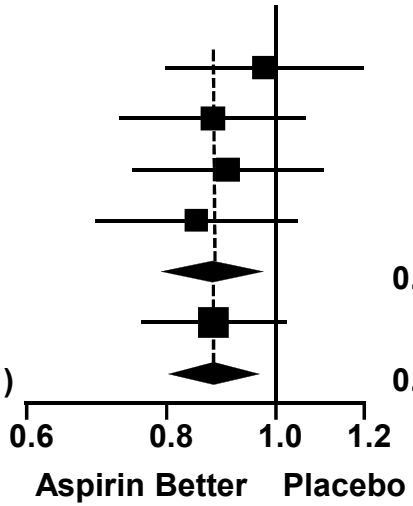
* Hepatobiliary and pancreas

Effect of aspirin on Serious Vascular Events



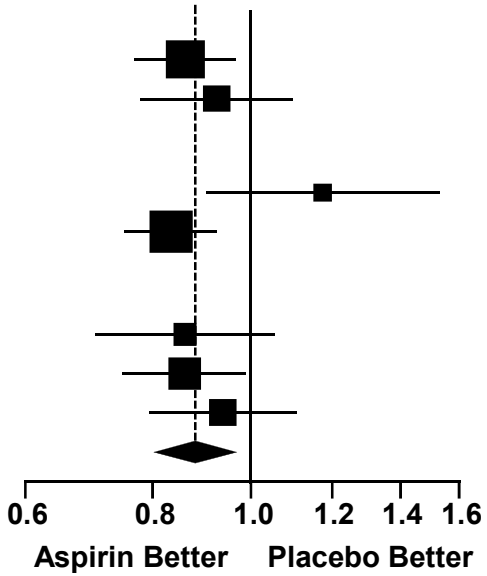
Components of the primary efficacy outcome plus revascularization

Type of Event	Aspirin (N=7740) no. of participants with events	(%)	Placebo (N=7740) 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)**
Any arterial revascularization	340	(4.4)	384	(5.0)
Any serious vascular event or revascularization	**833**	**(10.8)**	**936**	**(12.1)**



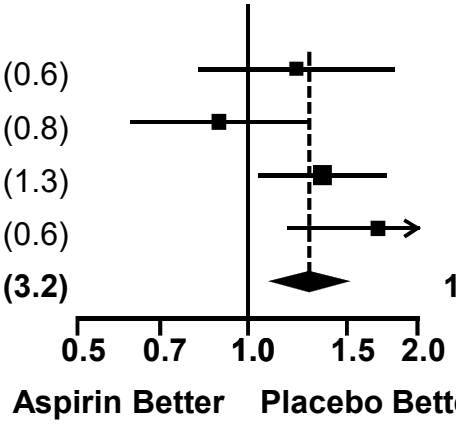
Effects of aspirin assignment on SVE or revascularization in different types of participant

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)**



Effect of aspirin on major bleed

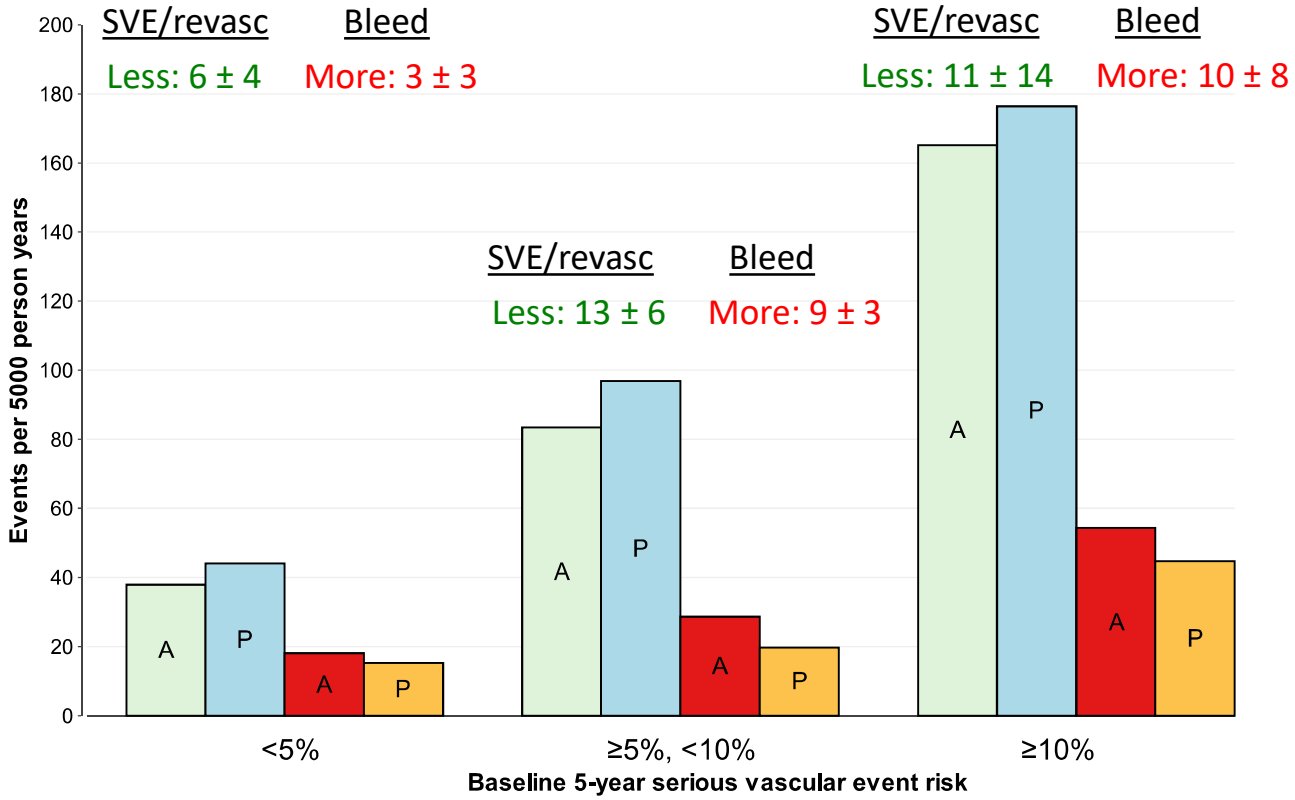
Type of Event	Aspirin (N=7740) no. of participants with events (%)	Placebo (N=7740) no. of participants with events (%)	Rate Ratio (95% CI)	Absolute Difference (%)
Major bleed				
Intracranial hemorrhage	55 (0.7)	45 (0.6)		0.1
Sight threatening eye bleed	57 (0.7)	64 (0.8)		-0.1
Serious gastrointestinal 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



Summary

- 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 but also significantly increased the risk of major bleeding
- 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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

Effect of aspirin on major bleed