Effects of aspirin on dementia and cognitive impairment in the ASCEND trial

Sarah Parish and Jane Armitage

on behalf of the ASCEND Study Collaborative Group

MRC Population Health Research Unit

Disclosures and funding

ASCEND was funded by the British Heart Foundation, UK Medical Research Council, and Alzheimer's Research UK, with some support from Bayer (aspirin), Abbott, Mylan and Solvay (fish oils)

Designed, conducted and analysed independently of the funders

University of Oxford is the trial sponsor

Department policy of not accepting personal payments from industry

Background

Daily low-dose aspirin reduces the risk of major occlusive vascular events but is associated with an increased risk of serious bleeding.

Aspirin may prevent cognitive impairment through the avoidance of ischemic strokes and transient ischaemic attacks (TIAs), but could increase impairment through an increased risk of intracranial bleeds and microbleeds.

Previous randomized trials of aspirin have not convincingly detected any effect of aspirin use on dementia incidence or cognitive impairment.

ASCEND trial design

Eligibility: Age ≥ 40 years; any DIABETES
No prior cardiovascular disease

Participants: 15,480 UK patients

Randomization: Aspirin 100 mg daily vs placebo
(and Omega-3 fatty acids 1 g capsule/day vs placebo)

Follow-up: Mean 7.4 years in trial + 1.8 years post trial;
>99% complete for morbidity & mortality

Data: 99% with linkage to electronic hospital admission records

ASCEND Study Collaborative Group: Trials 2016 / Am Heart J 2018 / NEJM 2018

ASCEND: Baseline demographics

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%)

Dementia outcomes

Key outcomes* considered:

- Broad dementia outcome: dementia, cognitive impairment, delirium/confusion, dementia medications, referral to memory clinic, geriatric psychiatry
- Narrow dementia outcome: dementia
- Cognitive function z-score at final follow-up, based on either Telephone Interview for Cognitive Status (TICSm) and verbal fluency or the Healthy Minds test developed by UK Biobank

Dementia outcomes defined from:

- Hospitalisations or serious events reported by participants during the trial
- ICD10-code diagnoses in electronic hospital admission data and death records
- Other indications of cognitive impairment in follow-up and electronic records

**For the pre-specified Data Analysis Plan see: https://ascend.medsci.ox.ac.uk/professionals*

Observational analyses of dementia risk associated with non-fatal vascular events or major bleeds

Poisson regression analyses using 2-year intervals of age at risk spent with or without the event.

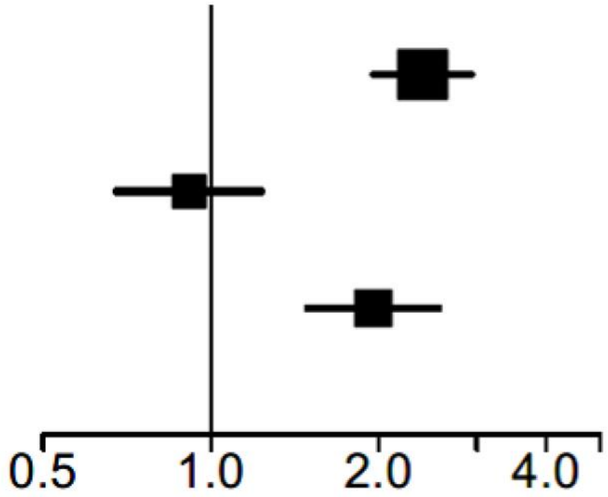
Dementias diagnosed after a disabling stroke or intracranial bleed are excluded

Analyses adjusted for the number of non-dementia-related hospital admissions* (0, 1, ≥2) during the interval, randomized treatment allocation, sex, prior diseases and baseline predictors of dementia including a hospital diagnosis based frailty score.

*to mitigate against bias caused by hospital admissions for other causes bringing forward the recording of a dementia diagnosis.

Observational analyses of dementia risk associated with non-fatal vascular events or major bleeds

Non−fatal incident event	NE_{dem} / NE	Rate ratio for the broad dementia outcome (95% CI)
Serious vascular event	133 / 990	2.40 (1.97, 2.92)
Revascularization	55 / 694	0.91 (0.68, 1.23)
Major bleed	59 / 496	1.96 (1.49, 2.56)

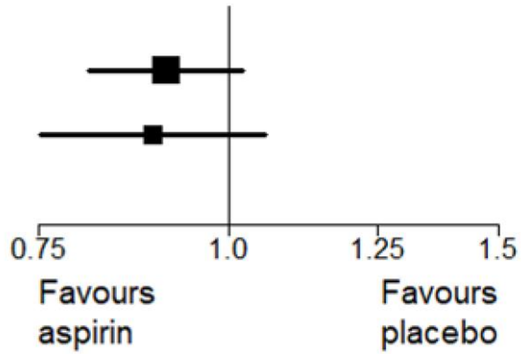


NE Number with non-fatal incident event
NE_{dem} Number with non-fatal incident event and, subsequently, the broad dementia outcome

OXFORD POPULATION HEALTH
UNIVERSITY OF OXFORD

Randomized effects of aspirin on dementia and cognitive function

Dementia outcomes*	Aspirin (N=7714)	Placebo (N=7713)	Rate ratio (95% CI)
	No. (%) with event		
Broad dementia outcome	548 (7.1%)	598 (7.8%)	0.91 (0.81, 1.02)
Narrow dementia outcome	254 (3.3%)	283 (3.7%)	0.89 (0.75, 1.06)

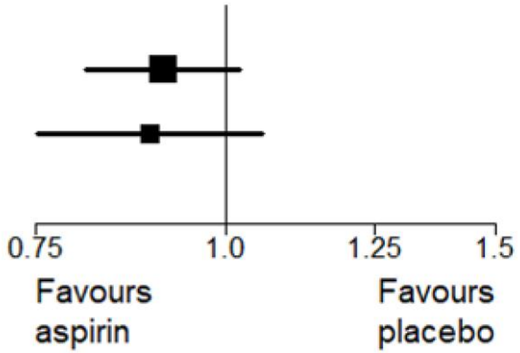


*Analyses restricted to those without the broad dementia outcome prior to randomisation

OXFORD POPULATION HEALTH
UNIVERSITY OF OXFORD

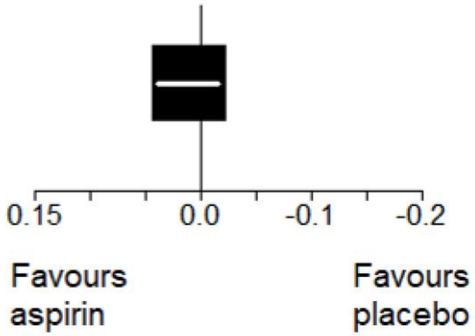
Randomized effects of aspirin on dementia and cognitive function

Dementia outcomes*	Aspirin (N=7714)	Placebo (N=7713)	Rate ratio (95% CI)
	No. (%) with event		
Broad dementia outcome	548 (7.1%)	598 (7.8%)	0.91 (0.81, 1.02)
Narrow dementia outcome	254 (3.3%)	283 (3.7%)	0.89 (0.75, 1.06)



*Analyses restricted to those without the broad dementia outcome prior to randomisation

Cognitive score**	Aspirin (N=4535)	Placebo (N=4480)	Cognitive z score difference (95% CI)
	Mean (SE) cognitive z score		
TICSm+VF or Healthy Minds (metaanalysed)	0.004 (0.015)	-0.002 (0.015)	0.012 (-0.016, 0.039)



**Analyses restricted to survivors able to respond to request for cognitive function test

OXFORD POPULATION HEALTH
UNIVERSITY OF OXFORD

Summary: dementia in ASCEND

- ASCEND provides randomized evidence of the effects of 100 mg daily aspirin on dementia and cognitive impairment, based on 1146 incident ‘broad dementia’ events
- No statistically significantly effect on dementia outcomes
- Results excluded proportional harms >2% and benefits of >19%
- Trials with larger numbers of incident dementia cases are needed to assess whether any modest proportional 15-18% benefits of 5-7 years aspirin use exist
- In the UK, routine electronic health data provided a cost-effective means of assessing the impact of vascular preventive therapies on dementia

https://ascend.medsci.ox.ac.uk/

OXFORD POPULATION HEALTH
UNIVERSITY OF OXFORD