A risk based approach to the role of aspirin on cardiovascular risk reduction in a healthy older cohort

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Declaration of interest

- I have nothing to declare

ASCEND

A Study of Cardiovascular Events iN Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

ARRIVE

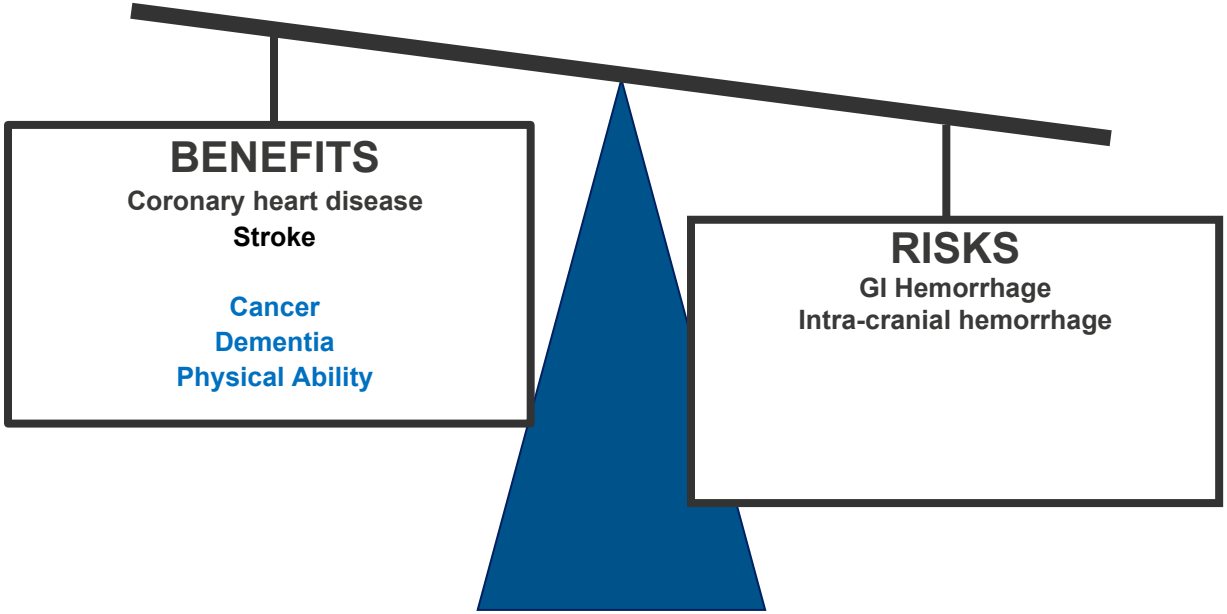
Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial

J Michael Gaziano, Carlos Brotons, Rosa Coppolecchia, Claudio Cricelli, Harald Darius, Philip B Gorelick, George Howard, Thomas A Pearson, Peter M Rothwell, Luis Miguel Ruilope, Michal Tendera, Gianni Tognoni, the ARRIVE Executive Committee

The aspirin balance with a focus on what's important for the elderly

ASPirin in Reducing Events in the Elderly
ASPREE

ASPREE TRIAL



ASPrin in Reducing Events in the Elderly (ASPREE) – Trial Design

Randomized placebo-controlled trial.

- 19,114 Men and Women
- 100 mg enteric-coated aspirin or placebo

- **In Australia** – 16,703 participants
  - 16 sites across Victoria, Tasmania, South Australia and Canberra
  - Conducted in general practices based on successful ANBP2 model.
- **In USA** – 2,411 participants
  - 34 Sites across including Minneapolis, Chicago, San Antonio, Pittsburg, North Carolina
  - Recruitment emphasis on minorities – Blacks and Hispanics (aged >65yrs)
  - Conducted primarily in clinical centres/ family practice
- Follow-up - median 4.8 years

Primary endpoint – prolongation of disability-free life.

SECONDARY OUTCOMES:

- All-cause Mortality

COMPOSITE PRIMARY OUTCOME:

- Dementia
- Persistent Physical Disability
- Fatal and non-fatal CVD (including stroke)
- Fatal and nonfatal Cancer
- Mild Cognitive Impairment
- Depression
- Serious bleeding

Disability-free survival defined as; being alive and free of dementia or persistent physical disability

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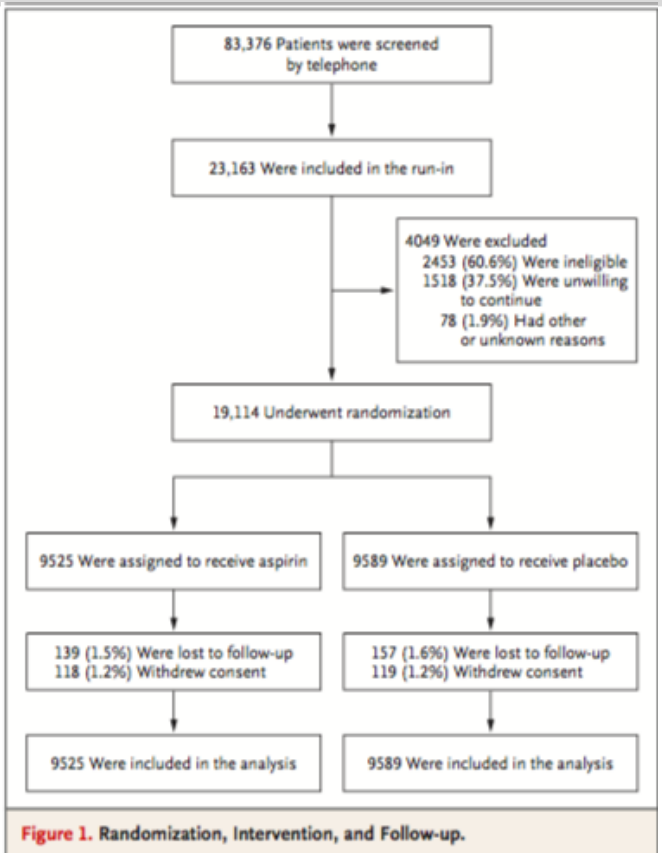

Figure 1. Randomization, Intervention, and Follow-up.

Table 1. Demographic Characteristics and Illness History of the Participants at Randomization, According to Prespecified Subgroups and Trial Group.*

Characteristic	Aspirin (N=9525)	Placebo (N=9589)
Age — no. (%)†		
65–73 yr	4719 (49.5)	4823 (50.3)
≥74 yr	4806 (50.5)	4766 (49.7)
Female sex — no. (%)	5373 (56.4)	5410 (56.4)
Country — no. (%)		
Australia	8322 (87.4)	8381 (87.4)
United States	1203 (12.6)	1208 (12.6)
Race or ethnic group — no. (%)‡		
White		
Australia	8169 (85.8)	8193 (85.4)
United States	539 (5.7)	549 (5.7)
Black	451 (4.7)	450 (4.7)
Hispanic	240 (2.5)	248 (2.6)
Other	126 (1.3)	149 (1.6)
Body-mass index§	28.1±4.8	28.1±4.7
Current smoking — no. (%)	352 (3.7)	383 (4.0)
Diabetes mellitus — no. (%)¶	1027 (10.8)	1030 (10.7)
Hypertension — no. (%)‖	7065 (74.2)	7148 (74.5)
Dyslipidemia — no. (%)**	6159 (64.7)	6308 (65.8)
Personal history of cancer — no. (%)	1827 (19.2)	1833 (19.1)
Previous regular aspirin use — no. (%)††	1053 (11.1)	1041 (10.9)
Frailty — no. (%)‡‡		
Not frail	5603 (58.8)	5643 (58.8)
Prefrail	3707 (38.9)	3740 (39.0)
Frail	215 (2.3)	206 (2.1)

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The aspirin balance with a focus on what's important for the elderly

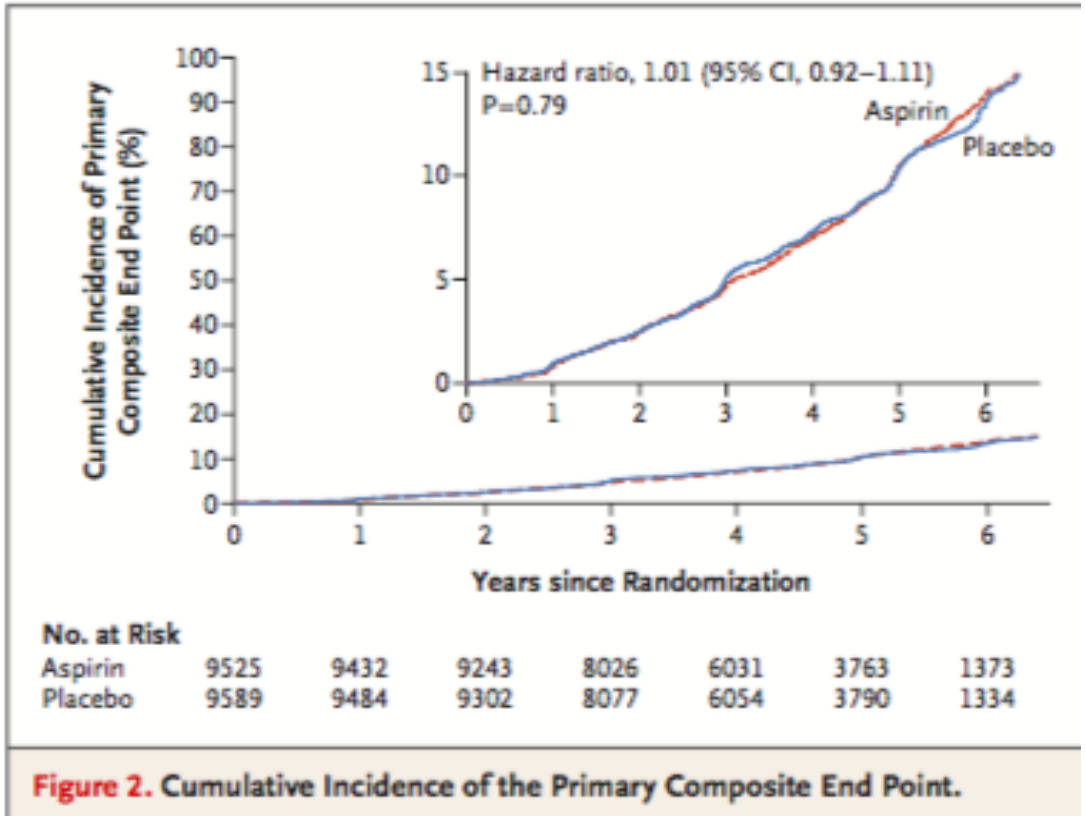
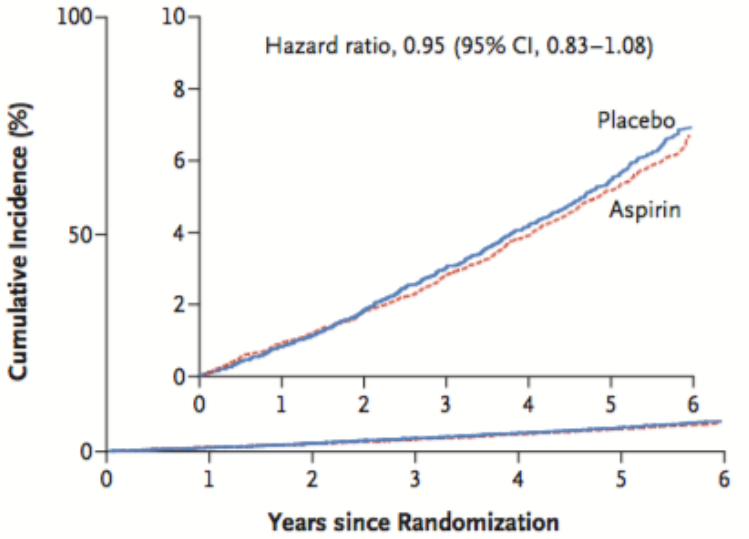


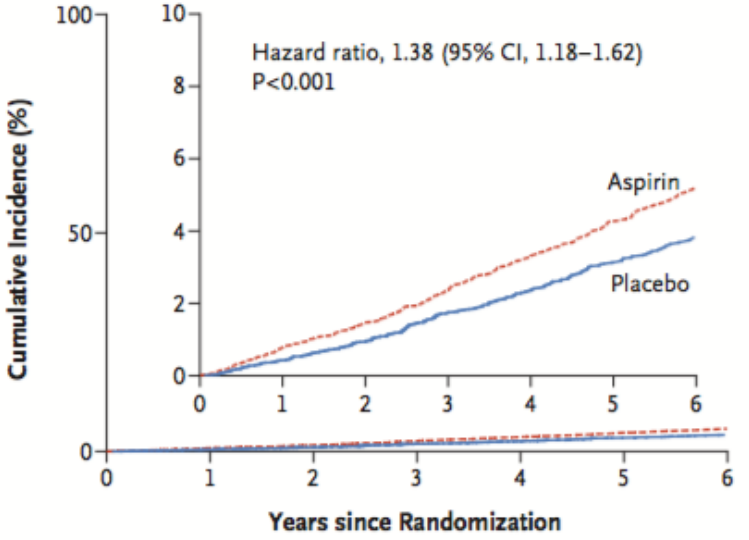
Figure 2. Cumulative Incidence of the Primary Composite End Point.

The aspirin balance with a focus on what's important for the elderly



No. at Risk							
Aspirin	9525	9322	9068	7820	5827	3568	1234
Placebo	9589	9387	9119	7843	5839	3578	1223

Figure 1. Cumulative Incidence of Cardiovascular Disease.



No. at Risk							
Aspirin	9525	9337	9094	7833	5826	3574	1248
Placebo	9589	9424	9192	7930	5935	3632	1244

Figure 2. Cumulative Incidence of Major Hemorrhage.

Current Analysis Aims

To determine whether the baseline levels of CVD risk influenced the effects of aspirin on

- Disability free-survival (DDD)
- Cardiovascular events (CVD)
- Major Bleeding

Baseline Levels of Risk

Framingham Modified Risk Equation[1]

Ages 65-74 years
Gender,
total cholesterol (TC),
high-density lipoprotein (HDL)
SBP
diabetes
antihypertensive medication use
current smoking

Outcomes

Fatal and Non-Fatal CHD Events
Fatal and non-fatal ischaemic stroke
+ Heart Failure

[1] D'Agostino RB, etal . Circulation. 2008;117(6):743

ACC/AHA ASCVD Pooled Risk Equation[2]

Age 65-79 years
Gender, **Ethnicity,**
total cholesterol (TC),
high-density lipoprotein (HDL)
SBP
diabetes
antihypertensive medication use
current smoking

Outcomes

Fatal and Non-Fatal CHD Events
Fatal and non-fatal ischaemic stroke

[2] Goff David C, Circulation. 2014;129(25_suppl_2):S49-S73

For ≥ 80 years

risk on the basis of presence of multiple conventional CVD risk factors

Gender,
hypercholesterolaemia,
hypertension,
Current smoking,
Diabetes
obesity
reduced renal function

Outcomes

FH – CVD Events
ASCVD Events

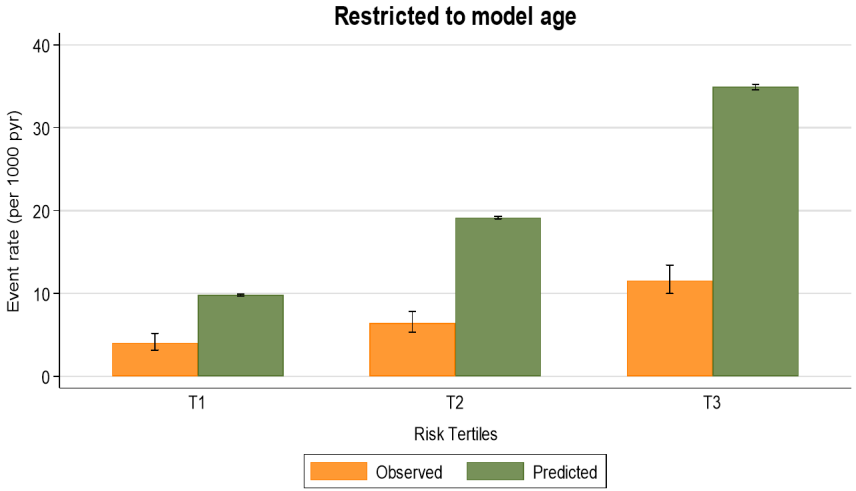
ASPREE Cohort by Baseline levels of CVD risk

	Framingham predicted risk tertiles among 65-74 yrs (N=10918)			ASCVD predicted risk tertiles among 65-79 yrs (N=15825)			Presence of risk factor among those aged ≥80 years (N=2928)		
	T1	**T2**	**T3**	**T1**	**T2**	**T3**	**0/1**	**2/3**	**>3**
Participants number	3652	3645	3621	5304	5285	5238	674	2054	200
Mean predicted risk %, range	10.1, 1.7-14.5	19.6, 14.5-25.5	37.1, 25.6-92.9	13.4, 3.3-18.2	22.6, 18.2-27.0	35.9, 27.0-78.5	NA	NA	NA
Age (year, mean±SD)	71.3±1.8	71.5±1.7	71.7±1.7*	71.4±2.2	73.0±2.5	74.9±2.9*	83.1±3.0	82.9±2.8	82.7±2.5
Men (%)	3.8	44.7	86.5*	12.6	52.4	67.3*	19.0	44.3	80.5*
Smoking Current (%)	1.3	3.3	9.3*	1.8	3.6	7.2*	0.3	2.3	5.5*
SBP (mmHg, mean±SD)	128±13	140±15	147±15*	129±14	139±14	149±14*	133±16	145±16	144±17*
DBP (mmHg, mean±SD)	75±9	79±9	81±9*	75±9	78±10	80±10*	73±10	76±10	75±9*
Obese (%)	25.8	32.1	36.6*	29.3	31.0	33.5*	3.1	22.2	75.0*
Total Cholesterol (mmol/L)	5.28±0.94	5.28±1.01	5.23±1.02*	5.39±0.98	5.24±0.95	5.13±1.01*	5.08±0.84	5.28±1.01	4.67±1.08
Lipid lowering drug (%)	36.8	32.9	32.1*	32.6	32.5	37.7*	8.9	34.9	69.0*
Antihypertensive (%)	37.0	49.7	64.0*	35.4	50.6	68.8*	27.9	65.9	84.0*
Diabetes %	1.2	5.9	18.8*	0.9	3.3	21.8*	0.3	6.1	60.0*

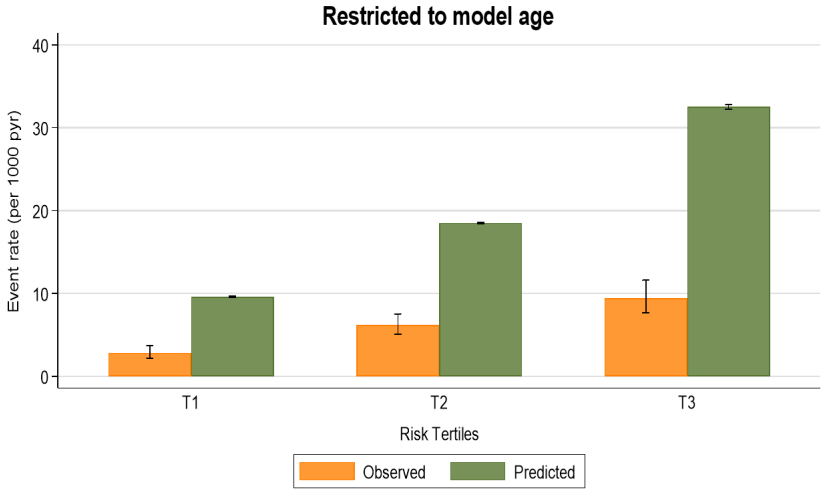
** P-value for trend <0.05*

Observed versus Predicted Events

Framingham CVD risk (65-74yrs)

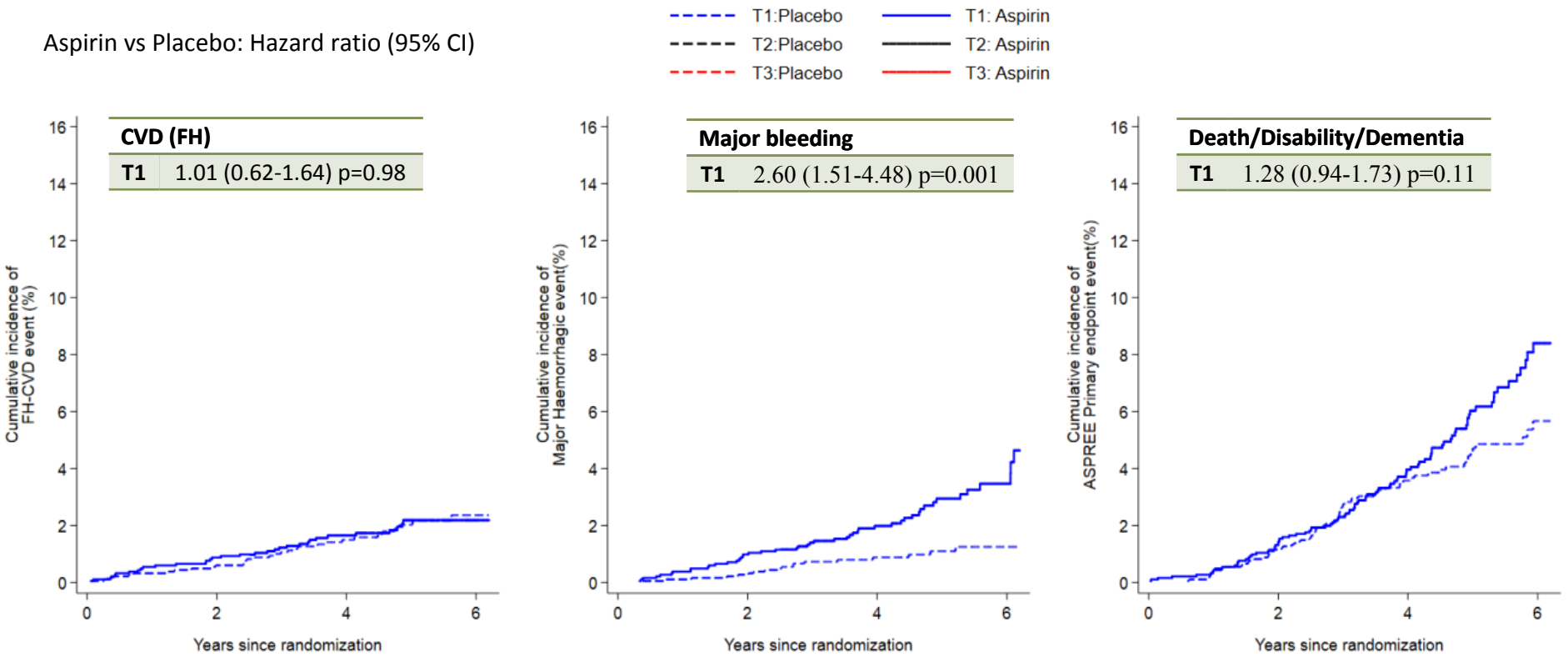


ASCVD risk (65-79yrs)



Framingham Risk Model (65-74yrs): Low Risk – T1

Aspirin vs Placebo: Hazard ratio (95% CI)



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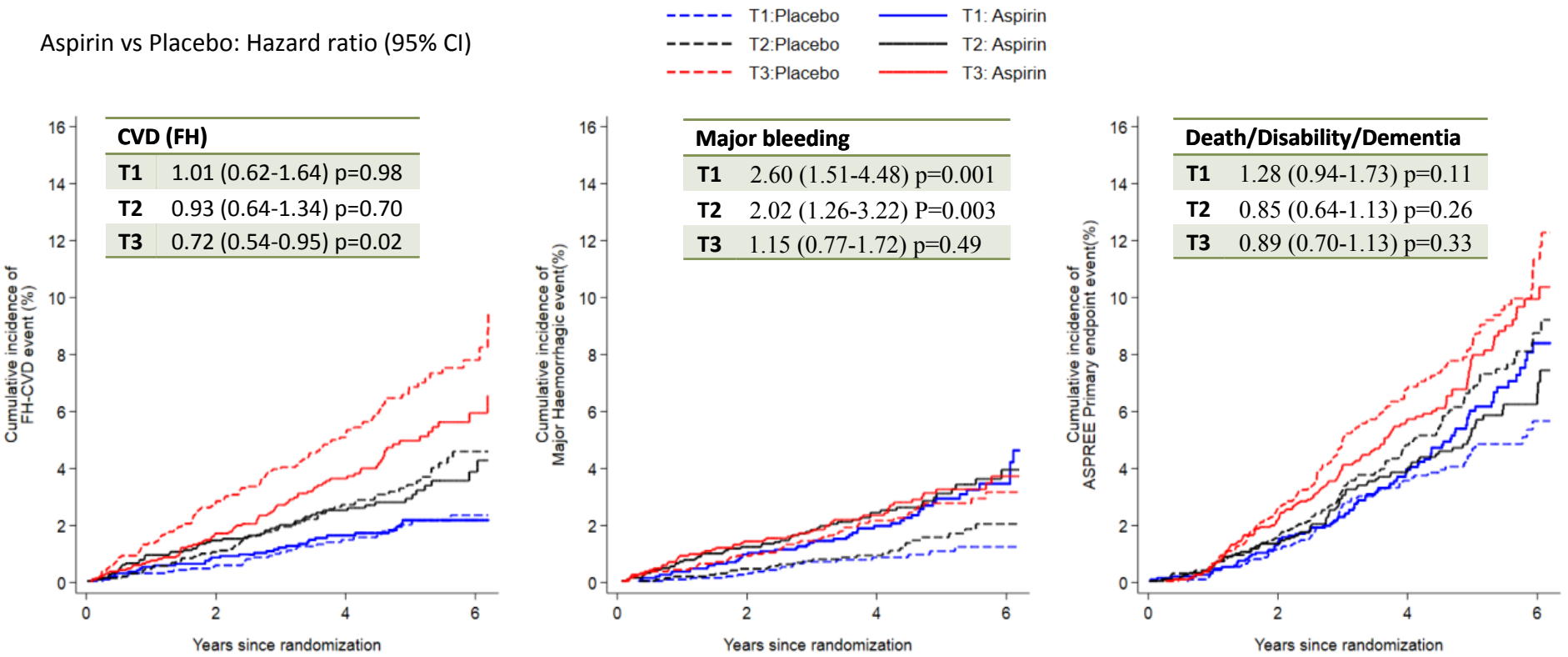
Framingham Risk Model (65-74yrs): Risk Tertiles

Aspirin vs Placebo: Hazard ratio (95% CI)



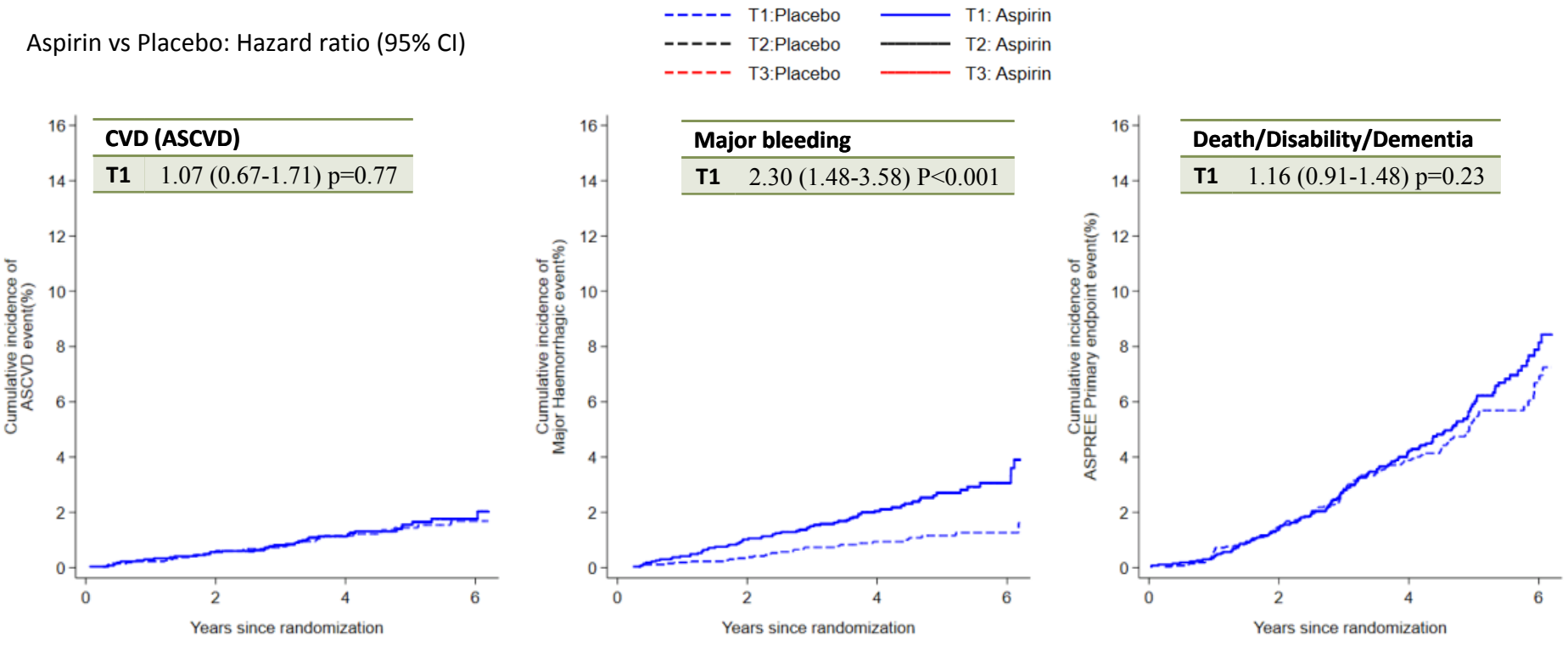
CVD (FH)	
T1	1.01 (0.62-1.64) p=0.98
T2	0.93 (0.64-1.34) p=0.70
T3	0.72 (0.54-0.95) p=0.02

Major bleeding	
T1	2.60 (1.51-4.48) p=0.001
T2	2.02 (1.26-3.22) P=0.003
T3	1.15 (0.77-1.72) p=0.49

Death/Disability/Dementia	
T1	1.28 (0.94-1.73) p=0.11
T2	0.85 (0.64-1.13) p=0.26
T3	0.89 (0.70-1.13) p=0.33

ASCVD Pooled Risk Equations (65-79yrs): Low Risk – T1

Aspirin vs Placebo: Hazard ratio (95% CI)



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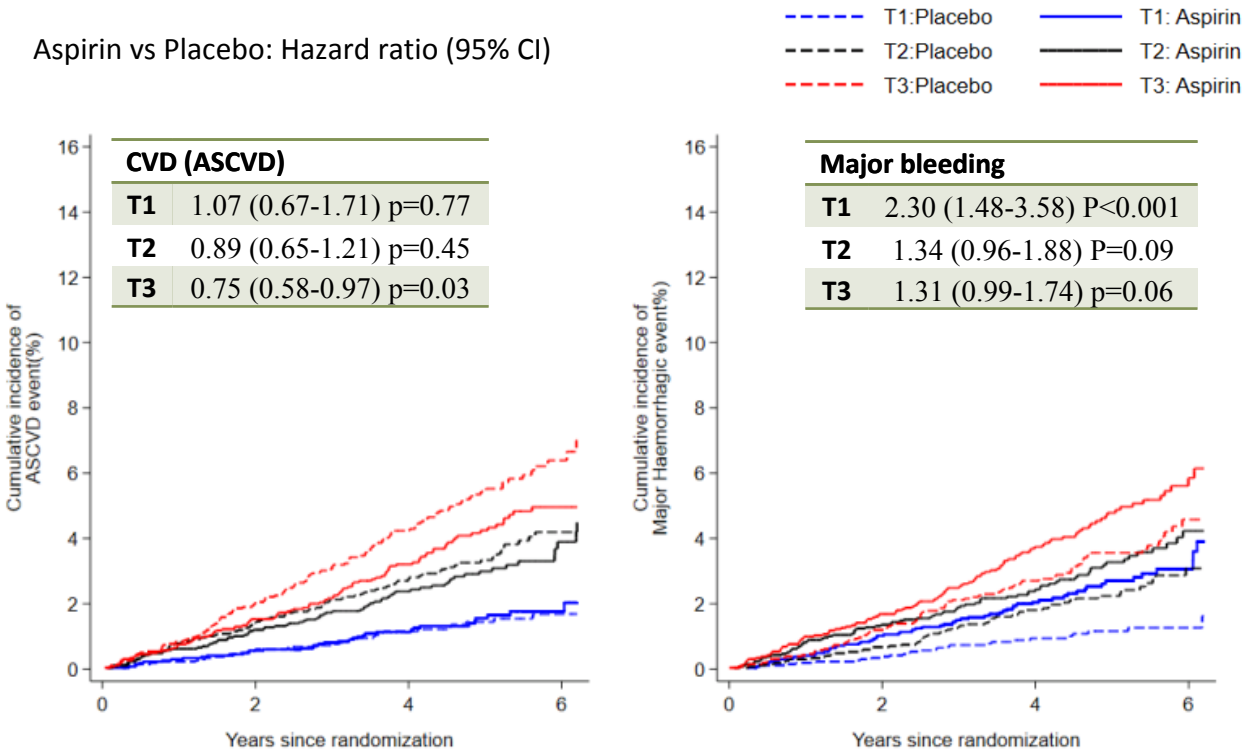
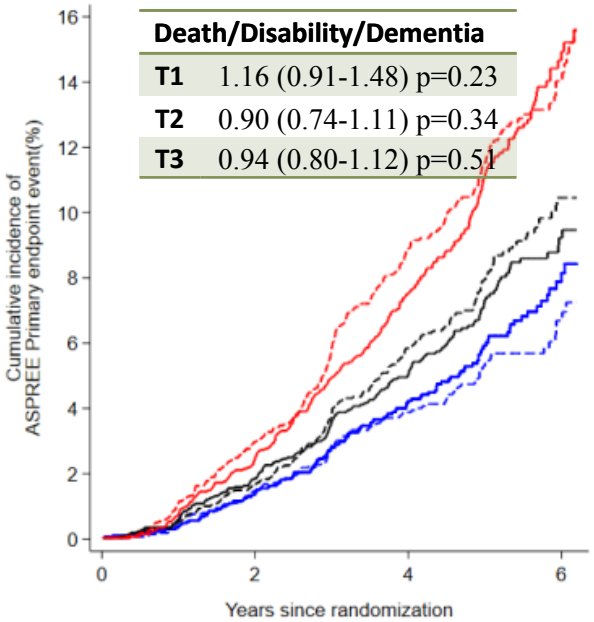
ASCVD Pooled Risk Equations (65-79yrs): Risk Tertiles

Aspirin vs Placebo: Hazard ratio (95% CI)



CVD (ASCVD)	
T1	1.07 (0.67-1.71) p=0.77
T2	0.89 (0.65-1.21) p=0.45
T3	0.75 (0.58-0.97) p=0.03

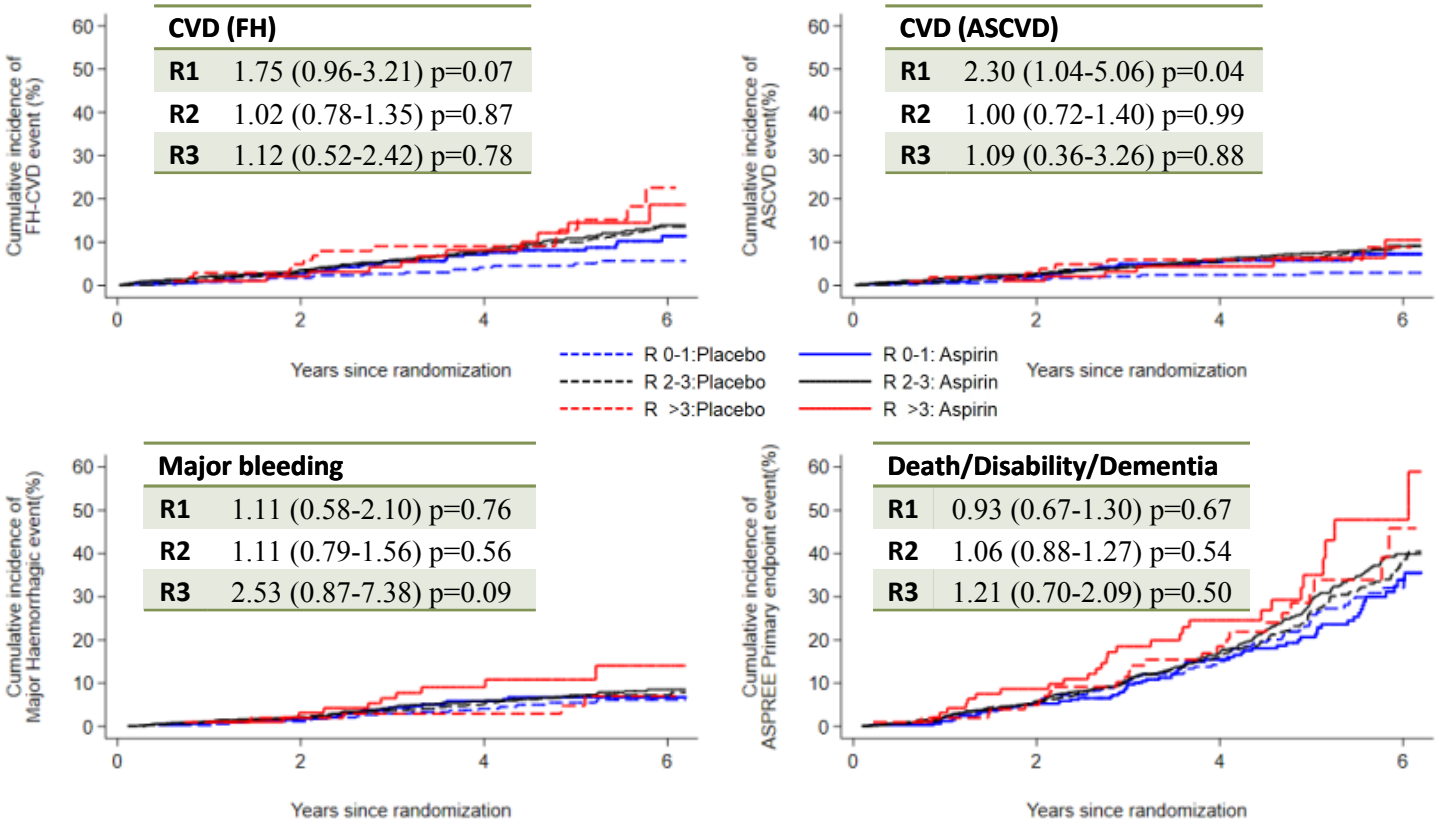
Major bleeding	
T1	2.30 (1.48-3.58) P<0.001
T2	1.34 (0.96-1.88) P=0.09
T3	1.31 (0.99-1.74) p=0.06



Death/Disability/Dementia	
T1	1.16 (0.91-1.48) p=0.23
T2	0.90 (0.74-1.11) p=0.34
T3	0.94 (0.80-1.12) p=0.51

Over 80's – Risk Factor Clustering

Aspirin vs Placebo:
Hazard ratio (95% CI)



Limitations

- Choice of 10-year Risk Equations – Framingham and ASCVD
- Lack of suitable risk prediction equations for over 80s
- Non pre-specified post-hoc analysis of the ASPREE study

ASPREE Main Trial

As a population strategy, findings do not support aspirin for primary prevention in the elderly as the risks outweighed the benefits

A risk based approach?

No CVD or DDD benefits and increased bleeding in low risk elderly

Modest CVD but no DDD and increased bleeding in high risk elderly

Over 80s

Clustering of conventional risk factors does not identify high CVD risk groups

No CVD or DDD benefits and increased bleeding in over 80's age group

Acknowledgements – ASPREE Study

ASPREE Study Group

J.J. McNeil, R.L. Woods, M.R. Nelson, C.M. Reid, B. Kirpach, R. Wolfe, E. Storey, R.C. Shah, J.E. Lockery, A.M. Tonkin, A.B. Newman, J.D. Williamson, K.L. Margolis, M.E. Ernst, W.P. Abhayaratna, N. Stocks, S.M. Fitzgerald, S.G. Orchard, R.E. Trevaks, L.J. Beilin, G.A. Donnan, P. Gibbs, C.I. Johnston, J. Ryan, B. Radziszewska, R. Grimm, and A.M. Murray, for the ASPREE Investigator Group*

Study Staff

Volunteers