The ASPREE Trial:

EFFECTS OF ASPIRIN ON DISABILITY-FREE SURVIVAL IN THE HEALTHY ELDERLY

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From Willow to Wonder Drug

- ***1934 BC:*** First record of Willow Bark as Analgesic
- ***1736:*** Edward Stone (1702–1768) uses Willow Bark to treat fever
- ***1828:*** Johann Buchner (1783–1852) first refined willow bark into yellow crystals and named it Salicin
- ***1938***: Raffaele Piria (1814–1865) produced a stronger compound from the crystals isolated from willow bark, which he named salicylic acid
- ***1918:*** Flu Pandemic leads to widespread Aspirin use
- ***1950's:*** First descriptions of Aspirin for primary prevention of MI
- ***1967***: Aspirin found to inhibit platelet function
- ***1971:*** Aspirin shown to inhibit Prostaglandin Synthesis
- ***1975:*** Aspirin found to reduce Thromboxane A2 Synthesis
- ***1978:*** Secondary Prevention of Stroke
- ***1988:*** ISIS-2 Trial → secondary prevention of MI

Desborough, M. J. R., & Keeling, D. M. (2017). ***The aspirin story - from willow to wonder drug. British Journal of Haematology, 177(5), 674–683.***

Introduction

- Substantial demographic shift toward an aging society .
- Cardiovascular diseases are among the principal causes of disability and death in older persons, and therefore, preventive interventions for such diseases are a high priority.
- Low-dose aspirin efficacy has been established in ***secondary prevention*** trials, in which the benefits associated with reducing the rates of both myocardial infarction and ischemic stroke have appeared to outweigh the risk of hemorrhage.
- ***Primary prevention trials:***
- -- Risk vs Benefits more balanced
- -- ***Elderly Population:***
- **---** Increased risk for CVD vs Increased risk of bleeding
- --- Limited number or geriatric patients included on previous primary prevention trials

Hypothesis

- ASPREE (**ASP**irin in **R**educing **E**vents in the Elderly) is an international randomized, double-blind, placebo-controlled trial in 19,114 older people There were approximately 9,500 people in both the aspirin group and the placebo group. The study started in 2010 and enrolled participants mostly aged 70 years and older. The trial finished in 2017.

- ***Among healthy, community-dwelling seniors, does low-dose aspirin reduce death, dementia, or persistent physical disability when compared with placebo?***

Evidence Base Review: PICOTT

Population	19,114 older people. There were approximately 9,500 people in both the aspirin group and the placebo group.
Intervention	100 mg of enteric-coated Aspirin (n=9,500)
Comparison	Placebo (n= 9,500)
Outcome	**Main:** Disability-free survival (*all-cause mortality, dementia, or persistent physical disability.*) **Secondary:** All-cause mortality, Dementia, Persistent Physical Disability, Major Hemorrhagic Event
Type of Question	Therapy
Type of Study	Multicenter, randomized, double-blind, placebo-controlled

Population

From March 2010 through December 2014, a total of 19,114 community-dwelling adults from Australia and the United States who were 70 years of age or older (or ≥65 years of age among blacks and Hispanics in the United States) were enrolled in the trial

•Age ≥70 years; age ≥65 if in the US and black or Hispanic

•Prior CVD including MI, HF, angina, CVA/TIA, carotid stenosis >50% or prior CEA/stent, prior PCI/angioplasty/CABG, or AAA
•Atrial fibrillation
•Dementia or modified MMSE score <78/100
•Severe physical disability (e.g., unable to perform ADLs)
•High risk of bleeding or anemia (Hgb <12 in males or <11 g/dL in females)
•Life expectancy <5 years.
•Current use of antiplatelet or anticoagulant
•Aspirin use for secondary prevention
•Uncontrolled hypertension
•Not willing to stop aspirin use, if currently taking for primary prevention
•Compliance <80% during 4-week run-in
•Other trial participation

Population

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)

Fried Frailty Criteria

Appendix 1: Fried Frailty Index derived from Cardiovascular Health Study

Criterion	Frailty Status
Shrinking	**Frailty cut point:** **Baseline:** Self reported unintentional weight loss ≥10lb in previous year **Follow-up:** Unintentional weight loss ≥5% of previous year's body weight *OR* BMI <18.5kg/m^2
Physical endurance/energy	*Geriatric Depression Scale:* 1. *Do you feel full of energy?* 2. *During the last 4 weeks how often you rested in bed during day?* Response options: Every day, every week, once, not at all. **Frailty cut point:** No to 1 and every day or every week to 2.
Low physical activity	*Frequency of mildly energetic, moderately energetic and very energetic physical activity.* Response options: ≥3 times per week, 1-2 times per week, 1-3 times per month, hardly ever/never **Frailty cut point:** Hardly ever/never for very energetic physical activity AND for moderately energetic physical activity.
Weakness	Hand grip strength in Kg: GRIP-D hand held dynamometer, dominant hand, average of 3 measures. **Frailty cut point:** **Grip strength:** lowest 20% (by gender, body mass index) *Men* BMI ≤24 ≤29 BMI 24.1–26 ≤30 BMI 26.1–28 ≤30 BMI >28 ≤32 *Women* BMI ≤23 ≤17 BMI 23.1–26 ≤17.3 BMI 26.1–29 ≤18 BMI >29 ≤21
Slow walking speed	Walking time in seconds (usual pace) over 15 feet **Frailty cut point:** Slowest 20%, stratified by gender and median standing height. *Men* Height ≤173 cm ≥7 seconds Height >173 cm ≥6 seconds *Women* Height ≤159 cm ≥7 seconds Height >159 cm ≥6 seconds *OR* Time to complete "timed up and go test" (TUG) **Frailty cut point:** TUG time ≥19 seconds

Frail: ≥3 criteria present; **Intermediate or Pre-Frail:**1 or 2 criteria present; **Robust :** 0 criteria present

Methods

Critical Review Checklist

1. Were patients randomized?
2. Was randomization concealed?
3. Were patients analyzed in the groups to which they were randomized?
4. Were the groups similar?
5. Where patients blinded?
6. Where providers blinded?
7. Was follow up completed?

Randomization

Aspirin (n= 9,525)

Placebo (n= 9,589)

Randomization Process

- Randomization was stratified according to trial center and age (65 to 79 years or ≥80 years).
- Trial participants, investigators, and general practitioner associate investigators were unaware of the trial-group assignments
- Adherence to the trial intervention was assessed annually by means of tablet counts on returned bottles of aspirin or placebo.
- Committees whose members were unaware of the trial-group assignments were responsible for adjudication of all potential clinical end-point events

Follow up

Median follow-up: 4.7 years

> 90% of the due trial visits were completed each year.

Aspirin: 62.1% & Placebo: 64.1%

- Aspirin: 139 (1.5%) Were lost to follow-up & 118 (1.2%) Withdrew consent
- Placebo: 157 (1.6%) Were lost to follow-up & 119 (1.2%) Withdrew consent
- Analysis was intention to treat

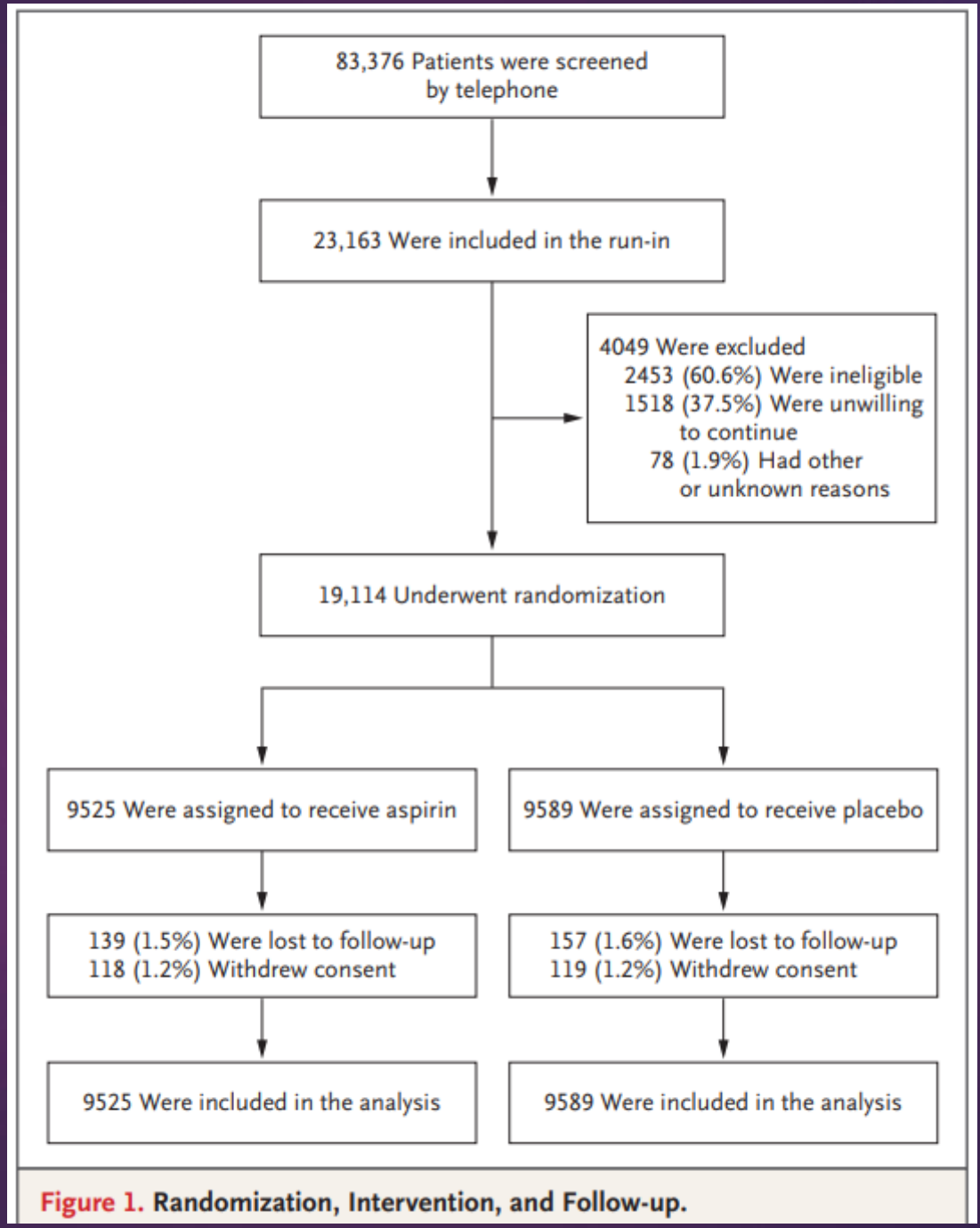


Figure 1. Randomization, Intervention, and Follow-up.

Adherence

Table S7: Adherence to Study Drug and Open Label Use of Aspirin by Trial Group

	Aspirin (N=9,525)			Placebo (N=9,589)		
Visit	Eligible* N	On study drug† N (%)	On open label aspirin‡ N (%)	Eligible* N	On study drug† N (%)	On open label aspirin‡ N (%)
Baseline	9525	9447 (99.2%)		9589	9505 (99.6%)	
Year 1	9467	7872 (83.2%)	94 (1.0%)	9534	8071 (84.7%)	127 (1.3%)
Year 2	9364	7056 (75.4%)	283 (3.0%)	9420	7321 (77.7%)	317 (3.4%)
Year 3	8227	5695 (69.2%)	274 (3.3%)	8304	5928 (71.4%)	286 (3.4%)
Year 4	6226	3976 (63.9%)	265 (4.3%)	6290	4152 (66.0%)	250 (4.0%)
Year 5	3987	2235 (56.1%)	169 (4.2%)	4033	2342 (58.1%)	171 (4.2%)
Year 6	1485	729 (49.1%)	137 (9.2%)	1456	735 (50.5%)	118 (8.1%)

Adherence

Table S6: Medication Adherence and Pill Count By Trial group

	Aspirin	Placebo
Number of participants	9,525	9,589
Number of pills consumed	10,962,411	11,336,214
% compliance	72.9%	74.3%
During the final year of the study, participants taking any study medication (%)	62.1%	64.1%
During the final year of the study, participants taking >80% of study pills as a proportion of participants taking any study medication (%)	86.8%	87.5%

'During the final year of the study' refers to any annual visit from July 2016 – June 2017.

Critical Review Checklist

1. Were patients randomized? ✓
2. Was randomization concealed? ✓
3. Were patients analyzed in the groups to which they were randomized? ✓
4. Were the groups similar? ✓
5. Where patients blinded? ✓
6. Where providers blinded? ✓
7. Was follow up completed? ✓

Critical Review Checklist

8. Was the method appropriate?
9. What outcome measures were used and were they appropriate?
10. Are the statistical tools adequate?
11. Was power and significance p level established?
12. Is the study sufficiently powered to eliminate errors?

Statistical Analysis

- ***Kaplan–Meier:*** Probability of remaining event-free
- ***Cox proportional-hazards model:*** time-to-event end points and to evaluate effects in subgroups with the use of interaction terms
- ***Safety Analysis - α:*** < 0.05
- ***Haybittle–Peto:*** 1893 primary end-point events had occurred
- ***P Value:*** 0.05

Critical Review Checklist

8. Was the method appropriate? ✓
9. What outcome measures were used and were they appropriate? ✓
10. Are the statistical tools adequate? ✓
11. Was power and significance p level established? ✓
12. Is the study sufficiently powered to eliminate errors? ✓ ✗

Results

Primary Endpoints

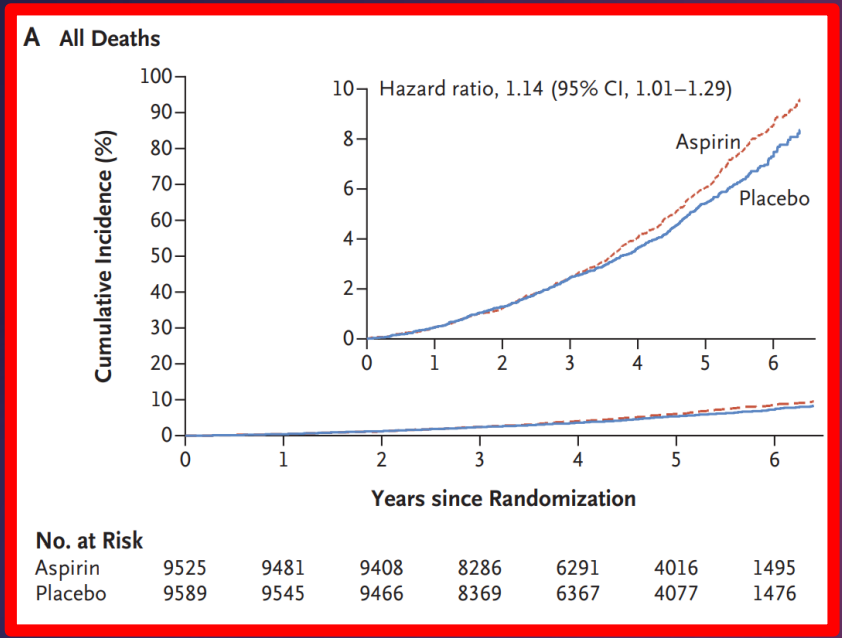
Table 2. Composite Primary End Point, Including the Components, and Secondary End Points of Death, Dementia, Persistent Physical Disability, and Major Hemorrhage.*

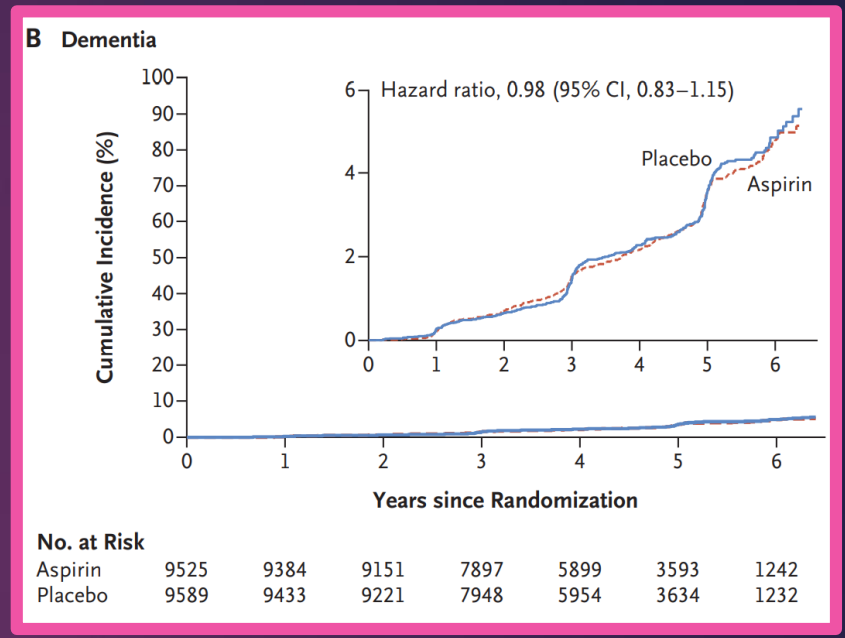
End Point	Aspirin (N = 9525)		Placebo (N = 9589)		Hazard Ratio (95% CI)	P Value
	no. of participants with event	*rate per 1000 person-yr*	*no. of participants with event*	*rate per 1000 person-yr*		
Primary end point†	921	21.5	914	21.2	1.01 (0.92–1.11)	0.79
Death from any cause	480	11.2	431	10.0	—	—
Dementia	274	6.4	275	6.4	—	—
Persistent physical disability	167	3.9	208	4.8	—	—

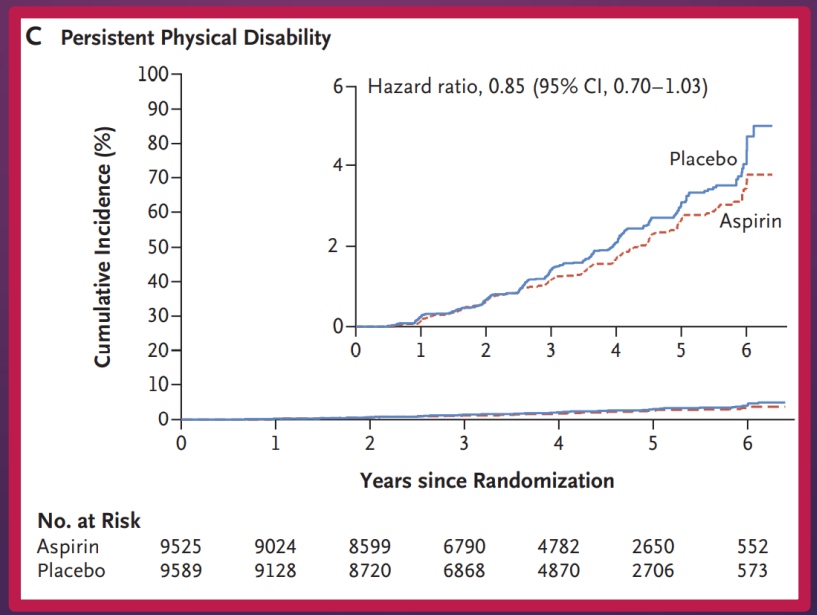
Secondary Endpoints

Secondary end points‡						
Death from any cause	558	12.7	494	11.1	1.14 (1.01–1.29)	—
Dementia	283	6.7	292	6.9	0.98 (0.83–1.15)	—
Persistent physical disability	188	4.9	224	5.8	0.85 (0.70–1.03)	—
Major hemorrhagic event	361	8.6	265	6.2	1.38 (1.18–1.62)	<0.001
Clinically significant bleeding	312	7.4	225	5.3	—	—
Hemorrhagic stroke	49	1.2	40	0.9	—	—

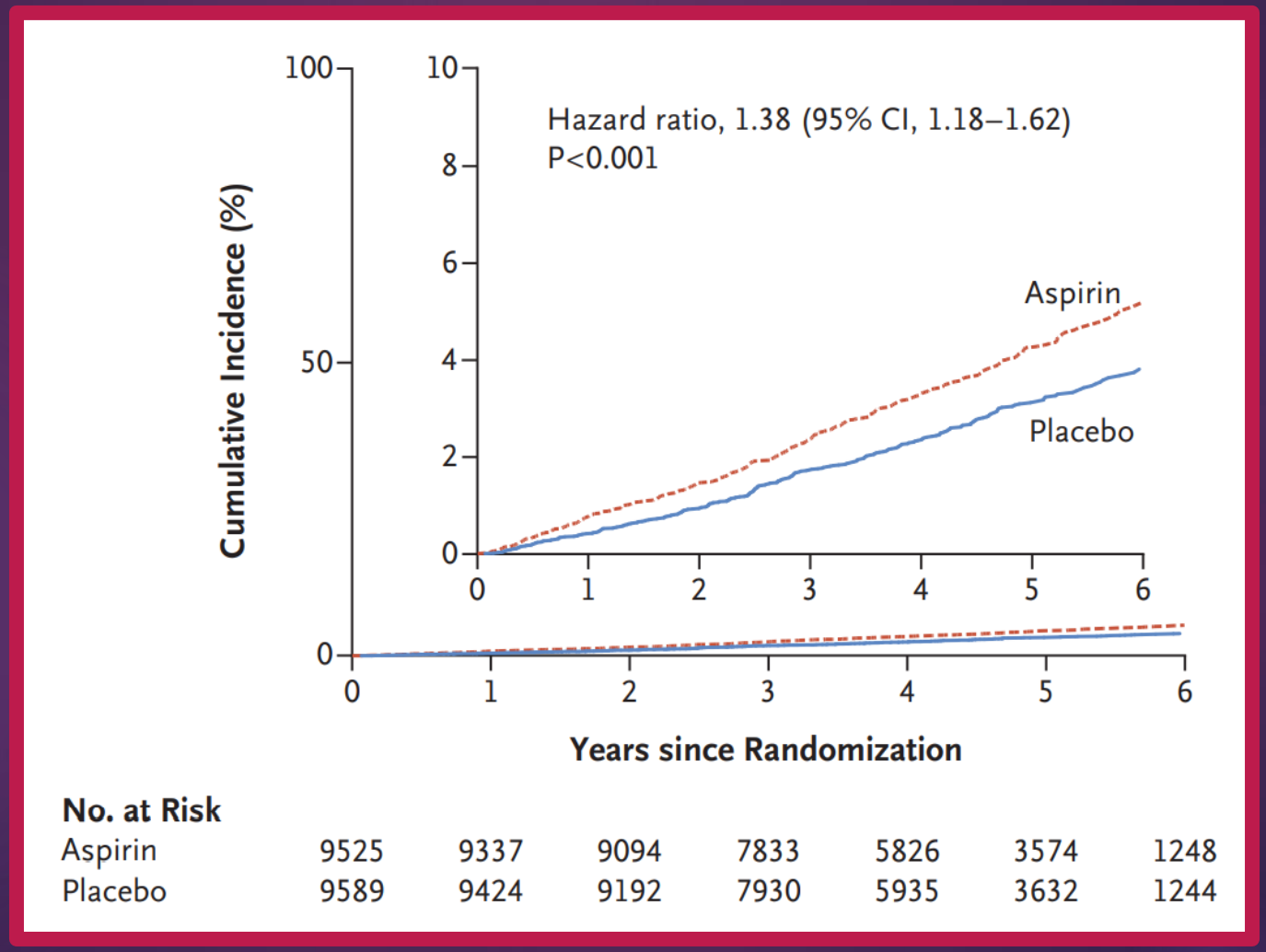
Secondary Endpoints







Secondary Endpoints



Discussion

The use of low-dose aspirin did not result in a significantly lower rate of the primary end point of disability-free survival *(death, dementia, persistent physical disability)* than placebo after a median follow-up of 4.7 years.

No significant difference in the rate of major CVD events (hazard ratio, 0.95; 95% confidence interval [CI], 0.83 to 1.08)

Rates of ***dementia*** were similar in the two groups and there was no evidence of an effect of aspirin on the rate of ***persistent physical disability***.

Discussion

Increase in all-cause mortality in individuals randomized to aspirin (***HR 1.14***; 95% CI 1.01 to 1.29).

The incidence of major hemorrhage was higher in the aspirin group than in the placebo group and amounted to an additional 2.4 serious bleeding events per 1000 person-years of exposure.

Discussion

The trial results also do not rule out a favorable effect of aspirin if its administration had been commenced at an earlier age or continued for a longer period of time.

This trial did not directly address the question of whether healthy older persons who have been using aspirin for primary prevention should continue or discontinue its use.

Limitations – Critique

- Relatively ***short duration of the intervention***, which may be important for detecting an effect of aspirin on conditions such as ***Alzheimer's disease***, and ***cancer*** , which have ***long latencies*** between their biologic substrates and clinical presentation.

- The trial also focused on a specific age range and had limited statistical power on which to base firm conclusions about the effect ***of aspirin on mortality*** in ***subgroups of the U.S. population.***

- Low adherence to ***aspirin*** (60 to 70%)

Key points

Question

Among healthy, community-dwelling seniors, does low-dose aspirin reduce death, dementia, or persistent physical disability when compared with placebo?

Findings

In this DBRCT, which included over 19,000 patients of ages 70 and above (65> for Black and Latino), low-dose aspirin did not reduce incident ***death, dementia, or persistent physical disability*** when compared with placebo and was associated with increased risk of ***major hemorrhage*** and ***all-cause mortality*****

Meaning

This study ***does not support initiation*** of aspirin on a routine basis for primary prevention of ***ASCVD***, all-cause ***mortality, dementia, or persistent physical disability***.

Questions? Opinions? Suggestions?