Madrid, 24 de Octubre de 2019

OCTAVAS JORNADAS CIENTÍFICAS DEL

CEIPV

Comité Español Interdisciplinario para la Prevención Vascular

DOCUMENTO DE AUTORIZACIÓN

PARA LA UTILIZACIÓN DE PRESENTACIÓN

MESA REDONDA: CONTROVERSIAS EN SALUD VASCULAR

TEMA: El uso de la aspirina en prevención primaria: posicionamiento del CEIPV

Carlos Brotons.
EAP Sardenya. Barcelona

eap sardenya Centre Universitari

Institut sant pau Investigacions Biomèdiques | Barcelona

CONFLICTO DE INTERESES

- *Miembro del comité ejecutivo del estudio ARRIVE, y coordinador español*

RESUMEN

- *Contextualización del tema (aspirina en prevención primaria)*
- *Resultados de los recientes ensayos clínicos-ARRIVE, ASCEND, ASPREE*
- *Análisis beneficio/riesgo*
- *Recomendaciones de las Guías*
- *Conclusiones*

CONTEXTUALIZACIÓN

Millones de personas toman la aspirina en

prevención primaria sin consejo médico

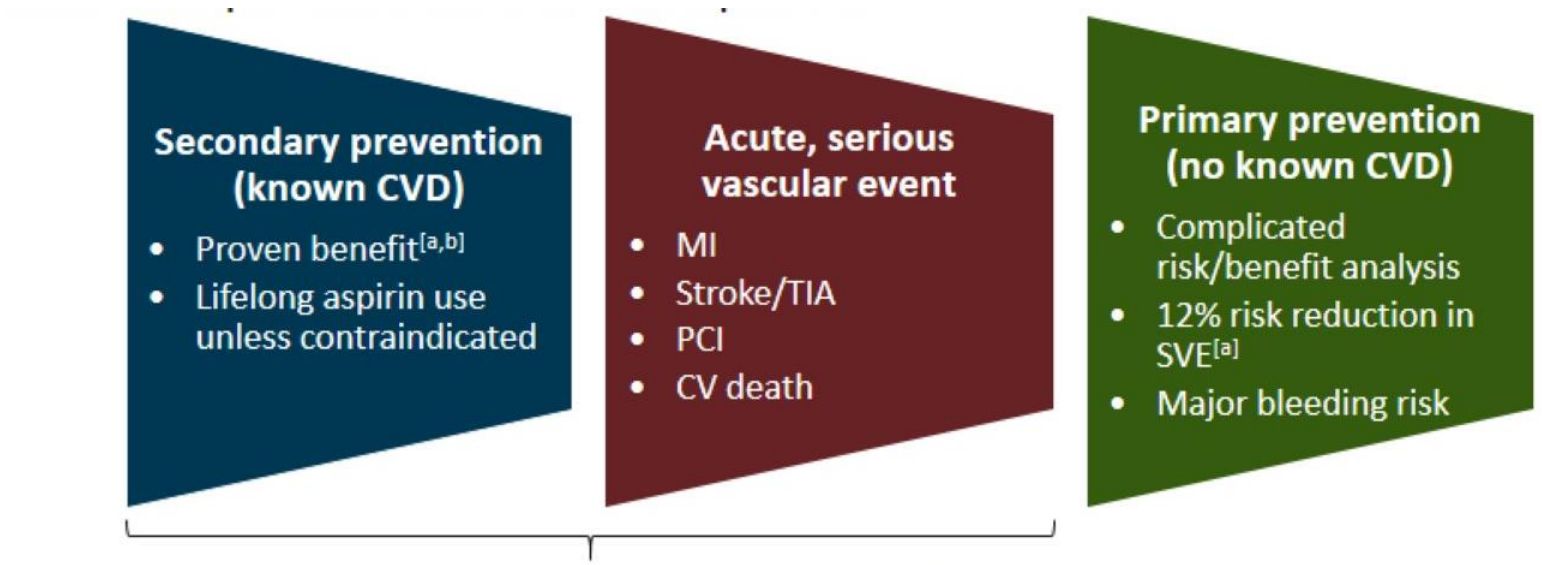
- *Nearly **25%** of adults without cardiovascular (CV) disease may be taking aspirin daily for primary prevention, **about 29 million people in US**.*
- *Of that group, **23**% were taking aspirin **without a physician's recommendation**, corresponding to about **6.6 million adults**.*
- *Nearly **50%** of people **at least 70 years** of age were on aspirin for primary CV prevention.*

Colin W. O'Brien. Annals of Internal Medicine 2019

CONTEXTUALIZACIÓN

- Más de 400 estudios han probado la hipótesis que la inhibición plaquetaria mediante aspirina reduce el riesgo en pacientes con SCA/ictus y en aquellos pacientes con enfermedad CV establecida

- En prevención primaria es más complicado porque el riesgo absoluto CV es menor y el riesgo de complicaciones puede ser comparable al de prevención secundaria



a. Antithrombotic Trialists Collaboration. *Lancet*. 2009;373:1849-1860.
b. Berger JS, et al. *Am J Med*. 2008;121:43-49.

CONTEXTUALIZACIÓN

UNIVERSITY OF OXFORD

6 older primary prevention trials

Trial	Number	Mean duration of follow-up (years)	Target population	Eligible age (years) at entry	Aspirin regimen
British Doctors' Study	5139	5.6	Male doctors	19-90	500 mg daily
US Physicians' Health Study	22071	5.0	Male doctors	45 -73	325 mg alt days
Thrombosis Prevention Trial	5085	6.7	Men with risk factors for CHD	45-69	75 mg daily
Hypertension Optimal Treatment Trial	18790	3.8	Men and women with DBP 100-115 mm Hg	50 - 80	75 mg daily
Primary Prevention Project	4495	3.7	Men and women with 1 or more risk factors for CHD	45-94	100 mg daily
Women's Health Study	39876	10.0	Female health professionals	45 or older	100 mg alt days

Jane Armitage. ESC 2019

CONTEXTUALIZACIÓN

Summary from ATTC meta-analysis Lancet 2009

- 12% proportional reduction in risk of Serious Vascular Events
- Absolute benefit 6 per 10,000 per year (mainly non-fatal MI)

- 54% proportional increase in risk of major bleeding
- Absolute hazard 3 per 10,000 per year

Estos ensayos se han llevado a cabo antes del amplio uso en la población de las estatinas y otros fármacos de protección cardiovascular

Jane Armitage. ESC 2019

CONTEXTUALIZACIÓN

UNIVERSITY OF OXFORD

More recent primary prevention trials

Trial	Number	Mean duration of follow-up (years)	Target population	Eligible age (years) at entry	Aspirin regimen
POPADAD	1276	6.7	Diabetes & ABPI ≤99	≥40	100 mg daily
JPAD	2539	4.4	Diabetes	30 -85	81 or 100 mg
AAA	3350	8.2	ABPI ≤95	50-75	100 mg daily
JPPP	14464	6.5	Men with risk factors for CHD	60 - 85	75 mg daily

Jane Armitage. ESC 2019

3 Primary prevention trials with low-dose aspirin

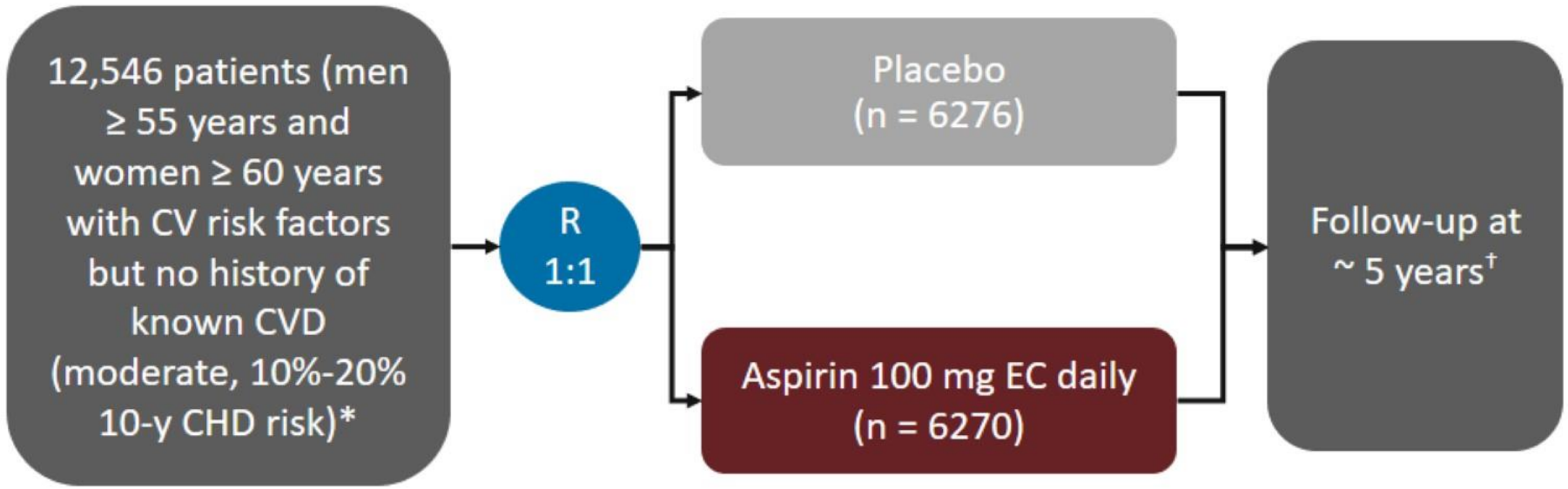
ASPREE Australia/US	Elderly	19,114	74yr	Disability-free survival
ARRIVE Europe/US	Moderate CV risk	12,546	64yr	CV composite
ASCEND UK	T2Diabetes	15480	63yr	CV composite

All community based
All used 100mg/d EC
All placebo controlled

Gaziano et al Lancet 2018 I ASCEND study collab. NEJM 2018

ARRIVE Study Design

Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel group study (Germany, Italy, Ireland, Poland, Spain, United Kingdom, United States)

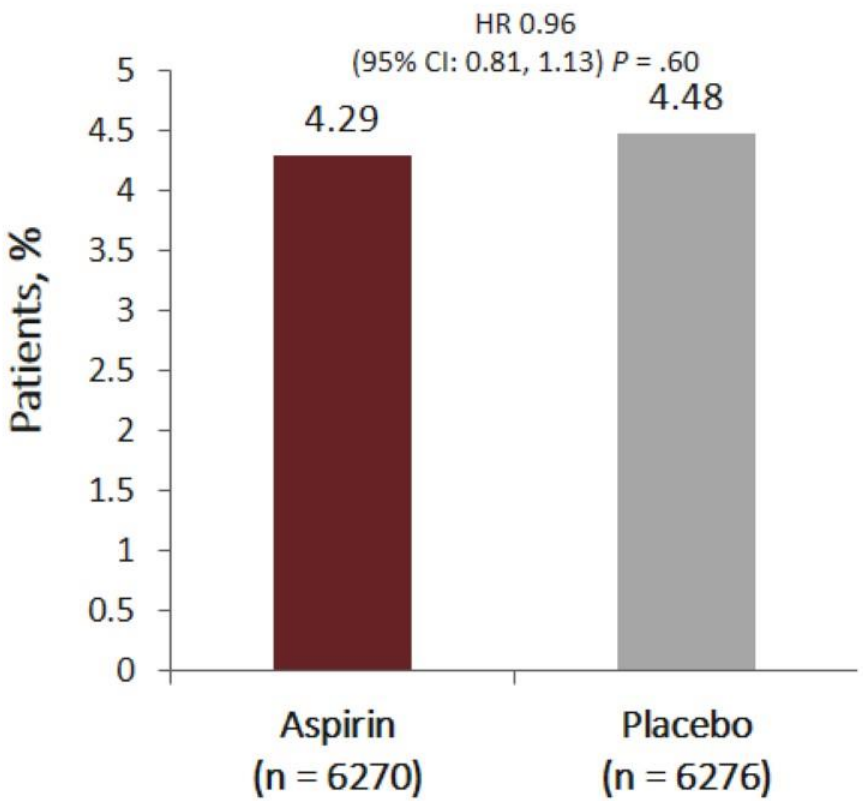


- Primary efficacy endpoint: time to the first occurrence of the composite outcome of MI, stroke, CV death, UA, or TIA
- Primary safety endpoints: hemorrhagic events and other AEs

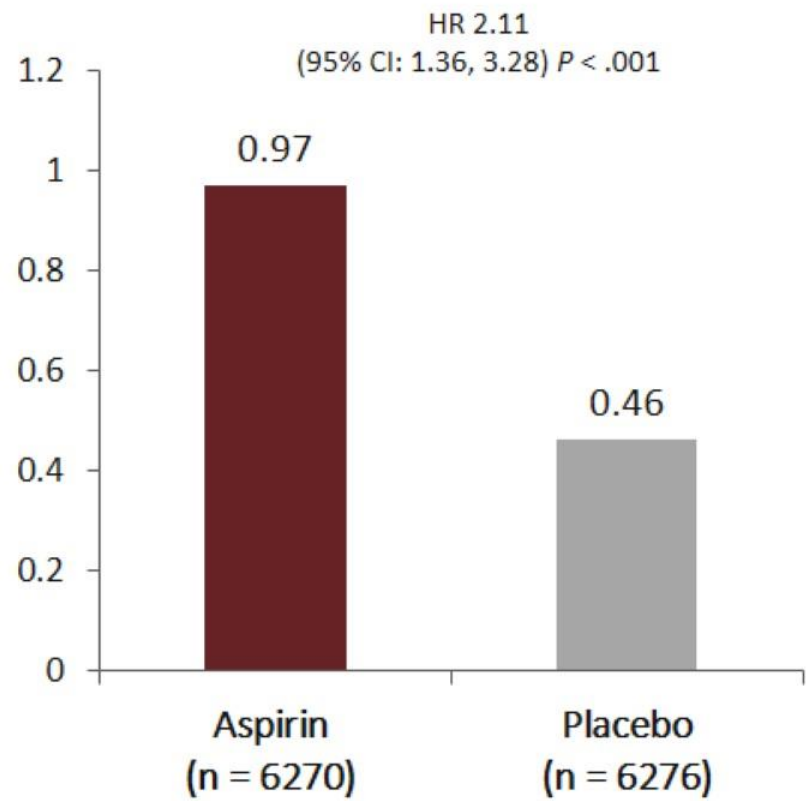
*Mean age: 64 years; 30% of patients enrolled were women. †Study duration: July 5, 2007 to November 15, 2016.
ClinicalTrials.gov. NCT00501059; Gaziano JM, et al. *Lancet*. 2018;392:1036-1046.

ARRIVE Results

Primary Endpoint*



GI Bleeding

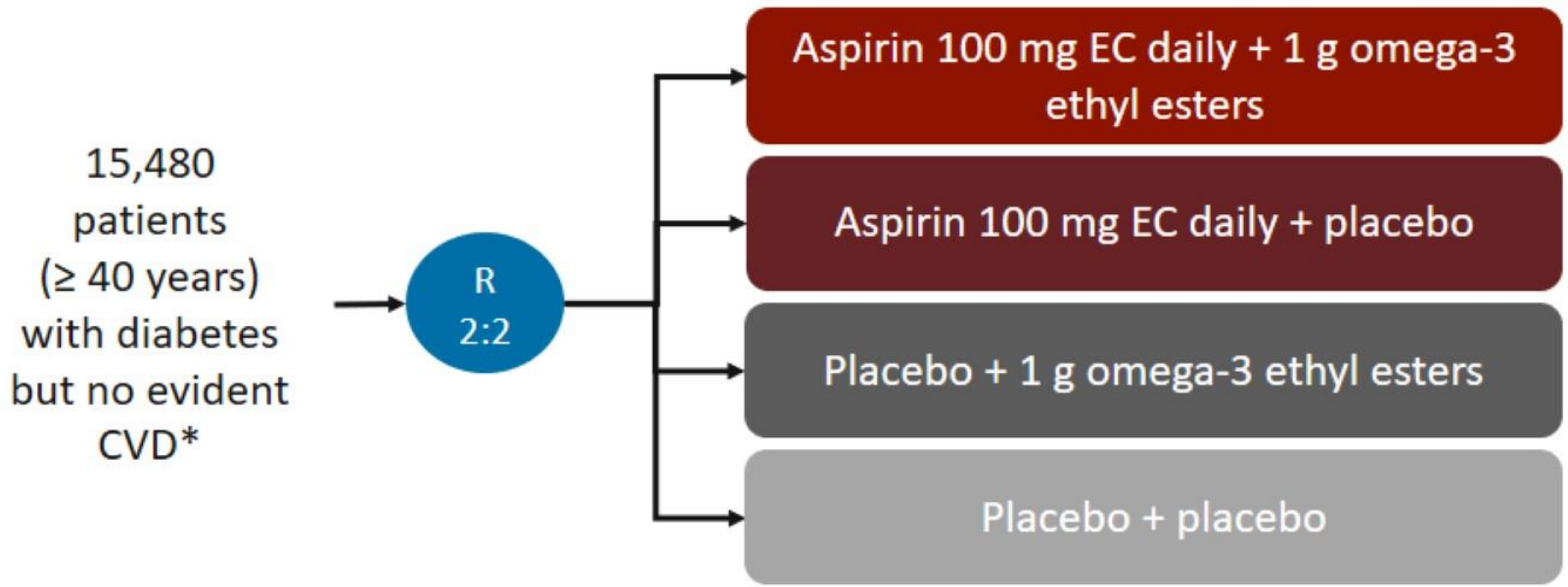


*Intention-to-treat analysis.

Gaziano JM, et al. *Lancet*. 2018;392:1036-1046.

ASCEND Study Design

Phase 4, double-blind, randomized, 2 x 2 factorial primary prevention study in patients with diabetes but no CVD (United Kingdom)



- Primary efficacy outcome: first SVE (MI, stroke, TIA) or death from any vascular cause (excluding ICH)
- Primary safety outcome: first major bleeding event (ie, ICH, sight-threatening bleeding, GI bleeding, or other serious bleeding)
- Secondary outcomes: included GI tract cancer

*Mean age: 63 years; 37% of patients enrolled were women. 94% of patients in aspirin and placebo groups had T2D.

ASCEND Study Collaborative Group. *N Engl J Med*. 2018;379:1529-1539; ClinicalTrials.gov. NCT00135226.

ASCEND Results

- Over a mean follow-up of 7.4 years*, fewer SVEs but more major bleeding occurred in the aspirin group compared with placebo (including statin therapy)
  - 12% reduction in SVE (8.5% vs 9.6%); RR 0.88 (95% CI: 0.79, 0.97); *P* = .01
  - 29% increased risk for major bleeding event (4.1% vs 3.2%); RR 1.29 (95% CI: 1.09, 1.52); *P* = .003
    - Mostly GI or extracranial bleeding
  - No significant difference in incidence of GI or other cancers
    - Long-term follow-up is planned

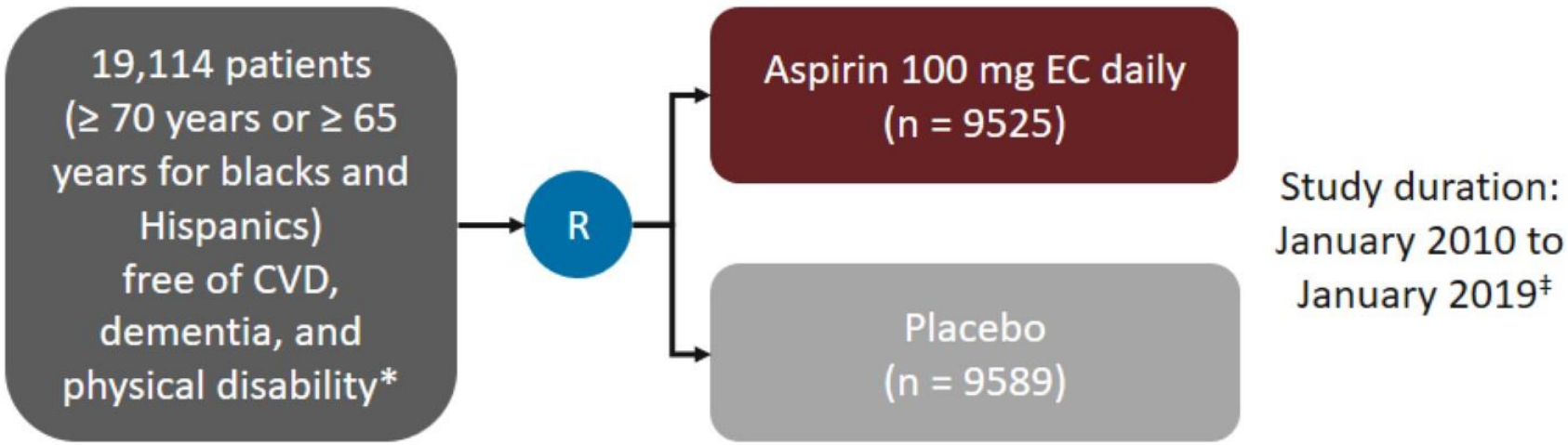
In patients with diabetes and no evident CVD, aspirin use should be individualized

*Final data collection date for primary outcome measure: March 2018.

ASCEND Study Collaborative Group. *N Engl J Med*. 2018;379:1529-1539; ClinicalTrials.gov. NCT00135226.

ASPREE Study Design

Double-blind, randomized, primary prevention study in the older population (United States, Australia)

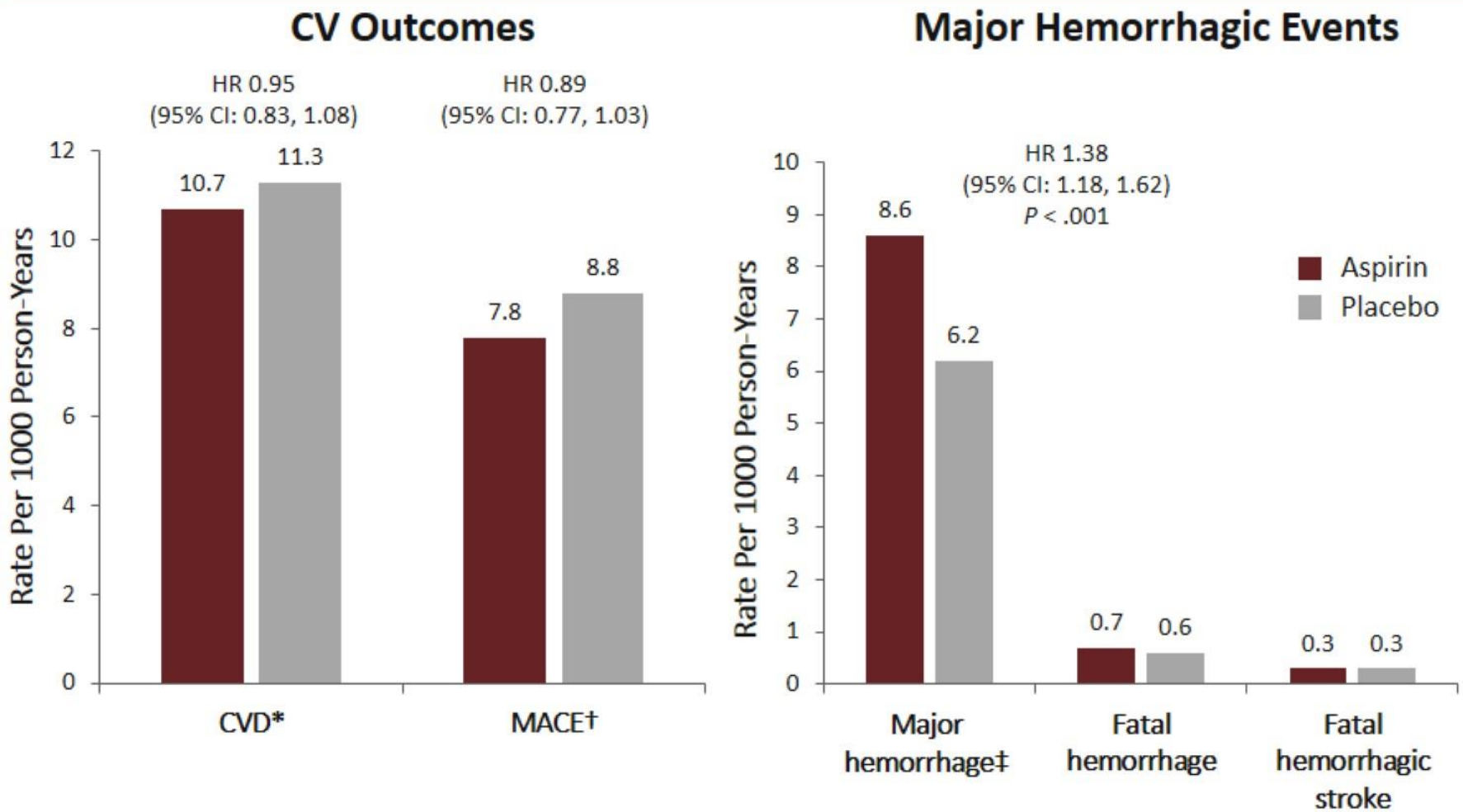


- Primary efficacy endpoints: disability-free survival (comprising all-cause mortality, incident dementia, or persistent physical disability)
- Primary safety endpoints: major hemorrhagic events (hemorrhagic stroke and CSB†)
- Secondary endpoints: fatal and nonfatal CV events and cancer

*Median age: 74 years; 56% of patients enrolled were women; 11% had diabetes. †Includes nonstroke clinically significant intracranial and extracranial bleeding. ‡Last update posted on December 19, 2018.

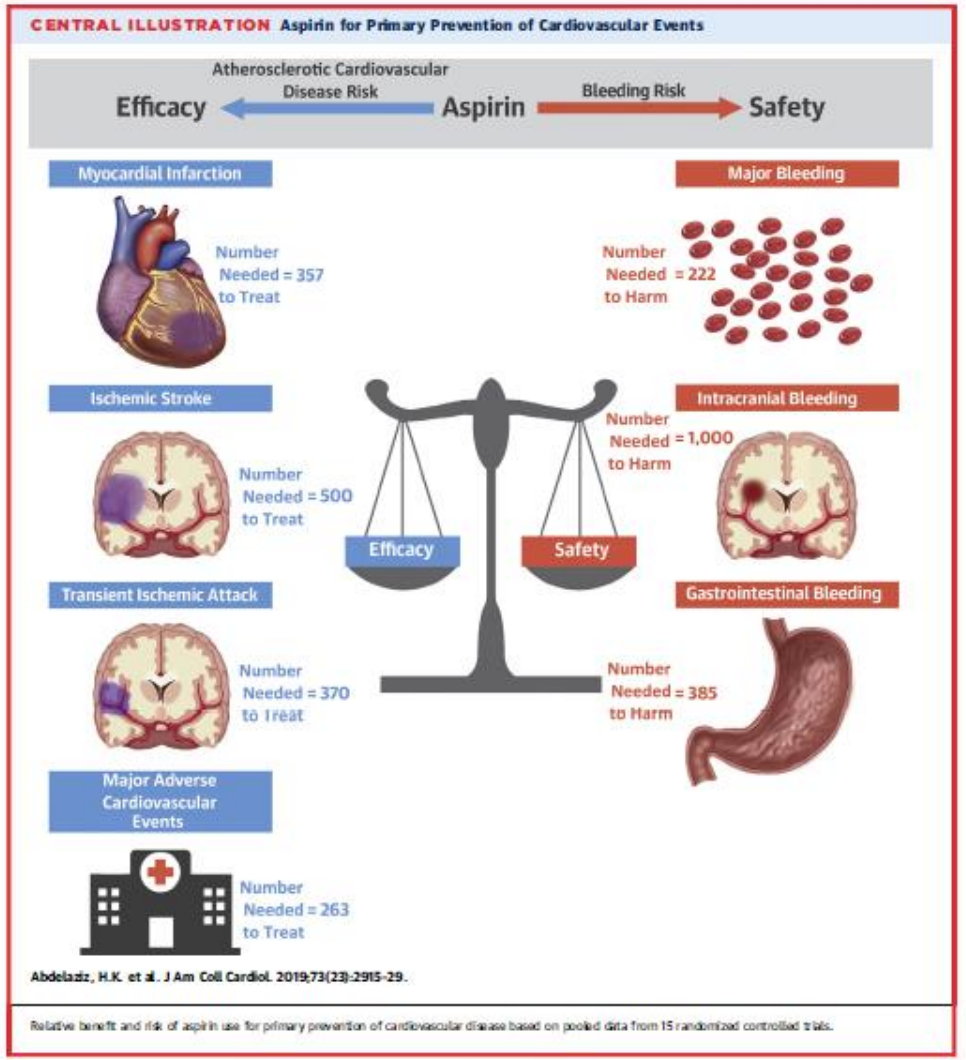
ASPREE Investigator Group. *Contemp Clin Trials.* 2013;36:555-564; ClinicalTrials.gov. NCT01038583.

ASPREE Results
CV Outcomes and Safety



*Composite of fatal CHD (including any death), nonfatal MI, fatal or nonfatal stroke, or hospitalization for HF. †Composite of fatal CHD (excluding death from HF), nonfatal MI, or fatal or nonfatal ischemic stroke. ‡Composite of hemorrhagic stroke, symptomatic intracranial or extracranial bleeding that led to transfusion, hospitalization, surgery, or death.

McNeil JJ, et al. *N Engl J Med*. 2018;379:1509-1518.



A C C VOL . 7 3 , N O . 2 3 , 2 0 1 9
Abdelaziz et al.
J U N E 1 8 , 2 0 1 9 : 2 9 1 5 – 2 9 Aspirin for Primary Prevention of CVD
2917

Análisis beneficio-riesgo: caso clínico

Paciente varón 65 años, diabético, ex-fumador, PAS 130, LDL 72 mg/dl, en tratamiento hipolipemiante e hipertenso.

Si 1000 pacientes de estas mismas características tomaran aspirina durante 5 años, se podrían evitar **12 eventos CVD**, y se podrían provocar **8 hemorragias mayores**

¿Cuál sería el mejor scenario?
¿Cuál sería el peor scenario?

Selak et al. Personalized Prediction of Cardiovascular Benefits and Bleeding Harms From Aspirin for Primary Prevention
A Benefit–Harm Analysis. *Ann Intern Med.* doi:10.7326/M19-1132 (sep 2019)

Table 1. Clinical Example* and Interpretation† of Personalized Benefit-Harm Calculation‡

Outcome	Expected Number of Events per 1000 Persons With These Same Characteristics Over 5 y			
	Pretreatment Risk (i.e., Without Aspirin)‡	Posttreatment Risk (i.e., With Aspirin)§	Difference With Aspirin	Net Effect of Aspirin‖
Main calculation (using point estimate of HR for effect of aspirin on major bleeds and CVD)				
Major bleeds	19	27	+8	−4
CVD	117	105	−12	
Worst-case scenario (using upper limit of 95% CI for HR for effect of aspirin on major bleeds and CVD)				
Major bleeds	19	30	+11	+6
CVD	117	112	−5	
Best-case scenario (using lower limit of 95% CI for HR for effect of aspirin on major bleeds and CVD)				
Major bleeds	19	25	+6	−12
CVD	117	99	−18	

Selak et al. Personalized Prediction of Cardiovascular Benefits and Bleeding Harms From Aspirin for Primary Prevention
A Benefit–Harm Analysis. *Ann Intern Med.* doi:10.7326/M19-1132 (sep 2019)

Aspirin Use

Recommendations for Aspirin Use		
COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age.
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.

2019 ACC/AHA guidelines on the Primary Prevention of CVD

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.	III	B	464

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Antiplatelet therapy (e.g. with aspirin) is not recommended for people with DM who do not have CVD.	III	A

Recommendations for Antiplatelet Therapy in Primary Prevention in Diabetes Mellitus

ESC European Society of Cardiology

Recommendations	Class	Level
In patients with DM at high/very high risk, aspirin (75–100 mg/day) may be considered in primary prevention in the absence of clear contraindications.	IIb	A
In patients with DM at moderate CV risk, aspirin for primary prevention is not recommended.	III	B
Gastric protection		
When low-dose aspirin is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding.	IIa	A

©ESC

www.escardio.org/guidelines

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

CONCLUSIONES

1 Escenario: Paciente no diabético, sin enfermedad cardiovascular de muy alto, alto o moderado riesgo CV

NO se recomienda aspirina en prevención primaria de la enfermedad CV

CONCLUSIONES

2 Escenario: Paciente diabético, sin enfermedad cardiovascular de alto o muy alto riesgo CV

Se podría considerer aspirina para la prevención primaria de la enfermedad CV (se debe considerer la utilización de IBPs)

CONCLUSIONES

3 Escenario: Paciente sin enfermedad CV, diabético de moderado/alto riesgo CV, o paciente NO diabético de alto o muy alto riesgo CV, que ya está tomando aspirina.

Discutir con el paciente riesgos/beneficios y preferencias (*shared-decision making*)



eap sardenya

Institut sant pau
Investigacions Biomèdiques | Barcelona



cbrotons@eapsardenya.cat