Conoscere e Curare il Cuore 2019

SABATO 2 MARZO

CHI HA BISOGNO DELL'ACIDO ACETILSALICILICO? FACCIAMO CHIAREZZA DOPO TANTI STUDI.

Claudio Borghi

Cattedra di Medicina Interna
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N.Rockwell,
Waiting room

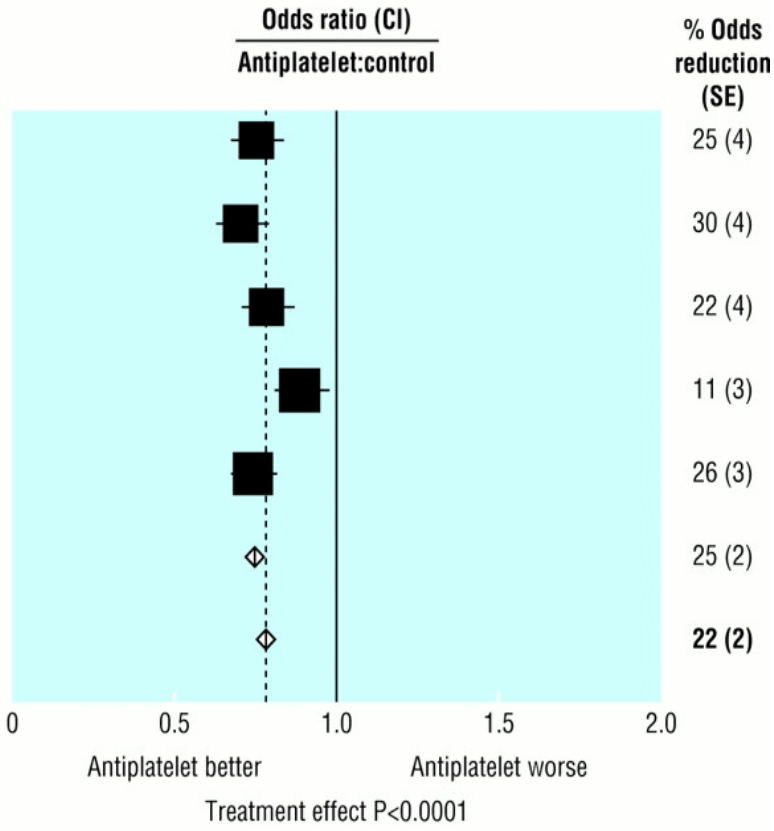
Proportional effects of antiplatelet therapy on vascular events in five main high risk categories

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	-159.8	567.6	25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	-181.5	519.2	30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	-152.1	625.8	22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	-94.6	795.3	11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	-222.3	737.0	26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	-715.7	2449.6	25 (2)
All trials	**195**	**7705/71 912 (10.7)**	**9502/72 139 (13.2)**	**-810.3**	**3244.9**	**22 (2)**

Heterogeneity of odds reductions between:

5 categories of trial: χ^2=21.4, df=4; P=0.0003

Acute stroke *v* other: χ^2=18.0, df=1; P=0.00002



Antithrombotic Trialists- Collaboration, BMJ 2002

The absolute risk of vascular complications is the major determinant of the absolute benefit of antiplatelet prophylaxis.

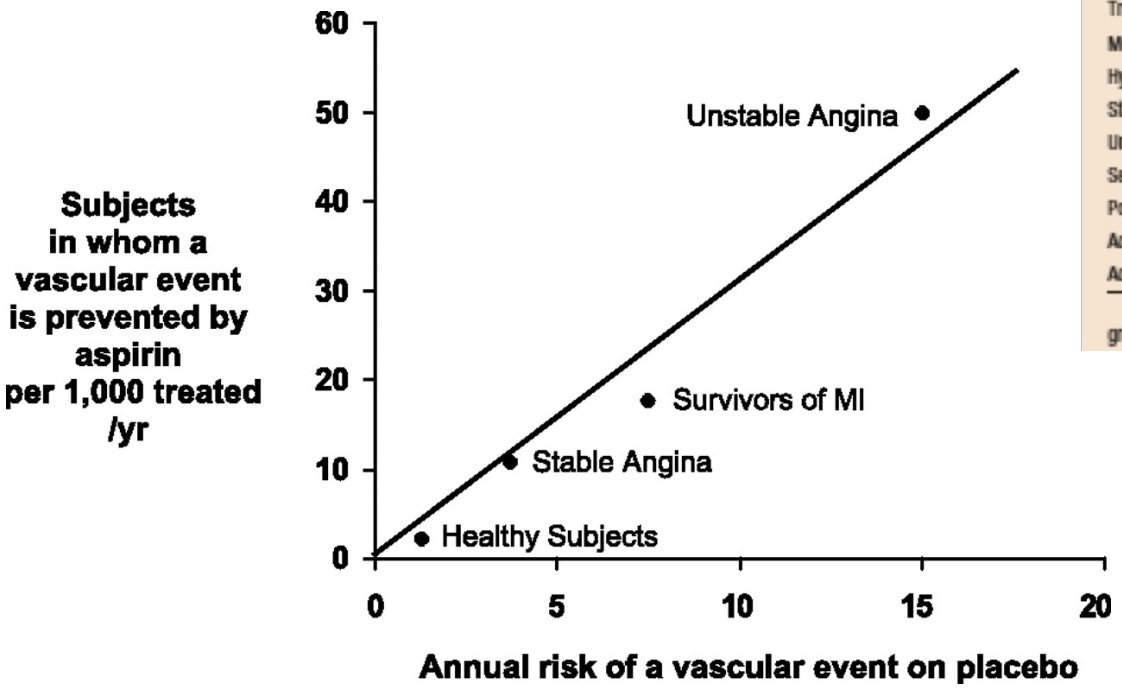


Table. Vascular Disorders for Which Aspirin Has Been Shown to Be Effective and Lowest Effective Dose

Disorder	Lowest Effective Daily Dose (mg)
Transient ischemic attack and ischemic stroke*	50
Men at high cardiovascular risk	75
Hypertension	75
Stable angina	75
Unstable angina*	75
Severe carotid artery stenosis*	75
Polycythemia vera*	100
Acute myocardial infarction	160
Acute ischemic stroke*	160

*Higher doses have been tested in other trials and not found to confer any greater risk reduction.

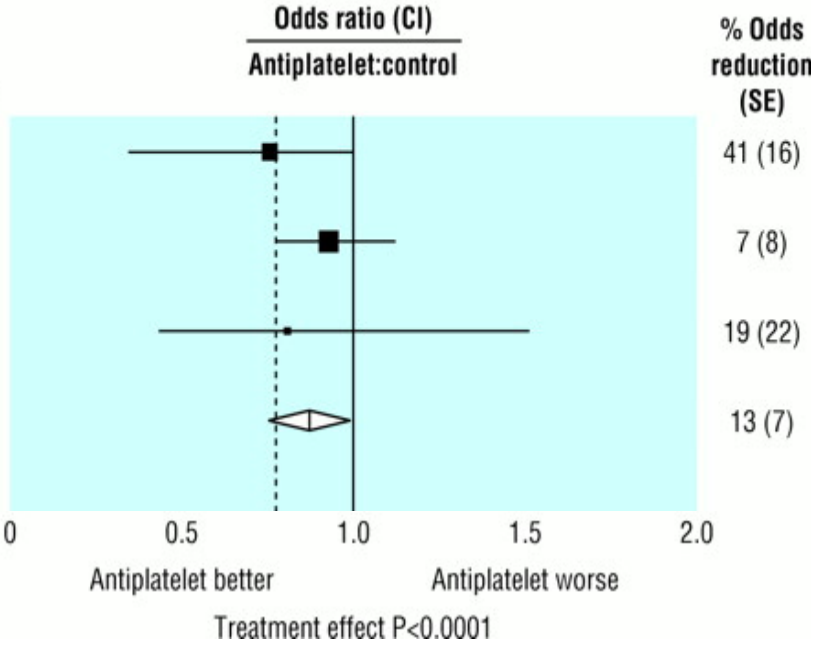
CHEST
The Cardiopulmonary and Critical Care Journal

Eikelboom J W et al. Chest 2012;141:e89S-e119S

Proportional effects of antiplatelet therapy on vascular events in patients with other high risk conditions

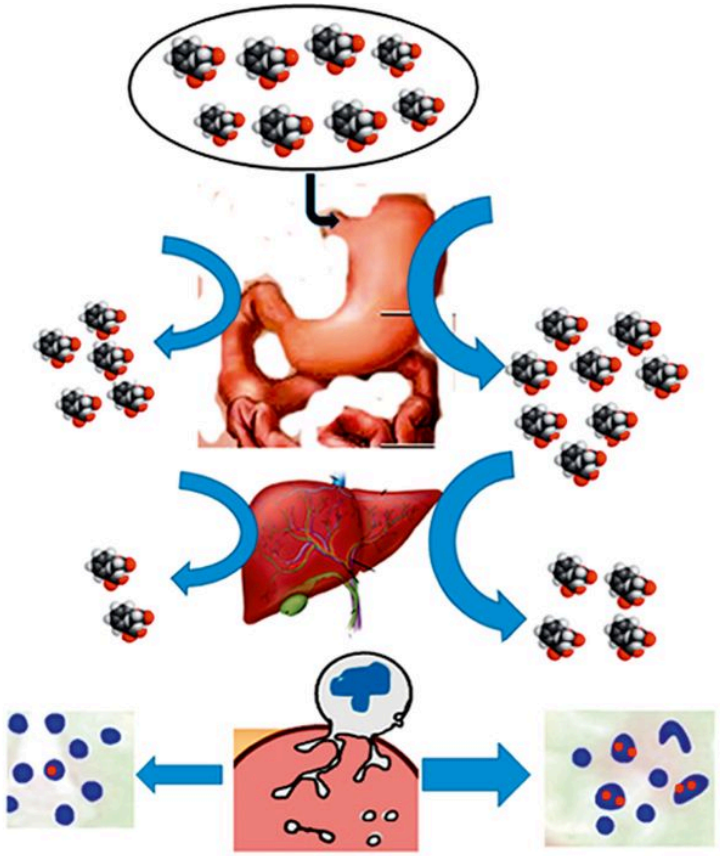
	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Haemodialysis	14	38/1333 (2.9)	67/1371 (4.9)	-12.2	23.4	41 (16)
Diabetes	9	403/2568 (15.7)	426/2558 (16.7)	-12.7	164.4	7 (8)
Carotid disease	6	36/339 (10.6)	43/337 (12.8)	-3.6	17.1	19 (22)
Subtotal	29	477/4240 (11.3)	536/4266 (12.6)	-28.5	204.9	13 (7)

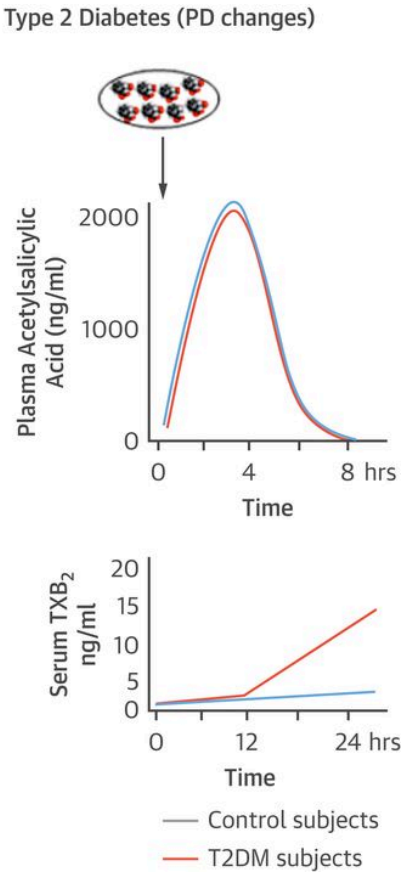
Heterogeneity between 7 subtotals other than acute stroke: χ^2=15.4, df=6; P=0.02

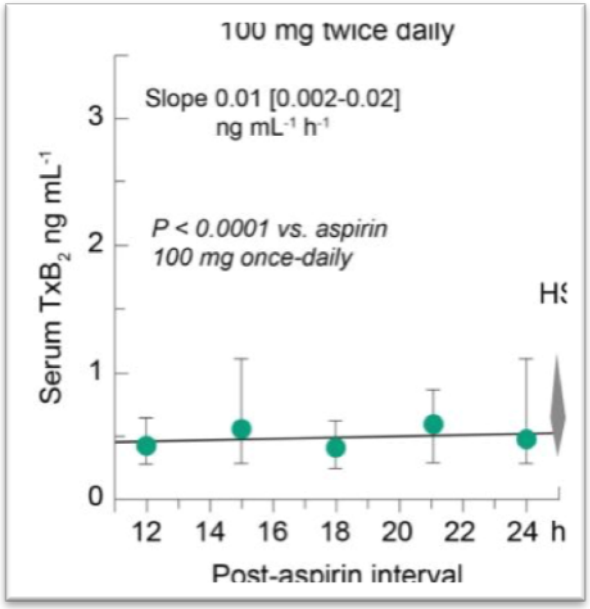


Antithrombotic Trialists- Collaboration, BMJ 2002

Distinct Mechanisms May Contribute to Variable Aspirin Responsiveness in patients with Diabetes







Rocca B et al, Journal of Thrombosis and Haemostasis 2012; 10 (7): 1220-1230

Patrono C & Rocca B, JACC 2017;69:613-615

Recommendations	Class[a]	Level[b]	Ref[c]
In acute coronary syndromes, a $P2Y_{12}$ inhibitor for 12 months is recommended in addition to aspirin, unless there are contra-indications such as excessive risk of bleeding.	I	A	455–457
$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.	IIb	A	458–461
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of ischaemic and bleeding risks of the patient.	IIb	A	462, 463
In the chronic phase (>12 months) after MI, aspirin is recommended.	I	A	464
In patients with non-cardioembolic ischaemic stroke or TIA, prevention with aspirin only, or dipyridamole plus aspirin or clopidogrel alone is recommended.	I	A	465–467
Prasugrel is not recommended in patients with stable CAD. Ticagrelor is not recommended in patients with stable CAD without a previous ACS.	III	C	463
In patients with non-cardioembolic cerebral ischaemic events, anticoagulation is not recommended.	III	B	468, 469
Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.	III	B	464

European recommendations for antiplatelet therapy in CV prevention

Piepoli M et al, The 6th Joint Task Force of ESC, Eur Heart J,2012

ASA and combination treatment

Norman Rockwell
Triple self-portrait
(1960)

PCI patients

ASA + Clopidogrel
Prasugrel
Ticagrelor

Stable ATS disease

ASA + NOAC (Rivaroxaban)

10.3 Prevention of hypertension and pre-eclampsia

Women at high or moderate risk of pre-eclampsia should be advised to take 100–150 mg of aspirin daily from week 12 to weeks 36–37.[364,365]

High risk of pre-eclampsia includes any of the following:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

Moderate risk of pre-eclampsia includes more than one of the following risk factors:

- first pregnancy
- age 40 years or older
- pregnancy interval of more than 10 years
- BMI of ≥35 kg/m^2 at first visit
- family history of pre-eclampsia
- multiple pregnancy.

ESC European Society of Cardiology
European Heart Journal (2018) **00**, 1–83
doi:10.1093/eurheartj/ehy340

ESC GUIDELINES

2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

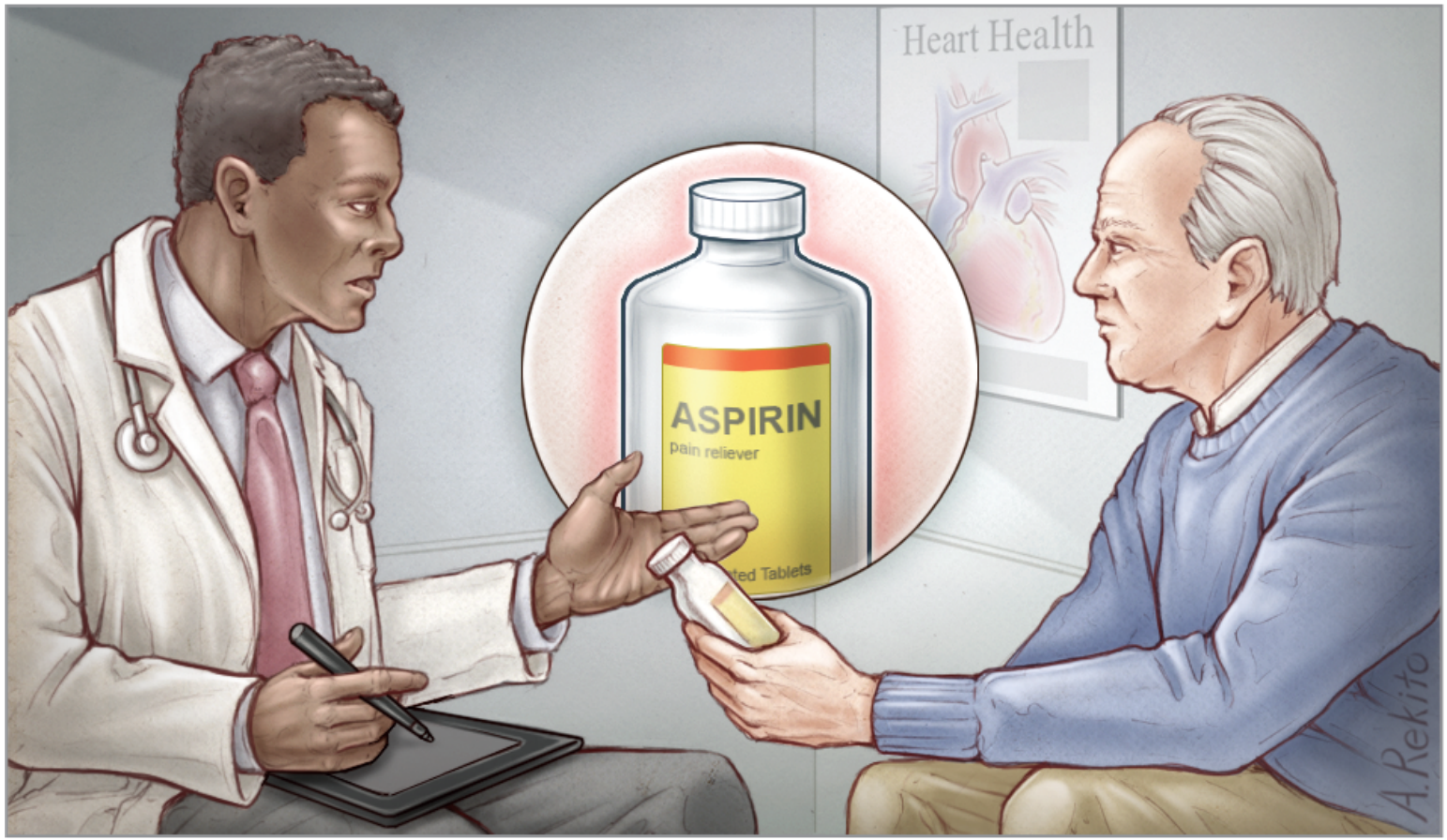
The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

Endorsed by: the International Society of Gender Medicine (IGM), the German Institute of Gender in Medicine (DGesGM), the European Society of Anaesthesiology (ESA), and the European Society of Gynecology (ESG)

JAMA CARDIOLOGY PATIENT PAGE

I Do Not Have Heart Disease—Should I Be Taking Aspirin?

Heart attack and stroke are sudden, symptomatic events that can lead to hospitalization and death.



Karmal KN et al, JAMA 2018

Factors affecting the relevance of primary prevention studies with ASA

- Type of tablets
- Nr of administrations (o.i.d, alternate days, etc)
- Sample size
- Difference in baseline CV risk among patients
- Emphasis on secondary objectives (i.e. CHD/stroke)
- Discrepancies patients/outcomes (e.g. PAD vs.CHD)

Results of different meta-analyses of primary prevention trials with ASA

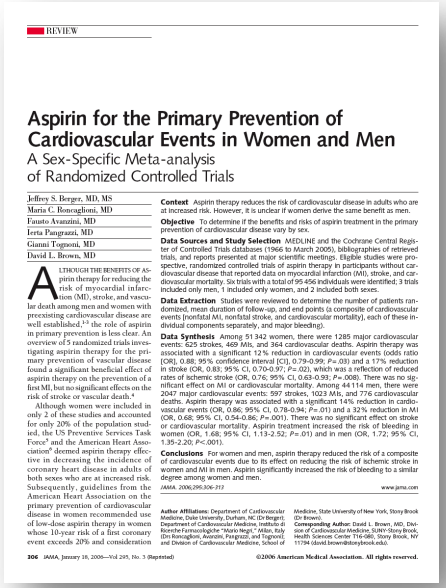
6 studies

Meta-analysis	Major vascular events	Major coronary events	Any stroke	Vascular death	Any death
ATT Collaboration:[1] rate ratio (95% CI)	0.88 (0.82–0.94)	0.82 (0.75–0.90)	0.95 (0.85–1.06)	0.97 (0.87–1.09)	0.95 (0.88–1.02)
Raju *et al.*:[30] relative risk (95% CI)	0.88 (0.83–0.94)	0.83 (0.69–1.00)	0.93 (0.82–1.05)	0.96 (0.84–1.09)	0.94 (0.88–1.00)
Bartolucci *et al.*:[31] odds ratio (95% CI)	0.87 (0.80–0.93)	0.85 (0.69–1.02)	0.92 (0.83–1.02)	0.96 (0.80–1.14)	0.93 (0.87–1.00)

9 studies

Patrono C. Eur Heart J. 2013 Nov;34(44):3403-11

ASA for the Primary Prevention of Cardiovascular Events in Women and Men: A Sex-Specific Meta-analysis of Randomized Controlled Trials



REVIEW

Aspirin for the Primary Prevention of Cardiovascular Events in Women and Men

A Sex-Specific Meta-analysis of Randomized Controlled Trials

Jeffrey S. Berger, MD, MS
Maria C. Roncaglioni, MD
Fausto Avanzini, MD
Ierta Pangrazzi, MD
Gianni Tognoni, MD
David L. Brown, MD

Context Aspirin therapy reduces the risk of cardiovascular disease in adults who are at increased risk. However, it is unclear if women derive the same benefit as men.

Objective To determine if the benefits and risks of aspirin treatment in the primary prevention of cardiovascular disease vary by sex.

Data Sources and Study Selection MEDLINE and the Cochrane Central Register of Controlled Trials databases (1966 to March 2005), bibliographies of retrieved trials, and reports presented at major scientific meetings. Eligible studies were prospective, randomized controlled trials of aspirin therapy in participants without cardiovascular disease that reported data on myocardial infarction (MI), stroke, and cardiovascular mortality. Six trials with a total of 95 456 individuals were identified; 3 trials included only men, 1 included only women, and 2 included both sexes.

Data Extraction Studies were reviewed to determine the number of patients randomized, mean duration of follow-up, and end points (a composite of cardiovascular events [nonfatal MI, nonfatal stroke, and cardiovascular mortality], each of these individual components separately, and major bleeding).

Data Synthesis Among 51 342 women, there were 1285 major cardiovascular events: 625 strokes, 469 MIs, and 364 cardiovascular deaths. Aspirin therapy was associated with a significant 12% reduction in cardiovascular events (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.79-0.99; *P*=.03) and a 17% reduction in stroke (OR, 0.83; 95% CI, 0.70-0.97; *P*=.02), which was a reflection of reduced rates of ischemic stroke (OR, 0.76; 95% CI, 0.63-0.93; *P*=.008). There was no significant effect on MI or cardiovascular mortality. Among 44 114 men, there were 2047 major cardiovascular events: 597 strokes, 1023 MIs, and 776 cardiovascular deaths. Aspirin therapy was associated with a significant 14% reduction in cardiovascular events (OR, 0.86; 95% CI, 0.78-0.94; *P*=.01) and a 32% reduction in MI (OR, 0.68; 95% CI, 0.54-0.86; *P*=.001). There was no significant effect on stroke or cardiovascular mortality. Aspirin treatment increased the risk of bleeding in women (OR, 1.68; 95% CI, 1.13-2.52; *P*=.01) and in men (OR, 1.72; 95% CI, 1.35-2.20; *P*<.001).

Conclusions For women and men, aspirin therapy reduced the risk of a composite of cardiovascular events due to its effect on reducing the risk of ischemic stroke in women and MI in men. Aspirin significantly increased the risk of bleeding to a similar degree among women and men.

JAMA. 2006;295:306-313
www.jama.com

Author Affiliations: Department of Cardiovascular Medicine, Duke University, Durham, NC (Dr Berger); Department of Cardiovascular Medicine, Instituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy (Drs Roncaglioni, Avanzini, Pangrazi, and Tognoni); and Division of Cardiovascular Medicine, School of Medicine, State University of New York, Stony Brook (Dr Brown).
Corresponding Author: David L. Brown, MD, Division of Cardiovascular Medicine, SUNY-Stony Brook, Health Sciences Center T16-080, Stony Brook, NY 11794 (david.brown@stonybrook.edu).

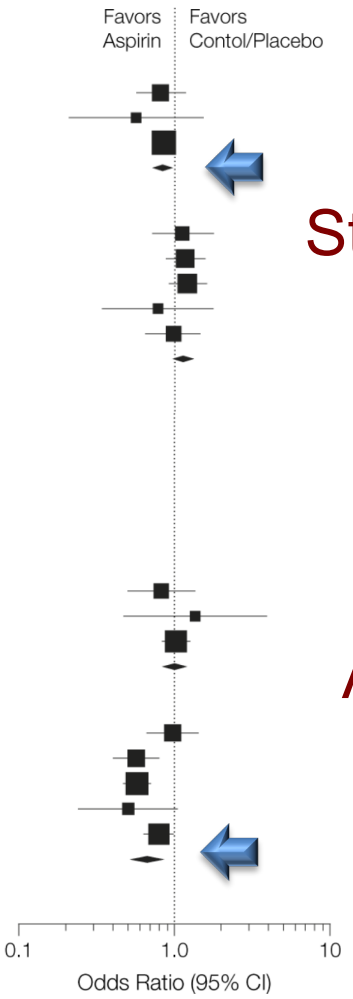
306 JAMA, January 18, 2006—Vol 295, No. 3 (Reprinted)

Stroke

Study, y	Events, No./Total: Aspirin	Events, No./Total: Control/Placebo	Odds Ratio (95% CI)
Women			
HOT,[12] 1998	54/4437	67/4446	0.81 (0.56-1.16)
PPP,[17] 2001	6/1277	11/1306	0.56 (0.21-1.51)
WHS,[9] 2005	221/19934	266/19942	0.84 (0.70-1.01)
Total	281/25648	344/25694	0.83 (0.70-0.97)
Men			
BDT,[15] 1988	61/3429	27/1710	1.13 (0.72-1.78)
HOT,[12] 1998	94/4962	80/4945	1.17 (0.87-1.57)
PHS,[14] 1989	119/11037	95/11034	1.22 (0.93-1.59)
PPP,[17] 2001	10/949	13/963	0.78 (0.34-1.78)
TPT,[16] 1998	47/2545	48/2540	0.98 (0.65-1.47)
Total	331/22922	266/21192	1.13 (0.96-1.33)

Myocardial Infarction

Study, y	Events, No./Total: Aspirin	Events, No./Total: Control/Placebo	Odds Ratio (95% CI)
Women			
HOT,[12] 1998	29/4437	35/4446	0.83 (0.51-1.36)
PPP,[17] 2001	8/1277	6/1306	1.37 (0.47-3.95)
WHS,[9] 2005	198/19934	193/19942	1.03 (0.84-1.25)
Total	235/25648	234/25694	1.01 (0.84-1.21)
Men			
BDT,[15] 1988	80/3429	41/1710	0.97 (0.66-1.42)
HOT,[12] 1998	54/4962	93/4945	0.57 (0.41-0.81)
PHS,[14] 1989	139/11037	239/11034	0.58 (0.47-0.71)
PPP,[17] 2001	11/949	22/963	0.50 (0.24-1.04)
TPT,[16] 1998	154/2545	190/2540	0.80 (0.64-0.99)
Total	438/22922	585/21192	0.68 (0.54-0.86)



Stroke

AMI

Berger JS et a, JAMA. 2006;295(3):306-313

Duble-faced Janus
II° century a.c.
Musem of S.Francesco
Trevi, Italy

Results of recent meta-analyses of ASA for the primary prevention of CVD: **bleeding outcomes**

Author (year of publication)	Number of participants[a] (number of studies)	Results (aspirin versus placebo)		
		Haemorrhagic stroke	Major bleeding	NNH major bleeding
ATTC [1] 2009	95 000 (6)	1.32 (0.91–1.91)	1.54 (1.30–1.82)	–
Raju *et al.* [4] 2011	100 076 (9)	1.36 (1.01–1.82)	1.66 (1.41–1.95)	300 (109 gastrointestinal[b])
Bartolucci *et al.* [2] 2011	100 038 (9)	n/a	n/a	–
Seshasai *et al.* [3] 2012	102 621 (9)	n/a	1.31 (1.14–1.50)	109

NNH, number needed to harm.
[a]Some of the analyses were limited to fewer participants according to data availability, e.g. BDT did not report gastrointestinal bleeding, HOT did not provide separate data on ischaemic and haemorrhagic stroke.
[b]Raju *et al.* reported major and gastrointestinal bleeding separately; Seshasai *et al.* reported all nontrivial bleeding combined.

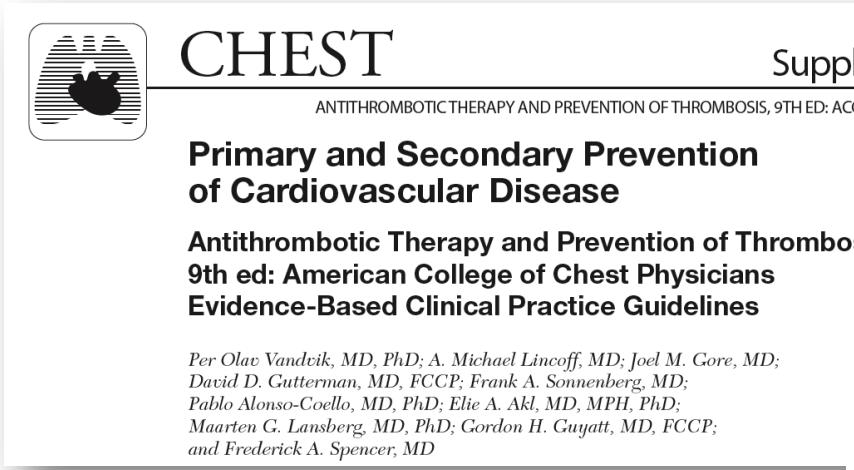
Raju NC & Elkelboom JW, Curr Opin in Cardiol 2012

ESC-European recommendations for antiplatelet therapy in CV prevention

Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.	III	B	464

Piepoli M et al, The 6th Joint Task Force of ESC, Eur Heart J,2016

Antiplatelet therapy (e.g. with aspirin) is not recommended for people with DM who do not have CVD.	III	A	398



CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Primary and Secondary Prevention of Cardiovascular Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Per Olav Vandvik, MD, PhD; A. Michael Lincoff, MD; Joel M. Gore, MD; David D. Gutterman, MD, FCCP; Frank A. Sonnenberg, MD; Pablo Alonso-Coello, MD, PhD; Elie A. Akl, MD, MPH, PhD; Maarten G. Lansberg, MD, PhD; Gordon H. Guyatt, MD, FCCP; and Frederick A. Spencer, MD

Recommendation

2.1. For persons aged 50 years or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in MI is closely balanced

RCT of Low-Dose ASA for Primary Prevention

High risk of CVD

Study (Ref. #)	Regimen(s)	Treatment Duration	N	Eligibility	Primary Endpoint	End Date
ACCEPT-D (23)	Aspirin 100 mg versus open control; simvastatin for all	5 yrs	5,170	Diabetes, no CVD	CV death, nonfatal stroke, nonfatal MI, other CV hospitalization	2015
ARRIVE (25)	Aspirin 100 mg versus placebo	5 yrs	~12,000	10-20% estimated 10-yr risk of CHD	MI, stroke, CV death, unstable angina, TIA	2016
ASPREE (24)	Aspirin 100 mg versus placebo	5 yrs	~19,000	Elderly, no diabetes or CVD	Death, dementia or significant disability	2017
ASCEND (22)	Aspirin 100 mg versus placebo (ω3FA vs. placebo)	7.5 yrs	~15,000	Diabetes, no CVD	MI, stroke or TIA, or CV death	2018

ACCEPT-D = Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trials in Diabetes; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = ASPirin in Reducing Events in the Elderly; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; FA = fatty acids; MI = myocardial infarction; TIA = transient ischemic attack.

High risk of cancer

Study	Regimen(s)	Treatment Duration	N	Eligibility	Primary Endpoint	End Date
AspECT	Aspirin 300 mg versus placebo	8 yrs	2,500	Barrett's esophagus	Death/adenocarcinoma or high-grade metaplasia	2017
seAFOod	Aspirin 300 mg versus placebo (EPA versus placebo)	1 yr	904	Multiple adenomas at BCSP	≥1 adenoma at 1-yr screen	NA
ASCOLT	Aspirin 200 mg versus placebo	3 yrs	2,660	Dukes C or high-risk Dukes B cancer	5-yr disease-free survival	2022
Add-Aspirin	Aspirin 100 mg versus aspirin 300 mg versus placebo	5 yrs	9,920	CRC, breast, gastroesophageal, prostate cancer	Disease-free survival (death for gastroesophageal)	2025

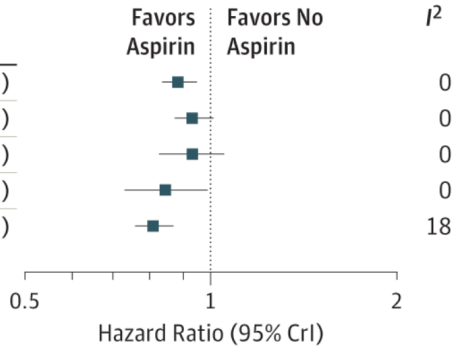
ASCOLT = Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers; AspECT = Aspirin and Esomeprazole Chemoprevention Trial; BCSP = bowel cancer screening program; CRC = colorectal cancer; EPA = eicosapentaenoic acid; NA = not available; seAFOod = Systematic Evaluation of Aspirin and Fish Oil.

Patrono C. J Am Coll Cardiol. 2015 Jul 7;66(1):74-85

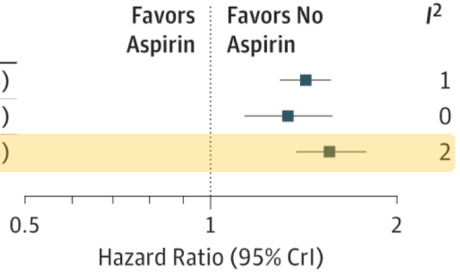
From: **Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis**

Cardiovascular and Bleeding Outcomes in all patients. The composite cardiovascular (CV) outcome consisted of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke.

Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Composite CV outcome	11	2911	79717	3072	78147	0.38 (0.20 to 0.55)	0.89 (0.84-0.95)
All-cause mortality	13	3622	81623	3588	80057	0.13 (-0.07 to 0.32)	0.94 (0.88-1.01)
CV mortality	13	995	81623	997	80057	0.07 (-0.04 to 0.17)	0.94 (0.83-1.05)
Myocardial infarction	13	1469	81623	1599	80057	0.28 (0.05 to 0.47)	0.85 (0.73-0.99)
Ischemic stroke	10	831	65316	942	63752	0.16 (0.06 to 0.30)	0.81 (0.76-0.87)



Bleeding Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Increase, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Major bleeding	11	1195	74715	834	73143	0.47 (0.34 to 0.62)	1.43 (1.30-1.56)
Intracranial bleeding	12	349	80985	257	79419	0.11 (0.04 to 0.18)	1.34 (1.14-1.57)
Major GI bleeding	10	593	70336	380	70465	0.30 (0.20 to 0.41)	1.56 (1.38-1.78)



NNT=265 vs NNH= 210

Zheng SL et al, JAMA. 2019;321(3):277-287.

Research

JAMA | Original Investigation

Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events

A Systematic Review and Meta-analysis

Sean L. Zheng, BM, BCh, MA, MRCP; Alistair J. Roddick, BSc

13 studies (up to 2019)
164.225 patients
Median follow-up: 5 years

CONCLUSIONS AND RELEVANCE The use of aspirin in individuals without cardiovascular disease was associated with a lower risk of cardiovascular events and an increased risk of major bleeding. This information may inform discussions with patients about aspirin for primary prevention of cardiovascular events and bleeding.

*" Consequently, the decision to use aspirin for primary prevention may need to be made on an individual basis, accounting for the patient's risk of bleeding and **their views on the balance of risk vs benefit**.[34] "*

Zheng SL et al, JAMA. 2019;321(3):277-287.

CLINICAL GUIDELINE

Annals of Internal Medicine

Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement

Kirsten Bibbins-Domingo, PhD, MD, MAS, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2009 USPSTF recommendation on aspirin use to prevent cardiovascular disease (CVD) events and the 2007 recommendation on aspirin and nonsteroidal anti-inflammatory drug use to prevent colorectal cancer (CRC).

Methods: The USPSTF reviewed 5 additional studies of aspirin for the primary prevention of CVD and several additional analyses of CRC follow-up data. The USPSTF also relied on commissioned systematic reviews of all-cause mortality and total cancer incidence and mortality and a comprehensive review of harms. The USPSTF then used a microsimulation model to systematically estimate the balance of benefits and harms.

Population: This recommendation applies to adults aged 40 years or older without known CVD and without increased bleeding risk.

Recommendations: The USPSTF recommends initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. (B recommendation)

The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin. (C recommendation)

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years. (I statement)

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older. (I statement)

Ann Intern Med. 2016;164:836-845. doi:10.7326/M16-0577 **www.annals.org**

For author affiliation, see end of text.

This article was published at www.annals.org on 12 April 2016.

* For a list of members of the USPSTF, see the **Appendix** (available at www.annals.org).

Sensitivity analyses for the efficacy of low-dose aspirin on cardiovascular events based on the intention-to-treat cohort of the JPAD study.

ORIGINAL RESEARCH ARTICLE

Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

10-Year Follow-Up of a Randomized Controlled Trial

BACKGROUND: The long-term efficacy and safety of low-dose aspirin for primary prevention of cardiovascular events in patients with type 2 diabetes mellitus are still inconclusive.

METHODS: The JPAD trial (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes) was a randomized, open-label, standard care–controlled trial examining whether low-dose aspirin affected cardiovascular events in 2539 Japanese patients with type 2 diabetes mellitus and without preexisting cardiovascular disease. Patients were randomly allocated to receive aspirin (81 or 100 mg daily; aspirin group) or no aspirin (no-aspirin group) in the JPAD trial. After that trial ended in 2008, we followed up with the patients until 2015, with no attempt to change the previously assigned therapy. Primary end points were cardiovascular events, including sudden death, fatal or nonfatal coronary artery disease, fatal or nonfatal stroke, and peripheral vascular disease. For the safety analysis, hemorrhagic events, consisting of gastrointestinal bleeding, hemorrhagic stroke, and bleeding from any other sites, were also analyzed. The primary analysis was conducted for cardiovascular events among patients who retained their original allocation (a per-protocol cohort). Analyses on an intention-to-treat cohort were conducted for hemorrhagic events and statistical sensitivity.

RESULTS: The median follow-up period was 10.3 years; 1621 patients (64%) were followed up throughout the study; and 2160 patients (85%) retained their original allocation. Low-dose aspirin did not reduce cardiovascular events in the per-protocol cohort (hazard ratio, 1.14; 95% confidence interval, 0.91–1.42). Multivariable Cox proportional hazard model adjusted for age, sex, glycemic control, kidney function, smoking status, hypertension, and dyslipidemia showed similar results (hazard ratio, 1.04; 95% confidence interval, 0.83–1.30), with no heterogeneity of efficacy in subgroup analyses stratified by each of these factors (all interaction P>0.05). Sensitivity analyses on the intention-to-treat cohort yielded consistent results (hazard ratio, 1.01; 95% confidence interval, 0.82–1.25). Gastrointestinal bleeding occurred in 25 patients (2%) in the aspirin group and 12 (0.9%) in the no-aspirin group (P=0.03), and the incidence of hemorrhagic stroke was not different between groups.

CONCLUSIONS: Low-dose aspirin did not affect the risk for cardiovascular events but increased risk for gastrointestinal bleeding in patients with type 2 diabetes mellitus in a primary prevention setting.

CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00110448.

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Sources of Funding, see page 667

Key Words: aspirin ■ diabetes mellitus ■ hemorrhage ■ primary prevention

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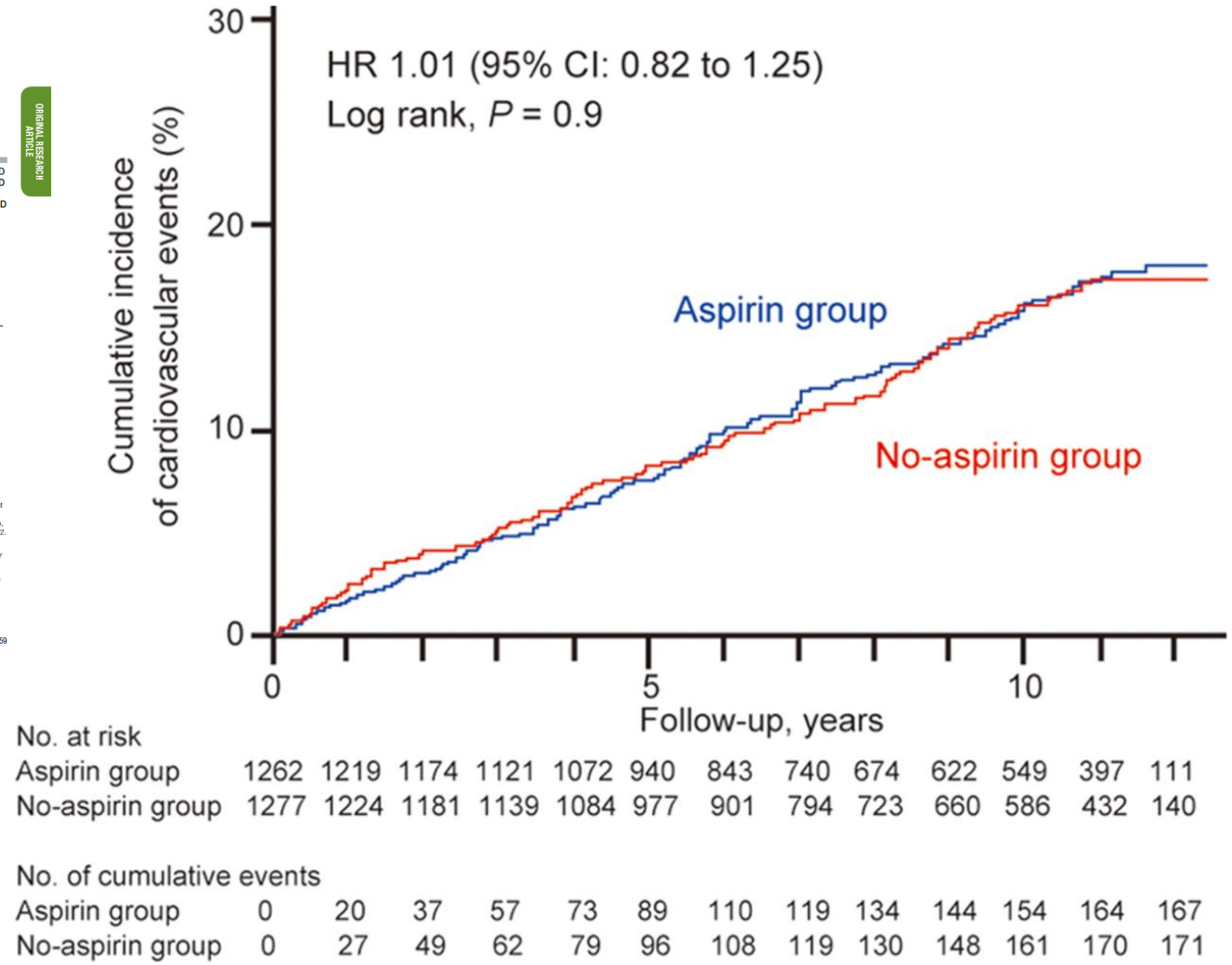
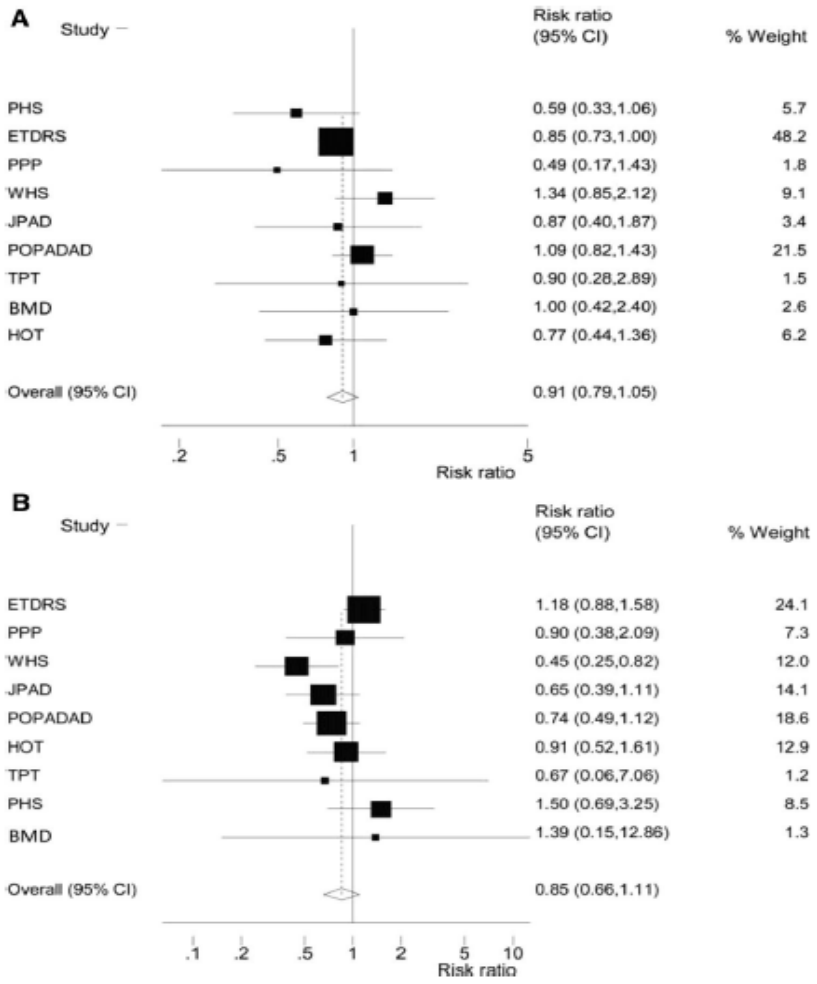
February 14, 2017 659



American Heart Association.

Yoshihiko Saito et al. Circulation. 2017;135:659-670

Metanalysis of trials examining the effects of ASA on primary prevention of CV diseases in DM



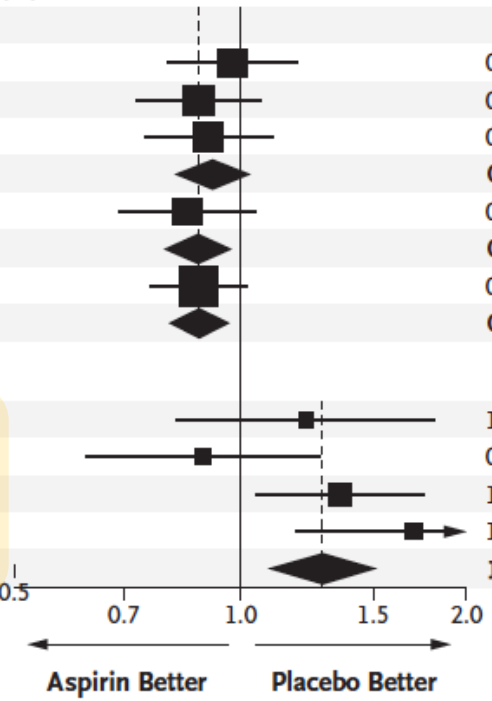
CHD

Stroke

Pignone M et al Circulation 2010

Relative rate of major vascular outcomes and major bleeding in the ASCEND study

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

This article was published on August 26, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1804988

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

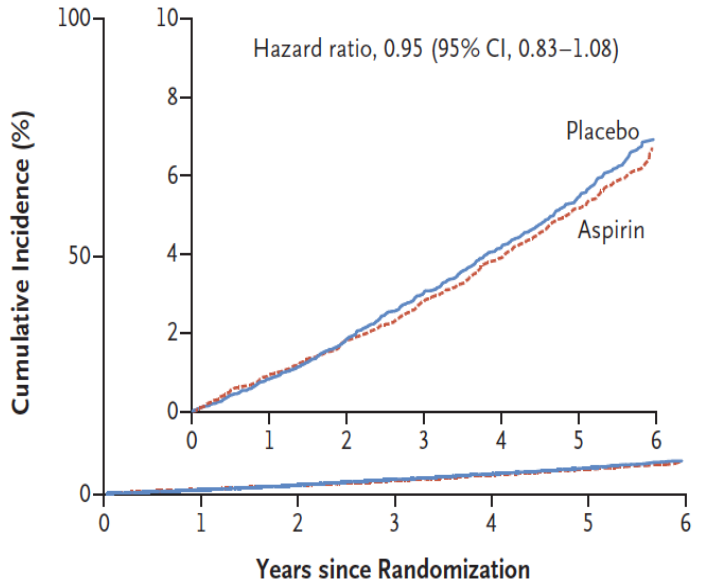
J.J. McNeil, R. Wolfe, R.L. Woods, A.M. Tonkin, G.A. Donnan, M.R. Nelson, C.M. Reid, J.E. Lockery, B. Kirpach, E. Storey, R.C. Shah, J.D. Williamson, K.L. Margolis, M.E. Ernst, W.P. Abhayaratna, N. Stocks, S.M. Fitzgerald, S.G. Orchard, R.E. Trevaks, L.J. Beilin, C.I. Johnston, J. Ryan, B. Radziszewska,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

CONCLUSIONS

The use of low-dose aspirin as a primary prevention strategy in older adults resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo. (Funded by the National Institute on Aging and others; ASPREE ClinicalTrials.gov number, NCT01038583.)

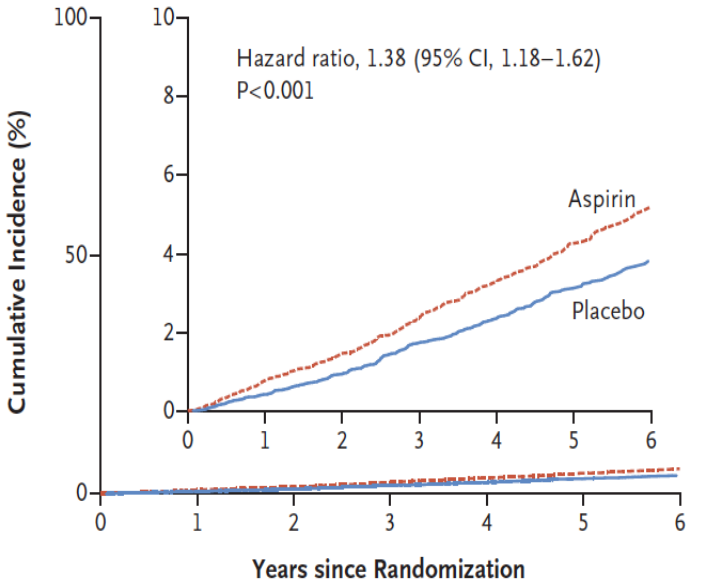
Cumulative incidence of CV disease and major hemorrhage in the ASPREE-3 study

Major CV disease (secondary end-point)



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

Major Hemorrhage (secondary end-point)



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

n.19114, ASA 100 mg/day

This article was published on September 16, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1805819

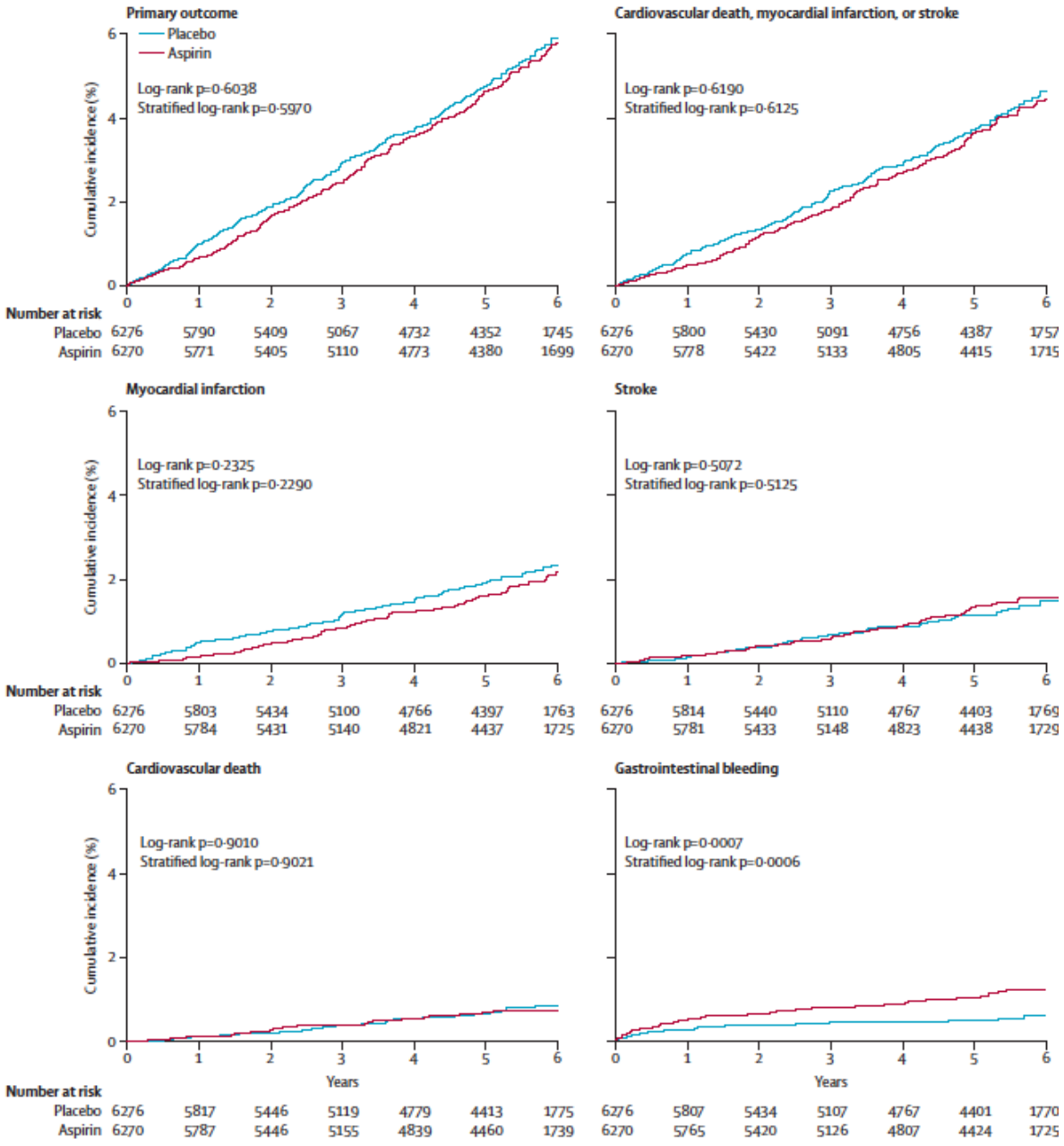
Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial

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

Methods ARRIVE is a randomised, double-blind, placebo-controlled, multicentre study done in seven countries. Eligible patients were aged 55 years (men) or 60 years (women) and older and had an average cardiovascular risk, deemed to be moderate on the basis of the number of specific risk factors. We excluded patients at high risk of gastrointestinal bleeding or other bleeding, or diabetes.

Interpretation The event rate was much lower than expected, which is probably reflective of contemporary risk management strategies, making the study more representative of a low-risk population. The role of aspirin in primary prevention among patients at moderate risk could therefore not be addressed. Nonetheless, the findings with respect to aspirin's effects are consistent with those observed in the previously published low-risk primary prevention studies.

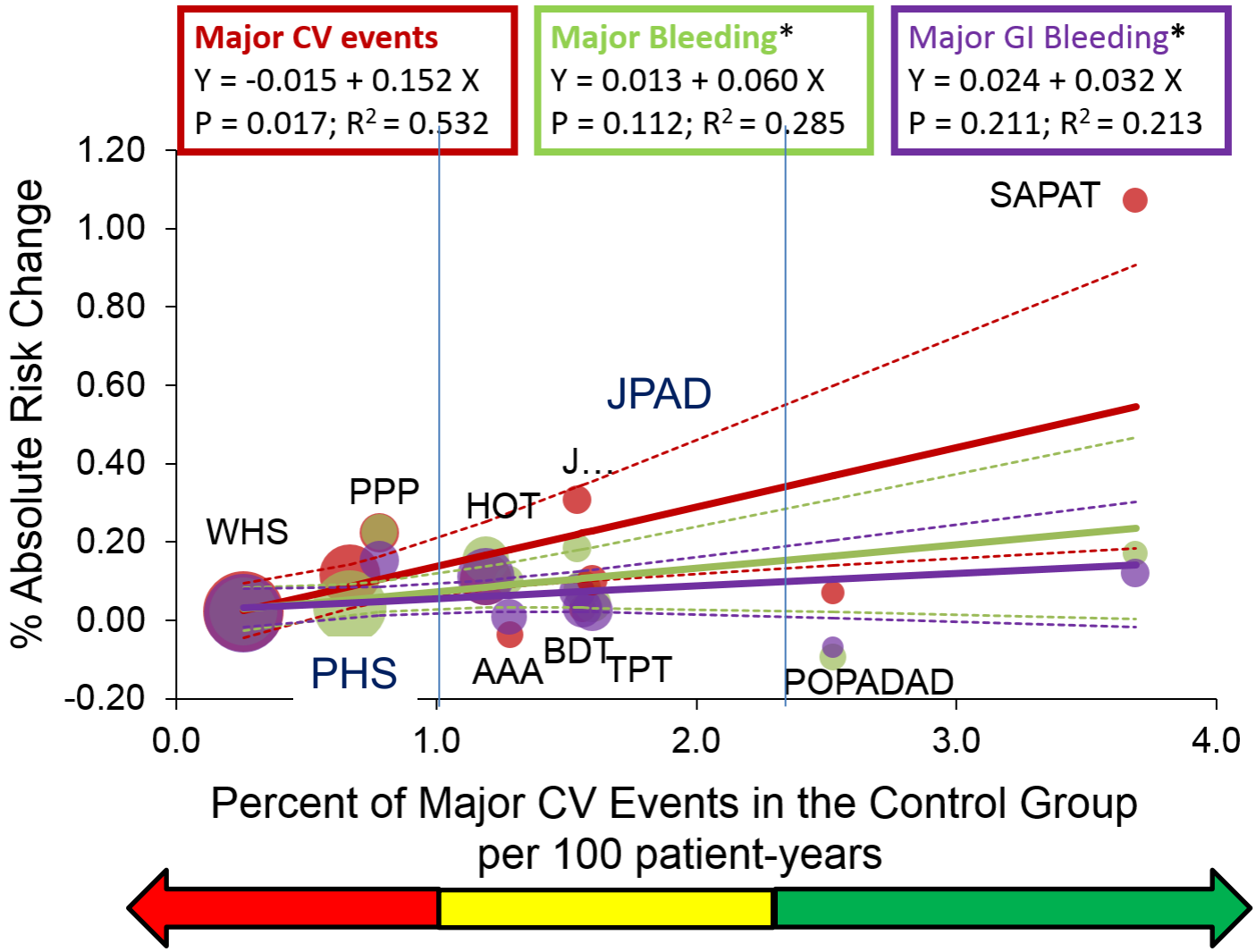
Lancet 2018



Incidence of primary outcome, components of the primary outcome in the ARRIVE Study

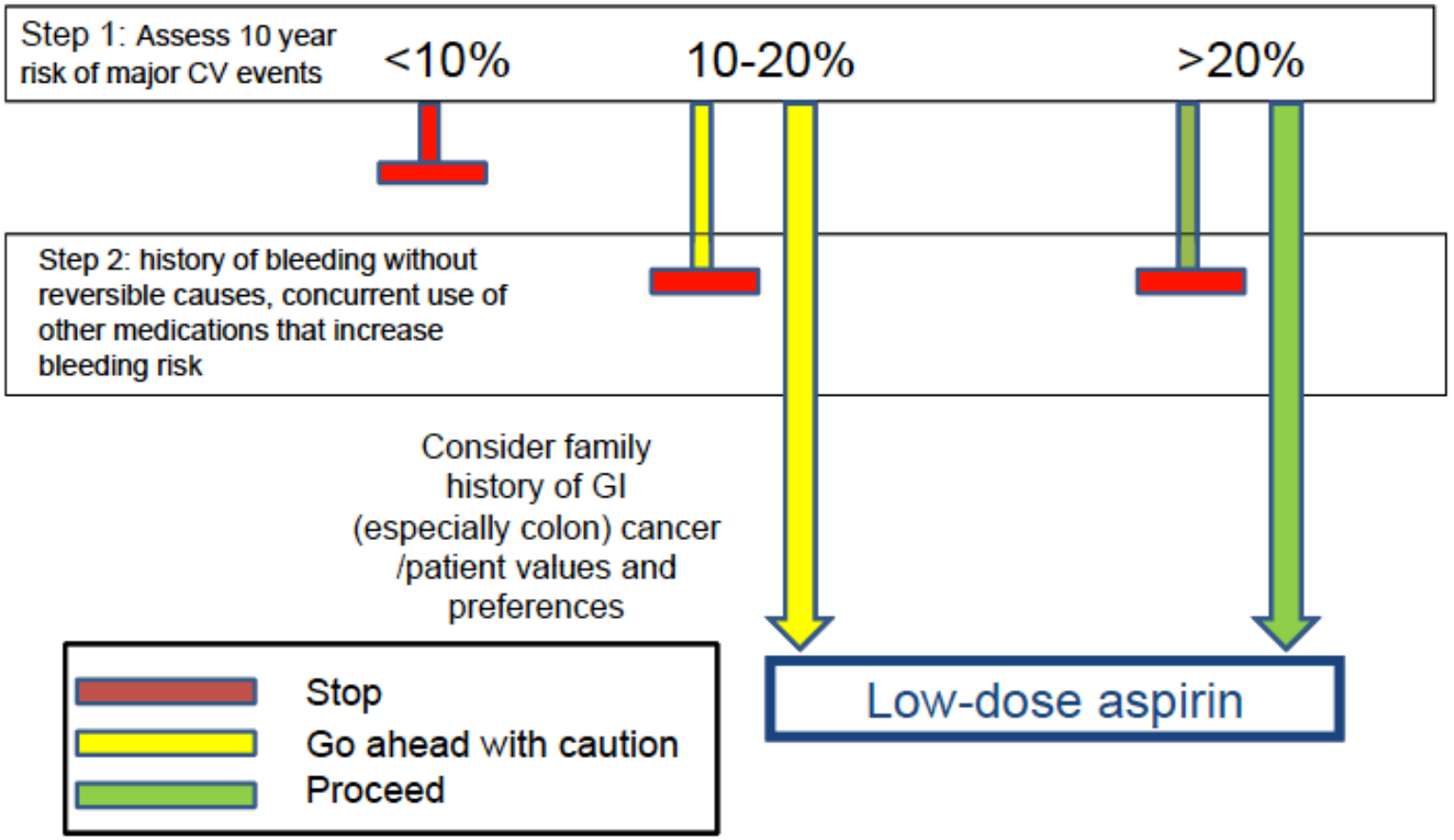
Gaziano JM et al, Lancet 2018

Absolute risk change (CV events and bleeding) and baseline CV risk in patients treated with ASA in primary prevention

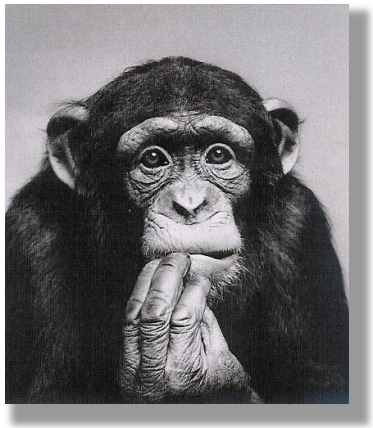


Halvorsen S, et al, JACC 2014

Practical stepwise approach to the use of ASA in primary CV prevention (ESC-WG on Thrombosis)



Halvorsen S, et al, JACC 2014



Final considerations

- The preventive role of ASA is well defined in patients *with* previous CVD or TOD (secondary prevention-SP).
- In patients *without* previous CVD (PP) the CV benefit of ASA is evident in almost all RCT, but it must be discounted against risk and relevance of bleeding, (GI vs. other major) that is the "discriminating" feature.
- Primary CV prevention with ASA can be recommended in:
  - *high CV risk pts (> 15-20% risk CVD/10 yrs) without major bleeding risk*
  - *patients with DM (twice-daily administration/low dose?),*
  - *pregnant subjects at risk of PE.*
- The conclusions of RCT are often limited by study designs and future analysis should consider *relevance of CV prevention vs. bleeding and patients selection* ahead of sample size and treatment options.