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ANTIAGREGACIÓN EN PREVENCIÓN PRIMARIA

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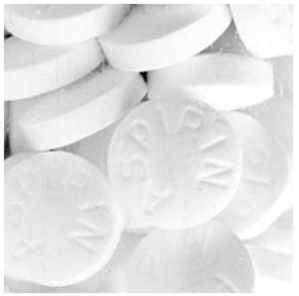
Antiagregación en prevención primaria
Punto de partida

- Menor beneficio que en prevención secundaria
- El beneficio cardiovascular obtenido está muy cercano al daño potencial (hemorragias principalmente digestivas)
- Prioritario el abordaje de otras medidas que implican menos riesgo y que son potencialmente más efectivas
  - cambios en el estilo de vida
  - tratamiento de la dislipemia
  - control de las cifras tensionales

Mecanismo de acción de la aspirina

- **Dosis bajas de aspirina** (75 a 100 mg) producen un efecto antitrombótico por acetilación irreversible de la ciclooxigenasa-1 (COX-1) plaquetaria, que inhibe la generación de tromboxano A2
- **Dosis más altas de aspirina** también inhiben la COX-2, bloqueando la producción de prostaglandinas y produciendo efectos analgésicos y antipiréticos



Grandes ECAs de prevención primaria de la ECV con ácido acetil salicílico

TABLE 1 Characteristics of Individual Trials of Aspirin in Primary Prevention

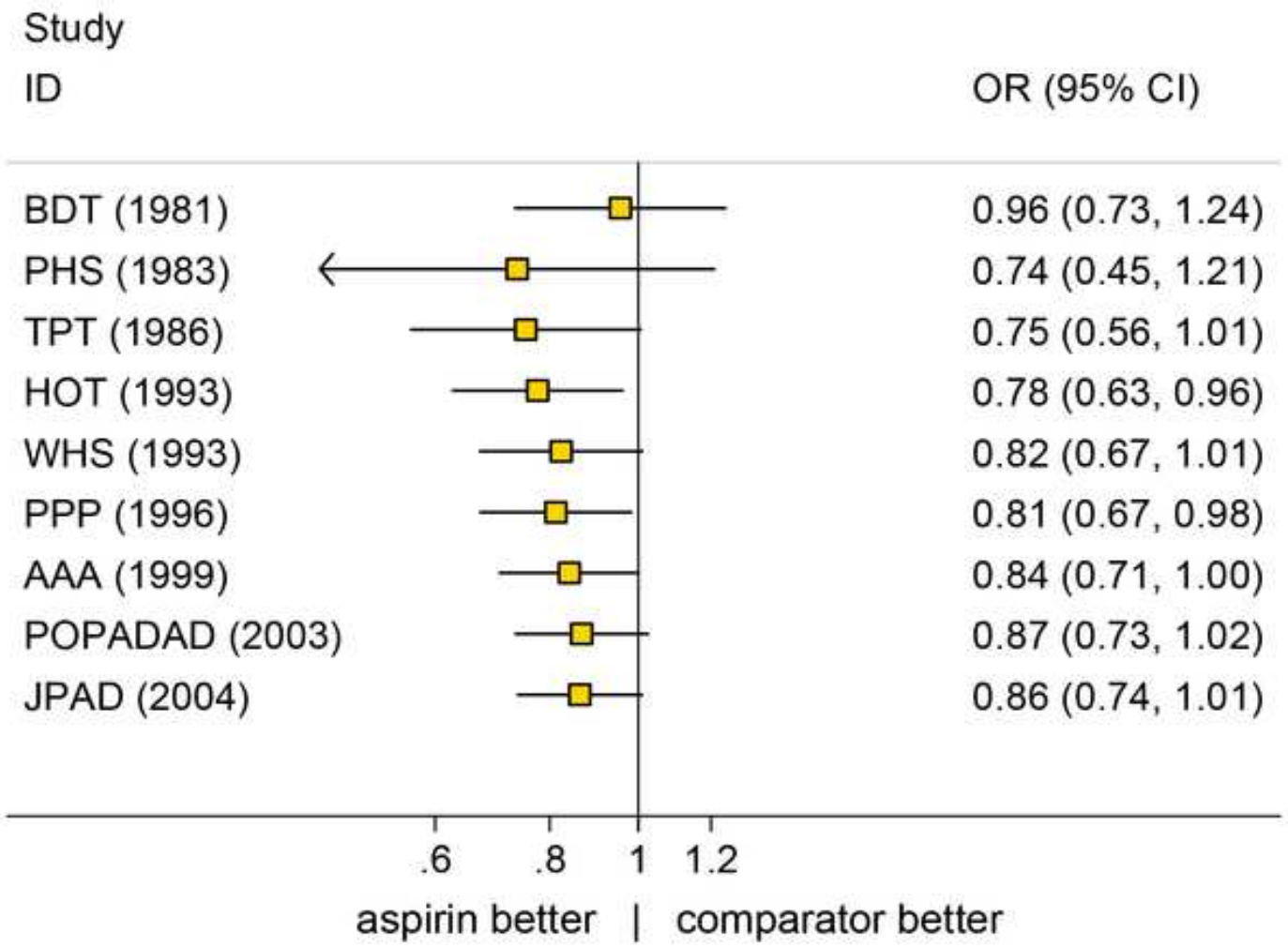
Trial, Year	Participants	Male, %	Mean Age, yrs	Aspirin Dose, mg	Duration of Follow-Up, yrs*	Primary Endpoint
BDT, 1988	5,139	100	63.6	500 or 300 daily	6.0	MI, stroke, or CV death
PHS, 1989	22,071	100	53.8	325 alternate day	5.02	MI, stroke, or CV death
HOT, 1998	18,790	53	61.5	75 daily	3.8	Major CV events
TPT, 1998	5,085	100	57.5	75 daily	6.4	Major coronary event
PPP, 2001	4,495	42	64.4	100 daily	3.6	MI, stroke, or CV death
WHS, 2005	39,876	0	54.6	100 alternate day	10.1	MI, stroke, or CV death
POPADAD, 2008	1,276	44	60.3	100 daily	6.7	CV death, MI, stroke, or amputation
JPAD, 2008	2,539	55	64.5	81 or 100 daily	4.37	Any atherosclerotic event
AAA, 2010	3,350	28	61.6	100 daily	8.2	Fatal or nonfatal coronary event, stroke, or revascularization

*Duration of follow-up represents median follow-up for POPADAD and JPAD, mean follow-up for the other trials.

AAA = Aspirin for Asymptomatic Atherosclerosis; BDT = British Doctors Trial; CV = cardiovascular; HOT = Hypertension Optimal Treatment; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; MI = myocardial infarction; PHS = Physicians Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

Sigrun Halvorsen , Felicita Andreotti , Jurriën M. ten Berg , Marco Cattaneo , Sergio Coccheri , Roberto Marchioli...
Aspirin Therapy in Primary Cardiovascular Disease Prevention : A Position Paper of the European Society of Cardiology Working Group on Thrombosis Journal of the American College of Cardiology, Volume 64, Issue 3, 2014, 319 - 327

Figure 2. Cumulative random effects meta-analysis of odds ratio for total CHD.



Sutcliffe P, Connock M, Gurung T, Freeman K, et al. (2013) Aspirin in Primary Prevention of Cardiovascular Disease and Cancer: A Systematic Review of the Balance of Evidence from Reviews of Randomized Trials. PLoS ONE 8(12): e81970. doi:10.1371/journal.pone.0081970
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0081970

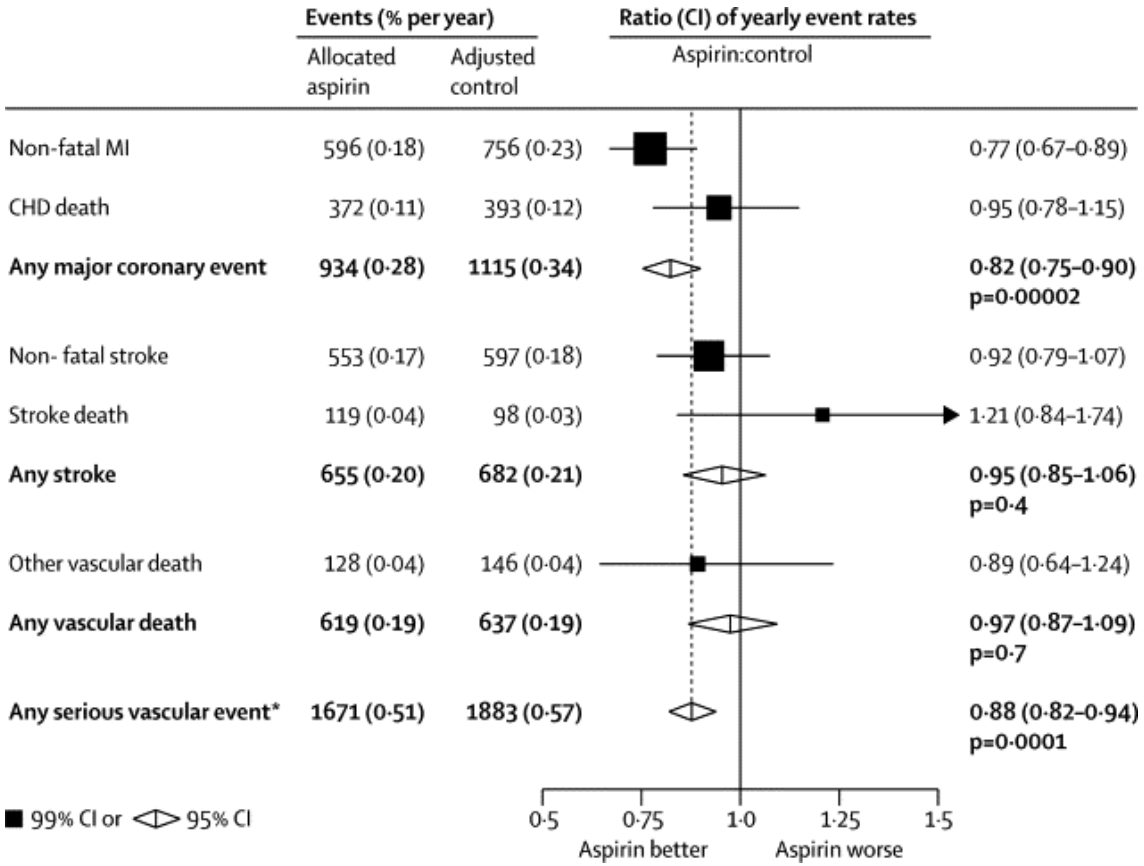


Figure 1 Serious vascular events in primary prevention trials—proportional effects of aspirin allocation Actual numbers for aspirin-allocated trial participants, and adjusted numbers for control-allocated trial participants, are presented, together with t...

Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials

The Lancet, Volume 373, Issue 9678, 2009, 1849 - 1860

http://dx.doi.org/10.1016/S0140-6736(09)60503-1

Prevención primaria de la enfermedad cardiovascular con aspirina (metaanálisis)

- Una reducción del 20% del riesgo de infarto de miocardio no nortal (OR 0,80; IC del 95% 0,67-0,96)
- No tiene impacto significativo sobre el accidente cerebrovascular no mortal (incluido el accidente cerebrovascular isquémico y hemorrágico)
- No hay impacto significativo en la mortalidad por ECV
- Produce un aumento del 54% en el RR de hemorragia extracraneal no mortal (RR 1.54, IC 95% 01,30 a 1,82)

Seshasai SR, Wijesuriya S, Sivakumaran R, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med 2012; 172:209.
Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373:1849.

Partnership for HEALTH

U.S. Preventive Services TASK FORCE

Heart and Circulation Clinician Fact Sheet

Using Aspirin for the Primary Prevention of Cardiovascular Disease

Your patients rely on you for accurate, up-to-date preventive health information. This fact sheet for clinicians provides information about the use of aspirin to prevent first myocardial infarctions in men and first ischemic strokes in women. It is designed to complement the patient brochures:

- *Talk With Your Health Care Provider About: Taking Aspirin to Prevent Heart Attacks—for Men*
- *Talk With Your Health Care Provider About: Taking Aspirin to Prevent Strokes—for Women*

Who should take aspirin to prevent cardiovascular disease?

The US Preventive Services Task Force (USPSTF) recommends the use of aspirin for the primary prevention of cardiovascular disease (CVD) when a *net* benefit is present. A *net* benefit means that the potential benefit from taking aspirin

How do I determine benefit?

An individual's potential clinical benefit from aspirin depends on his or her baseline risk.

ASPIRIN FOR THE PREVENTION OF CARDIOVASCULAR DISEASE
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Men Age 45-79 Years	Women Age 55-79 Years	Men Age < 45 Years	Women Age < 55 Years	Men & Women Age ≥ 80 Years
Recommendation	Encourage aspirin use when potential CVD benefit (MIs prevented) outweighs potential harm of GI hemorrhage	Encourage aspirin use when potential CVD benefit (strokes prevented) outweighs potential harm of GI hemorrhage	Do not encourage aspirin use for MI prevention	Do not encourage aspirin use for stroke prevention	No Recommendation
	GRADE: A		GRADE: D		GRADE: I (Insufficient Evidence)

How to Use This Recommendation

Shared decision making is strongly encouraged with individuals whose risk is close to (either above or below) the estimates of 10-year risk levels indicated below. As the potential CVD benefit increases above harms, the recommendation to take aspirin should become stronger.

To determine whether the potential benefit of MIs prevented (men) and strokes prevented (women) outweighs the potential harm of increased GI hemorrhage, both 10-year CVD risk and age must be considered.

Risk level at which CVD events prevented (benefit) exceeds GI harms			
Men		Women	
10-year CHD risk		10-year stroke risk	
Age 45 – 59 years	≥ 4%	Age 55 – 59 years	≥ 3%
Age 60 – 69 years	≥ 9%	Age 60 – 69 years	≥ 8%
Age 70 – 79 years	≥ 12%	Age 70 – 79 years	≥ 11%

The table above applies to adults who are not taking NSAIDs and who do not have upper GI pain or a history of GI ulcers.
NSAID use and history of GI ulcers raise the risk of serious GI bleeding considerably and should be considered in determining the balance of benefits and harms.
NSAID use combined with aspirin use approximately quadruples the risk of serious GI bleeding compared to the risk with aspirin use alone.
The rate of serious bleeding in aspirin users is approximately 2 – 3 times higher in patients with a history of GI ulcers.

Risk Assessment

For MEN: Risk factors for CHD include age, diabetes, total cholesterol level, HDL level, blood pressure, and smoking.
CHD risk estimation tool: http://healthlink.mcw.edu/article/923521437.html

For WOMEN: Risk factors for ischemic stroke include age, high blood pressure, diabetes, smoking, history of CVD, atrial fibrillation, and left ventricular hypertrophy.
Stroke risk estimation tool: http://www.westernstroke.org/PersonalStrokeRisk1.xls

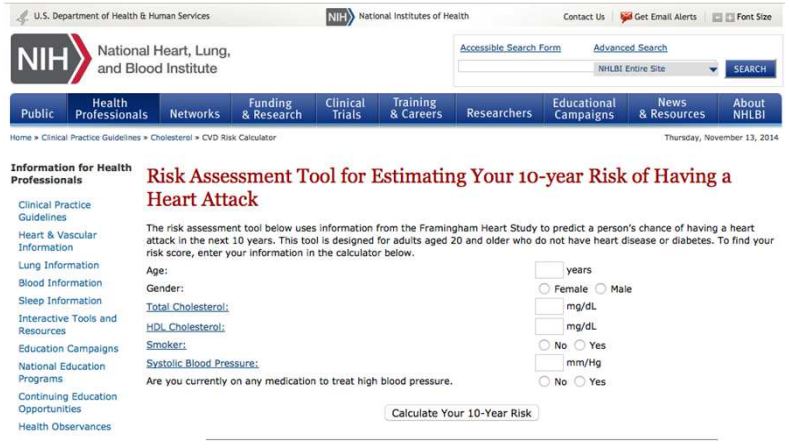
Relevant Recommendations from the USPSTF

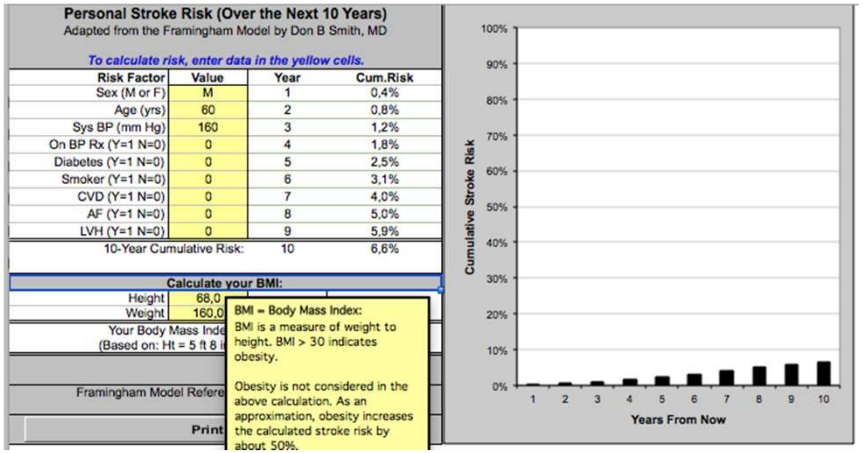
The USPSTF has made recommendations on screening for abdominal aortic aneurysm, carotid artery stenosis, coronary heart disease, high blood pressure, lipid disorders, and peripheral arterial disease. These recommendations are available at www.preventiveservices.ahrq.gov.

For the full recommendation statement and supporting documents, please go to: www.preventiveservices.ahrq.gov. Abbreviations: CHD = coronary heart disease, CVD = cardiovascular disease, GI = gastrointestinal, HDL = high-density lipoprotein, MI = myocardial infarction, NSAIDs = nonsteroidal anti-inflammatory drugs.

ASPIRIN FOR THE PREVENTION OF CARDIOVASCULAR DISEASE
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Men Age 45-79 Years	Women Age 55-79 Years
Recommendation	Encourage aspirin use when potential CVD benefit (MIs prevented) outweighs potential harm of GI hemorrhage	Encourage aspirin use when potential CVD benefit (strokes prevented) outweighs potential harm of GI hemorrhage
	GRADE: A	





http://cvdrisk.nhlbi.nih.gov/calculator.asp
http://www.westernstroke.org/index.php?header_name=stroke_tools.gif&main=stroke_tools.php

U.S. Preventive Services
TASK FORCE

ASPIRIN FOR THE PREVENTION OF CARDIOVASCULAR DISEASE
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

The following table provides the 10-year risk level at which the *net* benefit from aspirin becomes favorable.

Favorable Net Benefit from Aspirin Use			
Age	**10-year MI risk (men)**	**Age**	**10-year stroke risk (women)**
45–59	≥ 4 %	55–59	≥ 3 %
60–69	≥ 9 %	60–69	≥ 8 %
70–79	≥ 12 %	70–79	≥ 11 %

Shared decision making about the use of aspirin should be used with individuals

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Chest. Feb 2012; 141(2 Suppl): e637S–e668S. PMCID: PMC3278064
doi: 10.1378/chest.11-2306

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 with an increase in major bleeds. Whatever their risk status, people who are averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis. Individuals who value preventing an MI substantially higher than avoiding a GI bleed will be, if they are in the moderate or high cardiovascular risk group, more likely to choose aspirin.

Recommendations: Antiplatelet Agents (1)

- Consider aspirin therapy (75–162 mg/day) **C**
  - As a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%)
  - Includes most men >50 years of age or women >60 years of age who have at least one additional major risk factor
    - Family history of CVD
    - Hypertension
    - Smoking
    - Dyslipidemia
    - Albuminuria

ADA. VI. Prevention, Management of Complications. Diabetes Care 2014;37(suppl 1):S40

Aspirina y cáncer

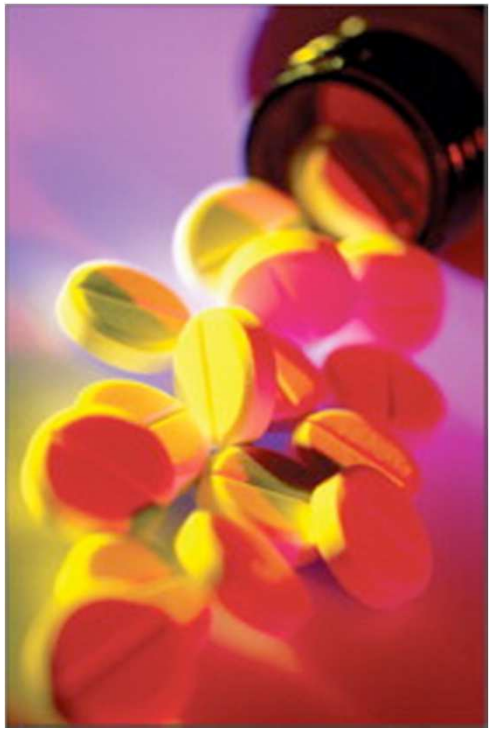


Table 1 Overall cancer incidence and mortality results from randomized trials of aspirin versus control

Table 1 | Overall cancer incidence and mortality results from randomized trials of aspirin versus control

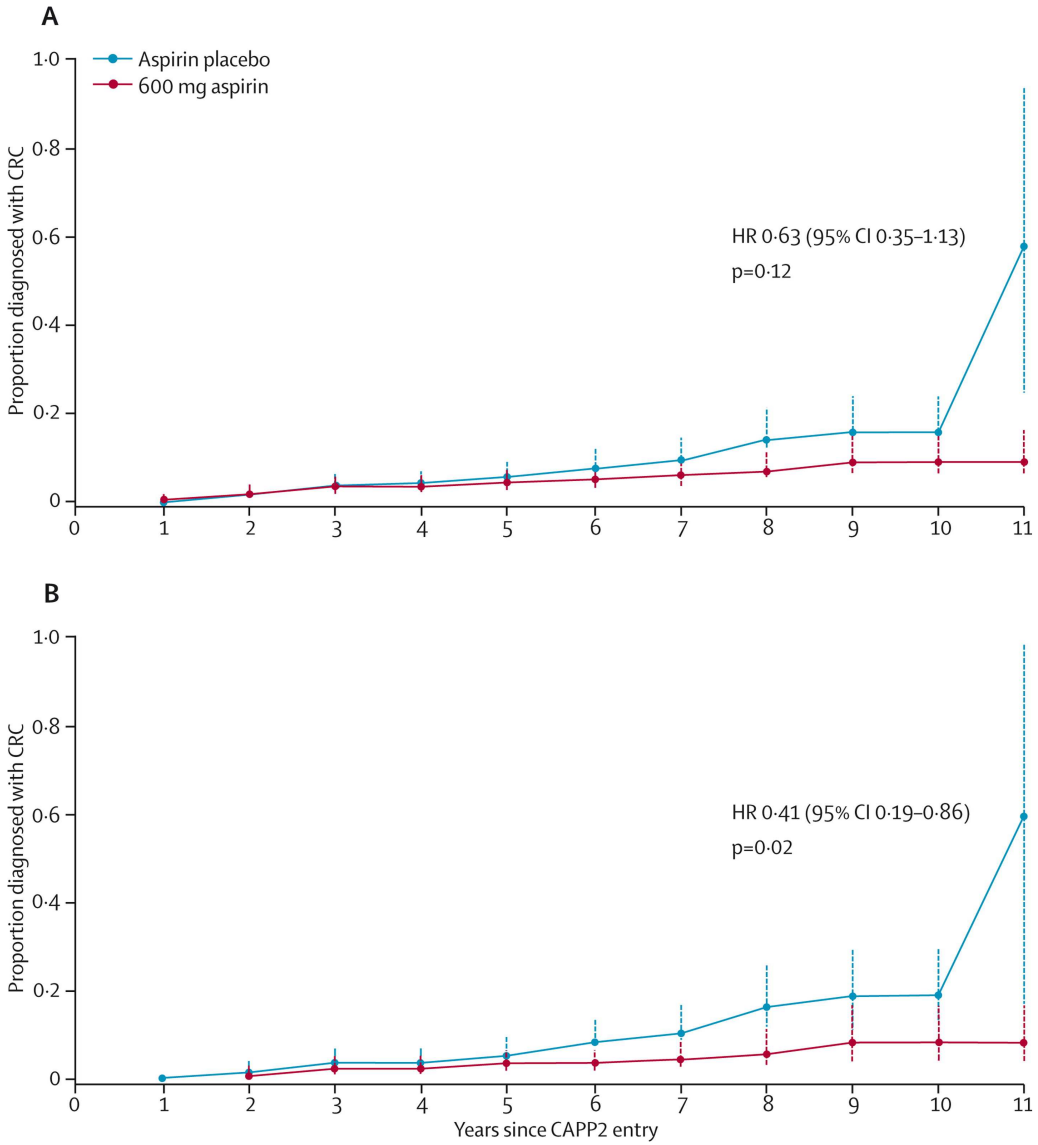
Study	Outcomes (participants)	Regimen	Intervention and follow-up period	Results: RR or OR (95% CI)
Cancer incidence				
Women's Health Study[8]	2,865 (39,876)	100 mg every other day	Mean 10-year intervention and follow-up period	1.01 (0.94–1.08) during full follow-up period 0.98 (0.89–1.09) during follow-up >5 years
Pooled analysis of 2 UK trials with long-term follow-up[29,*]	1,572 (7,588)	300–1,200 mg per day	Median 23 years follow up including mean 5-year intervention period	1.01 (0.88–1.16) for all cancers except colorectal 0.74 (0.56–0.97) for colorectal cancer
Pooled analysis of 6 trials of low-dose aspirin for primary prevention of vascular events[5]	1,632 (35,535)	75–100 mg per day	Mean intervention and follow-up period 4–8 years, depending on individual trial	0.88 (0.80–0.98) during full follow-up period 1.00 (0.88–1.15) during follow-up from 0 to <3 years 0.81 (0.67–0.98) during follow-up from 3 to <5 years 0.71 (0.57–0.89) during follow-up >5 years
Cancer mortality				
Women's Health Study[8]	583 (39,876)	100 mg every other day	Mean 10-year intervention and follow-up period	0.95 (0.81–1.11) during full follow-up period 0.96 (0.78–1.18) during following up >5 years
Pooled analysis of 3 UK trials of aspirin for prevention of vascular events with 20 years of follow up[6,‡]	1,634 (12,659)	75–1,200 mg per day	20 years of follow up, including a median intervention period of 4–7 years, depending on individual trial	0.80 (0.72–0.88) for all solid cancers 1.03 (0.74–1.43) for haematologic cancers Overall cancer mortality results below limited to participants scheduled for treatment for >5 years (1,378 deaths, 10,502 patients): 0.78 (0.70–0.87) during full 20-year follow up 0.79 (0.66–0.93) during follow up 0–10 years 0.77 (0.67–0.89) during follow up 10–20 years
Pooled analysis of 34 trials of daily aspirin for prevention of vascular events[5]	1,226 (69,224)	40–1,500 mg per day	Mean intervention and follow-up periods 1–8 years depending on individual trial	All 34 trials of daily aspirin at any dose: 0.85 (0.76–0.96) during full follow-up period 0.90 (0.76–1.06) during follow up 0 to <3 years 0.93 (0.75–1.16) during follow up 3 to <5 years 0.63 (0.49–0.82) during follow up >5 years Subset of 15 trials with doses ≤200 mg per day: 0.86 (0.75–0.99) during full follow-up period 1.01 (0.83–1.23) during follow up 0 to <3 years 0.87 (0.66–1.15) during follow up 3 to <5 years 0.63 (0.46–0.86) during follow up >5 years

*Overall cancer incidence not reported. Results specifically during intervention period not reported. ‡These analyses of cancer mortality include overlapping person time. Abbreviations: OR, odds ratio; RR, relative risk.

nature REVIEWS CLINICAL ONCOLOGY

Thun, M. J. *et al.* (2012) The role of aspirin in cancer prevention
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2011.199

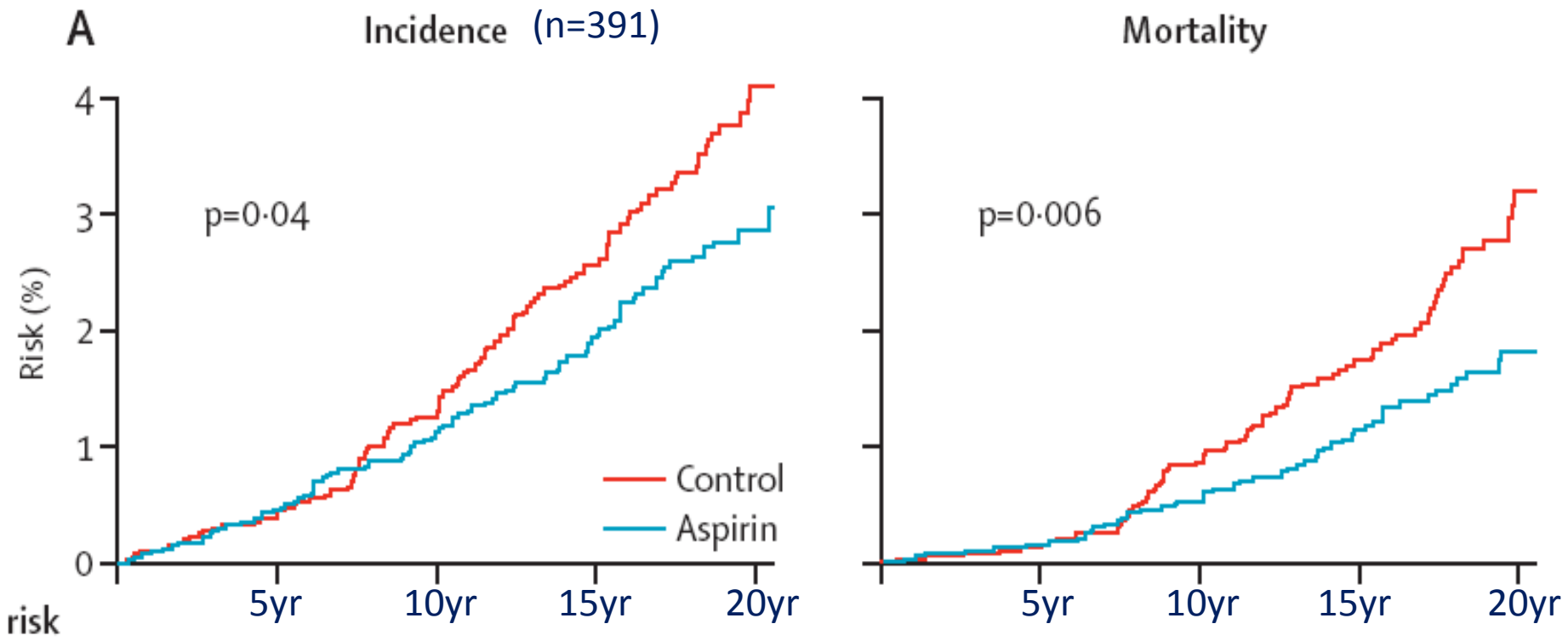
La administración de 600 mg diarios de aspirina durante una media de 25 meses redujo de forma considerable la incidencia de cáncer después de 55,7 meses entre los portadores de cáncer colorrectal hereditario. CAPP2



The Lancet 2011; 378:2081-2087

Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials

Peter M Rothwell, Michelle Wilson, Carl-Eric Elwin, Bo Norrving, Ale Algra, Charles P Warlow, Tom W Meade Lancet Oct 22 2010



Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials

Peter M Rothwell, F Gerald R Fowkes, Jill F F Belch, Hisao Ogawa, Charles P Warlow, Tom W Meade

Lancet Dec 7 2010

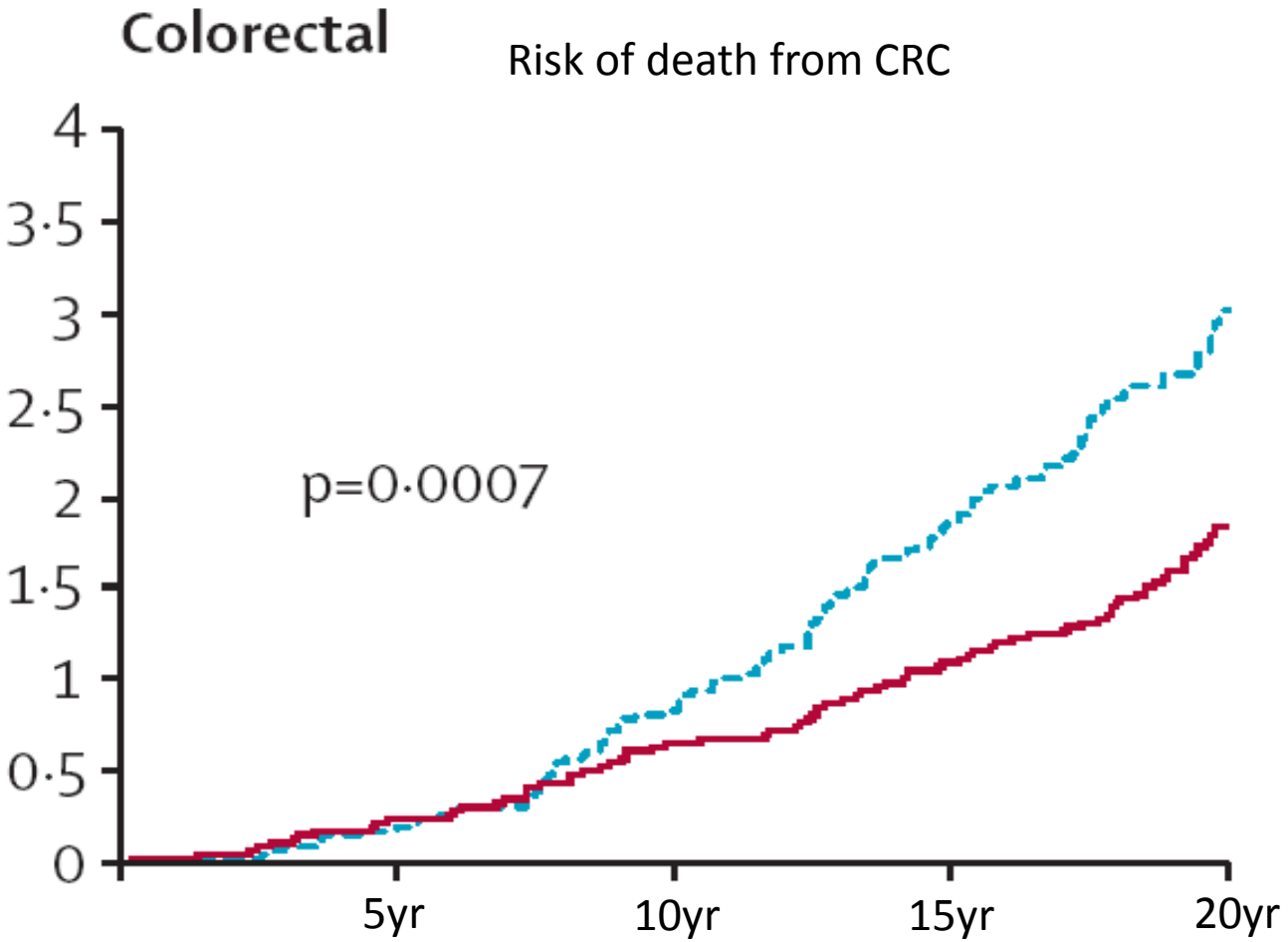
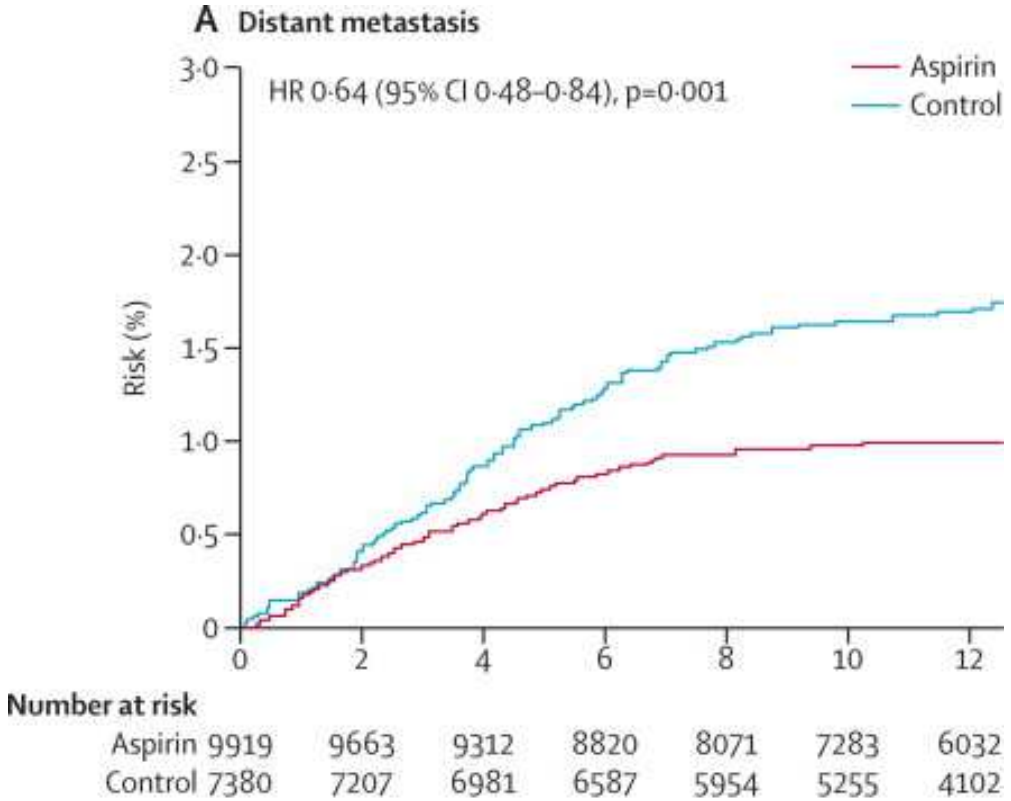


Figure 1 The effect of aspirin on risk of metastasis due to any incident cancer diagnosed during five trials of aspirin versus control Analysis is based on time from randomisation to diagnosis of metastasis during or after the trials.



Peter M Rothwell , Michelle Wilson , Jacqueline F Price , Jill FF Belch , Tom W Meade , Ziyah Mehta
Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials

The Lancet, Volume 379, Issue 9826, 2012, 1591 - 1601

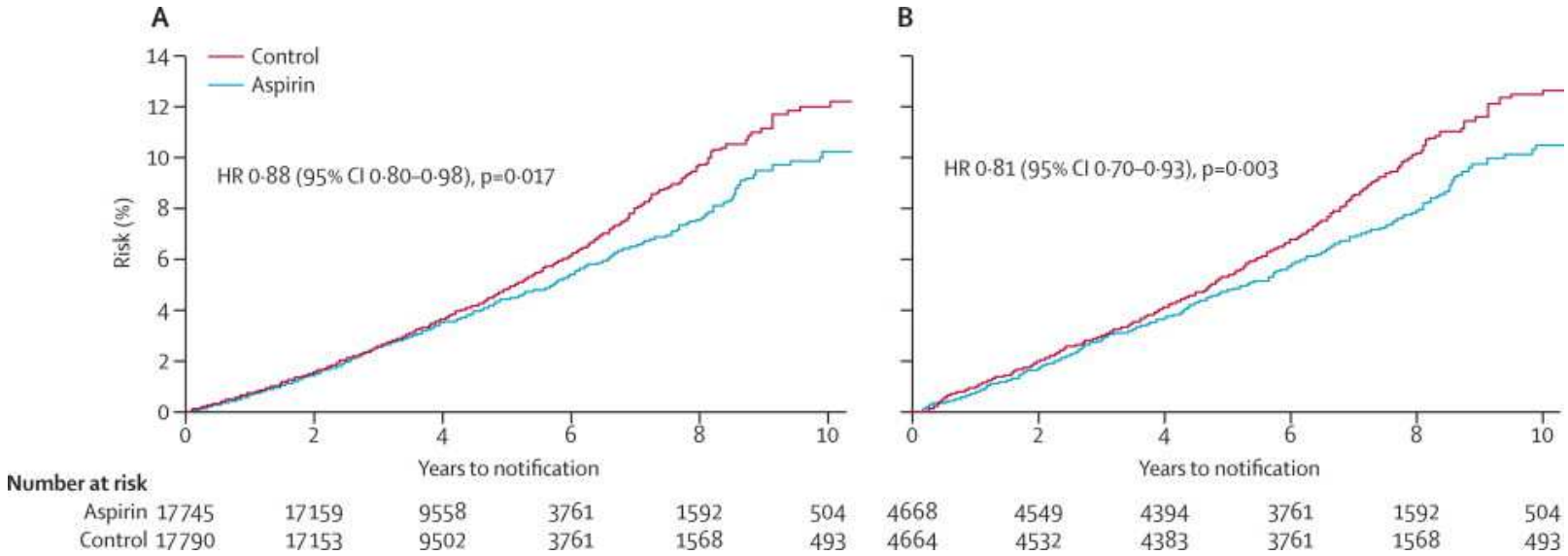


Figure 2 Pooled analysis of effect of allocation to aspirin on incidence of cancer during six randomised trials of daily low-dose (75–100mg daily) aspirin versus placebo in primary prevention of vascular events<ce:cross-refs refid="bib16 bib17 bib18 bib19 ...

Peter M Rothwell , Jacqueline F Price , F Gerald R Fowkes , Alberto Zanchetti , Maria Carla Roncaglioni , Gianni T...

Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials

The Lancet, Volume 379, Issue 9826, 2012, 1602 - 1612

http://dx.doi.org/10.1016/S0140-6736(11)61720-0

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Best Practice & Research Clinical Gastroenterology

Best Practice & Research Clinical Gastroenterology, Volume 26, Issue 4, 2012, e1 - e13

Mechanisms of the antitumoural effects of aspirin in the gastrointestinal tract☆

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Keywords:
Aspirin
Platelets
Cyclooxygenase
Tumourigenesis

A B S T R A C T

A recent clinical study showed that after five years of taking aspirin, at doses of at least 75 mg once daily, death rates were 54% less for gastrointestinal (GI) cancers. The finding of aspirin benefit at low-doses used for cardioprevention, locates the antiplatelet effect of aspirin at the centre of its antitumour efficacy. At low-doses, aspirin acts mainly by an irreversible inactivation of platelet cyclooxygenase (COX)-1 activity. We propose that platelet

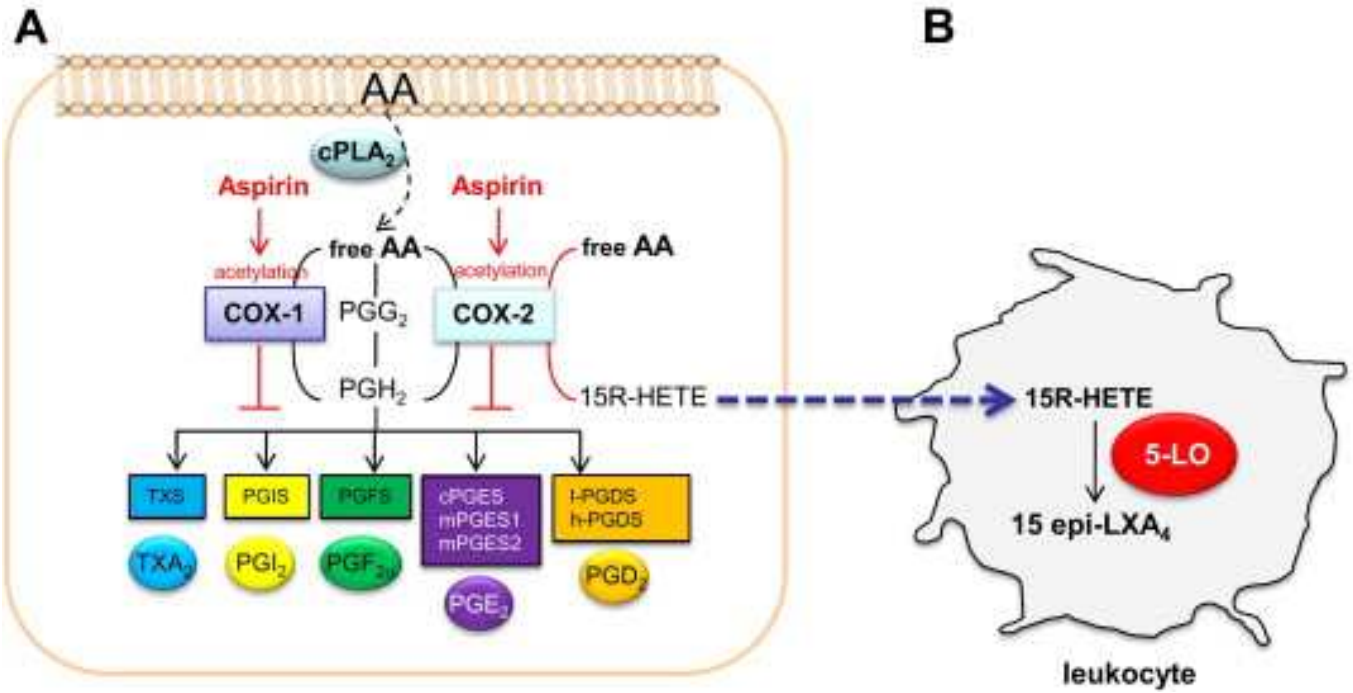


Fig. 1 Effects of aspirin on arachidonic acid metabolism. (A) Aspirin acetylates COX-1 enzyme, thus blocking the biosynthesis of prostanoids COX-1-derived. Differently, acetylated COX-2, conserves the catalytic ability to transform free AA to 15R-HETE. (B)...

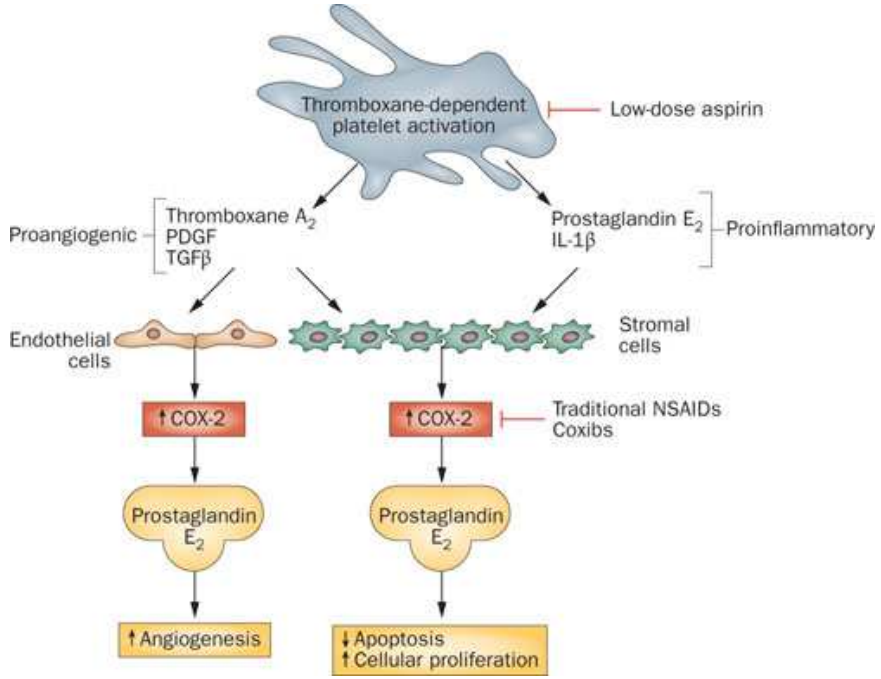
Annalisa Bruno , Melania Dovizio , Stefania Tacconelli , Paola Patrignani

Mechanisms of the antitumoural effects of aspirin in the gastrointestinal tract

Best Practice & Research Clinical Gastroenterology, Volume 26, Issue 4, 2012, e1 - e13

http://dx.doi.org/10.1016/j.bpg.2012.10.001

Figure 2 Hypothesized mechanism by which the inhibition of COX-1 in platelets by low-dose aspirin may suppress the induction of COX-2 in adjacent nucleated cells of the intestinal mucosa in early stage neoplasia



Thun, M. J. *et al.* (2012) The role of aspirin in cancer prevention
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2011.199

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Editorial

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Effects of aspirin on cancer initiation and progression

Expert Rev. Anticancer Ther. 13(2), 115–117 (2013)

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Stanley L Liauw

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"...during metastasis, platelets surround cancer cells in the bloodstream, which protects them from immune surveillance and promotes their colonization at distant sites."

It has long been recognized that an association between malignancy and hypercoagulability exists. This is thought to be due to cancer-mediated effects on the coagulation cascade. Conversely, there is now mounting evidence which suggests that factors involved in hemostasis and thrombosis can also influence carcinogenesis. Consequently, medications that interfere with coagulation have been investigated as potential cancer therapeutics. The suggestion that anticoagulants and antiplatelet drugs may have antineoplastic was an association between long-term daily aspirin use and a decreased overall incidence of cancer [4]. The chemopreventive effect of aspirin is most convincingly demonstrated in colorectal cancer. A large observational study with 662,424 adults showed a significant association between aspirin use and a decrease in mortality from colon cancer [3]. Furthermore, a randomized trial showed that among colorectal cancer patients, aspirin use was associated with a reduced incidence of recurrent colorectal adenomas [5].

La aspirina ralentiza el envejecimiento del genoma

Modulation of Age- and Cancer-Associated DNA Methylation Change in the Healthy Colon by Aspirin and Lifestyle

Faiza Noreen, Martin Röösli, Pawel Gaj, Jakub Pietrzak, Stefan Weis, Patric Urfer, Jaroslaw Regula, Primo Schär, Kaspar Truninger

Manuscript received September 2, 2013; revised April 23, 2014; accepted May 12, 2014.

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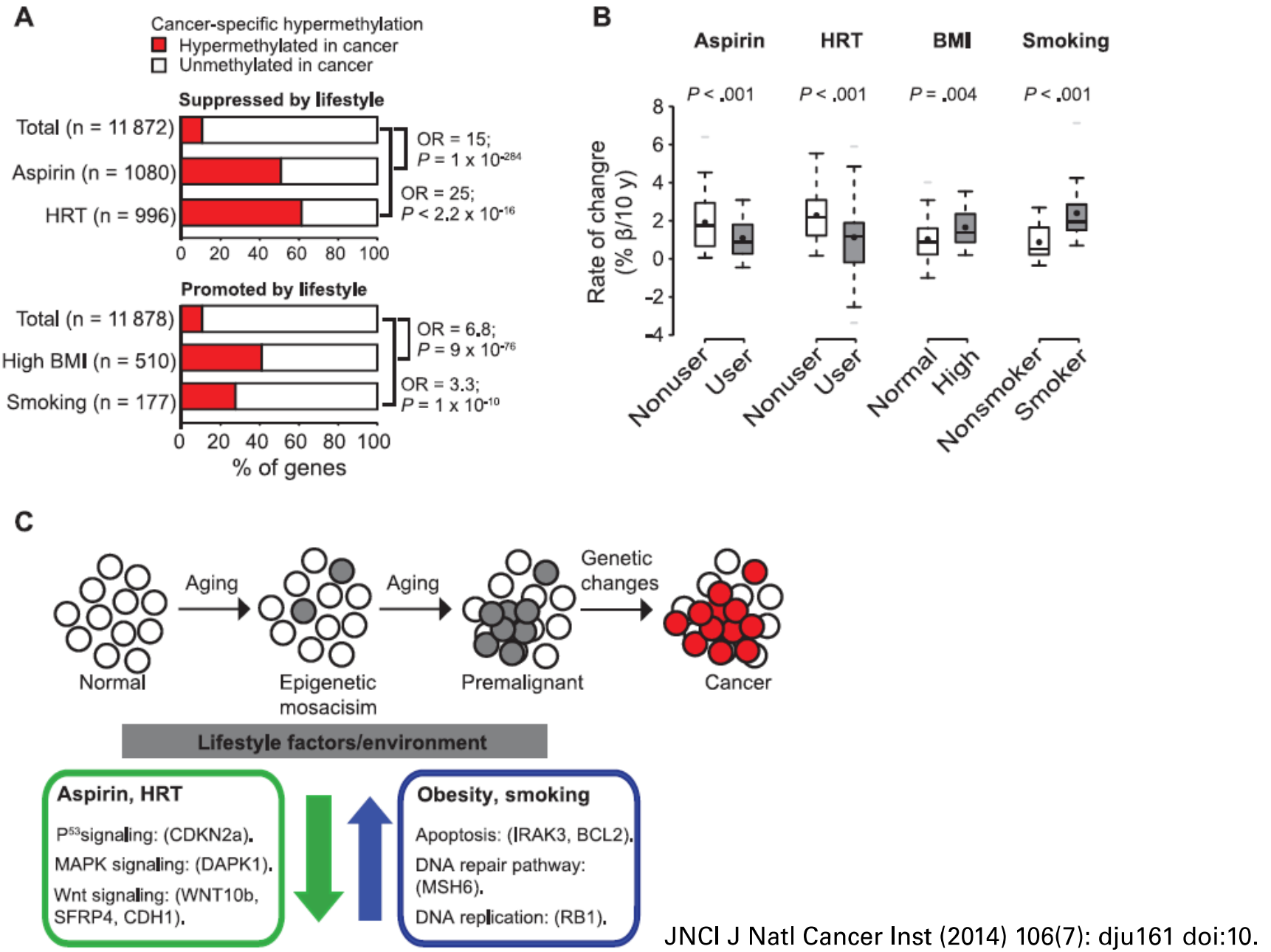
Background Aberrant DNA methylation in gene promoters is associated with aging and cancer, but the circumstances determining methylation change are unknown. We investigated the impact of lifestyle modulators of colorectal cancer (CRC) risk on the stability of gene promoter methylation in the colonic mucosa.

Methods We measured genome-wide promoter CpG methylation in normal colon biopsies (n = 1092) from a female screening cohort, investigated the interaction of lifestyle factors with age-dependent increase in methylation with log-linear multivariable regression, and related their modifying effect to hypermethylation in CRC. All statistical tests were two-sided.

Results Of 20025 promoter-associated CpGs analyzed, 1713 showed statistically significant age-dependent methylation gains. Fewer CpGs acquired methylation in users of aspirin (≥2 years) and hormonal replacement therapy (HRT age ≥50 years) compared with nonusers (43 vs 1355; 1 vs1377, respectively), whereas more CpGs were affected in smokers (≥20 years) and individuals with a body mass index (BMI) of 25 kg/m^2 and greater compared with control groups (180 vs 39; 554 vs 144, respectively). Fifty percent of the CpGs showing age-dependent methylation were found hypermethylated in CRC (odds ratio [OR] = 20; 95% confidence interval [CI] = 18 to 23; $P < 2 \times 10^{-16}$). These loci gained methylation with a higher median rate compared with age-only methylated sites ($P = 2 \times 10^{-76}$) and were enriched for polycomb regions (OR = 3.67). Importantly, aspirin ($P < .001$) and HRT use ($P < .001$) reduced the methylation rate at these cancer-related genes, whereas smoking ($P < .001$) and high BMI ($P = .004$) increased it.

Conclusions Lifestyle, including aspirin use, modulates age-associated DNA methylation change in the colonic epithelium and thereby impacts the evolution of cancer methylomes.

JNCI J Natl Cancer Inst (2014) 106(7): dju161 doi:10.1093/jnci/dju161



JNCI J Natl Cancer Inst (2014) 106(7): dju161 doi:10.

Low-dose Aspirin and Cancer Mortality: A Meta-analysis of Randomized Trials

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ABSTRACT

OBJECTIVE: Low-dose aspirin is a common strategy for preventing cardiovascular disease and associated mortality. A recent individual patient data meta-analysis of 8 trials of low- and high-dose aspirin, with long-term follow-up, found important reductions in cancer mortality. We aimed to determine whether cancer mortality also is reduced by low-dose aspirin in the shorter term.

METHODS: We conducted a comprehensive search of 10 electronic databases up to December 2011. We conducted a meta-analysis using data from all randomized clinical trials evaluating low-dose (75-325 mg) daily aspirin. We extracted data on non-cardiovascular disease mortality and cancer mortality. We pooled studies using a random-effects model and conducted a meta-regression. We supplemented this with a cumulative meta-analysis and trial sequential monitoring analysis.

RESULTS: Twenty-three randomized studies reported on nonvascular death. There were 944 nonvascular deaths of 41,398 (2.28%) patients receiving low-dose aspirin and 1074 nonvascular deaths of 41,470 (2.58%) patients not receiving aspirin therapy. The relative risk of nonvascular death was 0.88 (95% confidence interval [CI], 0.81-0.96, $I^2 = 0\%$). Eleven trials included data evaluating cancer mortality involving 16,066 patients. There were 162 of 7998 (2.02%) and 210 of 8068 (2.60%) cancer deaths among low-dose aspirin users versus non-aspirin users, respectively, reported over an average follow-up of 2.8 years. The relative risk of cancer mortality was 0.77 (95% CI, 0.63-0.95, $I^2 = 0\%$). Studies demonstrated a significant treatment effect after approximately 4 years of follow-up. The optimal information size analysis showed that a sufficient number of patients had been randomized to provide convincing evidence of a preventive role of low-dose aspirin in nonvascular deaths.

CONCLUSION: Nonvascular deaths, including cancer deaths, are reduced with low-dose aspirin.

 • *The American Journal of Medicine (2012) 125, 560-567*

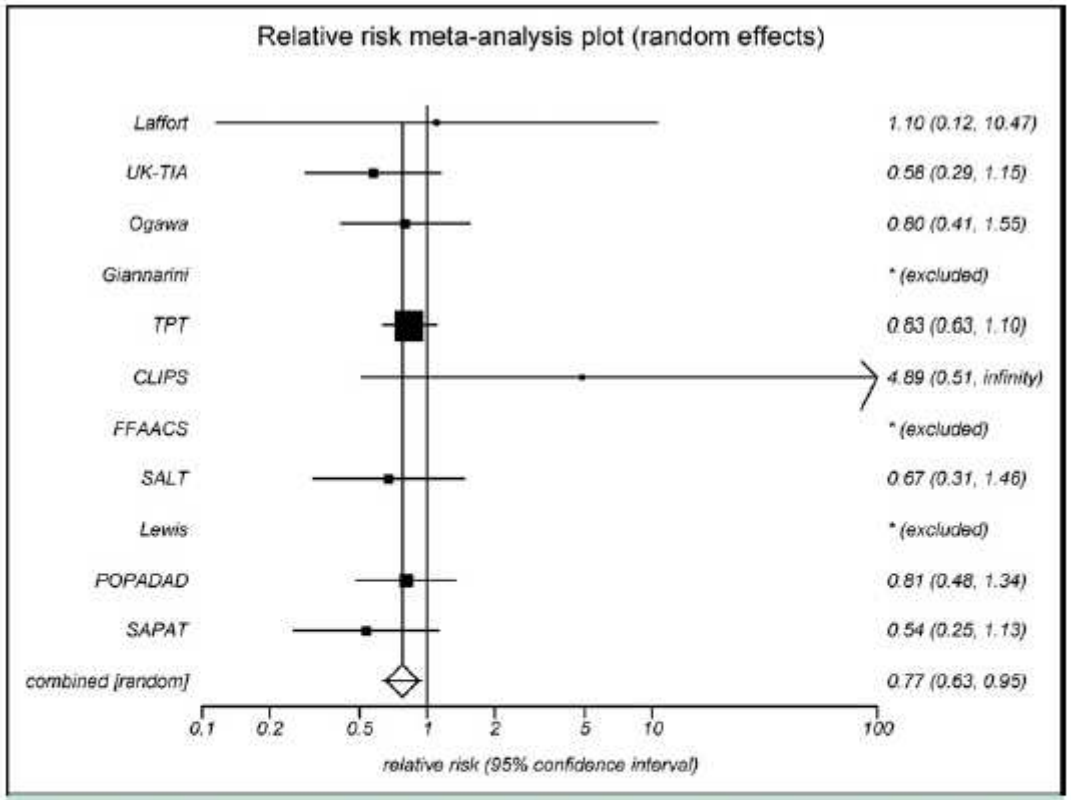

Figure 3 Cancer mortality. Forest plot shows the individual relative risk point estimates with 95% CI and the pooled overall relative risk estimate. UK-TIA = United Kingdom Transient Ischemic Attack; TPT = Thrombosis Prevention Trial; CLIPS = Critical Leg Ischaemia Prevention Study; FFAACS = Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontane; SALT = Swedish Aspirin Low-Dose Trial; POPADAD = Prevention Of Progression of Arterial Disease And Diabetes; SAPAT = Swedish Angina Pectoris Aspirin Trial.

Are we ready to recommend aspirin for cancer prevention?

Andrew T Chan , Nancy R Cook

The Lancet, Volume 379, Issue 9826, 2012, 1569 - 1571

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doi:10.1093/annonc/mdu225

Estimates of benefits and harms of prophylactic use of aspirin in the general population

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Background: Accumulating evidence supports an effect of aspirin in reducing overall cancer incidence and mortality in the general population. We reviewed current data and assessed the benefits and harms of prophylactic use of aspirin in the general population.

Methods: The effect of aspirin for site-specific cancer incidence and mortality, cardiovascular events was collated from the most recent systematic reviews. Studies identified through systematic Medline search provided data regarding harmful effects of aspirin and baseline rates of harms like gastrointestinal bleeding and peptic ulcer.

Results: The effects of aspirin on cancer are not apparent until at least 3 years after the start of use, and some benefits are sustained for several years after cessation in long-term users. No differences between low and standard doses of aspirin are observed, but there were no direct comparisons. Higher doses do not appear to confer additional benefit but increase toxicities. Excess bleeding is the most important harm associated with aspirin use, and its risk and fatality rate increases with age. For average-risk individuals aged 50–65 years taking aspirin for 10 years, there would be a relative reduction of between 7% (women) and 9% (men) in the number of cancer, myocardial infarction or stroke events over a 15-year period and an overall 4% relative reduction in all deaths over a 20-year period.

Conclusions: Prophylactic aspirin use for a minimum of 5 years at doses between 75 and 325 mg/day appears to have favourable benefit–harm profile; longer use is likely to have greater benefits. Further research is needed to determine the optimum dose and duration of use, to identify individuals at increased risk of bleeding, and to test effectiveness of *Helicobacter pylori* screening–eradication before starting aspirin prophylaxis.

Key words: aspirin, prevention, benefit-harm, cancer, cardiovascular disease, gastrointestinal bleeding

review

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Conclusiones:

- El uso de aspirina un mínimo de 5 años en dosis entre 75 y 325 mg / día parece tener un perfil beneficio-daño favorable
- Un uso más largo es probable que tenga mayores beneficios
- Se necesitan más investigaciones para:
  - determinar la dosis óptima y la duración del uso
  - identificar individuos en mayor riesgo de hemorragia
  - Probar la eficacia de la detección y erradicación del Helicobacter pylori detección antes de iniciar la profilaxis con aspirina

Estudios en marcha con aspirina en PP ECV

Online Supplemental Table 2: Ongoing randomized controlled trials of aspirin in the primary prevention of CV events.

	DESIGN	NUMBER of SUBJECTS	AGE RISK FACTORS	ASA DOSE CONTROL	OTHER THERAPIES	PRIMARY EFFICACY END POINT	FOLLOW-UP START / END
Individuals without CVD							
ARRIVE Aspirin to Reduce Risk of Initial Vascular Event	Randomised 1:1 Double blind Placebo control	~ 12,000 No known CVD Without diabetes	Men > 55 y with 2-4 RFs Women > 60 y with ≥ 3 RFs	100 mg daily Placebo		Nonfatal MI Nonfatal stroke CV death	~ 5 years Event driven
ASPREE Aspirin in Reducing Events in the Elderly	Randomised 1:1 Double blind Placebo control	~ 15,000 No overt CVD	Men and women ≥ 70 y Multiple RFs	100 mg daily Placebo		Major adverse CV events and dementia	~ 5 years
JPPP Japanese Primary Prevention Project	Randomised Open label Controlled Blind adjudication	14,466	Men and women 60-85 y with HT, diabetes or dyslipidemia	100 mg daily No ASA		Nonfatal MI Nonfatal stroke CV death	~ 4 years Enrollment 2005-2007
ASCEND A Study of Cardiovascular Events iN Diabetes	Randomised Double blind Placebo control 2x2 Factorial	15,480 Type I and II diabetes No overt CVD	Men and women ≥ 40 y With diabetes	100 mg daily Placebo	Omega-3 fatty acids 1 g daily or olive oil placebo	Nonfatal MI Nonfatal stroke* CV death	~ 7.5 years Start 2005 End ~ 2017
ACCEPT-D Aspirin and simvastatin Combination for CV Event Prevention Trial in Diabetes	Randomised Open label Controlled	5,170 Type I and II diabetes on, or eligible for, statin therapy No overt CVD	Men and women ≥ 50 y With diabetes on statin therapy	100 mg daily No ASA	Simvastatin 20 mg daily in all for LDL-C > 100 mg/dl	Nonfatal MI Nonfatal stroke CV death Hospital admission for CV cause	Event driven
ENVIS-ion Elderly NeuroVascular Imaging Study (ASPREE Substudy)	Randomised 1:1 Double blind Placebo control	~ 600 No overt CVD Normal cognitive function	Men and women ≥ 70 y Multiple RFs	100 mg daily Placebo		Brain lesions at magnetic resonance imaging	~ 3 years Start 2008

Sigrun Halvorsen , Felicita Andreotti , Jurriën M. ten Berg , Marco Cattaneo , Sergio Coccheri , Roberto Marchioli...

Aspirin Therapy in Primary Cardiovascular Disease Prevention : A Position Paper of the European Society of Cardiology Working Group on Thrombosis Journal of the American College of Cardiology, Volume 64, Issue 3, 2014, 319 - 327

Estudios en marcha para comprobar si aspirina reduce la incidencia y mortalidad por cáncer

Trials of Aspirin for Cancer Prevention

Trial Name	Trial Design	Status
CAPP3	Enrolling 3,000 people with Lynch syndrome. Trial will test whether 100, 300, and 600 mg of aspirin per day for 2 years, followed by 100 mg per day, can reduce the risk of all Lynch syndrome-related cancers.	Will begin enrolling in 2014
ASCOLT	Enrolling patients recently treated for colorectal cancer to see if 200 mg of aspirin per day for 3 years can improve disease-free or overall survival	Currently enrolling participants
ASPREE	Enrolling 19,000 healthy U.S. participants aged 65 or older to see if the overall benefits (prevention of heart disease, stroke, certain cancers, and dementia) of taking daily low-dose aspirin for 5 years outweigh the risks, especially bleeding. Incidence of nonfatal and fatal cancers is a secondary endpoint.	Currently enrolling participants
AspECT	Enrolled 2,500 participants to test whether two different doses of an acid reflux drug with or without aspirin can reduce the risk of esophageal cancer in people with Barrett esophagus	Ongoing, enrollment complete

National Cancer Institute
at the National Institutes of Health

http://www.cancer.gov/cancertopics/research-updates/2014/aspirin

Prevención primaria de la enfermedad cardiovascular y cáncer con aspirina

- Reducción del 20% respecto del riesgo de infarto de miocardio no nortal (OR 0,80; IC del 95% 0,67-0,96)
- No tiene impacto significativo sobre el accidente cerebrovascular no mortal (incluido el accidente cerebrovascular isquémico y hemorrágico)
- Reducción del riesgo aproximado del 12% de la incidencia de cáncer, potencialmente mayor con un tratamiento prolongado y que se producen después de un período de latencia prolongado (hasta 8 a 10 años)
- Aumento del 54% en el RR de hemorragia extracraneal no mortal (RR 1.54, IC 95% 01,30 a 1,82)
- Una posible reducción en el riesgo relativo de la mortalidad global (del orden de 6% a 8%)

UpToDate® **Aspirin in the primary prevention of cardiovascular disease and cancer**

El uso de aspirina en 1000 pacientes de 60 años y con un riesgo medio de EC (del 10% al 20% en 10 años) y con un riesgo medio de cualquier malignidad (aprox. el 12%) durante un período de 10 años resultaría en:

- 6 muertes menos
- 17 infartos de miocardio no mortales menos
- 6 cánceres menos
- Sin reducción significativa de los accidentes cerebrovasculares no mortales (incluye tanto a los accidentes cerebrovasculares isquémicos y hemorrágicos)
- 16 episodios más de sangrado importantes (hemorragia intracraneal más sangrado en el tracto gastrointestinal o de otros sitios que requiere hospitalización y / o transfusión)

UpToDate® **Aspirin in the primary prevention of cardiovascular disease and cancer**

UpToDate®

Aspirin in the primary prevention of cardiovascular disease and cancer

Estimated myocardial infarctions (MIs) prevented and estimated harms of using aspirin for 10 years in a hypothetical cohort of 1000 men

Variable	Estimated MIs prevented (per 1000 men), *n*		
10-year CHD risk, percent	**Age 45 to 59 years**	**Age 60 to 69 years**	**Age 70 to 79 years**
1	3.2	3.2	3.2
2	6.4	6.4	6.4
3	9.6	9.6	9.6
4	12.8	12.8	12.8
5	16	16	16
6	19.2	19.2	19.2
7	22.4	22.4	22.4
8	25.6	25.6	25.6
9	28.8	28.8	28.8
10	32	32	32
11	35.2	35.2	35.2
12	38.4	38.4	38.4
13	41.6	41.6	41.6
14	44.8	44.8	44.8
15	48	48	48
16	51.2	51.2	51.2
17	54.4	54.4	54.4
18	57.6	57.6	57.6
19	60.8	60.8	60.8
20	64	64	64
Type of event	**Estimated harms, *n***		
GI bleeding	8	24	36
Hemorrhagic stroke	1	1	1

Aspirin Therapy in Primary Cardiovascular Disease Prevention

A Position Paper of the European Society of Cardiology Working Group on Thrombosis

Sigrun Halvorsen, MD,* Felicita Andreotti, MD, PhD,† Jurriën M. ten Berg, MD,‡ Marco Cattaneo, MD,§ Sergio Coccheri, MD,|| Roberto Marchioli, MD,¶ João Morais, MD,# Freek W. A. Verheugt, MD,** Raffaele De Caterina, MD, PhD††

ABSTRACT

Although the use of oral anticoagulants (vitamin K antagonists) has been abandoned in primary cardiovascular prevention due to lack of a favorable benefit-to-risk ratio, the indications for aspirin use in this setting continue to be a source of major debate, with major international guidelines providing conflicting recommendations. Here, we review the evidence in favor and against aspirin therapy in primary prevention based on the evidence accumulated so far, including recent data linking aspirin with cancer protection. While awaiting the results of several ongoing studies, we argue for a pragmatic approach to using low-dose aspirin in primary cardiovascular prevention and suggest its use in patients at high cardiovascular risk, defined as ≥2 major cardiovascular events (death, myocardial infarction, or stroke) projected per 100 person-years, who are not at increased risk of bleeding. (J Am Coll Cardiol 2014;64:319–27) © 2014 by the American College of Cardiology Foundation.

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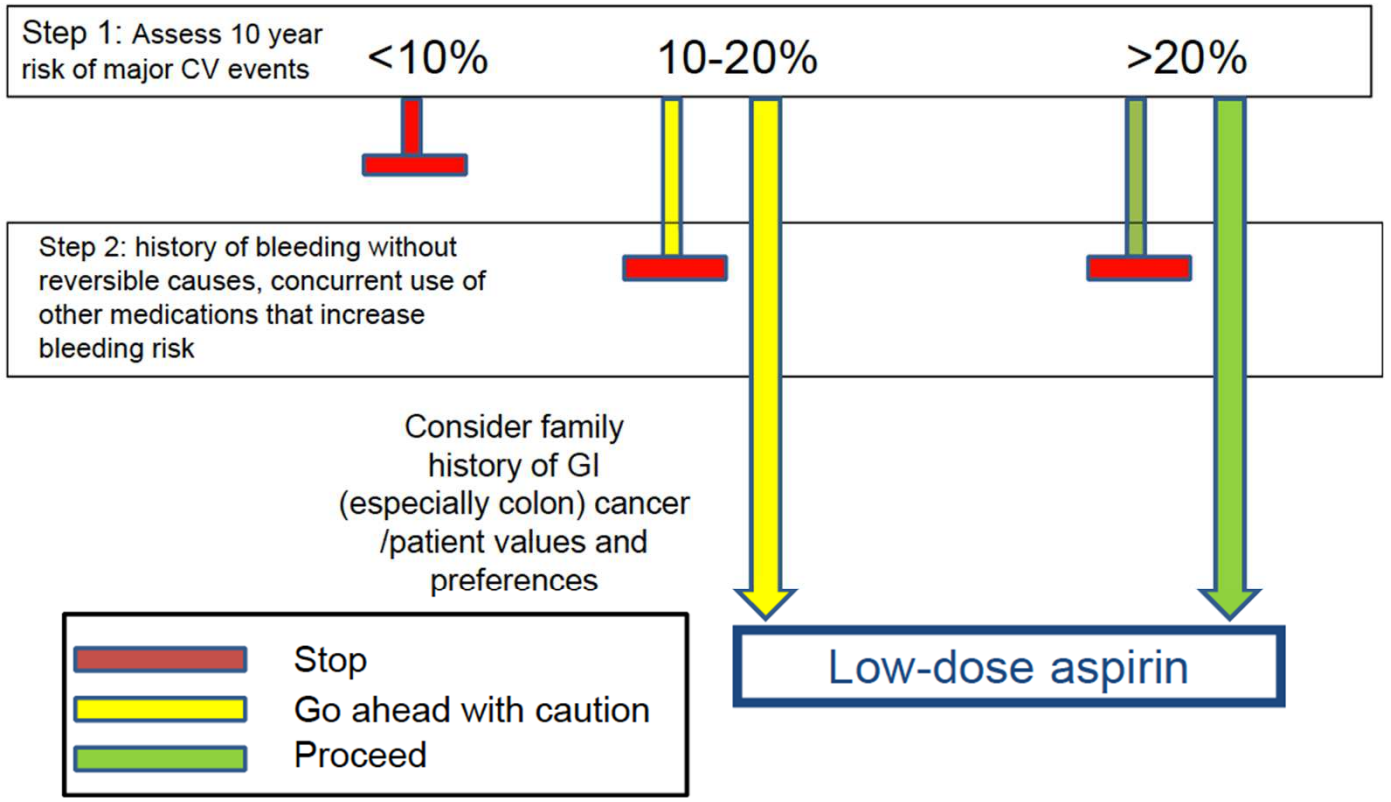

CENTRAL ILLUSTRATION **A Proposed Practical Stepwise Approach to the Use of Aspirin in Primary CV Prevention**

Sigrun Halvorsen , Felicita Andreotti , Jurriën M. ten Berg , Marco Cattaneo , Sergio Coccheri , Roberto Marchioli...
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