L'Acido Acetilsalicilico nella prevenzione cardio-oncologica: fatti e misfatti

Pietro Amedeo Modesti

Universita' degli Studi di Firenze

STEP 1. First paradigm change: 1950

From pain to cardiovascular prevention

1. *"Ingestion of 12 aspirin tablets daily resulted after five days in **spontaneous profuse nosebleed**. The test was repeated twice over, with precisely the same results."*

Craven L. Journal of Insurance Medicine, 1950

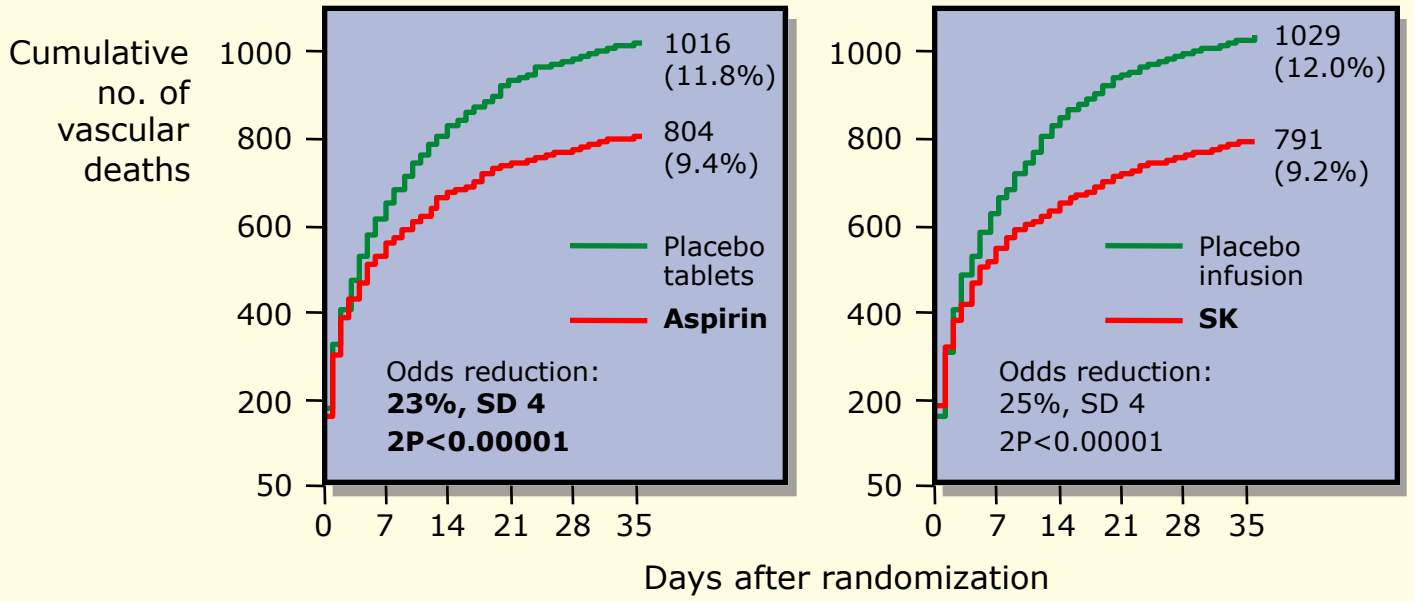
2. *"The value of Aspirin (acetylsalicylic acid) in the general **prophylaxis of coronary occlusion** is suggested by observations accumulated during the past seven years."*

Craven L. Mississippi Valley Medical Journal, 1953

ASA in acute myocardial infarction

ISIS-2: Second International Study of Infarct Survival

Vascular mortality over 35 days: individual therapies



The ISIS-2 collaborative group. *Lancet* 1988; ii: 349–60.

2002 ATTC: antiplatelet therapy and CV mortality

Patient type	Fatalities prevented per 1,000 treated	Significance vs control
History of MI	14	p=0.0006
Acute MI*	23	p<0.0001
History of stroke/TIA	7	p=0.04
Acute stroke*	5	p=0.05
All	**15% reduction**	**p<0.0001**

*Acute data are recorded within ~30 days of a CV event.
ATTC, Antithrombotic Trialists' Collaboration; CV, cardiovascular; MI, myocardial infarction; TIA, transient ischemic attack.

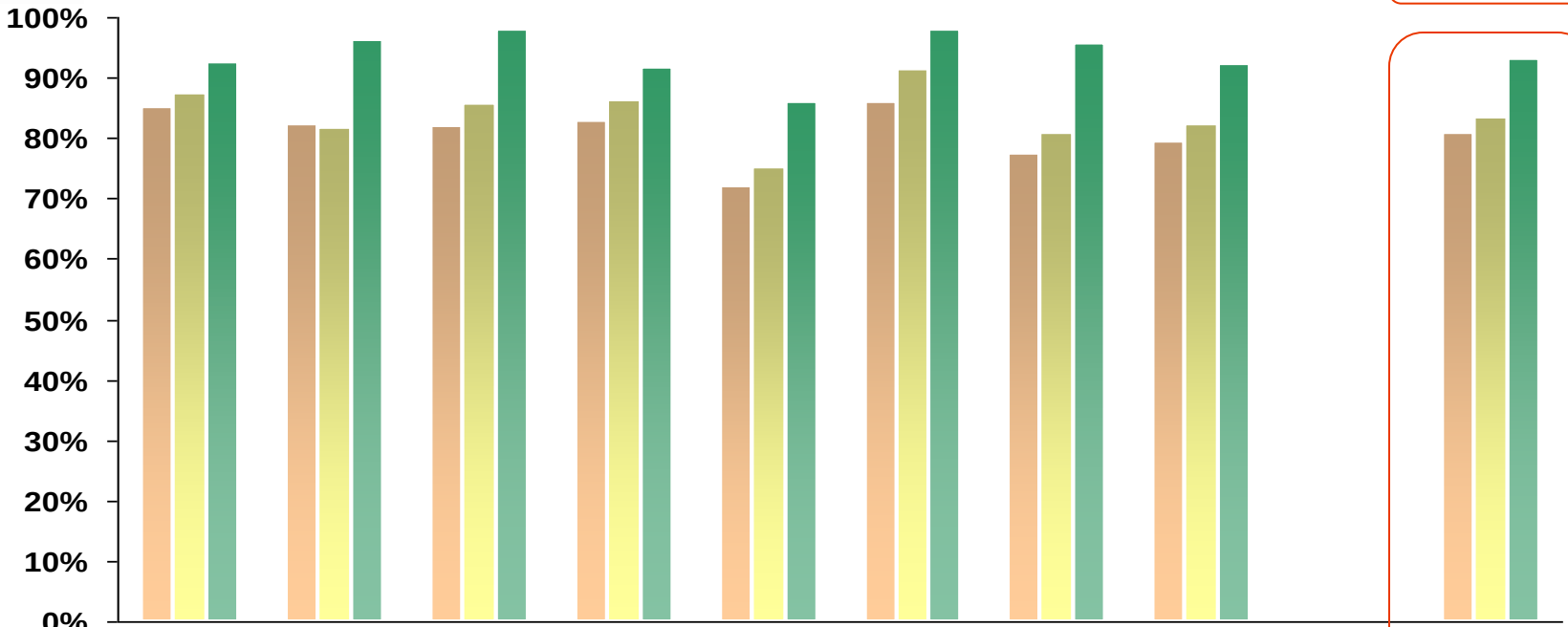
BMJ 2002; 324: 71–86.

Press Release - Over 40,000 lives lost worldwide every year because Aspirin is underused
EMBARGO: 00.01hrs GMT FRIDAY 11 JANUARY 2002

OVER 40,000 LIVES LOST WORLDWIDE EVERY YEAR BECAUSE ASPIRIN IS UNDERUSED

What's changed since then?

Medication Use: Antiplatelets



	Czech Rep.	Finland	France	Germany	Hungary	Italy	Nether-lands	Slovenia	ALL
Survey 1	85,2%	82,2%	82,1%	82,9%	72,0%	86,1%	77,5%	79,4%	80,8%
Survey 2	87,6%	81,9%	85,7%	86,3%	75,1%	91,5%	81,0%	82,3%	83,6%
Survey 3	92,5%	96,4%	98,1%	91,8%	86,1%	98,0%	95,7%	92,4%	93,2%

S2 vs. S1 : P=0.29
S3 vs. S2 : P=0.0002
S3 vs. S1 : P<0.0001

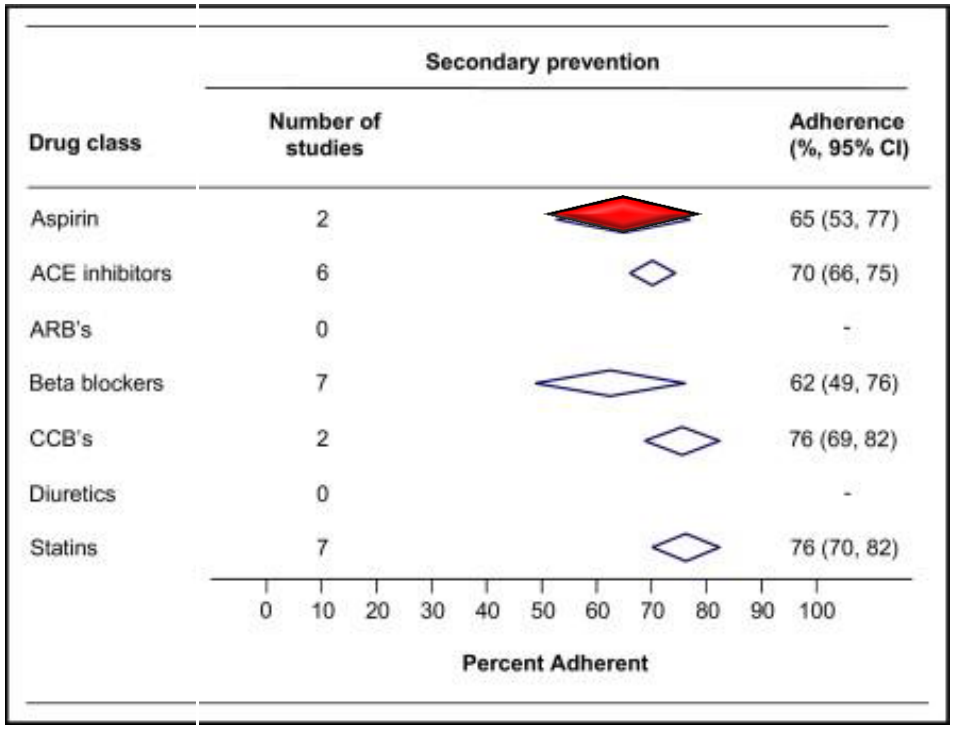
Kotseva K, et al. EUROASPIRE Study Group. Eur J Cardiovasc Prev Rehabil. 2010

1. Underuse of ASA in secondary prevention at community level (USA)

Adherence to Drugs That Prevent Cardiovascular Disease: Meta-analysis on 376,162 Patients

Sayed H. Naderi, BMedSci, Jonathan P. Bestwick, MSc, David S. Wald, MD

Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine, Queen Mary University of London, Charterhouse Square, London.



Meta-regression analysis showed a 0.15% decrease in adherence per month of follow-up (P = 0.07) (no effect on adherence of gender, age, or method of payment).

The American Journal of Medicine (2012) 125, 882-887

2. Underuse of ASA in secondary prevention at the global level (the world)

Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey

Salim Yusuf, Shofiqul Islam, Clara K Chow, Sumathy Rangarajan, Gilles Dagenais, Rafael Diaz, Rajeev Gupta, Roya Kelishadi, Romaina Iqbal, Alvaro Avezum, Annamarie Kruger, Raman Kutty, Fernando Lanas, Liu Lisheng, Li Wei, Patricio Lopez-Jaramillo, Aytekin Oguz, Omar Rahman, Hany Swidan, Khalid Yusoff, Witold Zatonski, Annika Rosengren, Koon K Teo, on behalf of the Prospective Urban Rural Epidemiology (PURE) Study Investigators

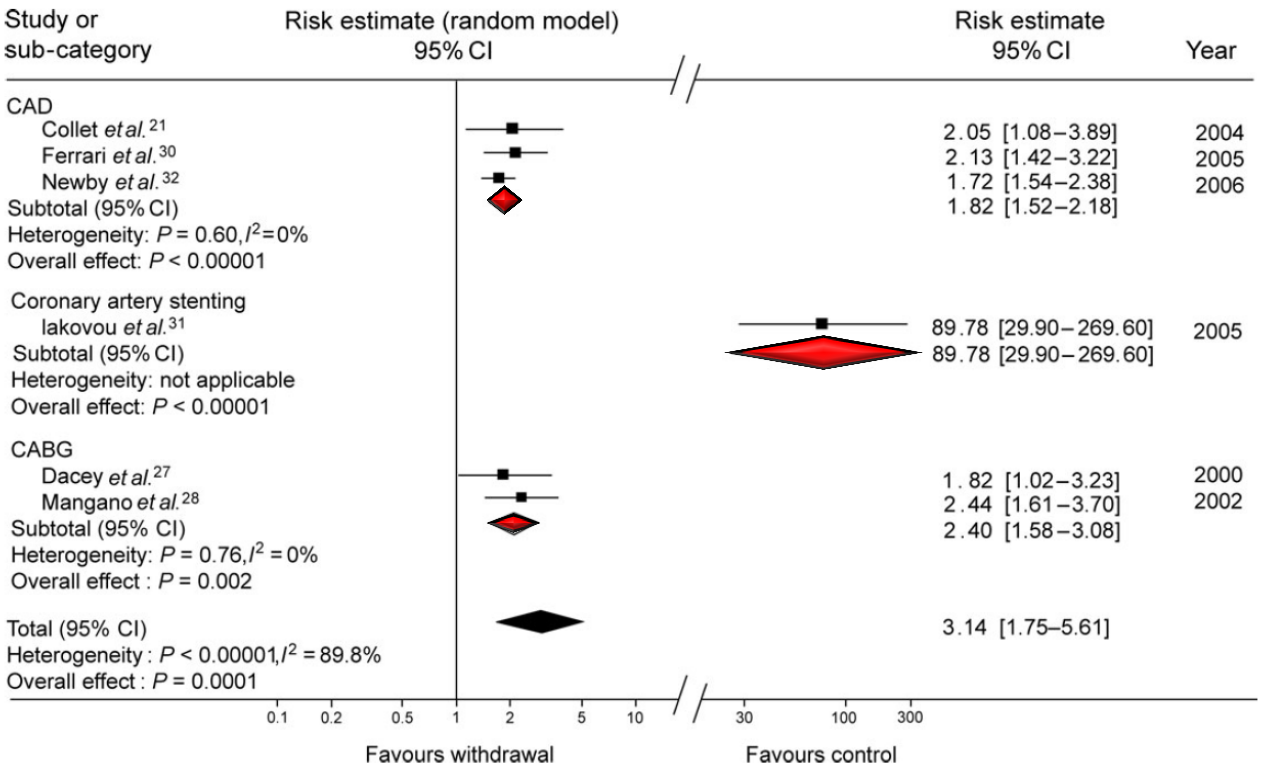
Drug use in participants with CAD or Stroke

	Overall	High-income countries	Low-income countries
CAD *(self reported: MI, CABG, PTCA, angina)*			
ASA	1460 (**25.8**%)	429 (**64.1**%)	80 (**11.0**%)
BP lowering drugs	2427 (43.0%)	524 (78.3%)	159 (21.8%)
Statins	942 (16.7%)	474 (70.9%)	33 (4.5%)
Stroke *(self reported)*			
ASA	557 (**24.3**%)	113 (**53.1**%)	13 (**3.8**%)
BP lowering drugs	916 (40.0%)	129 (60.6%)	45 (13.0%)
Statins	206 (9.0%)	110 (51.6%)	2 (0.6%)
CAD or Stroke			
ASA	1900 (**25.3**%)	521 (**62.0**%)	92 (**8.8**%)
BP lowering drugs	3146 (41.8%)	621 (73.8%)	200 (19.2%)
Statins	1096 (14.6%)	559 (66.5%)	34 (3.3%)

Yusuf S et al. Lancet 2011

3. The risk of ASA discontinuation in secondary prevention in the stent era

Risk of adverse thrombotic events in patients who discontinued aspirin (metanalysis of 6 studies)

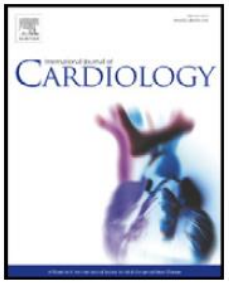


Biondi-Zoccai et al. ***Eur.Heart J.*** 2006

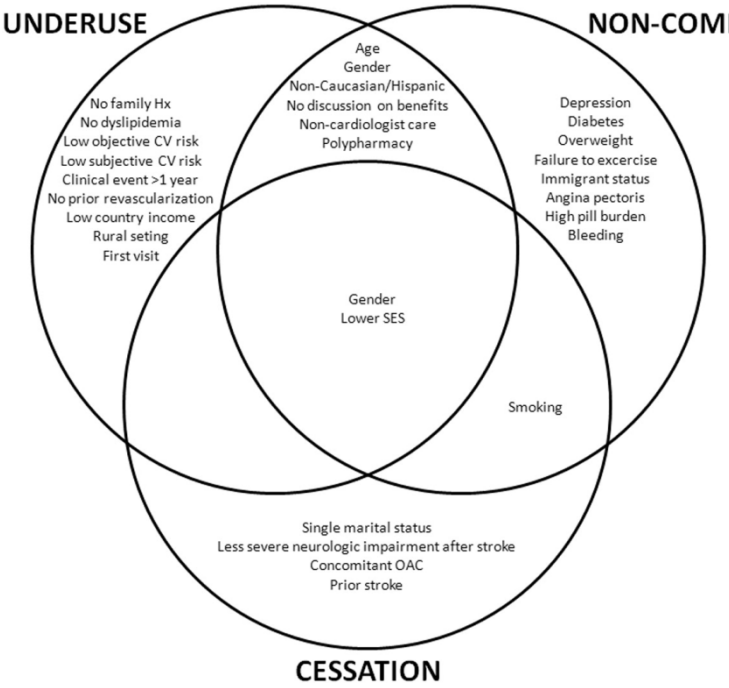
3. The risk of ASA discontinuation in secondary prevention

Aspirin underuse, non-compliance or cessation: Definition, extent, impact and potential solutions in the primary and secondary prevention of cardiovascular disease

Giuseppe Biondi-Zoccai [a,b,*], Yangfeng Wu [c], Carlos V. Serrano Jr. [d], Giacomo Frati [a,e], Pierfrancesco Agostoni [f], Antonio Abbate [b]



Older age, Female gender, **Hispanic ethnicity, Polipharmacy,** Clinical event >1 year before, No prior revascularization, **Low socio-economic status**, Non-cardiologist care, **Lower income country, Rural setting,** No discussion about aspirin risk–benefit profile.



Older age, Female gender, **Non-Caucasian ethnicity, Immigrant status,** Depression, Diabetes, Symptomatic angina pectoris, Smoking, Overweight, Failure to exercise regularly, **Low socio-economic status,** Polipharmacy, Non-cardiologist care.

Female gender, Smoking, Single marital status, **Lower educational level**, Oral anticoagulant therapy, Prior stroke, Less severe neurological impairment after stroke

Int. J. Cardiol. 2015; 182:148–154

European Heart Journal (2016) **37**, 2315–2381
doi:10.1093/eurheartj/ehw106

2016 European Guidelines on cardiovascular disease prevention in clinical practice

Recommendations for achieving medication adherence

Recommendations	Class[a]	Level[b]	Ref[c]
Simplifying the treatment regimen to the lowest acceptable level is recommended, with repetitive monitoring and feedback. In case of persistent non-adherence, multi-session or combined behavioural interventions are recommended.	I	A	481
It is recommended that physicians assess medication adherence, and identify reasons for non-adherence in order to tailor further interventions.	I	C	482–484
The use of the polypill and combination therapy to increase adherence to drug therapy may be considered.	IIb	B	485, 486

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Brief Review

Gaps in Hypertension Guidelines in Low- and Middle-Income Versus High-Income Countries

A Systematic Review

Mayowa Owolabi,* Paul Olowoyo,* J. Jaime Miranda, Rufus Akinyemi, Wuwei Feng, Joseph Yaria, Tomiwa Makanjuola, Sanni Yaya, Janusz Kaczorowski, Lehana Thabane, Josefien Van Olmen, Prashant Mathur, Clara Chow, Andre Kengne, Raelle Saulson, Amanda G. Thrift, Rohina Joshi, Gerald S. Bloomfield, Mulugeta Gebregziabher, Gary Parker, Charles Agyemang, Pietro Amedeo Modesti, Shane Norris, Luqman Ogunjimi, Temitope Farombi, Ezinne Sylvia Melikam, Ezinne Uvere, Babatunde Salako, Bruce Ovbiagele; for the COUNCIL Initiative†

***Hypertension*. 2016**

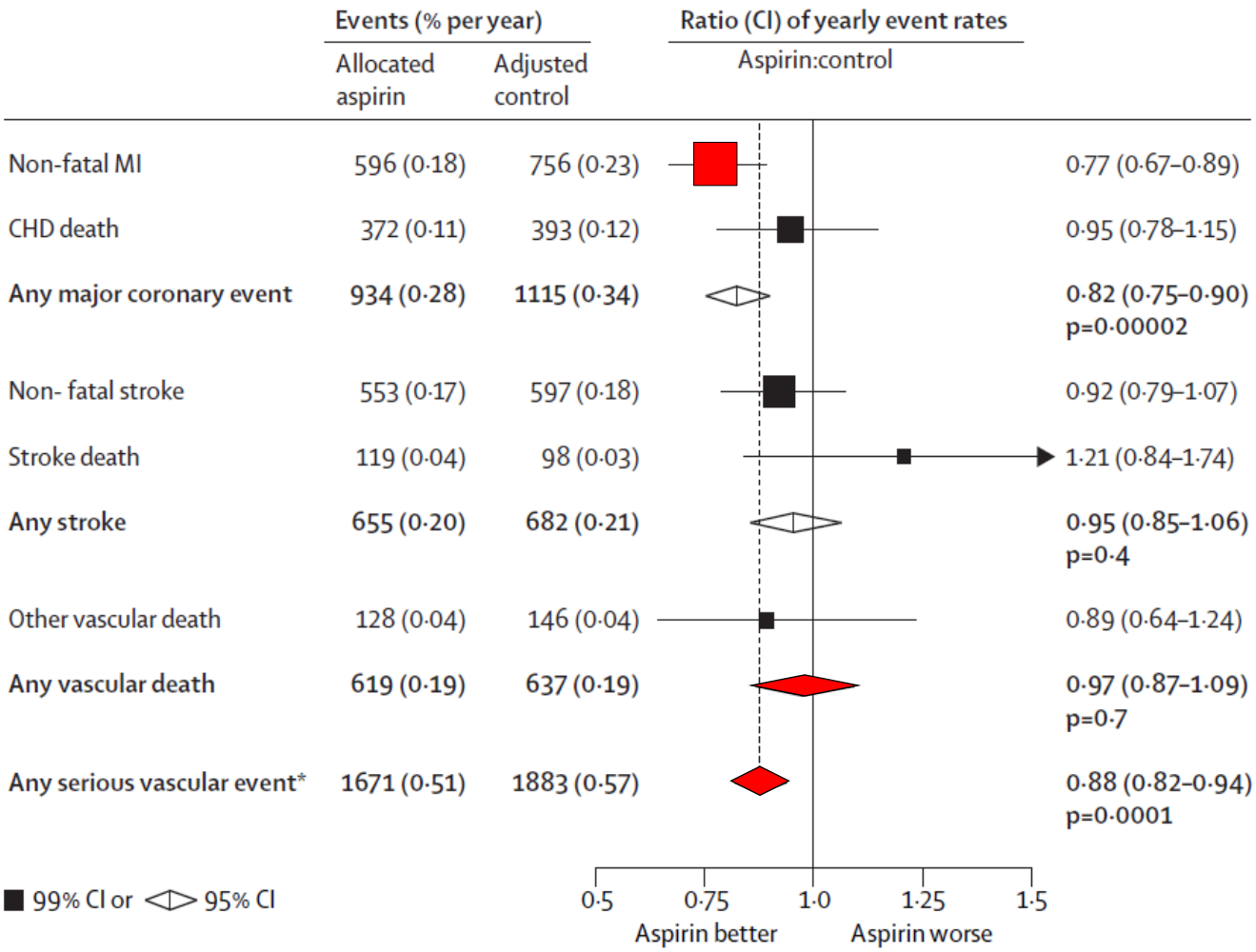
1.ASA – from Pain to Prevention

2.The tale of risk in primary prevention

Aspirin in Primary Prevention Trials

metanalysis of 6 studies

- serious CV events (myocardial infarction, stroke, or death from a vascular cause)



NNT per 5 years = 333

Antithrombotic Trialists' (ATT) Collaboration. ***Lancet 2009***; *373: 1849–60*

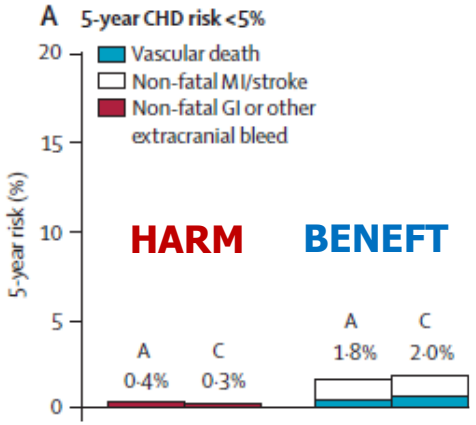
CV risk

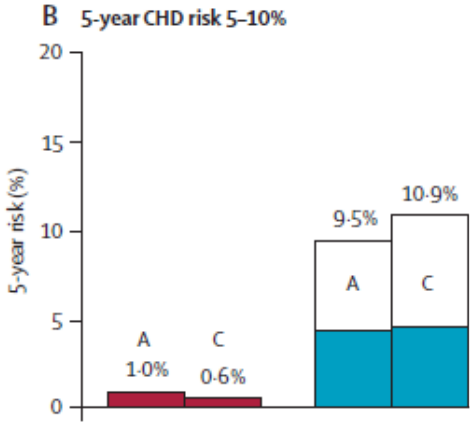
Physicians' Health Study

placebo group
4.0 events in 10 yrs

Table 3. Confirmed Deaths, According to Treatment Group.

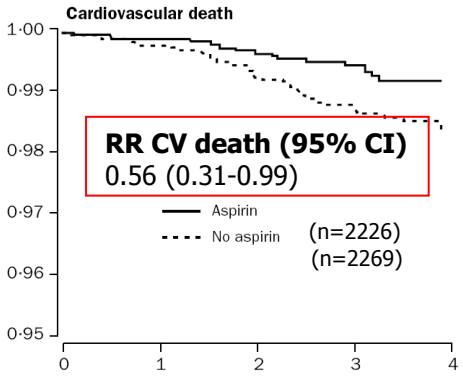
Cause*	Aspirin Group	Placebo Group	Relative Risk	95% Confidence Interval	P Value
Total cardiovascular deaths†	81	83	0.96	0.60–1.54	0.87
Acute myocardial infarction (410)	10	28	0.31	0.14–0.68	0.004
Other ischemic heart disease (411–414)	24	25	0.97	0.60–1.55	0.89
Sudden death (798)	22	12	1.96	0.91–4.22	0.09
Stroke (430, 431, 434, 436)‡	10	7	1.44	0.54–3.88	0.47
Other cardiovascular (402, 421, 424, 425, 428, 429, 437, 440, 441)	15	11	1.38	0.62–3.05	0.43



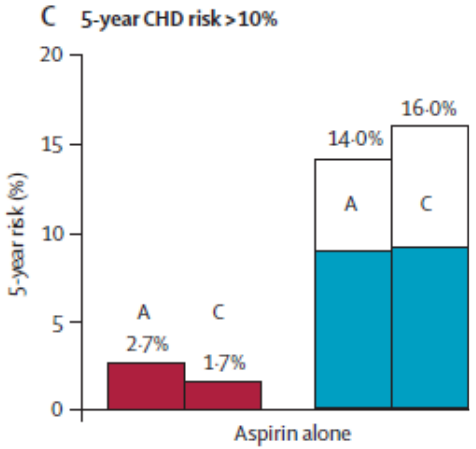


PRIMARY PREVENTION PROJECT (PPP)

placebo group
22.9 events in 10 yrs



THE LANCET • Vol 357 • January 13, 2001



Antithrombotic Trialists' (ATT) Collaboration. ***Lancet 2009**; 373: 1849–60*

CV risk

Physicians' Health Study

placebo grou
4.0 events i

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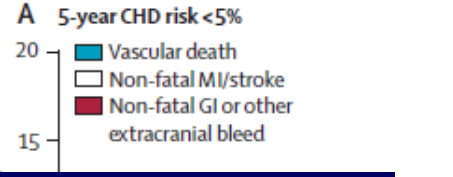
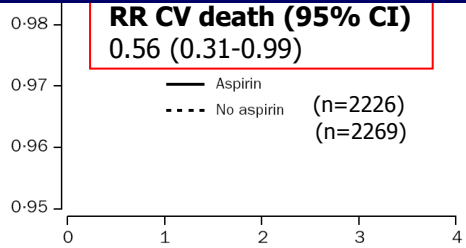


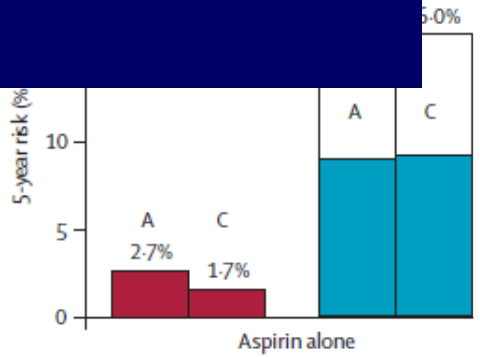
Aspirin in primary prevention studies
CV risk and ASA efficacy

Study	(year)	rate of CV events in placebo group (% per 10 years)	rate of CV mortality in placebo group (% per 10 years)	MI (p=)	CV death (p=)
WHS	(2006)	**2.6**	0.6	ns	ns
PHS	(1997)	**4.0**	1.0	**0.01**	ns
BDrT	(1988)	**6.0**	2.0	ns	ns
HOT	(2002)	**10.3**	3.9	**0.002**	ns
TPT	(2003)	**11.7**	4.0	**0.04**	ns
PPP	(2001)	**22.9**	4.5	**0.01**	**0.05**

PA Modesti - UNIFI



THE LANCET • Vol 357 • January 13, 2001

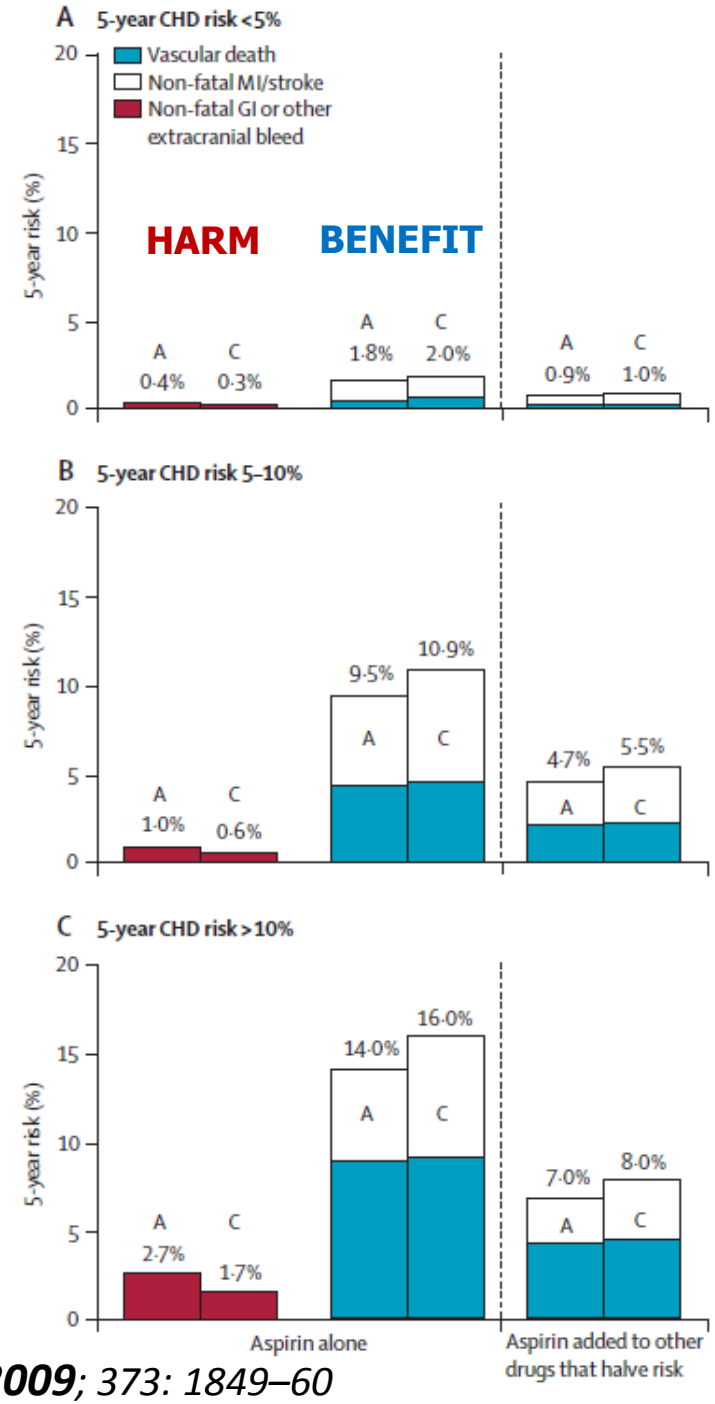


Antithrombotic Trialists' (ATT) Collaboration. ***Lancet 2009***; *373: 1849–60*

primary prevention in the real word

Modern measures (statins or others) could "per se" reduce CV risk by 50%

Absolute benefit of ASA could be about half as large as suggested



Antithrombotic Trialists' (ATT) Collaboration. ***Lancet 2009**; 373: 1849–60*

1. ASA – from Pain to Prevention

2. The tale of risk in primary prevention

3. ASA and Diabetes

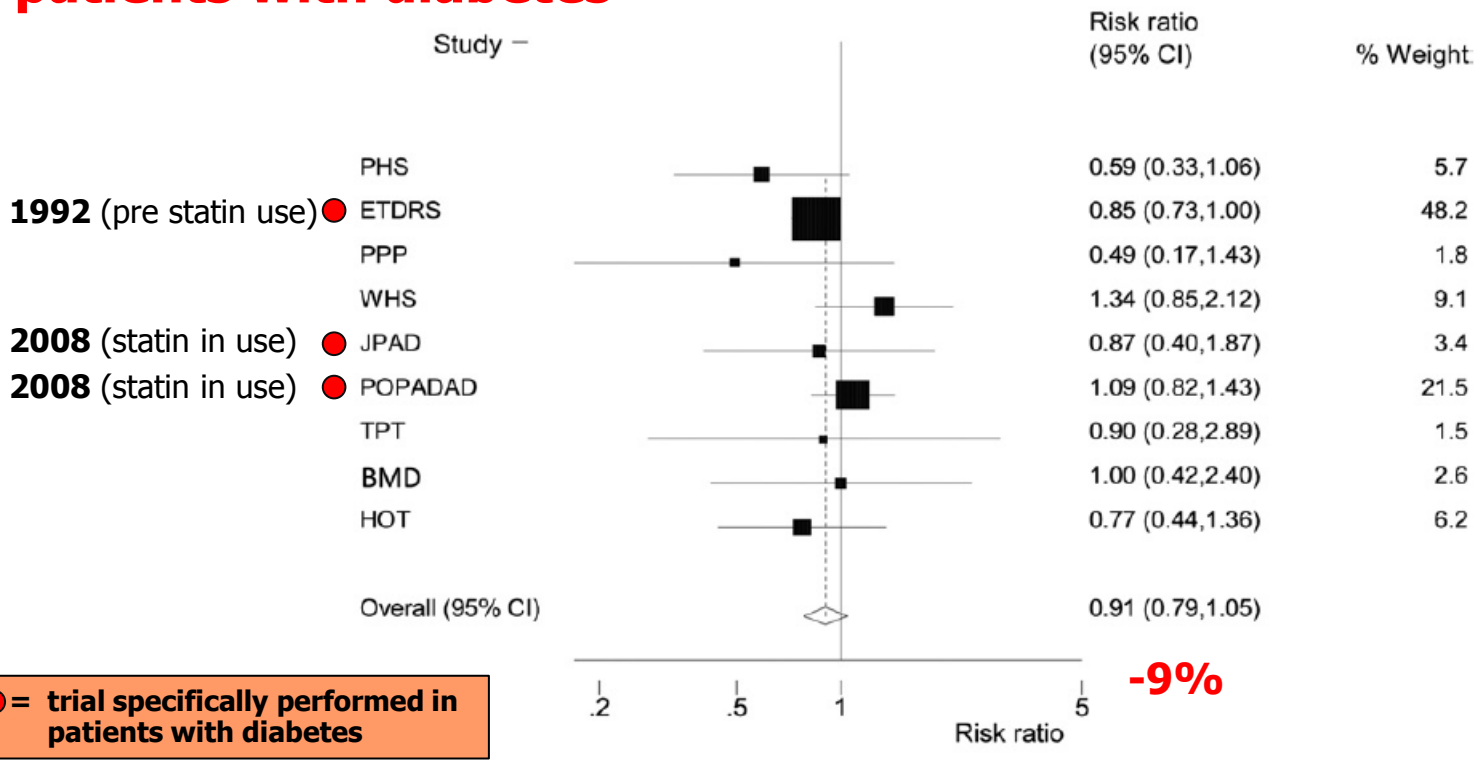
Journal of the American College of Cardiology
© 2010 by the American Diabetes Association, the American Heart Association, Inc., and the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 55, No. 25, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.04.003

EXPERT CONSENSUS DOCUMENT

Aspirin for Primary Prevention of Cardiovascular Events in People With Diabetes

A Position Statement of the American Diabetes Association, a Scientific Statement of the American Heart Association, and an Expert Consensus Document of the American College of Cardiology Foundation

Effects of ASA on risk of CAD disease events (non fatal and fatal MI) in patients with diabetes



● = trial specifically performed in patients with diabetes

JACC 2010

BMJ

RESEARCH

BMJ 2008;337:a1840

The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease

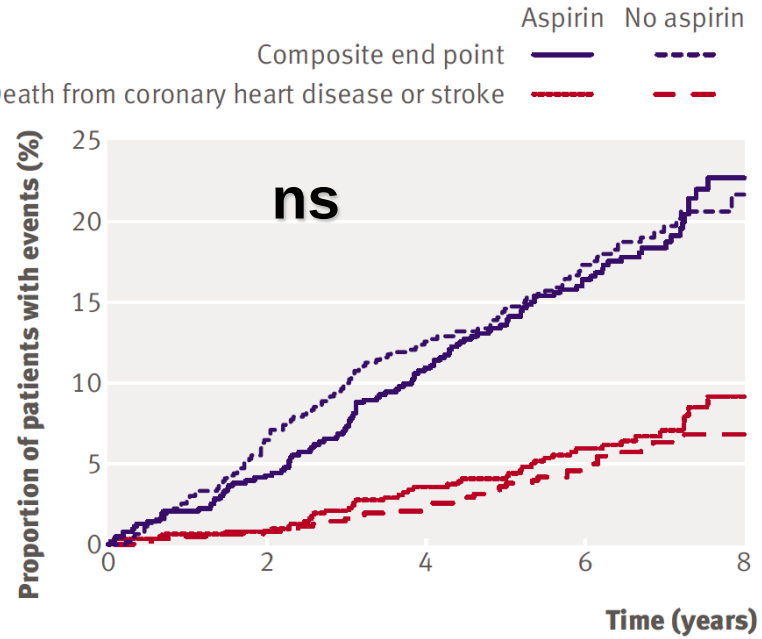
Inclusion criteria:
DM; ABI<0.99

ASA	**Placebo**
n=638	n=638

Primary end points
Composite of:
- fatal or nonfatal MI
- fatal or nonfatal stroke
- amputation

Death from CAD or stroke

Statin use
Not stated



Numbers at risk for composite end point

Aspirin	638	599	543	399	48
No aspirin	638	590	534	381	48

Study dimensioned with an expected CV risk of 40% per 10 years ***(event rate lower than expected)***

Underpowered study
1600 planned
1276 recruited

Low compliance
14% drop out at 1 yr
50% drop out at 5 yrs

ORIGINAL CONTRIBUTION

JAMA-EXPRESS

JAMA. 2008;300(18):2134-2141

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

A Randomized Controlled Trial

for the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators

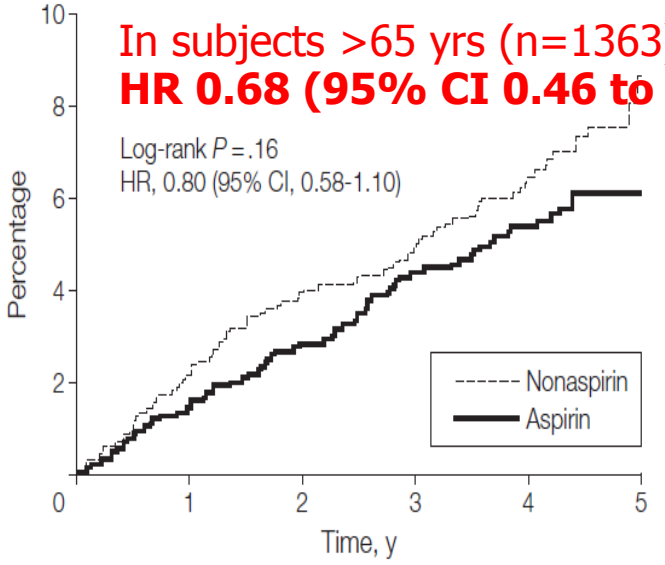
	Placebo	ASA
Subjects	1277	1262
Events	86	68
(events/10 yrs)	15.4	12.3
	(1/3 than expected)	

Primary end point: atherosclerotic events (fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease)

Statin use 26%

Figure 2. Total Percentage of Atherosclerotic Events According to Treatment Group

In subjects >65 yrs (n=1363)
HR 0.68 (95% CI 0.46 to 0.99)



No. at risk						
Nonaspirin	1277	1220	1165	1117	813	135
Aspirin	1262	1210	1159	1095	806	140

CI indicates confidence interval; HR, hazard ratio.

ONGOING TRIALS IN DIABETES

ACCEPT-D

Open Access

Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins

Giorgia De Berardis[1], Michele Sacco[1], Virgilio Evangelista[2], Alessandro Filippi[5], Carlo B Giorda[3], Gianni Tognoni[1], Umberto Valentini[4], Antonio Nicolucci*[1] and ACCEPT-D Study Group[1]

ASA **100 mg daily**

Adults **> 50** years

taking also simvastatin

n= **5170 pts**

ASCEND *A S*tudy of *C*ardiovascular *E*vents i*N D*iabetes

Recruitment is now Complete - 15,480 participants randomised. Follow-up to continue until 2017.

The ASCEND randomised trial should provide the first reliable evidence about the effects of aspirin and of omega-3 fatty acids in diabetes. ASCEND has recruited 15,000 people with diabetes (either type 1 or type 2) who were not known to have vascular disease. ASCEND volunteers are randomly allocated to take either 100mg aspirin daily or placebo (dummy) and 1 gram capsules containing naturally occurring omega-3 fatty acids ("fish-oils") or placebo capsules containing olive oil. If favourable results emerge, this could lead to the widespread use of these treatments in diabetes, and avoidance of many thousands of heart attacks and strokes.

Funding for the study is being provided by the British Heart Foundation, packaged aspirin and matching placebo is being provided by Bayer AG and packaged omega-3 fatty acid supplements and matching placebo capsules by Abbott Products Operations AG (formerly Solvay Pharmaceuticals). The trial is coordinated by the University of Oxford Clinical Trial Service Unit and started during 2004, and is scheduled to continue until 2017.

https://www.ctsu.ox.ac.uk/ascend/

UNIVERSITY OF OXFORD

Information for Patients and Carers
ASCEND
Clinical Trial Service Unit
Richard Doll Building University of Oxford
Old Road Campus, Headington
Oxford, OX3 7LF

Office telephone: 01865 743888
Office fax: 01865 743981
Freefone: 0800 585323

Clinical Trial Service Unit

MRC Medical Research Council

British Heart Foundation

ASA **100 mg daily**

Adults **> 40** years

with no previous events

n= **10000 pts**

ARRIVE **A**spirin to **R**educe **R**isk of **I**nitial **V**ascular **E**vents

Men aged ≥55 years with two to four CVD risk factors
Women aged ≥60 years with three or more CVD risk factors
CVD risk factors include elevated total and/or LDL cholesterol, low HDL cholesterol, cigarette smoking, elevated blood pressure, current use of medication to treat high blood pressure, and a family history of early CHD

ARRIVE
Aspirin to Reduce Risk of Initial Vascular Events

ASA **100 mg daily**

Men ≥**55** years
Women ≥**60** years

with 2-4 risk factors

n= **12000 pts**

AHA/ADA Scientific Statement

Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence

A Scientific Statement From the American Heart Association and the American Diabetes Association

Caroline S. Fox, MD, MPH, FAHA, Co-Chair; Sherita Hill Golden, MD, MHS, FAHA, Co-Chair; Cheryl Anderson, PhD, MPH, MS; George A. Bray, MD; Lora E. Burke, PhD, MPH, FAHA; Ian H. de Boer, MD, MS; Prakash Deedwania, MD, FAHA; Robert H. Eckel, MD; Abby G. Ershow, ScD, RD, FAHA; Judith Fradkin, MD; Silvio E. Inzucchi, MD; Mikhail Kosiborod, MD, FAHA; Robert G. Nelson, MD, PhD; Mahesh J. Patel, MD; Michael Pignone, MD, MPH; Laurie Quinn, PhD, RN; Philip R. Schauer, MD; Elizabeth Selvin, PhD, MPH, FAHA; Dorothea K. Vafiadis, MS, FAHA; on behalf of the American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research, and the American Diabetes Association

Recommendations

1. **Low-dose aspirin (75–162 mg/d) is reasonable among those with a 10-year CVD risk of at least 10% and without an increased risk of bleeding (*ACC/AHA Class IIa; Level of Evidence B*) (*ADA Level of Evidence C*).**
2. **Low-dose aspirin is reasonable in adults with diabetes mellitus at intermediate risk (10-year CVD risk, 5%–10%) (*ACC/AHA Class IIb; Level of Evidence C*) (*ADA Level of Evidence E*).**

Circulation. 2015;132:691-718.

Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association

Diabetes Care 2015;38:1777–1803 | DOI: 10.2337/dci15-0012

Caroline S. Fox, Co-Chair; Sherita Hill Golden, Co-Chair; Cheryl Anderson; George A. Bray; Lora E. Burke; Ian H. de Boer; Prakash Deedwania; Robert H. Eckel; Abby G. Ershow; Judith Fradkin; Silvio E. Inzucchi; Mikhail Kosiborod; Robert G. Nelson; Mahesh J. Patel; Michael Pignone; Laurie Quinn; Philip R. Schauer; Elizabeth Selvin; and Dorothea K. Vafiadis; on behalf of the American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research, and the American Diabetes Association

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Diabetes Care 2015;38:1777–1803

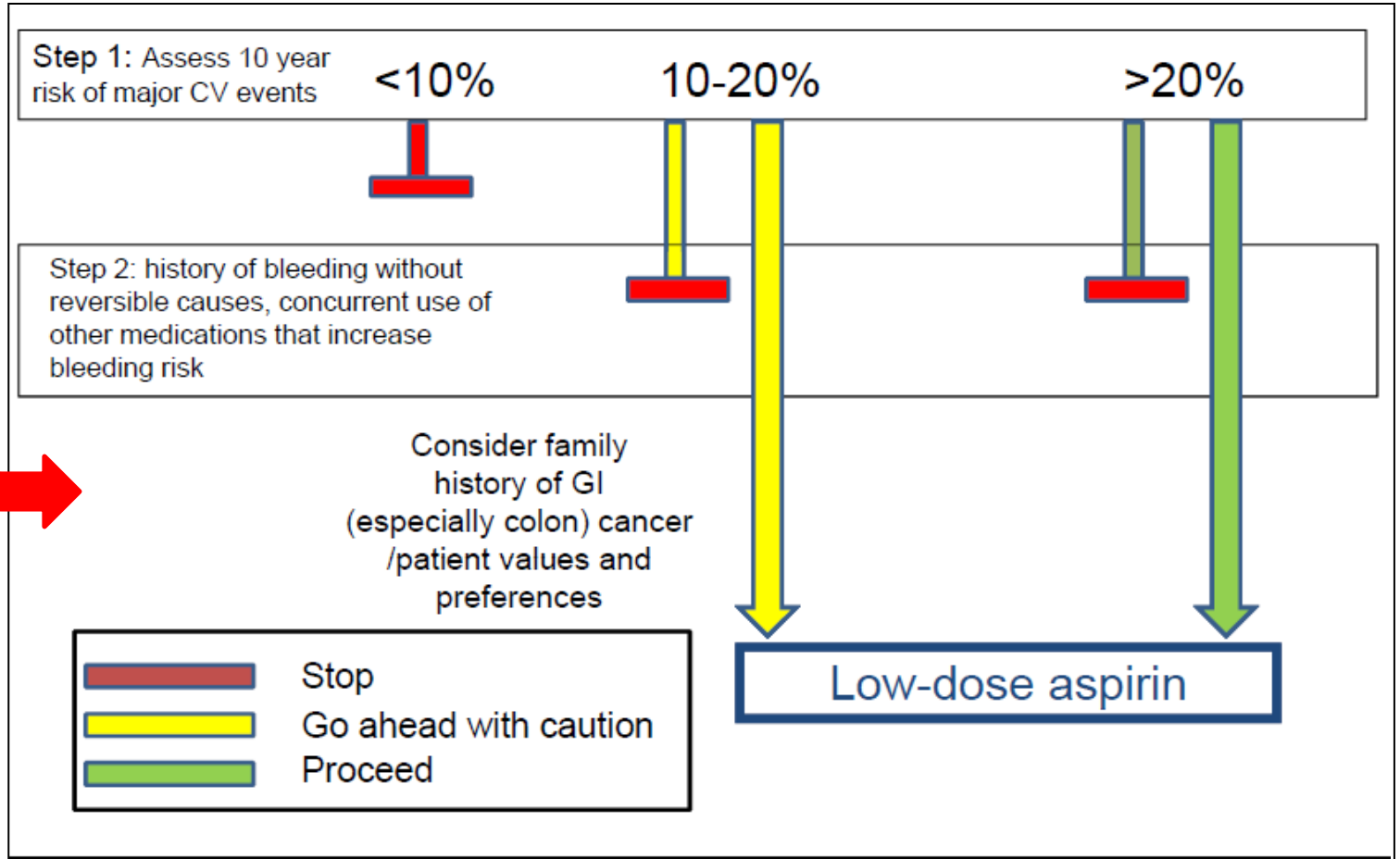
1. ASA – from Pain to Prevention

2. The tale of primary prevention
   when the low risk is too high?

3. ASA and Diabetes

4. A new paradigm change for ASA?

from cardiovascular to CANCER prevention



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

Halvorsen S et al. ***JACC*** 2014

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

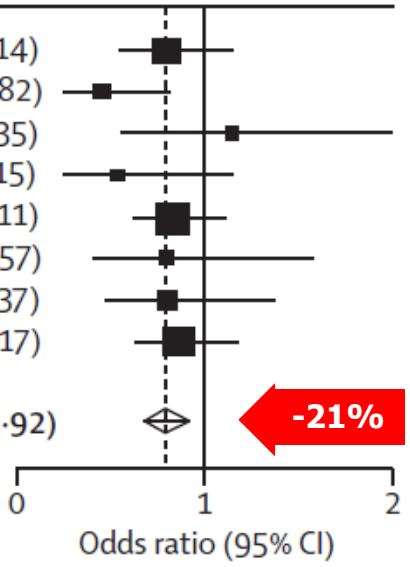
www.thelancet.com **Published online December 7, 2010 DOI:10.1016/S0140-6736(10)62110-1**

Trials selection critera: ***1.any dose aspirin (30-1200 mg daily)***
2.treatment duration >4 years

During trial (n=8) results

NNT 139

	Deaths due to cancer		Odds ratio (95% CI)
	Aspirin	Control	
BDAT[19]	75/3429	47/1710	0·79 (0·55–1·14)
UK-TIA[18]	21/1621	23/814	0·45 (0·25–0·82)
ETDRS[20]	16/1856	14/1855	1·14 (0·56–2·35)
SAPAT[22]	10/1009	19/1026	0·53 (0·25–1·15)
TPT[17]	87/2545	104/2540	0·83 (0·62–1·11)
JPAD[21]	15/1262	19/1277	0·80 (0·40–1·57)
POPADAD[23]	25/638	31/638	0·80 (0·47–1·37)
AAA[24]	78/1635	90/1675	0·86 (0·63–1·17)
Total	327/14035	347/11535	0·79 (0·68–0·92)



p_{sig}=0·003, p_{het}=0·84

Figure 1: Meta-analysis of the effect of aspirin on deaths due to cancer during all eligible randomised trials of aspirin versus control

1.riduzione mortalita' per cancro

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

www.thelancet.com **Published online December 7, 2010 DOI:10.1016/S0140-6736(10)62110-1**

post-trial follow-up (7 trials) Thrombosis Prevention Trial; British Doctors Aspirin Trial; Swedish Aspirin Low Dose Trial; UKTIA Aspirin Trial; Dutch TIA trial

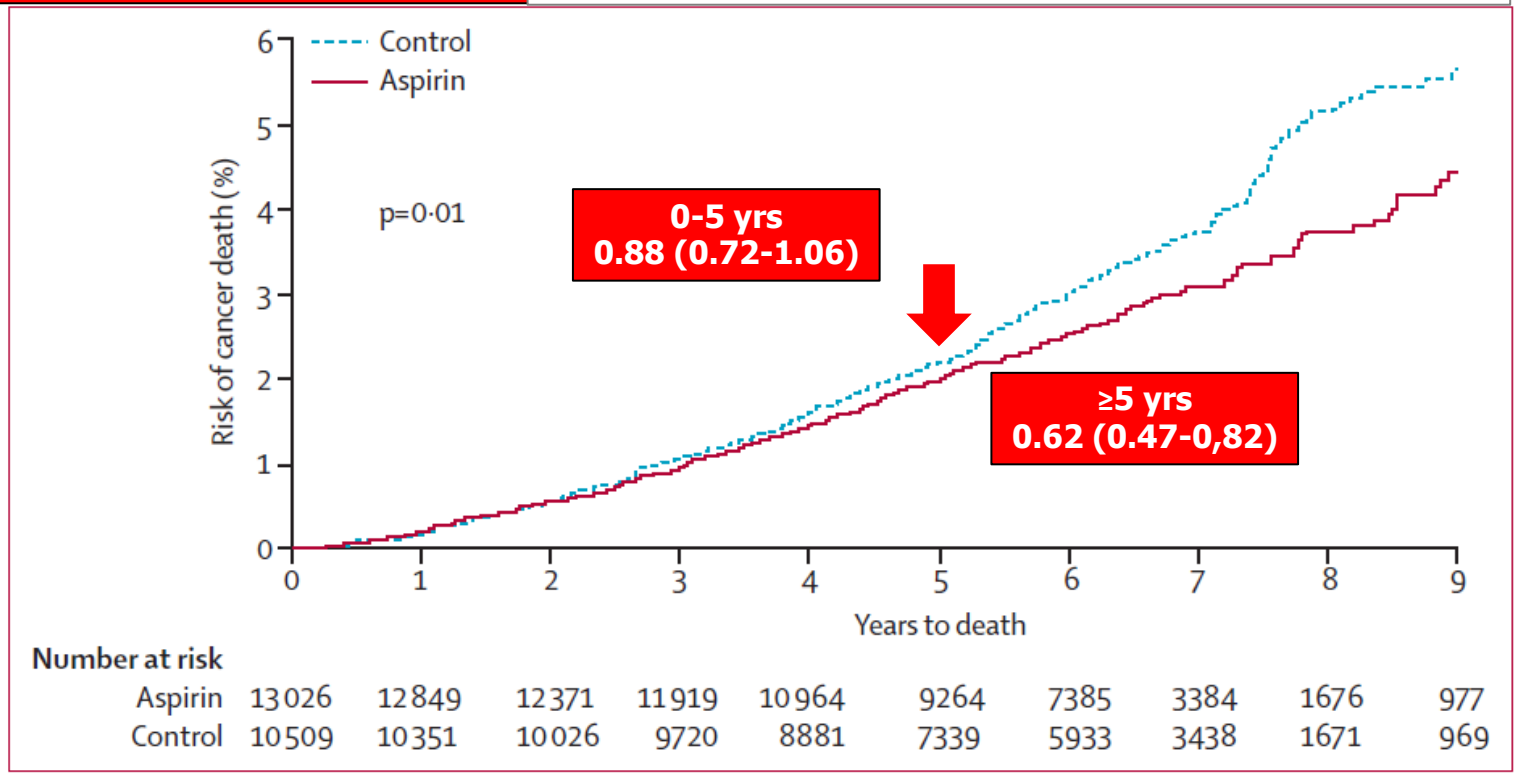


Figure 2: Effect of allocation to aspirin versus control on risk of death due to cancer during the trial treatment periods in a pooled analysis of the 23 535 patients in seven trials[17-21,23,24]

2.effetto tempo dipendente

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

Peter M Rothwell, Jacqueline F Price, F Gerald R Fowkes, Alberto Zanchetti, Maria Carla Roncaglioni, Gianni Tognoni, Robert Lee, Jill F F Belch, Michelle Wilson, Ziyah Mehta, Tom W Meade
www.thelancet.com Published online March 21, 2012 DOI:10.1016/S0140-6736(11)61720-0

incident cancer

major vascular events

bleeding

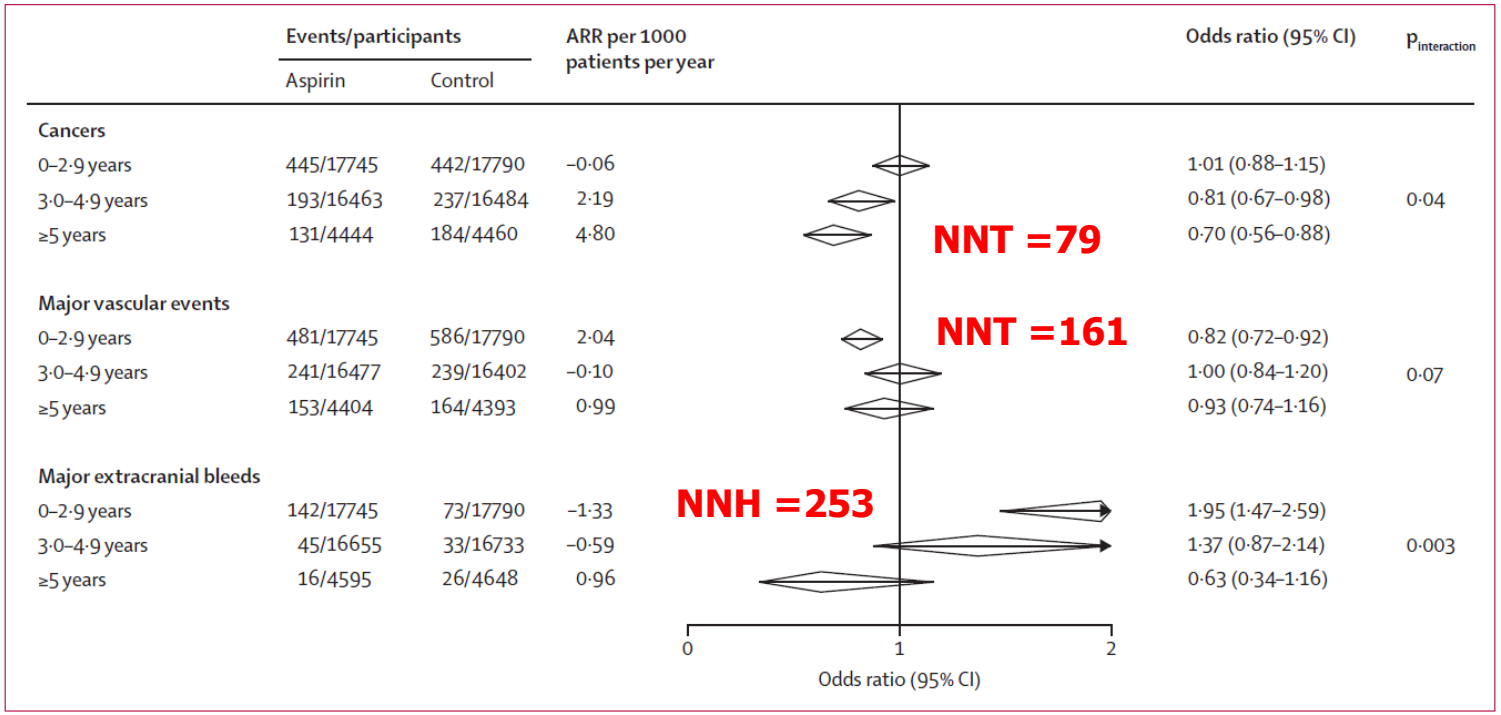


Figure 5: **Summary of meta-analyses of the effect of aspirin on risks of incident cancer, major vascular events, and major extracranial bleeds during six randomised trials of daily low-dose aspirin versus control in primary prevention of vascular events[16–21] stratified by period of trial follow-up (0–2·9, 3·0–4·9, ≥5 years)**
The number of participants at the start of each period was based on the number of individuals surviving free of the relevant outcome event at the start of the period, such that only first events of each type were included. The statistical significance of the interaction between the treatment effect and the period of follow-up was derived from a Cox model in which time was included as a continuous variable. ARR=absolute reduction in risk.

The Lancet, Volume 377, Issue 9759, Pages 31 - 41, 1 January 2011

3. non e' diagnosi precoce - incidenza di cancro si riduce dopo 3 anni di trattamento

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

colon cancer mortality **-48% after at least 2.5 years of ASA**
-52% after at least 5 years of ASA

	Incidence of colorectal cancer				Mortality due to colorectal cancer			
	n/N	HR (95% CI)	ARR (95% CI)	p	n/N	HR (95% CI)	ARR (95% CI)	p
All patients	196/8073	0·75 (0·56–0·97)	1·21% (0·19–2·22)	0·02	130/8073	0·61 (0·43–0·87)	1·36% (0·44–2·28)	0·005
Scheduled treatment ≥2·5 years	185/7383	0·69 (0·51–0·93)	1·33% (0·30–2·36)	0·003	119/7383	0·54 (0·36–0·80)	1·49% (0·55–2·43)	0·001
Scheduled treatment ≥5 years	135/5077	0·62 (0·43–0·94)	1·55% (0·34–2·76)	0·003	91/5077	0·48 (0·30–0·77)	1·76% (0·61–2·91)	0·001

Pooled analyses of trials of low-dose aspirin (75–300 mg daily) stratified according to the duration of scheduled treatment during the initial trial period. Data are hazard ratios (HR) from a Cox model and absolute reductions in 20-year risk (ARR) derived from life-tables. The p values are taken from the Cox model stratified by study and the analysis of patients with longer scheduled trial treatments includes all events from the time of randomisation. The p values therefore differ slightly from those obtained from the log-rank test in analyses from different timepoints in figure 2.

Table 2: Effect of low-dose (75–300 mg) aspirin versus control on subsequent long-term incidence and mortality due to colorectal cancer

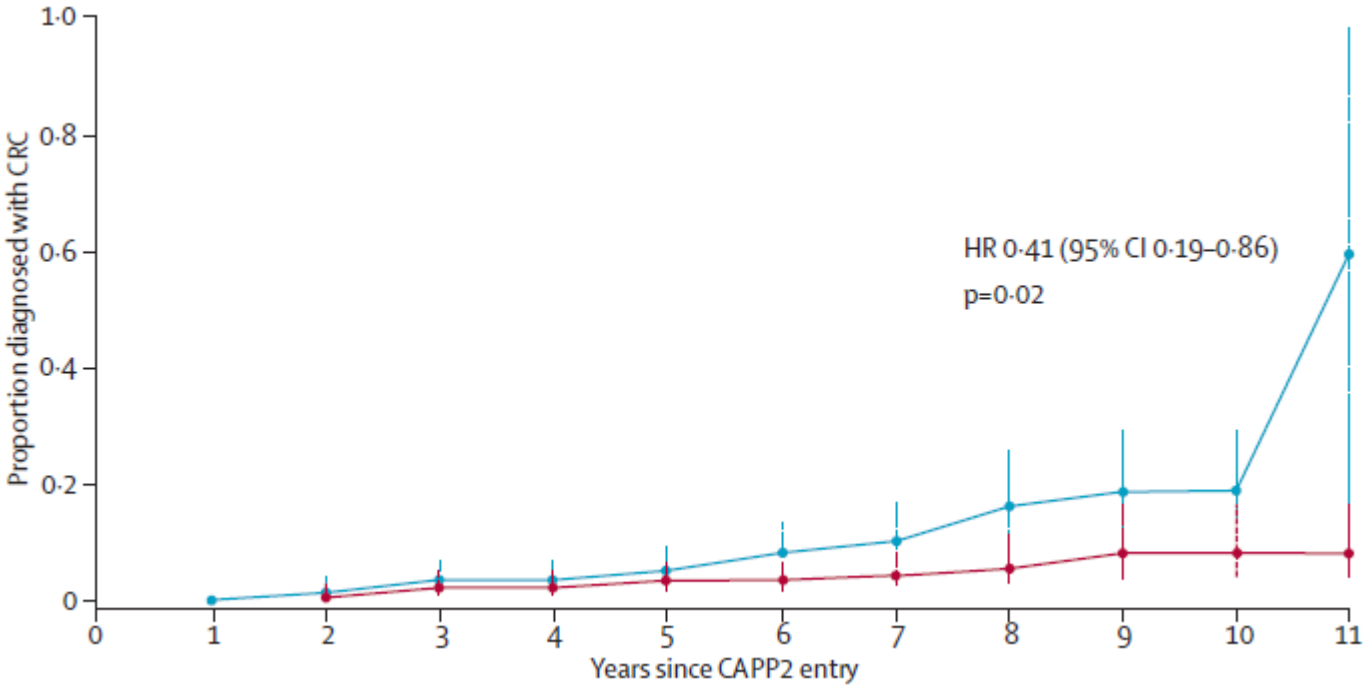
-52%

Trials selection critera: ***1.based in UK or Sweden***
2.treatment duration 2-5 years

4.effetto maggiore e piu' precoce nel cancro del colon

Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial

John Burn, Anne-Marie Gerdes, Finlay Macrae, Jukka-Pekka Mecklin, Gabriela Moeslein, Sylviane Olschwang, Diane Eccles, D Gareth Evans, Eamonn R Maher, Lucio Bertario, Marie-Luise Bisgaard, Malcolm G Dunlop, Judy W C Ho, Shirley V Hodgson, Annika Lindblom, Jan Lubinski, Patrick J Morrison, Victoria Murday, Raj Ramesar, Lucy Side, Rodney J Scott, Huw J W Thomas, Hans F Vasen, Gail Barker, Gillian Crawford, Faye Elliott, Mohammad Movahedi, Kirsi Pylvanainen, Juul T Wijnen, Riccardo Fodde, Henry T Lynch, John C Mathers, D Timothy Bishop, on behalf of the CAPP2 Investigators

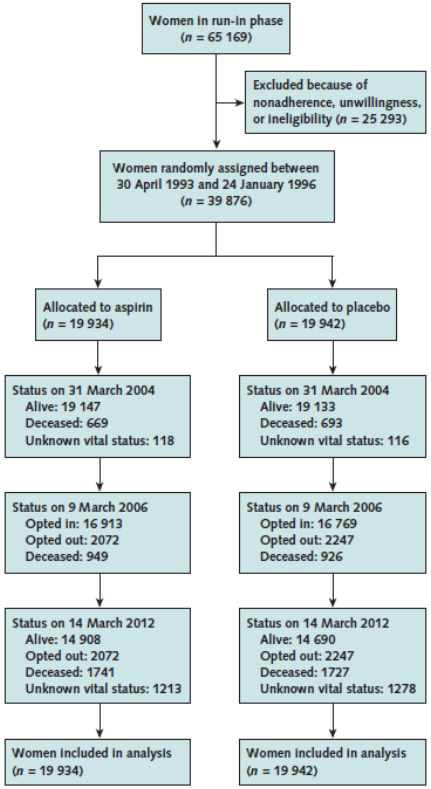


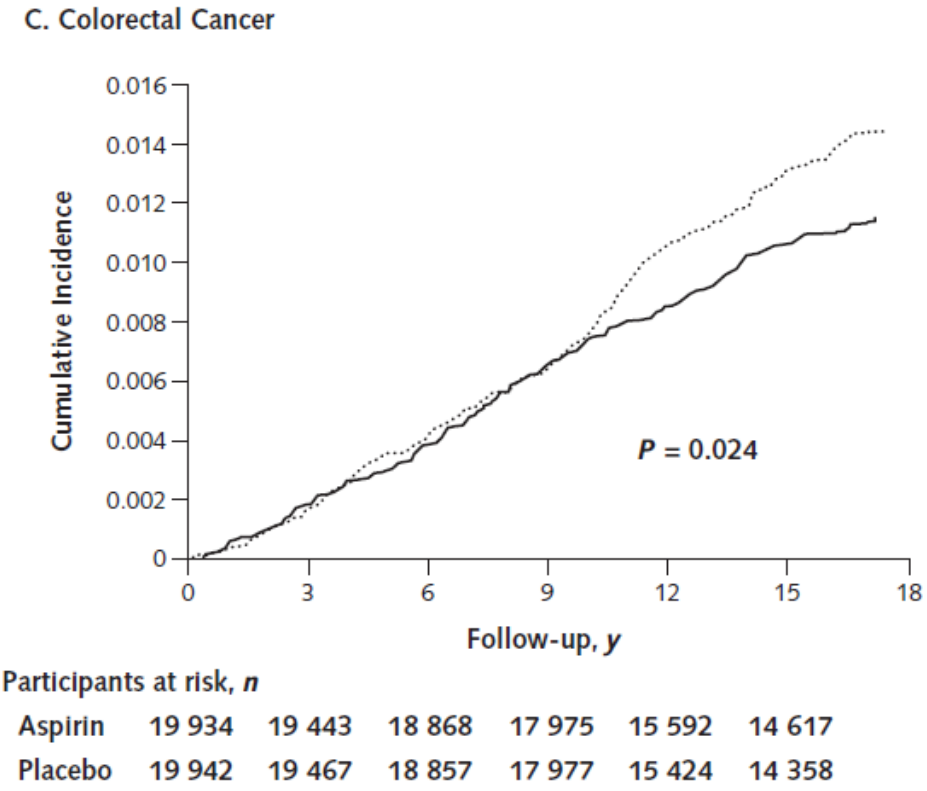
Lancet 2011; 378: 2081–87

Annals of Internal Medicine | ORIGINAL RESEARCH

Alternate-Day, Low-Dose Aspirin and Cancer Risk: Long-Term Observational Follow-up of a Randomized Trial

Nancy R. Cook, ScD; I-Min Lee, ScD; Shumin M. Zhang, ScD; M. Vinayaga Moorthy, PhD; and Julie E. Buring, ScD





Ann Intern Med. 2013;159:77-85.

Annals of Oncology 00: 1–10, 2014
doi:10.1093/annonc/mdu225

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

J. Cuzick[1*], M. A. Thorat[1], C. Bosetti[2], P. H. Brown[3], J. Burn[4], N. R. Cook[5], L. G. Ford[6], E. J. Jacobs[7], J. A. Jankowski[8,9], C. La Vecchia[2,10], M. Law[11], F. Meyskens[12], P. M. Rothwell[13], H. J. Senn[14] & A. Umar[15]

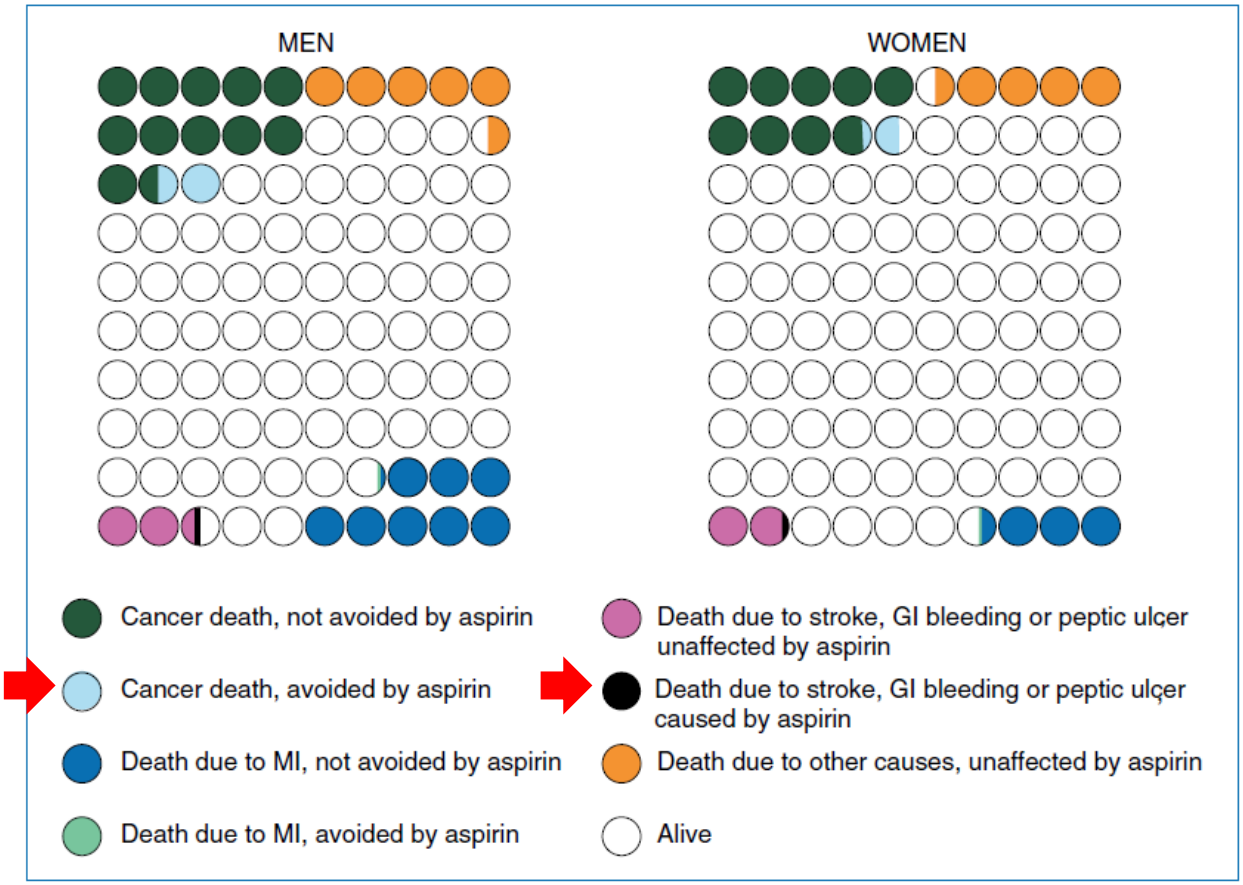


Figure 1. Cumulative effects of aspirin taken for 10 years starting at 55 years of age: on deaths over next 20 years in 100 average-risk men (A) and women (B).

Annals of Internal Medicine

CLINICAL GUIDELINE

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*

Table 1. Lifetime Events in 10 000 Men Taking Aspirin*

CVD Risk	Nonfatal MIs Prevented	Nonfatal Ischemic Strokes Prevented	CRC Cases Prevented	Serious GI Bleeding Events Caused	Hemorrhagic Strokes Caused	Net Life-Years Gained	QALYs Gained
Aged 50-59 y							
10%	225	84	139	284	23	333	588
15%	267	86	121	260	28	395	644
20%	286	92	122	248	21	605	834
Aged 60-69 y							
10%	159	66	112	314	31	−20	180
15%	186	80	104	298	24	96	309
20%	201	84	91	267	27	116	318

CRC = colorectal cancer; CVD = cardiovascular disease; GI = gastrointestinal; MI = myocardial infarction; QALY = quality-adjusted life-year.
* A complete set of results are available in the decision analysis report (28).

Annals of Internal Medicine

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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*

Table 2. Lifetime Events in 10 000 Women Taking Aspirin*

CVD Risk	Nonfatal MIs Prevented	Nonfatal Ischemic Strokes Prevented	CRC Cases Prevented	Serious GI Bleeding Events Caused	Hemorrhagic Strokes Caused	Net Life-Years Gained	QALYs Gained
Aged 50-59 y							
10%	148	137	139	209	35	219	621
15%	150	143	135	200	34	334	716
20%	152	144	132	184	29	463	833
Aged 60-69 y							
10%	101	116	105	230	32	−12	284
15%	110	129	93	216	34	17	324
20%	111	130	97	217	33	48	360

CRC = colorectal cancer; CVD = cardiovascular disease; GI = gastrointestinal; MI = myocardial infarction; QALY = quality-adjusted life-year.
* A complete set of results are available in the decision analysis report (28).

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Population	Adults aged 50 to 59 y with a ≥10% 10-y CVD risk	Adults aged 60 to 69 y with a ≥10% 10-y CVD risk	Adults younger than 50 y	Adults aged 70 y or older
Recommendation	Initiate low-dose aspirin use. Grade: B	The decision to initiate low-dose aspirin use is an individual one. Grade: C	No recommendation. Grade: I (insufficient evidence)	No recommendation. Grade: I (insufficient evidence)

Risk Assessment	Primary risk factors for CVD are older age, male sex, race/ethnicity, abnormal lipid levels, high blood pressure, diabetes, and smoking. Risk factors for GI bleeding with aspirin use include higher aspirin dose and longer duration of use, history of GI ulcers or upper GI pain, bleeding disorders, renal failure, severe liver disease, and thrombocytopenia. The USPSTF used a calculator derived from the ACC/AHA pooled cohort equations to predict 10-y risk for first atherosclerotic CVD event.			
Preventive Medication	Aspirin's anticlotting effect is useful for primary and secondary CVD prevention because it potentially decreases the accumulation of blood clots that form as a result of reduced blood flow at atherosclerotic plaques, thereby reducing hypoxic damage to heart and brain tissue. The mechanisms for inhibition of adenoma or colorectal cancer development are not yet well-understood but may result from aspirin's anti-inflammatory properties.			
Treatment and Dosage	A reasonable approach consistent with the evidence is to prescribe 81 mg/d (the most commonly prescribed dose in the United States), and assess CVD and bleeding risk factors starting at age 50 y and periodically thereafter, as well as when CVD and bleeding risk factors are first detected or change.			
Balance of Benefits and Harms	The benefits of aspirin use outweigh the increased risk for bleeding by a moderate amount.	The benefits of aspirin use outweigh the increased risk for bleeding by a small amount.	The evidence on aspirin use is insufficient and the balance of benefits and harms cannot be determined.	The evidence on aspirin use is insufficient and the balance of benefits and harms cannot be determined.

Ann Intern Med. 2016;164:836-845.

Question 1

Aspirin chemoprevention in the context of cancer screening

Adjunct or Substitute for Screening?

Outcome	Procedure	RR [95% CI]	Author
Mortality	Fecal occult blood testing	**0.84** [95% CI, 0.78–0.90]	*Hewitson P et al 2008*
		0.68 [95% CI, 0.56–0.82]	*Shaukat A et al 2013*
	Sigmoidoscopy screening	**0.72** [95% CI, 0.65–0.80]	*Elmunzer BJ et al 2012*
	Complete screening	**0.50** [95% CI, 0.35–0.64]	*Elmunzer BJ et al 2012*
	Colonoscopy with polypectomy	**0.47** (95% CI, 0.26–0.80)	*Winawer SJ et al 2009*
Incidence	Fecal occult blood testing	**0.80** [95% CI, 0.70–0.90]	*Mandel JS et al 2000*
	Sigmoidoscopy screening	**0.82** [95% CI, 0.73–0.91]	*Elmunzer BJ et al 2012*
	Complete screening	**0.68** [95% CI, 0.47–0.89]	*Elmunzer BJ et al 2012*

Chan AT, Ladabaum U Gastroenterology 2016

JAMA Oncol. doi:10.1001/jamaoncol.2015.6396
Published online March 3, 2016.

Original Investigation

Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer

Yin Cao, MPH, ScD; Reiko Nishihara, PhD; Kana Wu, MD, PhD; Molin Wang, PhD; Shuji Ogino, MD, PhD; Walter C. Willett, MD, DrPH; Donna Spiegelman, ScD; Charles S. Fuchs, MD, MPH; Edward L. Giovannucci, MD, MPH, ScD; Andrew T. Chan, MD, MPH

Nurses' Health Study (1980-2010), Health Professionals Follow-up Study (1986-2012)
(n=135 965 underwent follow-up for as long as 32 years)
ASA lowers the incidence of gastrointestinal tract cancers (**RR, 0.85; 95%CI, 0.80-0.91**)

Among subjects older than 50 years, regular aspirin could prevent:

33 colorectal cancers / 100 000 person-years (PAR 17.0%)
among those who had not undergone a lower endoscopy

18 colorectal cancers / 100 000 person-years (PAR 8.5%)
among those who had

CONCLUSIONS AND RELEVANCE Long-term aspirin use was associated with a modest but significantly reduced risk for overall cancer, especially gastrointestinal tract tumors. Regular aspirin use may prevent a substantial proportion of colorectal cancers and complement the benefits of screening.

Question 2

The mechanism

Question 2

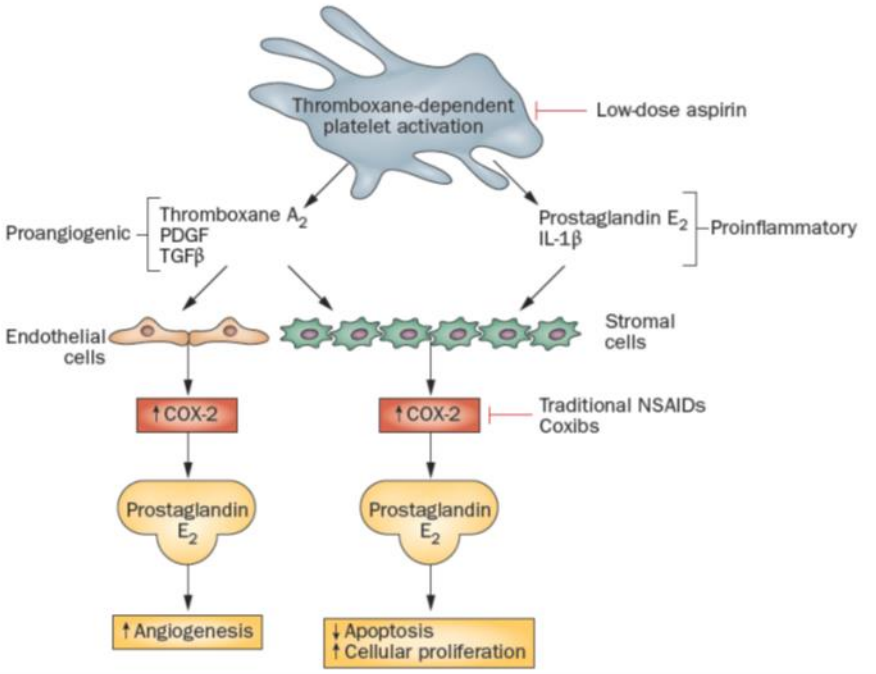
The mechanism

Cancer prevention at low doses (75-300 mg);

Dosing at 24h seems to be adequate;

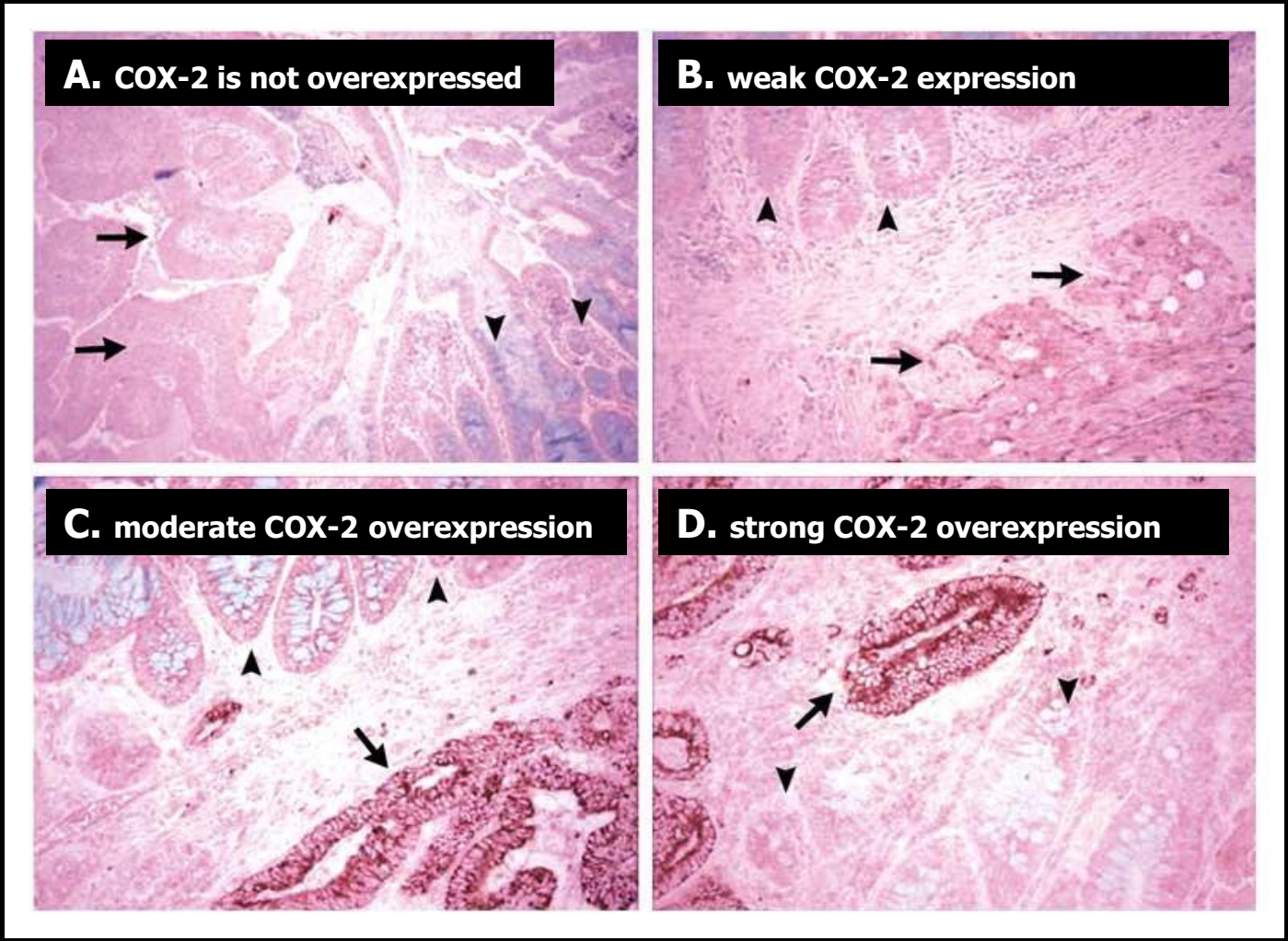
Clear reduction in colon cancer mortality with controlled release formulation (75 mg)

Features not compatible with a direct effect of ASA on COX-2



Thun MJ, Jacobs EJ, Patrono C *Nature Reviews* 2012

Aspirin use associated with reduced risk of CRC that overexpresses COX-2 (PTGS2)



Chan AT et al. N Engl J Med 2007;356:2131-2142.

Aspirin use associated with reduced risk of CRC that overexpresses COX-2 (PTGS2)

Table 2. Relative Risk of Colorectal Cancer in Relation to COX-2 Expression and Regular Aspirin Use.*

Variable	Women		Men		Total†	
	Nonregular Users of Aspirin	Regular Users of Aspirin	Nonregular Users of Aspirin	Regular Users of Aspirin	Nonregular Users of Aspirin	Regular Users of Aspirin
All colorectal cancer						
No. of cases/no. of person-yr	225/1,037,122	143/704,361	161/402,337	107/302,612	386/1,439,458	250/1,006,973
Age-adjusted relative risk (95% CI)	1.0	0.80 (0.65–0.99)	1.0	0.72 (0.56–0.92)	1.0	0.76 (0.65–0.89)
Multivariate relative risk (95% CI)‡	1.0	0.80 (0.65–0.99)	1.0	0.67 (0.52–0.86)	1.0	0.73 (0.62–0.86)
COX-2–positive cancer§						
No. of cases/no. of person-yr	154/1,037,181	88/704,404	117/402,372	64/302,652	271/1,439,553	152/1,007,056
Age-adjusted relative risk (95% CI)	1.0	0.72 (0.55–0.94)	1.0	0.59 (0.44–0.81)	1.0	0.66 (0.54–0.81)
Multivariate relative risk (95% CI)‡	1.0	0.72 (0.56–0.94)	1.0	0.56 (0.41–0.76)	1.0	0.64 (0.52–0.78)¶
COX-2–negative cancer‖						
No. of cases/no. of person-yr	71/1,037,259	55/704,435	44/402,442	43/302,668	115/1,439,702	98/1,007,104
Age-adjusted relative risk (95% CI)	1.0	0.98 (0.69–1.39)	1.0	1.04 (0.68–1.59)	1.0	0.99 (0.76–1.30)
Multivariate relative risk (95% CI)‡	1.0	0.98 (0.69–1.40)	1.0	0.97 (0.63–1.49)	1.0	0.96 (0.73–1.26)¶

* The women were participants in the Nurses' Health Study (NHS)[19,20] enrolled in 1980 and followed until 2002. The men were participants in the Health Professionals Follow-up Study (HPFS)[18] enrolled in 1986 and followed until 2002. In the NHS, regular aspirin use was based on previously described categorization as the consumption of at least two 325-mg tablets per week. Nonregular use was defined as the consumption of fewer than two tablets per week. In the HPFS, regular aspirin use was based on previously described categorization as the consumption of aspirin at least two times per week. Nonregular use was defined as the consumption of aspirin fewer than two times per week. Relative risks are for regular users as compared with nonregular users.

† Pooled data are from NHS and HPFS (P=0.33 with the use of Cochran's Q test for heterogeneity).

‡ Multivariate relative risks are adjusted for age, sex, smoking before 30 years of age (0 pack-years, 1 to 4 pack-years, 5 to 10 pack-years, 11 to 15 pack-years, or >15 pack-years); body-mass index (in quintiles); regular vigorous exercise (in quintiles of metabolic equivalent [MET] task score per week); colorectal cancer in a parent or sibling (yes or no); previous endoscopy (yes or no); history of polyps (yes or no); current multivitamin use (yes or no); consumption of beef, pork, or lamb as a main dish (0 to 3 times per month, once a week, 2 to 4 times per week, or ≥5 times per week); alcohol consumption (0 g, 0.1 to 4.9 g, 5.0 to 14.9 g, or ≥15.0 g per day); and energy-adjusted folate and calcium intake (in quintiles). For the analyses restricted to women, the multivariate models were also adjusted for postmenopausal hormone-replacement therapy (premenopausal women and postmenopausal women who never used, formerly used, or were currently using hormone-replacement therapy) and did not include sex. For the analyses restricted to men, the multivariate models did not include sex.

§ Cancers with immunohistochemical COX-2 staining of moderate to strong intensity are classified as COX-2–positive cancers.

¶ The P value for heterogeneity of the association of regular aspirin use with COX-2–positive cancer and of regular aspirin use with COX-2– negative cancer is 0.02 (χ^2=5.7, 1 degree of freedom).

‖ Cancers with no immunohistochemical COX-2 staining or with staining of weak intensity are classified as COX-2–negative cancers.

60–85% of CRCs over express COX-2

Chan AT et al. N Engl J Med 2007;356:2131-2142.

The NEW ENGLAND JOURNAL of MEDICINE

Aspirin use associated with reduced mortality in patients with PIK3CA-mutant cancers

ORIGINAL ARTICLE

Aspirin Use, Tumor *PIK3CA* Mutation, and Colorectal-Cancer Survival

Xiaoyun Liao, M.D., Ph.D., Paul Lochhead, M.B., Ch.B., Reiko Nishihara, Ph.D., Teppei Morikawa, M.D., Ph.D., Aya Kuchiba, Ph.D., Mai Yamauchi, Ph.D., Yu Imamura, M.D., Ph.D., Zhi Rong Qian, M.D., Ph.D., Yoshifumi Baba, M.D., Ph.D., Kaori Shima, D.D.S., Ph.D., Ruifang Sun, M.B., Katsuhiko Nosho, M.D., Ph.D., Jeffrey A. Meyerhardt, M.D., M.P.H., Edward Giovannucci, M.D., M.P.H., Sc.D., Charles S. Fuchs, M.D., M.P.H., Andrew T. Chan, M.D., M.P.H., and Shuji Ogino, M.D., Ph.D.

Mutations in **PIK3CA** (catalytic subunit alpha polypeptide inducing COX-2 overexpression) are present in 15 to 20% of colorectal cancers.

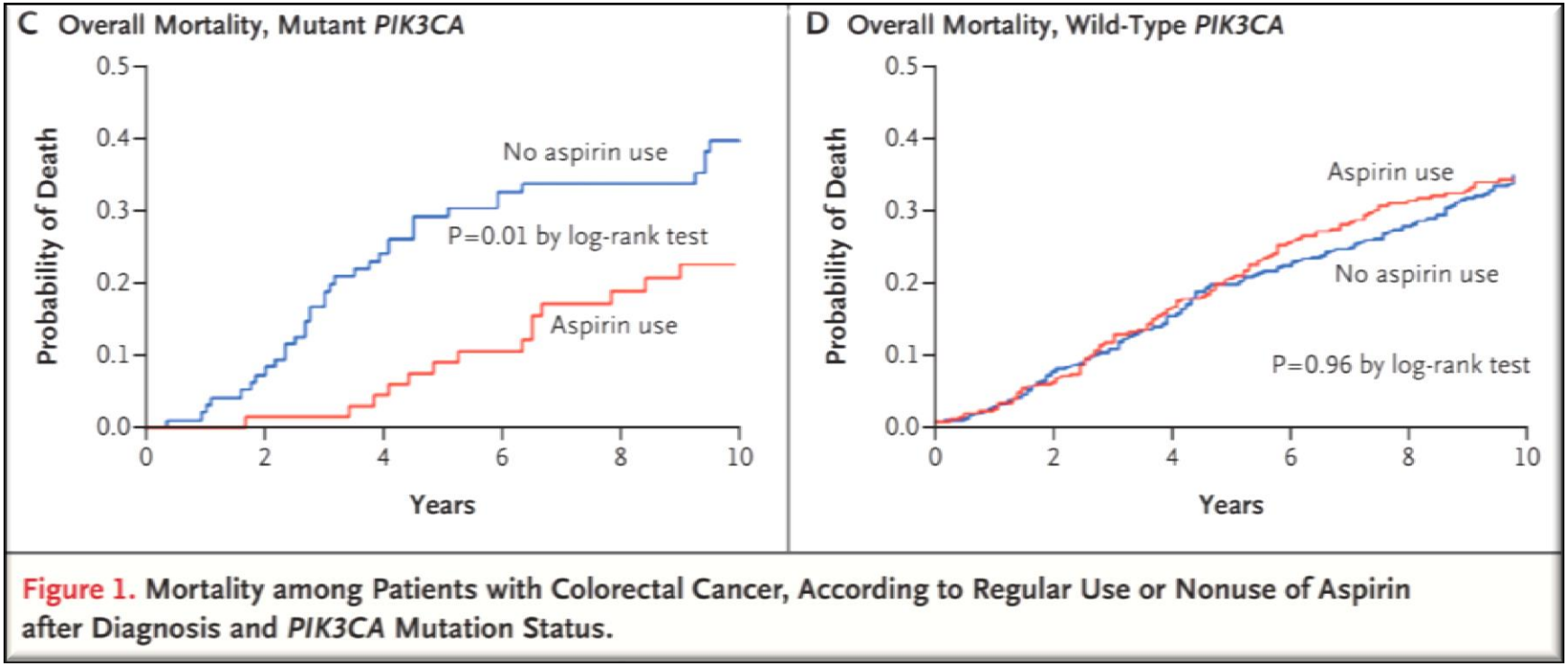


Figure 1. Mortality among Patients with Colorectal Cancer, According to Regular Use or Nonuse of Aspirin after Diagnosis and *PIK3CA* Mutation Status.

N Engl J Med 2012;367:1596-606.

Conclusion

1. Benefit of low-dose aspirin therapy is clear for the secondary prevention of CVD. However, aspirin therapy is underused for reasons not yet understood; aspirin withdrawal for emergency surgery;

2. For the primary prevention, Aspirin may be a potential low-cost alternative to endoscopic CRC screening in resource-limited settings or a complement in settings in which such programs are already implemented (screening adherence remains suboptimal).

3. Cost-effectiveness analyses: advances in genetic and molecular biomarkers as a basis for a precision medicine–based approach to disease prevention may be helpful (PIK3CA mutation - 15–20% of CRC - is now a potential biomarker of aspirin efficacy)

Conclusion

1. Benefit of low-dose aspirin therapy is clear for the secondary prevention of CVD. However, aspirin therapy is underused for reasons not yet understood; aspirin withdrawal for emergency surgery;

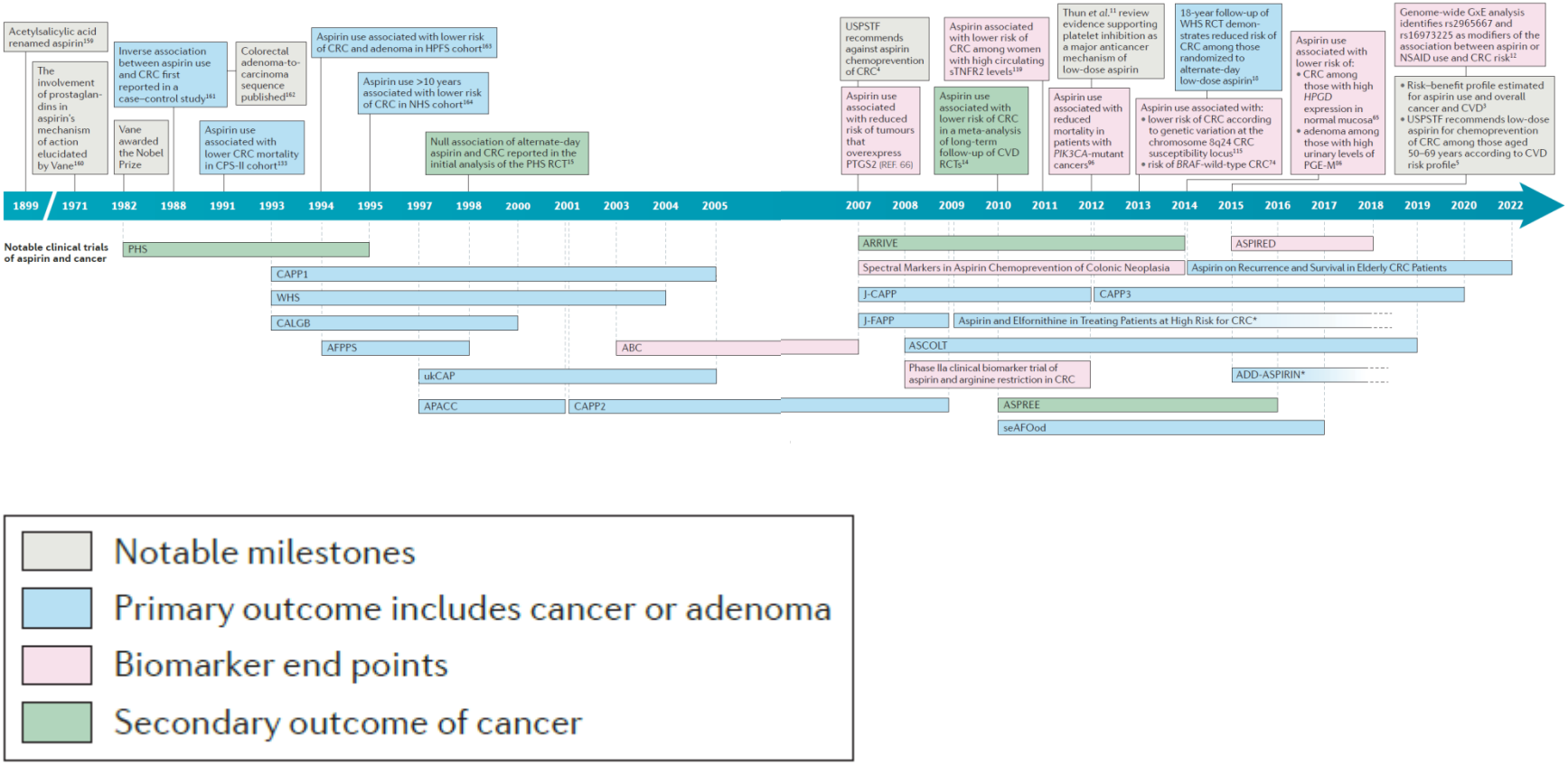
2. For the primary prevention, Aspirin may be a potential low-cost alternative to endoscopic CRC screening in resource-limited settings or a complement in settings in which such programs are already implemented (screening adherence remains suboptimal).

3. Cost-effectiveness analyses: advances in genetic and molecular biomarkers as a basis for a precision medicine–based approach to disease prevention may be helpful (PIK3CA mutation - 15–20% of CRC - is now a potential biomarker of aspirin efficacy)

The possibility to prevent serious cardiovascular events and colon cancer with a single, inexpensive pill makes low-dose aspirin therapy worth considering.

Il grande pubblico pensa che i libri, come le uova, guadagnino ad essere consumati freschi. E' per questa ragione che sceglie sempre le novità

Johann Wolfgang Goethe



Nature Reviews Cancer. 2016 Mar;16(3):173-86