Aspirin for Primary and Secondary Cardiovascular Prevention

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Advances in Cardiac Arrhythmias and Great Innovations in Cardiology

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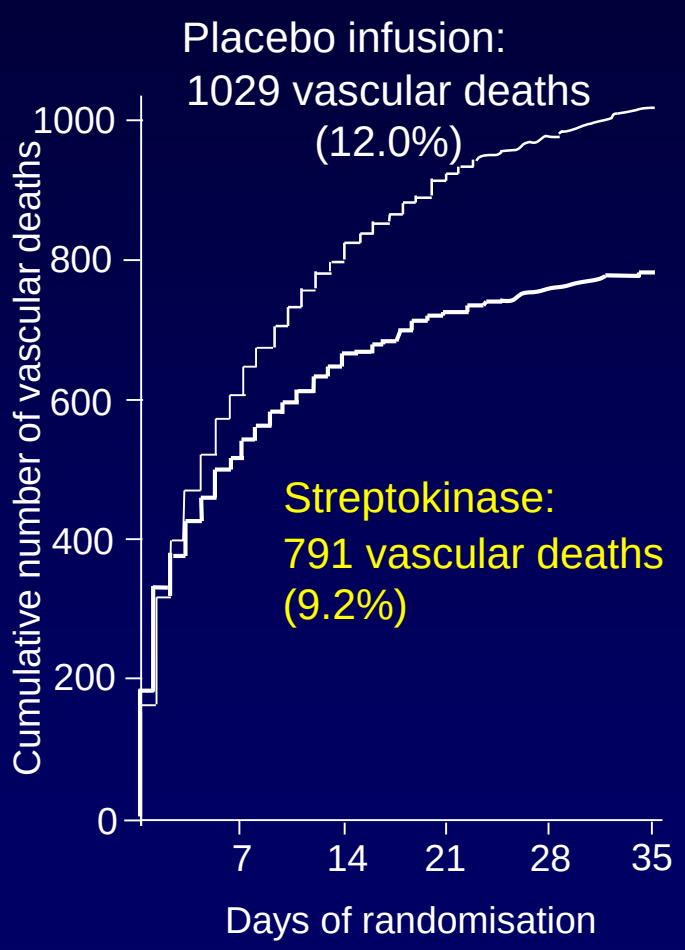
Disclosure

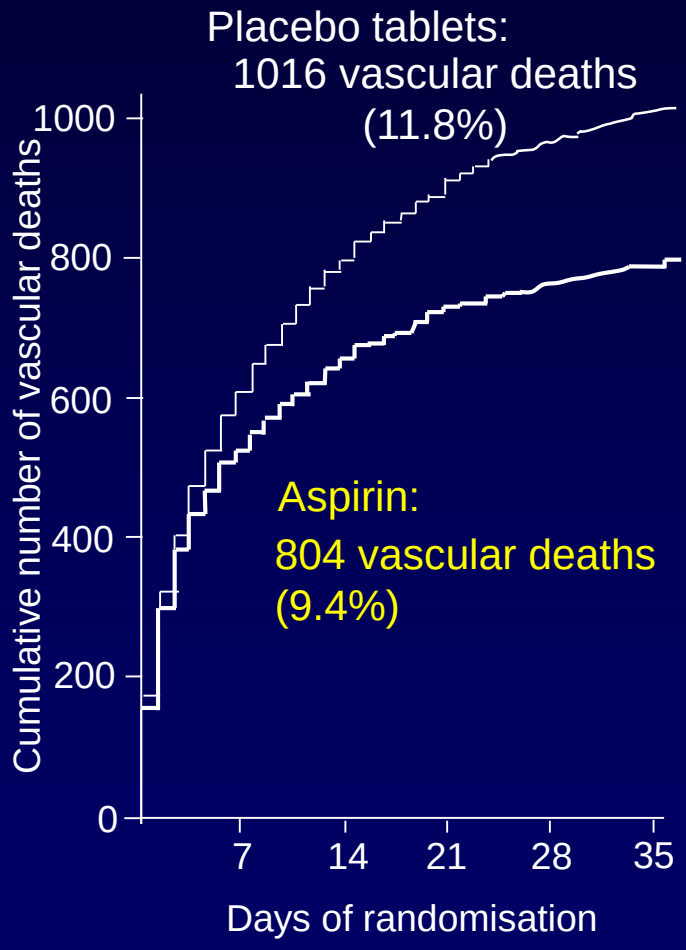
I am an unpaid member of the Scientific Advisory Board of the Aspirin Foundation.

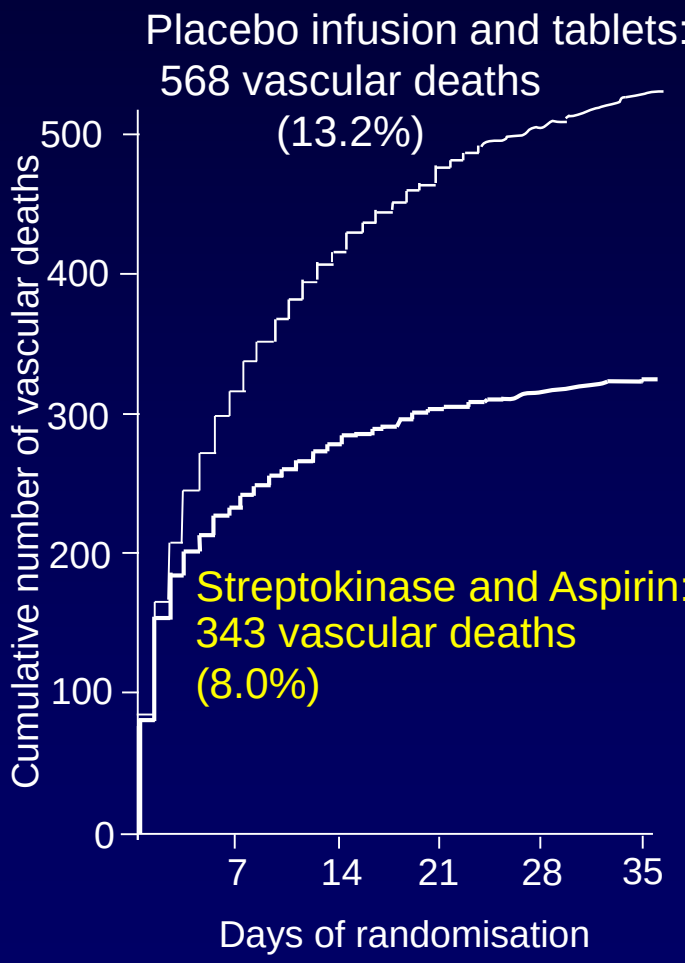
I have received grant support for investigator-initiated research from:

- European Commission, FP6 and FP7 Programmes
- Bayer AG

Randomised Trial of Intravenous Streptokinase, Oral Aspirin, Both, or Neither among 17187 Cases of Suspected Acute Myocardial Infarction: ISIS-2







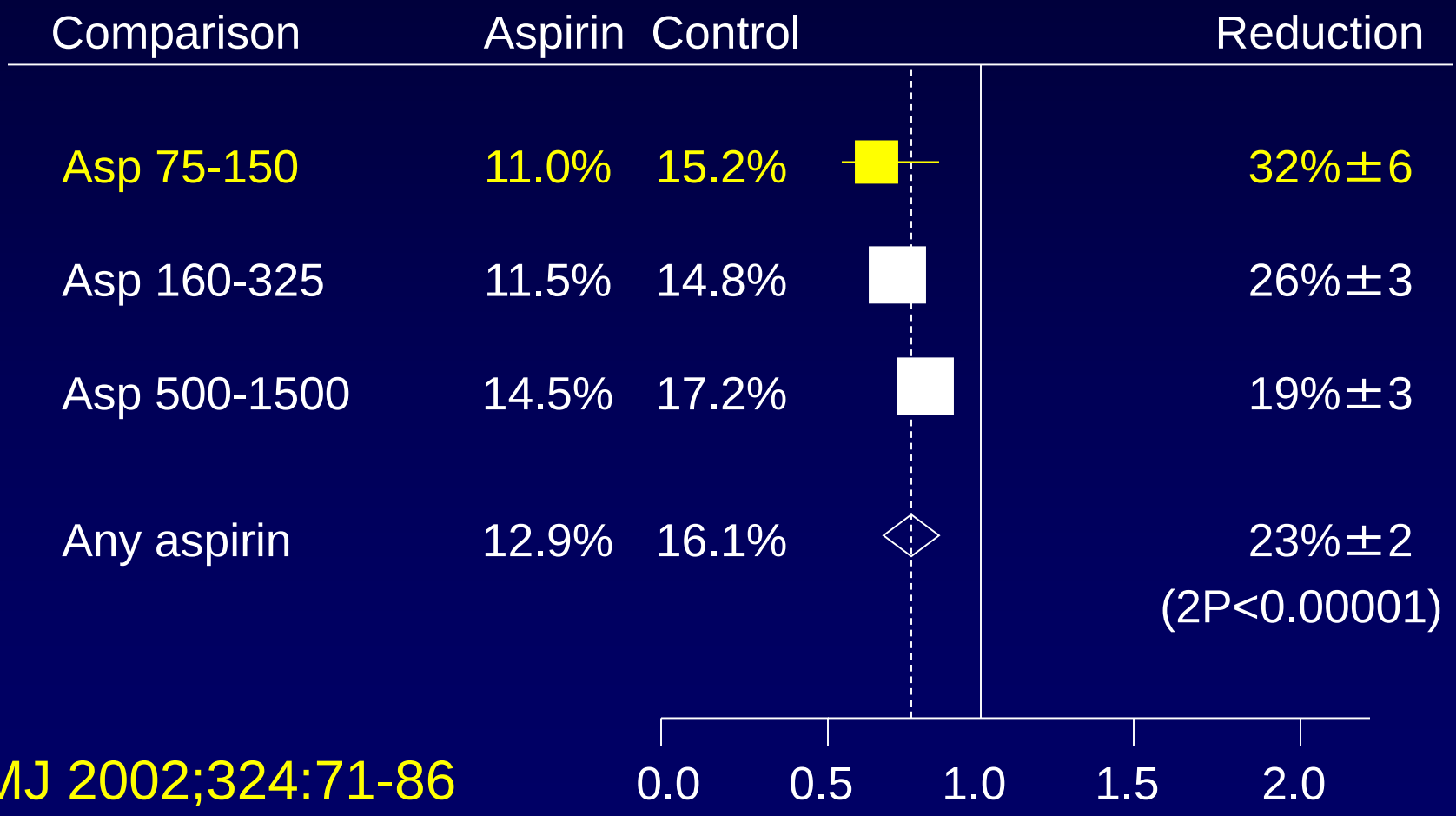
ISIS-2 Collaborative Group, Lancet 1988; II:349-360

Reduction in the Risk of Death or Acute MI in Placebo-Controlled Randomized Trials of Aspirin in Unstable Angina *

Trial	Daily Dose mg	Follow-up mo.	Risk Reduction %	P
Lewis et al, NEJM 1983	324	3	51	0.0005
Cairns et al, NEJM 1985	1300	18	51	0.008
RISC Group, Lancet 1990	75	3	64	0.0001

Patrono C, N Engl J Med 1994;330:1287-94

Antithrombotic Trialists' Collaboration
Meta-Analysis of Aspirin Trials in High-Risk Patients



BMJ 2002;324:71-86

European Heart Journal
doi:10.1093/eurheartj/ehv320

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

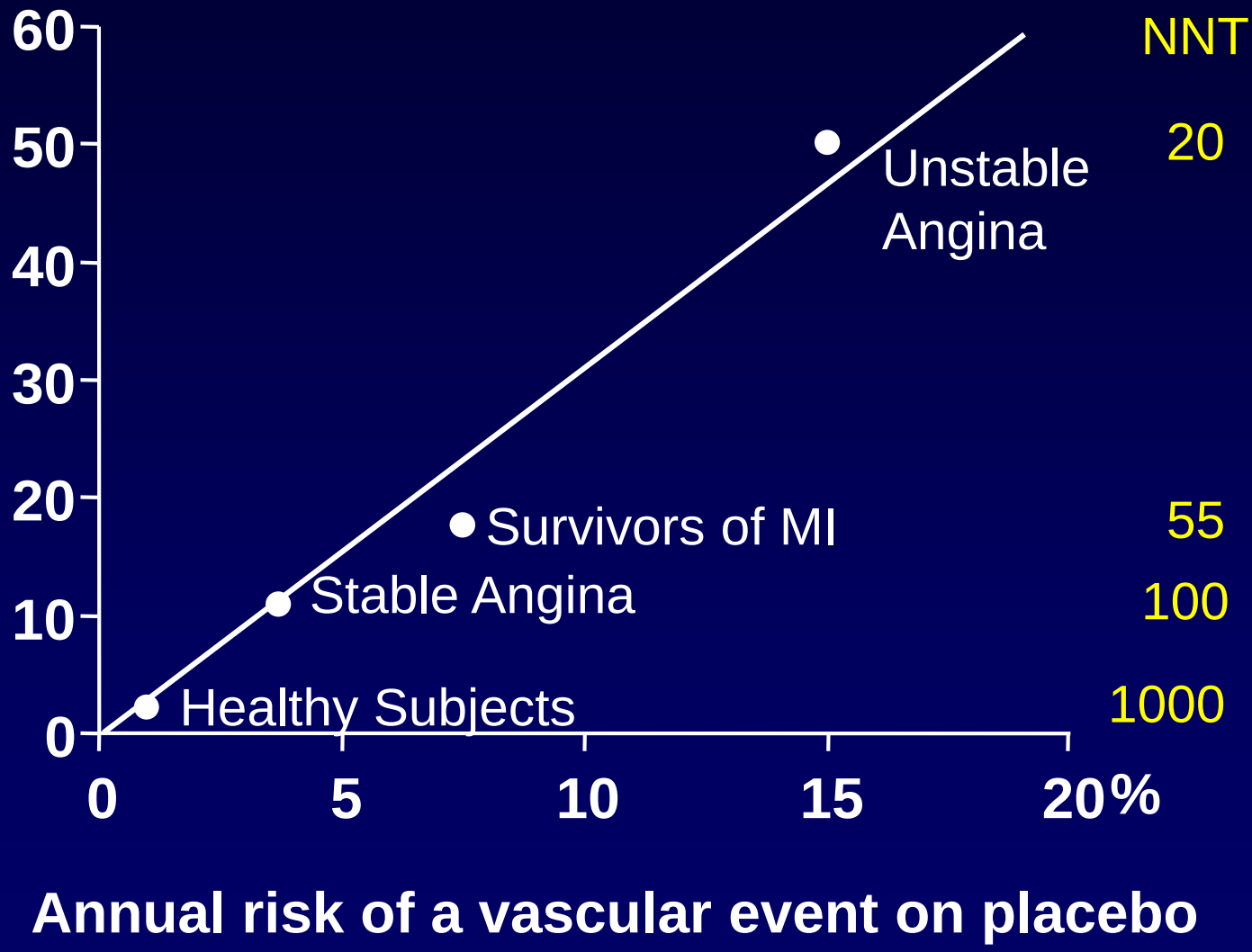
Authors/Task Force Members: Marco Roffi* (Chairperson) (Switzerland), Carlo Patrono* (Co-Chairperson) (Italy), Jean-Philippe Collet† (France), Christian Mueller† (Switzerland), Marco Valgimigli† (The Netherlands), Felicita Andreotti (Italy), Jeroen J. Bax (The Netherlands), Michael A. Borger (Germany), Carlos Brotons (Spain), Derek P. Chew (Australia), Baris Gencer (Switzerland), Gerd Hasenfuss (Germany), Keld Kjeldsen (Denmark), Patrizio Lancellotti (Belgium), Ulf Landmesser (Germany), Julinda Mehilli (Germany), Debabrata Mukherjee (USA), Robert F. Storey (UK), and Stephan Windecker (Switzerland)

Document Reviewers: Helmut Baumgartner (CPG Review Coordinator) (Germany), Oliver Gaemperli (CPG Review Coordinator) (Switzerland), Stephan Achenbach (Germany), Stefan Agewall (Norway), Lina Badimon (Spain),

Recommendations for platelet inhibition in NSTE-ACS		
Recommendations	Class[a]	Level[b]
Oral antiplatelet therapy		
Aspirin is recommended for all patients without contra-indications at an initial oral loading dose[c] of 150–300 mg (in aspirin-naïve patients) and a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications[d], for all patients at moderate- to high-risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[d]	I	B
• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B
$P2Y_{12}$ 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
It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.	III	B
Intravenous antiplatelet therapy		
GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications.	IIa	C
Cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI.	IIb	A
It is not recommended to administer GPIIb/IIIa inhibitors in patients in whom coronary anatomy is not known.	III	A

The Risk of Vascular Complications is the Major Determinant of the Absolute Benefit of Antiplatelet Therapy

Subjects in whom a vascular event is prevented by aspirin per 1,000 treated for 1 year

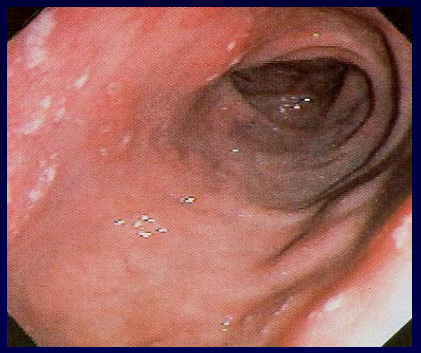


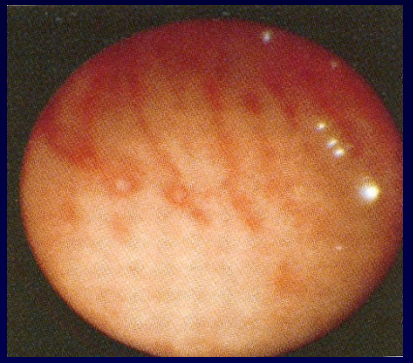
Patrono et al, Chest 2008;133:199S-233S

Gastrointestinal Lesions Induced by NSAIDs

1. Acute Mucosal Lesions:

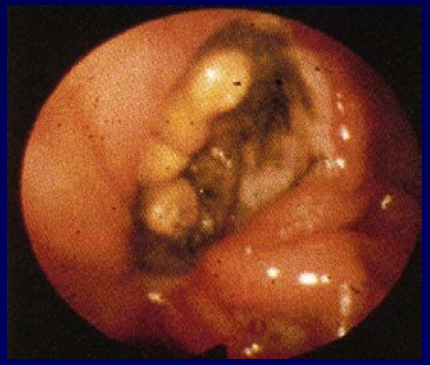
70-90% of patients

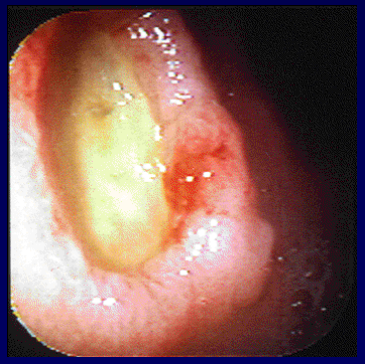




2. Chronic/Deep GD Ulcers

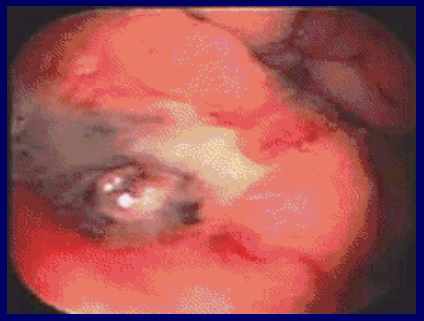
Endoscopic ulcers: 30-50% of patients
Symptomatic ulcers: <10% of patients

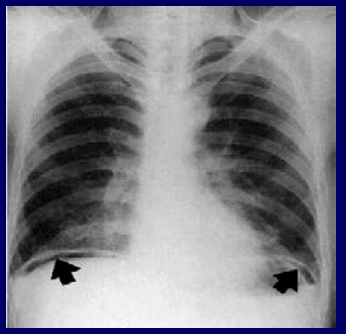




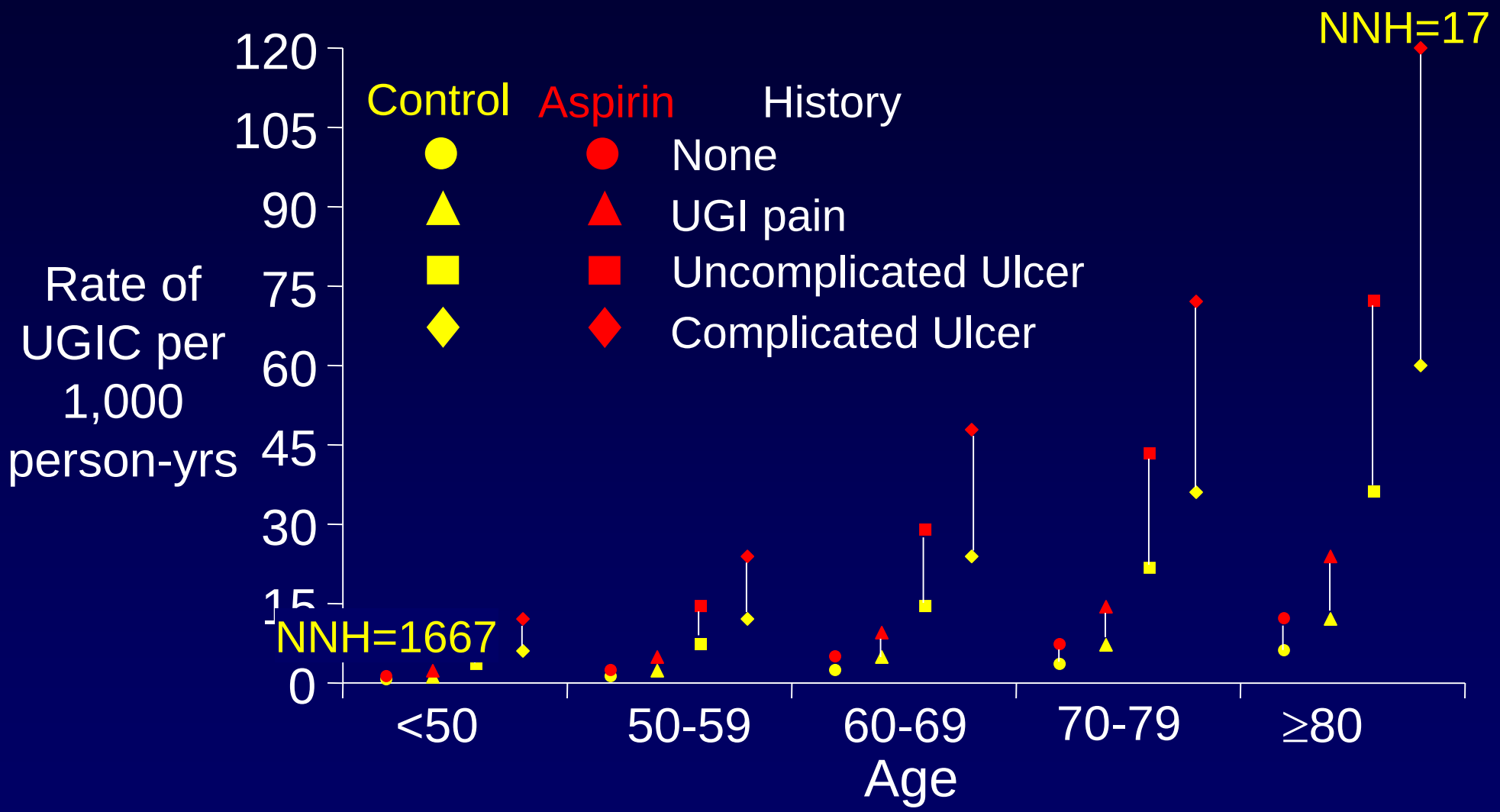
3. Complications:

1-2% of patients



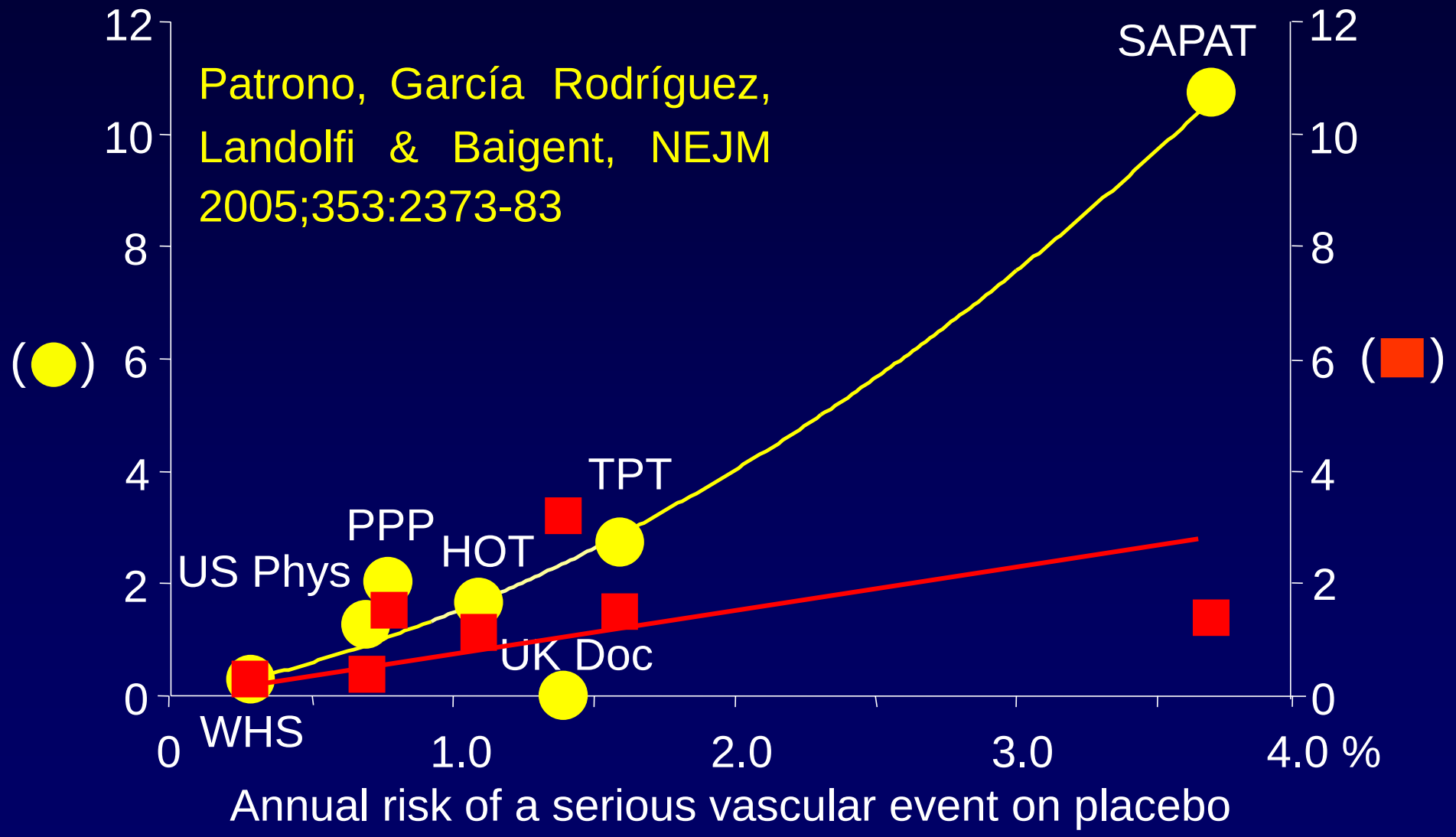


Estimates of UGIC Rates in Male Subjects, as a Function of Age, Prior History and Low-Dose Aspirin

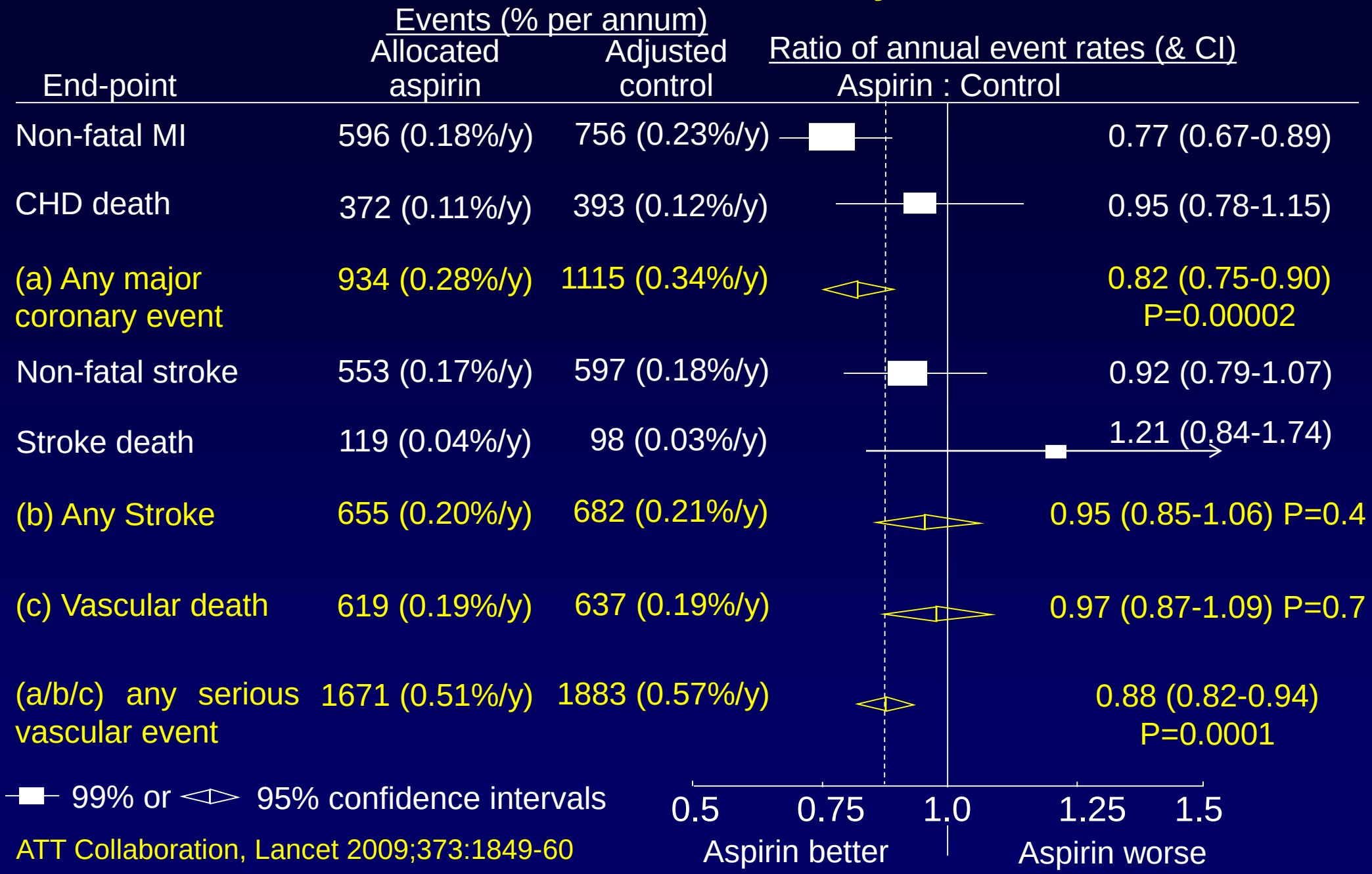


Patrono, García Rodríguez, Landolfi & Baigent, NEJM 2005; 353:2373-83

Vascular Events (●) Avoided vs Major Bleeds (■) Caused per 1,000 Treated with Aspirin per Year



Serious Vascular Events in Primary Prevention Trials



ATT Collaboration, Lancet 2009;373:1849-60

American College of Chest Physicians 2012 Guidelines

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).

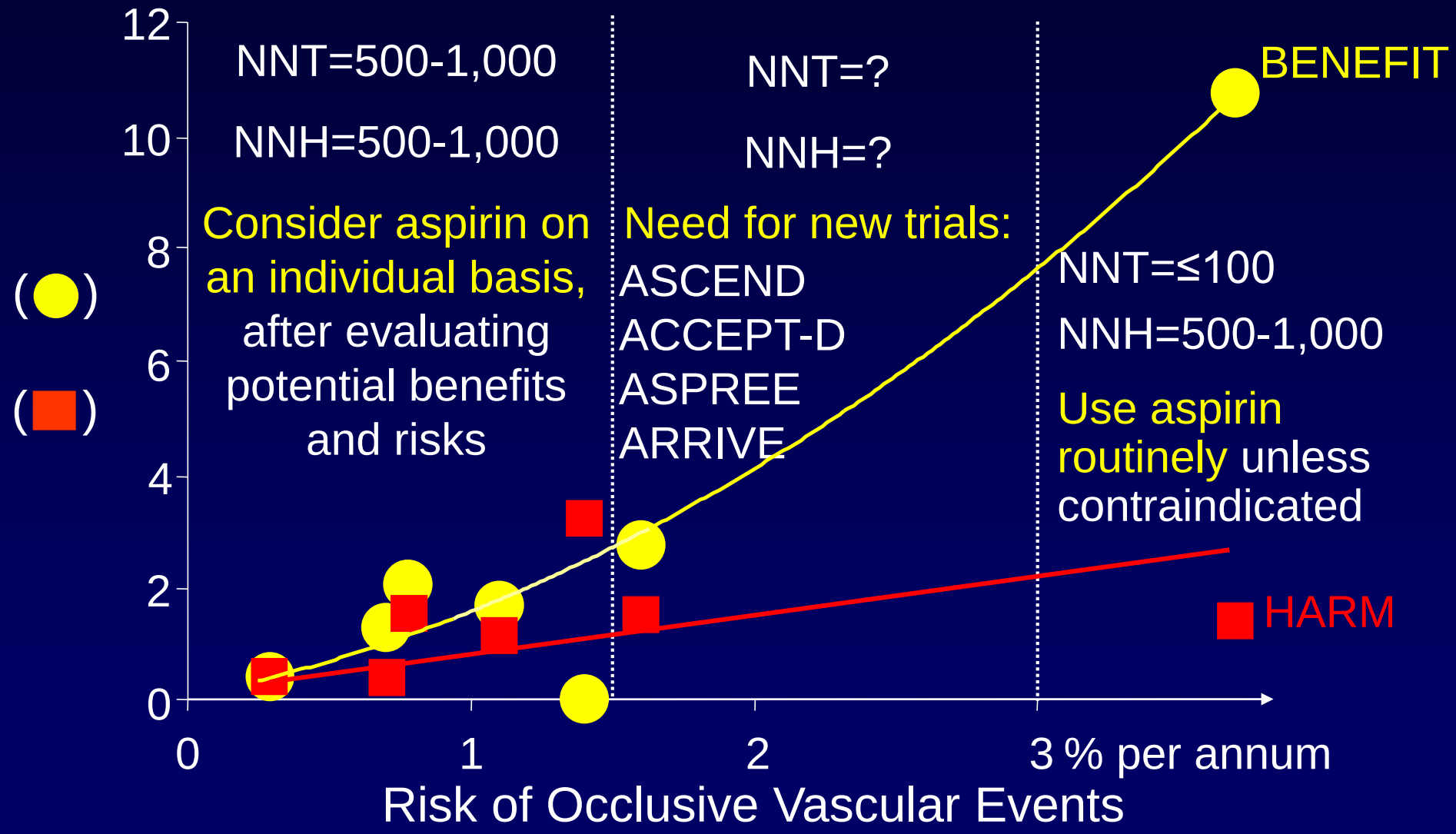
Vandvik et al, CHEST 2012; 141(Suppl):e637S–e668S

European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2012)

Aspirin cannot be recommended in primary prevention due to its increased risk of major bleeding (Grade IIIB).

Perk et al, Eur Heart J 2012; 33:1635-701

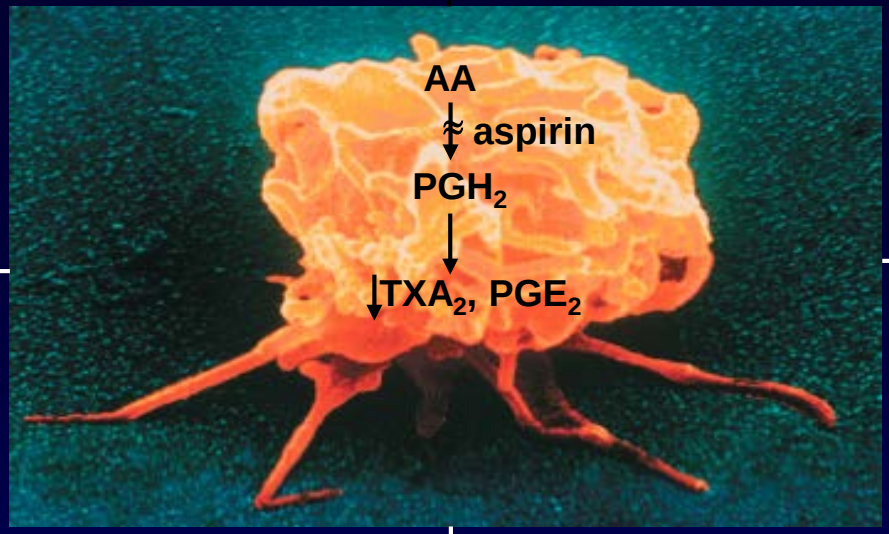
Vascular Events (●) Avoided vs Major Bleeds (■) Caused by Aspirin per 1,000 Treated per Year



Patrono, JACC 2015;66:74-85

Release of microparticles?

Patrono, JACC 2015;66:74-85



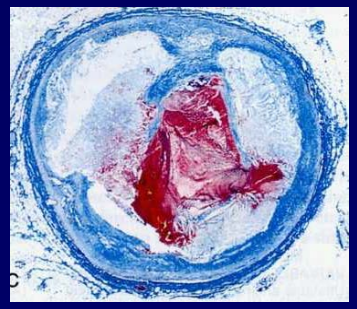
Platelet surface for clotting factors assembly

Release of pro-thrombotic prostanoids

Release of pro-inflammatory, mitogenic and pro-angiogenic autacoids

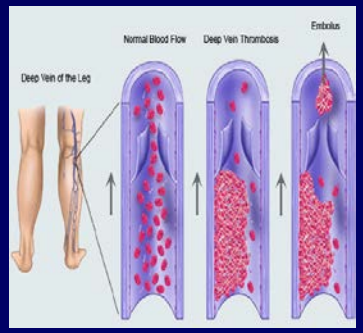
Coronary Atherothrombosis

- Evidence from >50 RCTs and meta-analyses



Venous Thromboembolism

- Evidence from several RCTs and meta-analyses

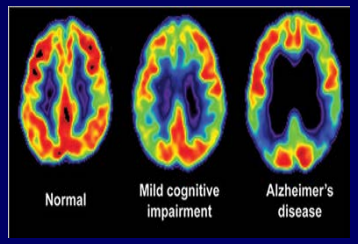


Colorectal Cancer

- Evidence from observational studies and meta-analyses
- Evidence from post-hoc long-term follow-up of RCTs and meta-analyses
- Currently being tested prospectively in primary prevention and adjuvant RCTs

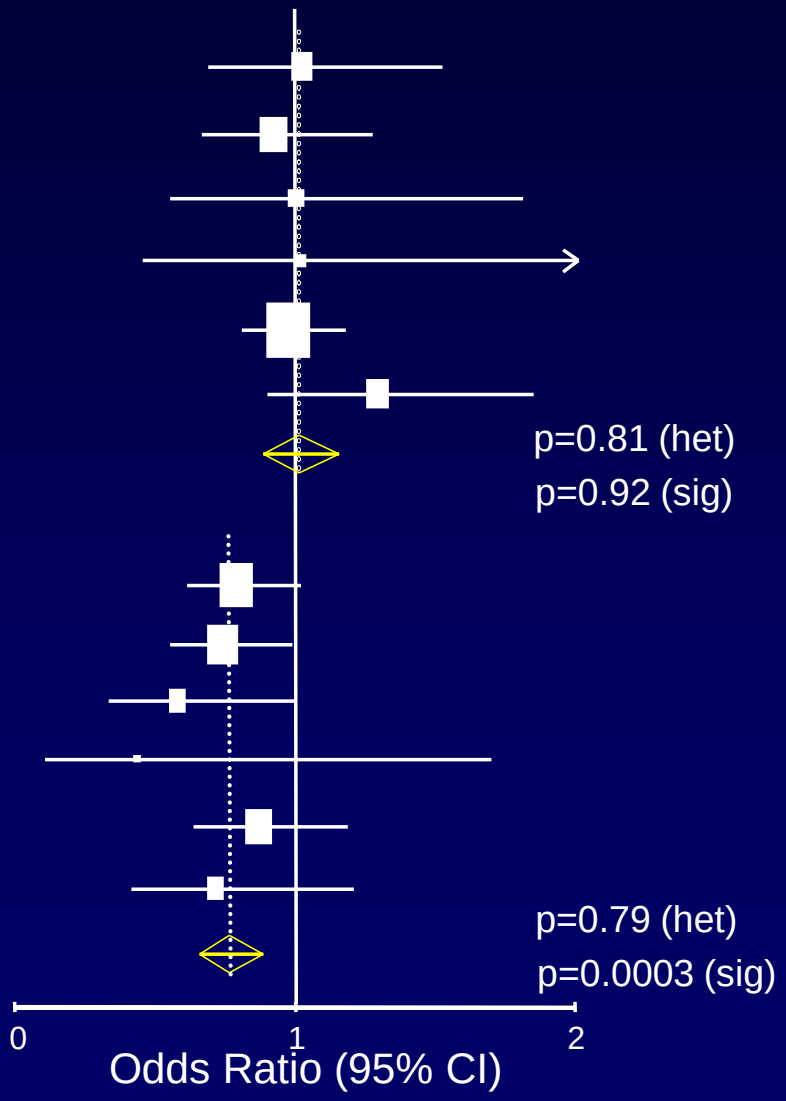
Cognitive Impairment

- Limited evidence from observational studies
- Currently being tested in the ASPREE primary preventional trial



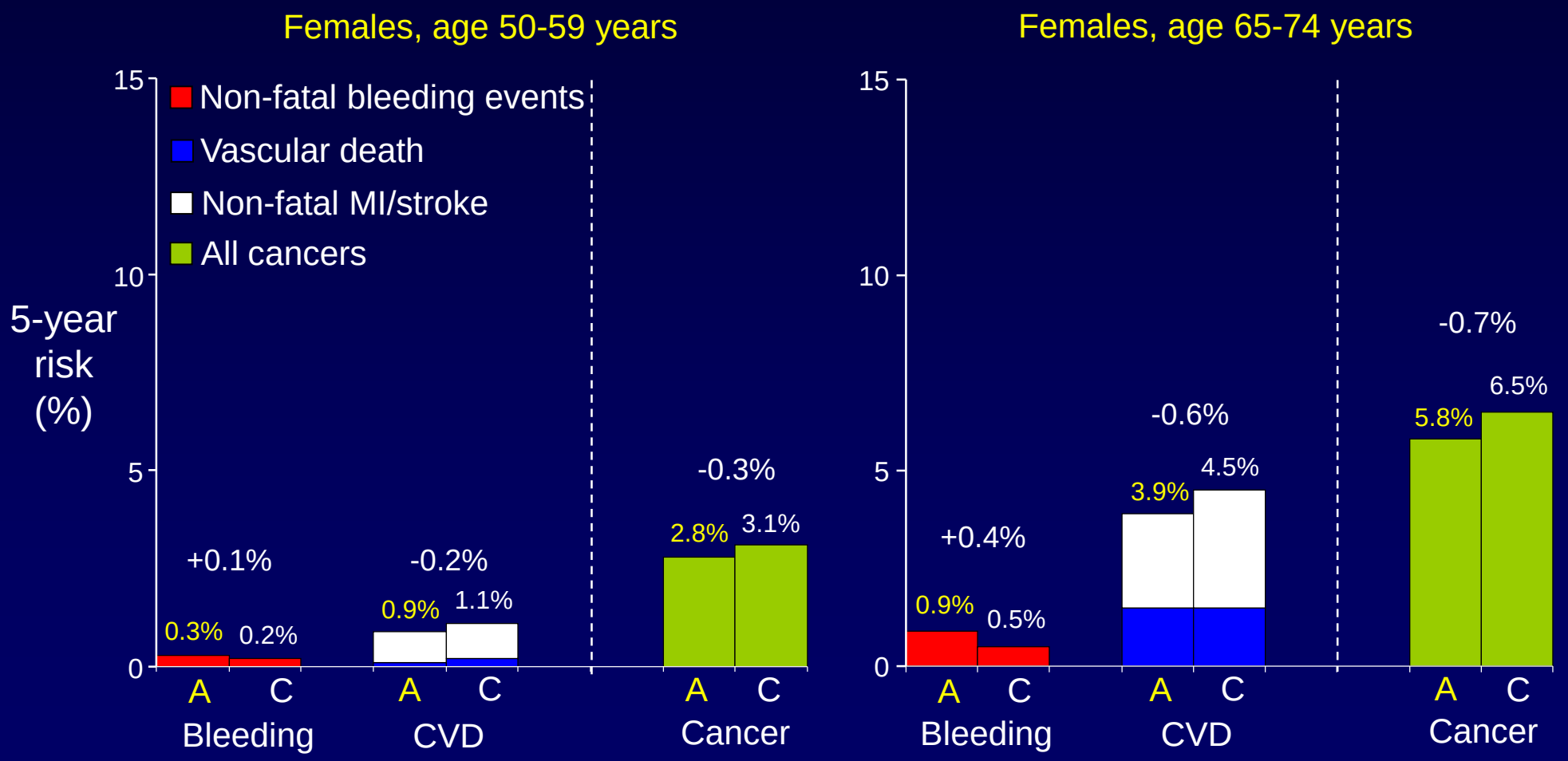
Cancer Incidence During Six Randomised Trials of Daily Low-Dose Aspirin in Primary Prevention of Vascular Events

Trial Follow-up	Events/Subjects		Odds	95%CI
	Aspirin	Control	Ratio	
0-2.9 years				
AAA	50/1675	49/1675	1.02	0.68-1.52
TPT	72/2545	78/2540	0.92	0.66-1.27
POPADAD	23/638	23/638	1.00	0.56-1.80
JPAD	12/1262	12/1277	1.01	0.45-2.26
HOT	219/9399	255/9391	0.97	0.81-1.17
PPP	69/2226	55/2269	1.29	0.90-1.84
TOTAL	445/17745	442/17790	1.01	0.88-1.15
≥3 years				
AAA	116/1593	145/1599	0.79	0.61-1.02
TPT	84/2431	112/2433	0.74	0.56-0.99
POPADAD	22/532	37/593	0.58	0.34-1.00
JPAD	3/1095	7/1117	0.44	0.11-1.69
HOT	75/9063	86/9029	0.87	0.64-1.18
PPP	24/1689	34/1713	0.71	0.42-1.21
TOTAL	324/16463	421/16484	0.76	0.66-0.88



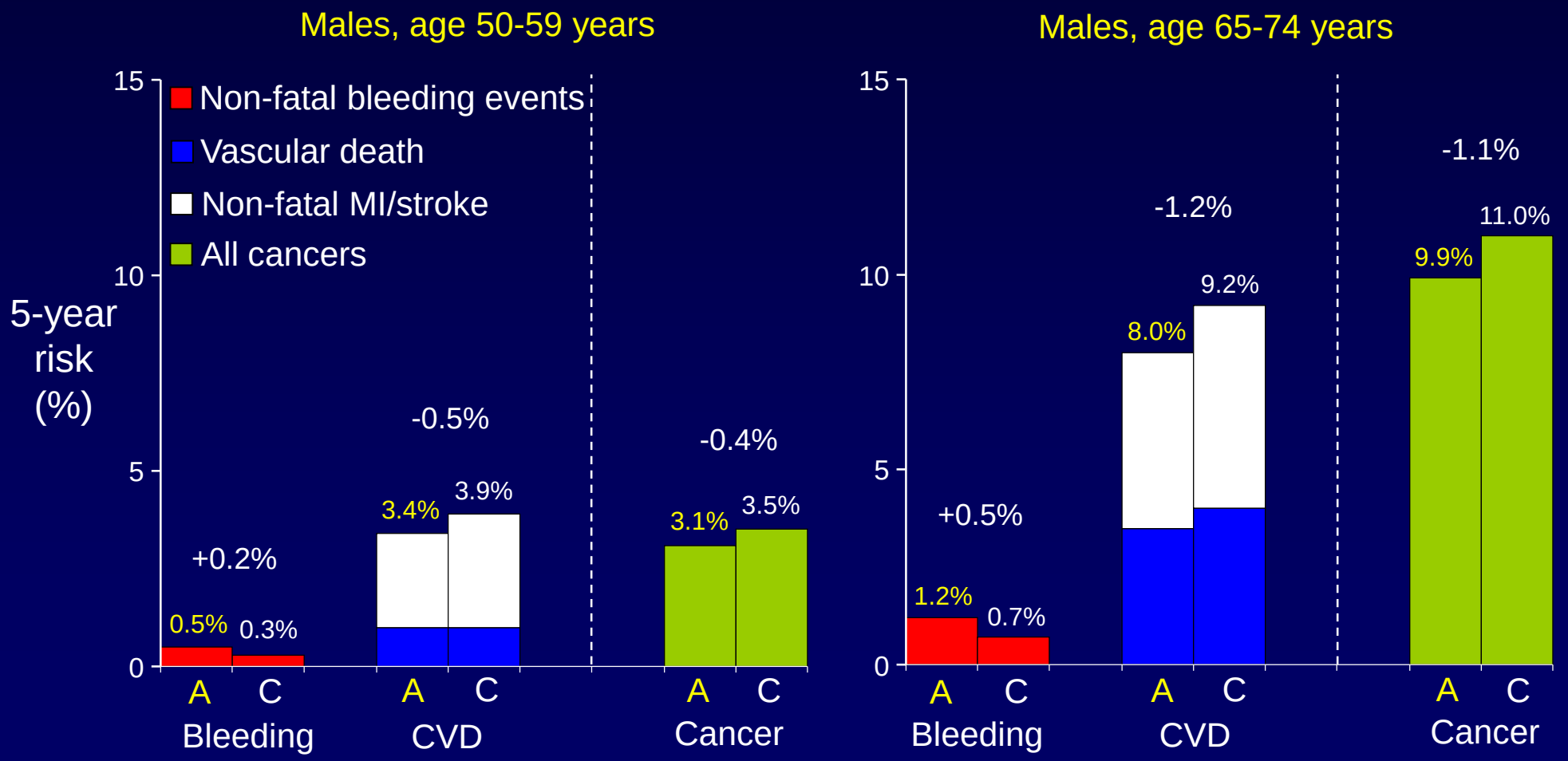
Rothwell et al, Lancet 2012;379:1602–1612

Five-Year Risk of Vascular Events and Major Bleeding Based on Primary Prevention Trials of Aspirin *vs* Placebo, and Hypothetical 10% Reduction in Cancer Incidence by Age and Sex



Thun, Jacobs, Patrono *Nature Rev Clin Oncol* 2012;9:259-67

Five-Year Risk of Vascular Events and Major Bleeding Based on Primary Prevention Trials of Aspirin *vs* Placebo, and Hypothetical 10% Reduction in Cancer Incidence by Age and Sex



Thun, Jacobs, Patrono *Nature Rev Clin Oncol* 2012;9:259-67

Draft Recommendation Statement
Aspirin to Prevent Cardiovascular Disease and Cancer

Population	Recommendation	Grade
Adults ages 50 to 59 years	The USPSTF recommends low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in adults ages 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
Adults ages 60 to 69 years	The decision to use low-dose aspirin to prevent CVD and colorectal cancer in adults ages 60 to 69 years who have a greater than 10% 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 use low-dose aspirin.	C

U.S. Preventive Services Task Force, September 15, 2015

Ongoing Randomised Trials of Aspirin vs Placebo: Low-Risk Individuals

Study	Regimen(s)	Treatment duration	N	Eligibility	Primary endpoint	Estimated total of all cancers		End date
						≤5 years	>5 years	
ACCEPT-D	A100 vs open control; simvastatin for all	5 y	5170	Diabetes, no CVD	CV death, non-fatal stroke, nonfatal MI, other CV hospitalisation	~300	-	2015
ARRIVE	A100 enteric coated vs P	5y	12,000	10-20% estimated 10y risk of CHD	MI, stroke, CV death, unstable angina, TIA	~800	-	2016
ASPREE	A100 vs P	5 y	19,000	Elderly, no diabetes or CVD	Death, dementia or significant disability	~1000	-	2017
ASCEND	A100 vs P (ω3FA vs P)	7.5 y	15,000	Diabetes, no CVD	MI, stroke or TIA, or CV death	~900	~500 in trial, then registry)	2018

Patrono, JACC 2015;66:74-85

Ongoing Randomised Trials of Aspirin vs Placebo: High-Risk Cancer Patients

Study	Regimen(s)	Treatment duration	N	Eligibility	Primary endpoint	Estimated total of all cancers		End date
						≤5 years	>5 years	
AspECT	A300 vs P	8 y	2500	Barrett's oesophagus	Death/adeno-carcinoma or high-grade metaplasia	~120	~100	2017
seAFOod	A300 vs P (EPA vs P)	1 y	904	Multiple adenomas at BCSP	≥1 adenoma at 1 year screen	<10	-	NA
ASCOLT	A200 vs P	3y	2660	Dukes C or high-risk Dukes B cancer	3 year disease-free survival	900	-	NA
ADD-Aspirin	A100 vs A300 vs P	5y	~9,920	CRC, breast, gastro-oesophageal, prostate ca	Disease-free survival (death for gastro-oesophageal)	3400	>1000	2025

Abbreviations: BCSP = Bowel Cancer Screening Programme; CRC = colorectal cancer

Patrono, JACC 2015;66:74-85

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Bianca Rocca

Alessandro Sgambato

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Michael Thun

Eric Jacobs

Medical Research Council UK

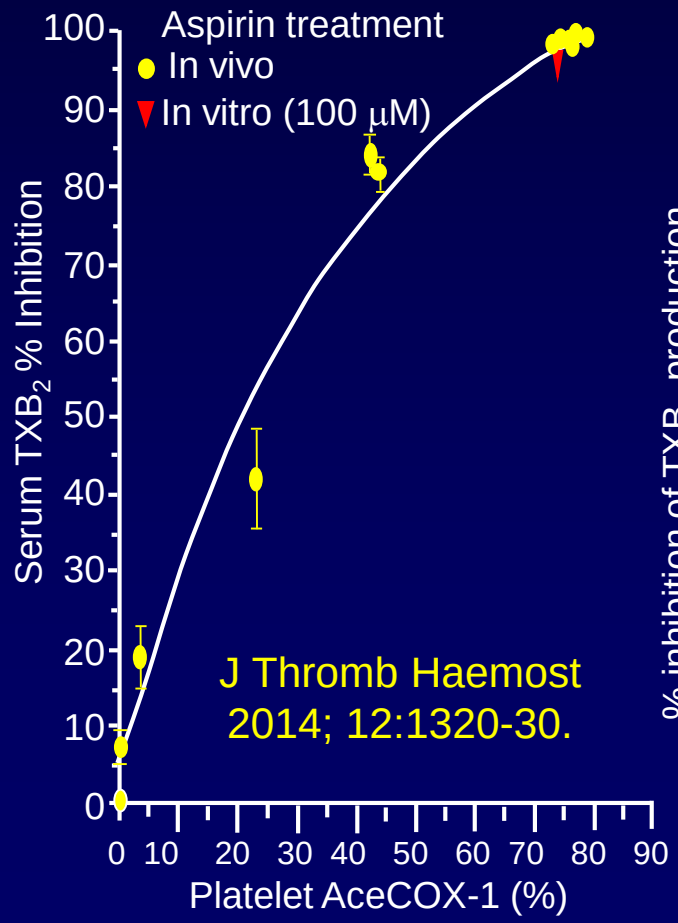
Ruth Langley

European Commission FP6, EICOSANOX

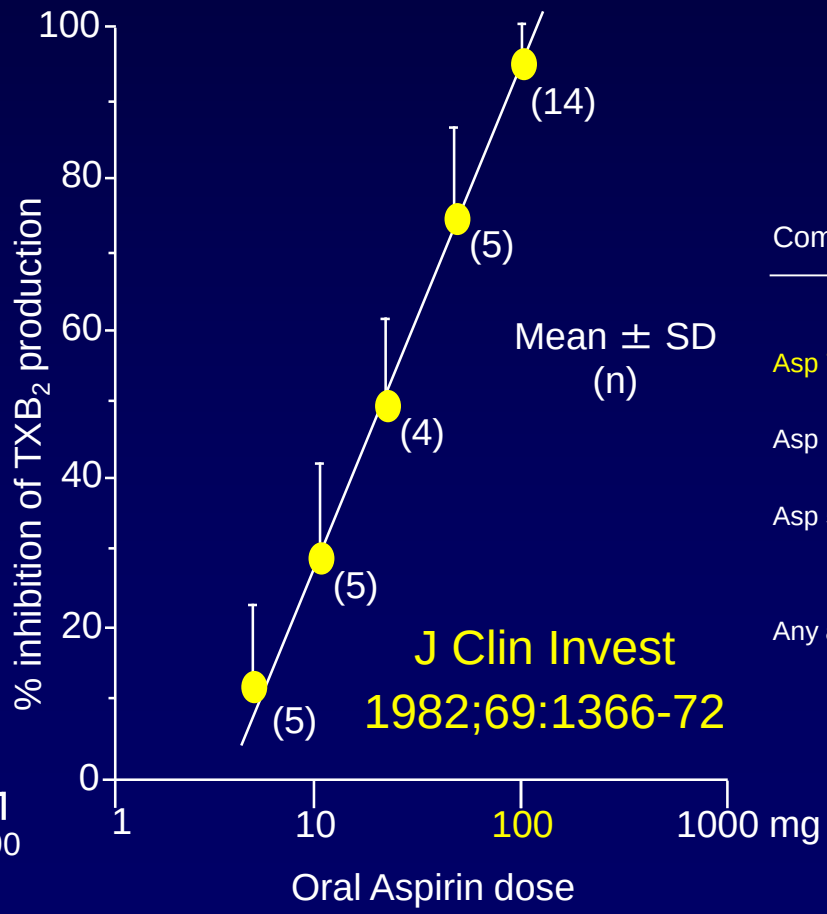
European Commission/EFPIA Innovative Medicines Initiative, SUMMIT

Acetylation of Platelet COX-1, Inhibition of TXA_2 Production and Reduction of Vascular Events by Aspirin are Saturable at Low Doses

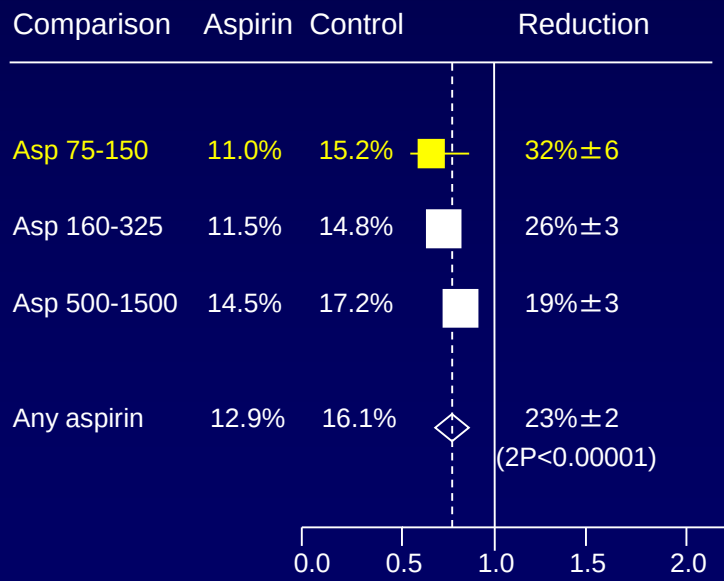
Acetylation of Platelet COX-1



Inhibition of TXA_2 Production



Reduction of Vascular Events in High-Risk Patients



BMJ 2002;324:71-86

Task Force on Antiplatelet Agents of the Working Group on Thrombosis of the European Society of Cardiology

"Hence, the currently available trial results do not seem to justify general guidelines advocating the routine use of aspirin in all asymptomatic individuals above a moderate level of coronary risk, unless additional long-term benefits of antiplatelet therapy become established".

Patrono et al, Eur Heart J 2011; 32:2922-32

Dropping Aspirin?

Pros

1. Reduced risk of bleeding in patients on DAPT
2. Reduced risk of GI damage
3. Reduced risk of inhibiting vascular PGI_2
4. Reduced risk of a pharmacodynamic interaction with ACE-inhibitors.

But

1. Increased risk of coronary atherothrombosis
2. Low-dose aspirin is not gastrotoxic
3. Low-dose aspirin does not inhibit PGI_2 production
4. Low-dose aspirin does not interfere with the antihypertensive effect of ACE-inhibitors.

Aspirin in the Secondary Prevention of CV Disease

From the Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services, Washington, DC (A.K.P.) and Chicago (J.M.G.); the Centers for Disease Control and Prevention, Atlanta (Y.H., J.S.W.); and the Center for Medicare and Medicaid Innovation, Baltimore (J.S.W.).

Parekh et al. N Engl J Med, 2013;368:204-5

Aspirin in the Secondary Prevention of CV Disease

Provision of aspirin to patients with coronary artery disease, atherosclerotic peripheral artery disease, or a history of cerebrovascular disease (transient ischemic attack or stroke) should be the norm; everyone without a contraindication should receive it.

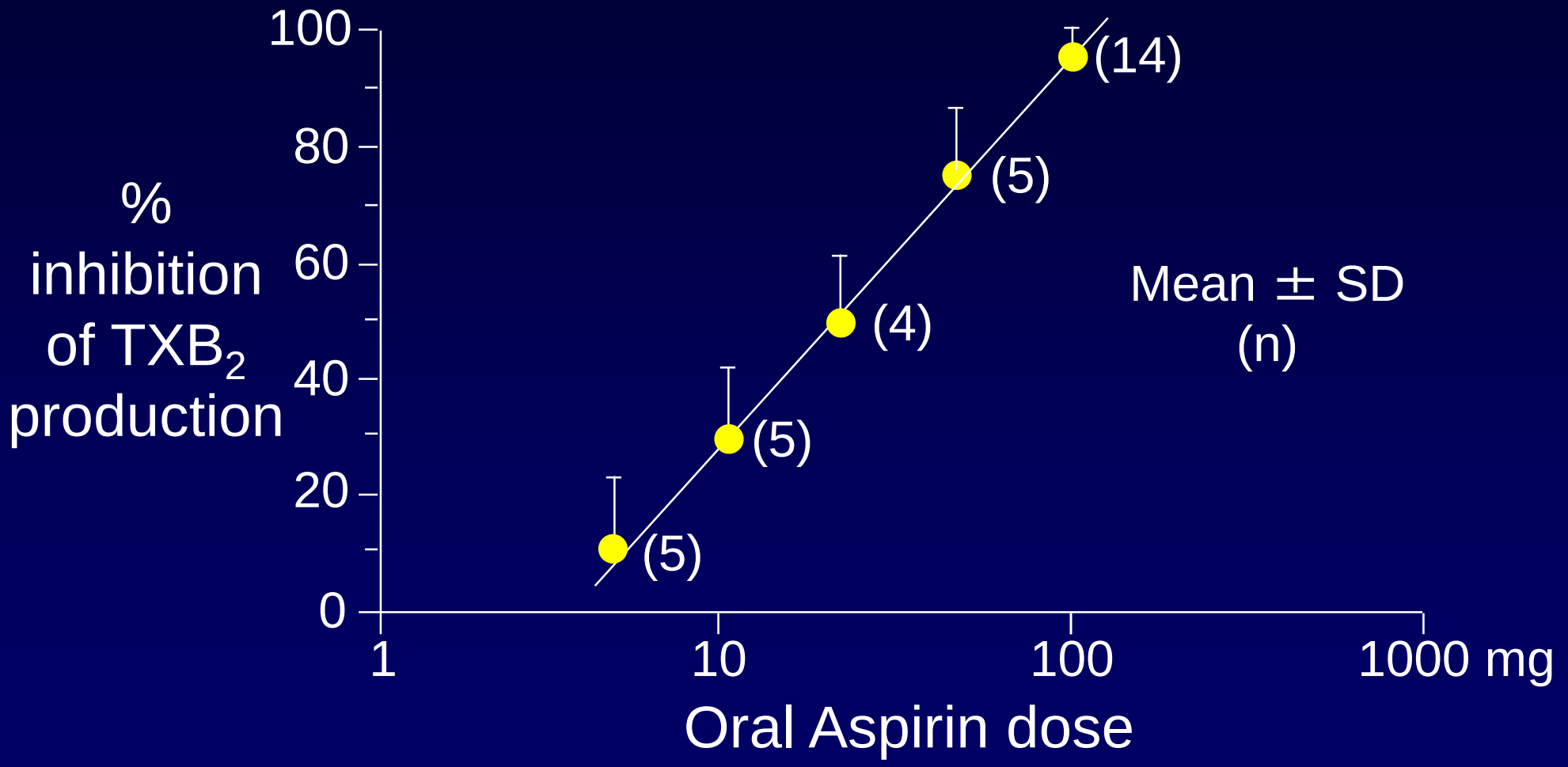
Parekh et al. N Engl J Med, 2013;368:204-5

Aspirin in the Secondary Prevention of CV Disease

Many heart attacks and strokes can be prevented by simplifying the message to both clinicians and their patients with a history of coronary artery disease, peripheral vascular disease, or stroke and no allergy or recent history of bleeding: it's good medicine to take a daily low-dose aspirin.

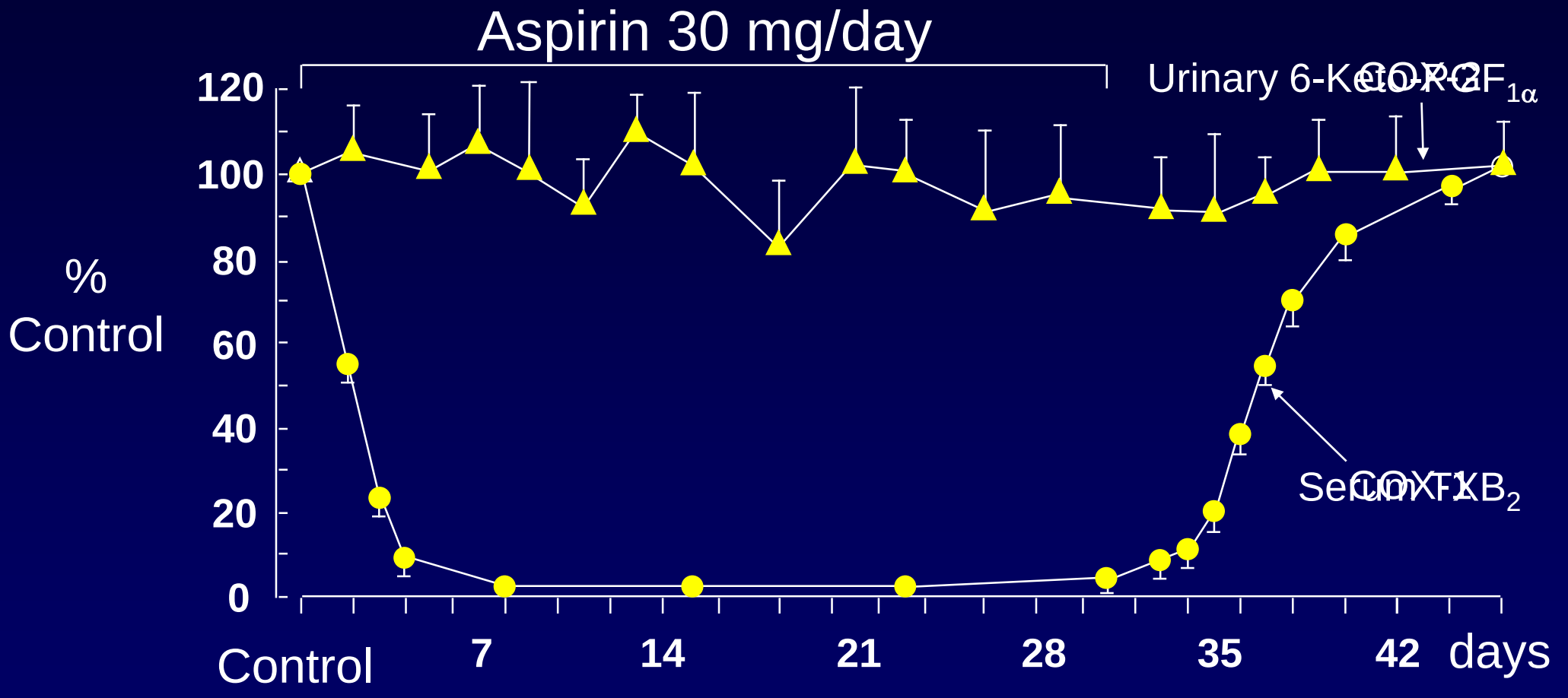
Parekh et al. N Engl J Med, 2013;368:204-5

Log-linear Inhibition of Platelet Cyclooxygenase Activity by Aspirin in Healthy Subjects



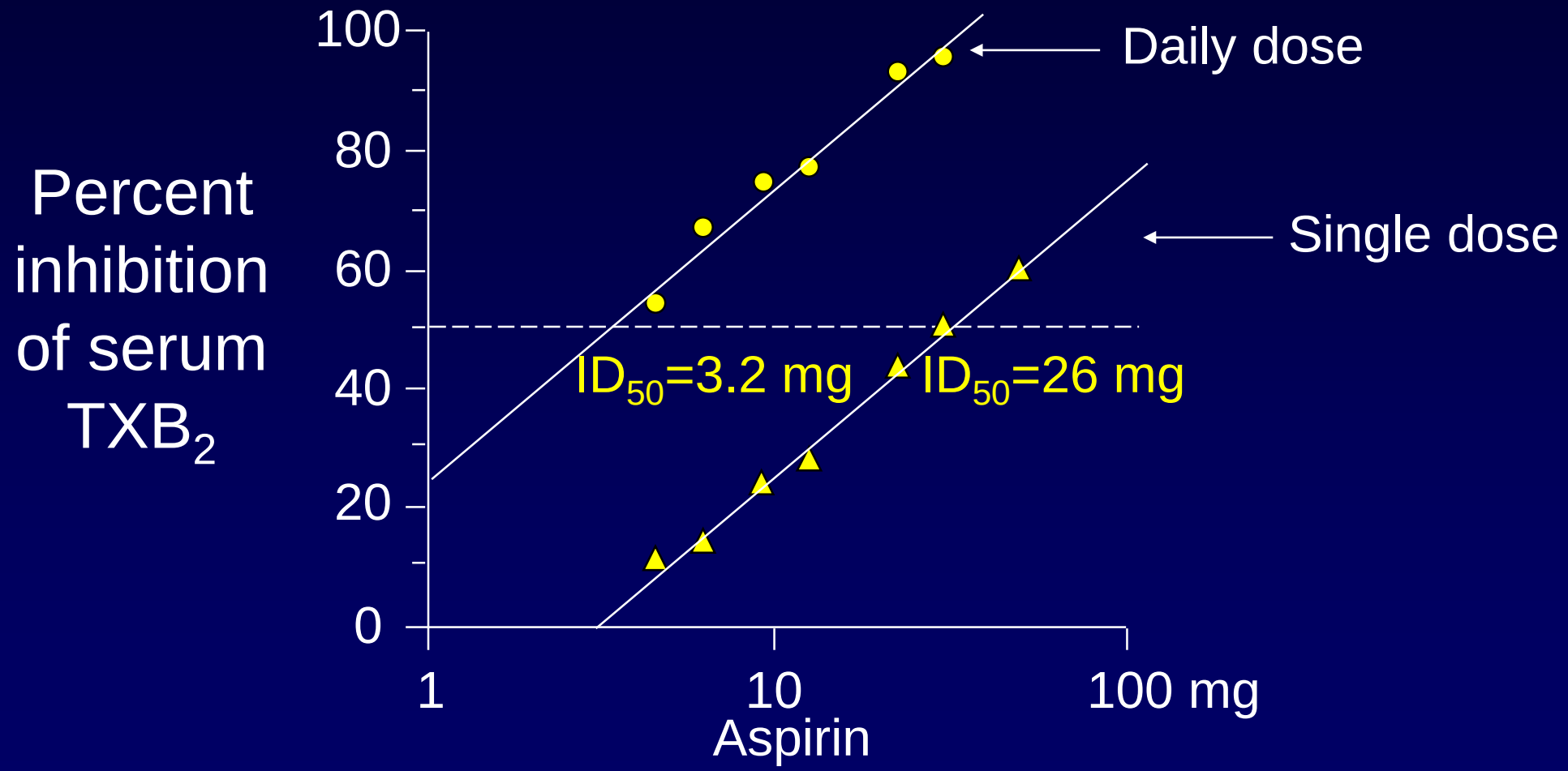
Patrignani, Filabozzi & Patrono, J Clin Invest 1982; 69:1366-72

Selective Cumulative Inhibition of Platelet TXA_2 Production by Low-Dose Aspirin in Healthy Subjects



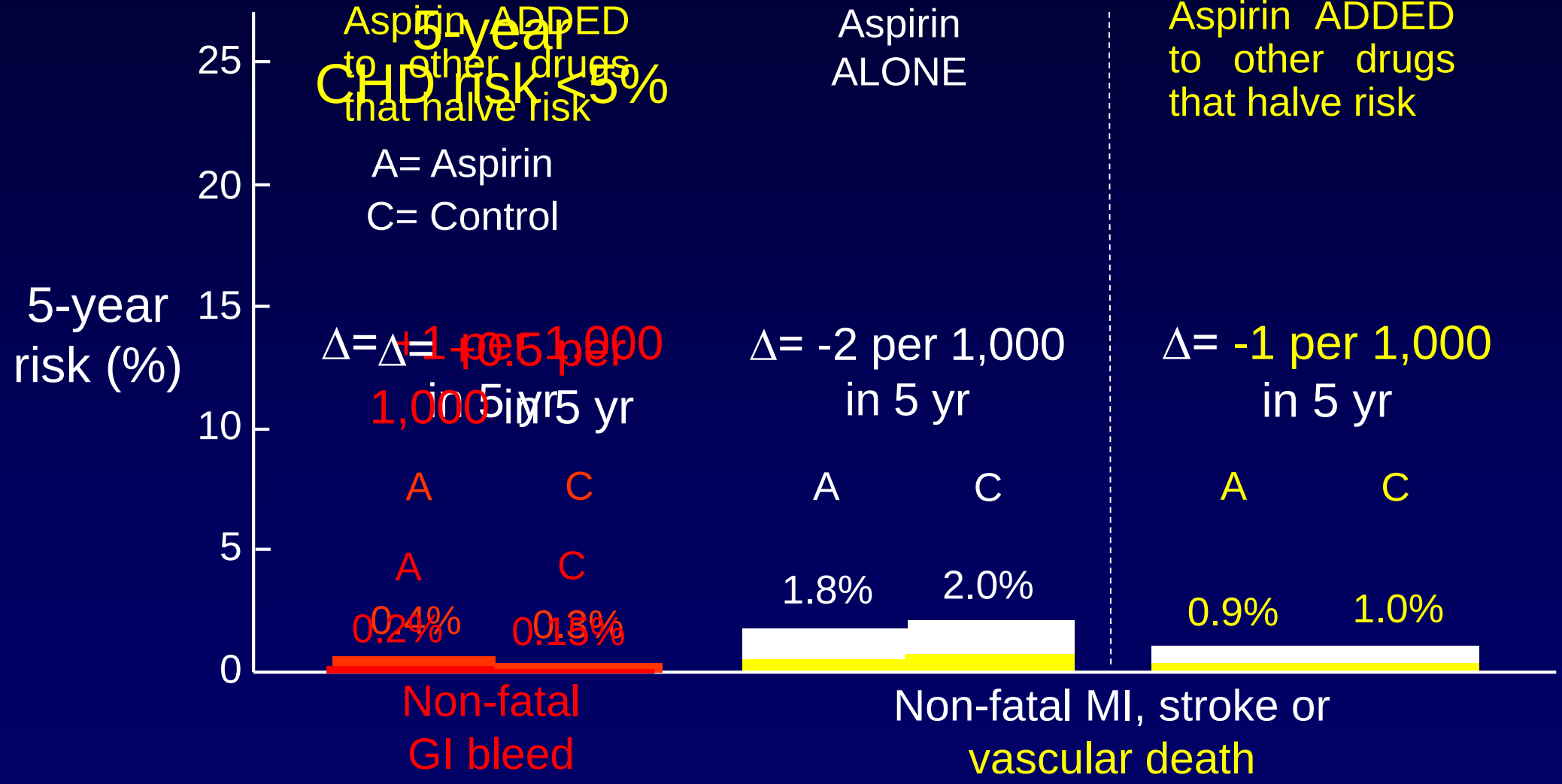
Patrignani, Filabozzi & Patrono, J Clin Invest 1982; 69:1366-72

Cumulative Inhibition of Platelet COX-1 by Low Doses of Aspirin Shifts the Dose-Response Curve by a Factor Equivalent to the Daily Platelet Turnover



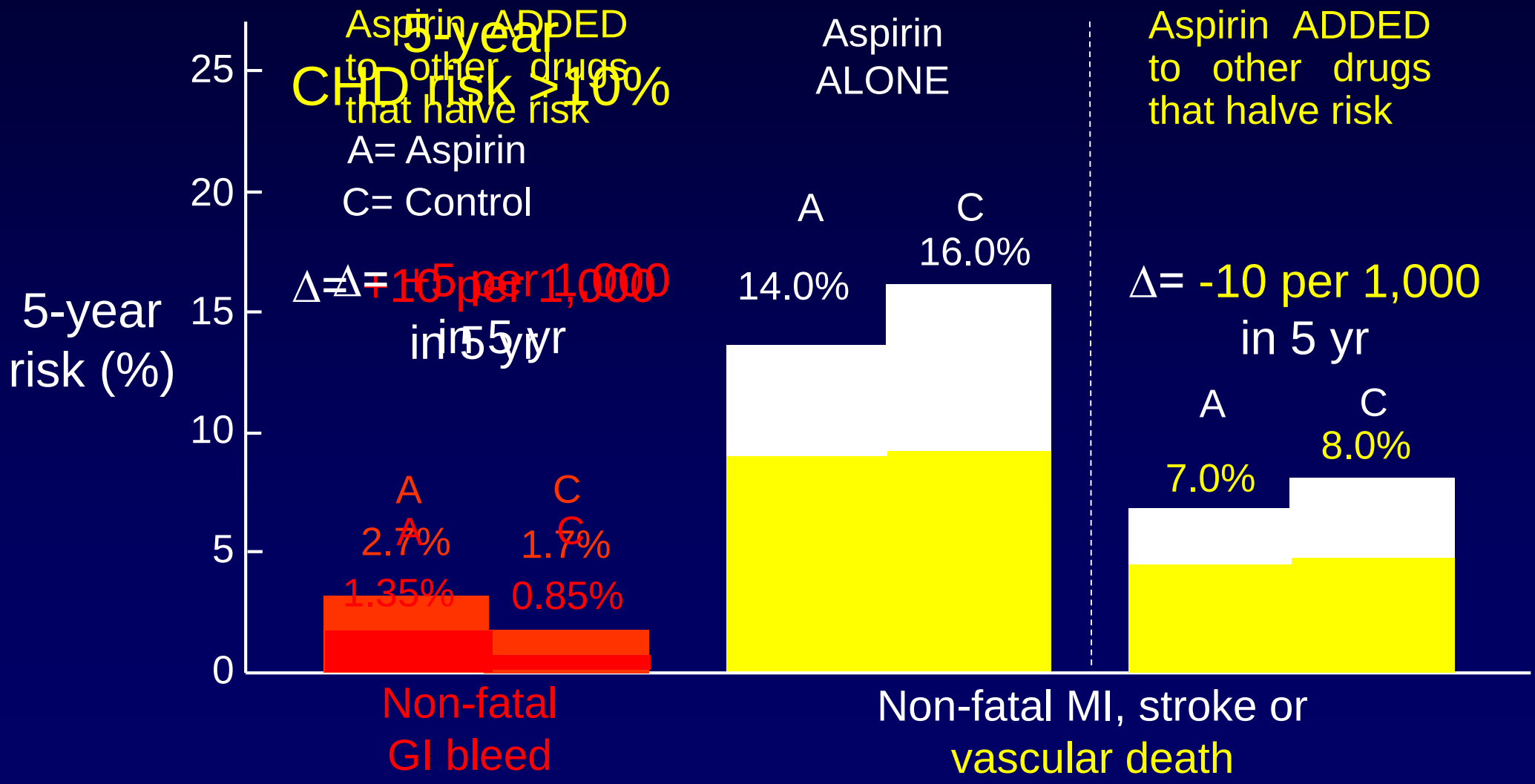
Patrono et al., Circulation 1985; 72:1177-84

Balancing the Benefits and Bleeding Risks of Aspirin, as a Function of CHD Risk



ATT Collaboration, Lancet 2009; 373:1849-60

Balancing the Benefits and Bleeding Risks of Aspirin, as a Function of CHD Risk

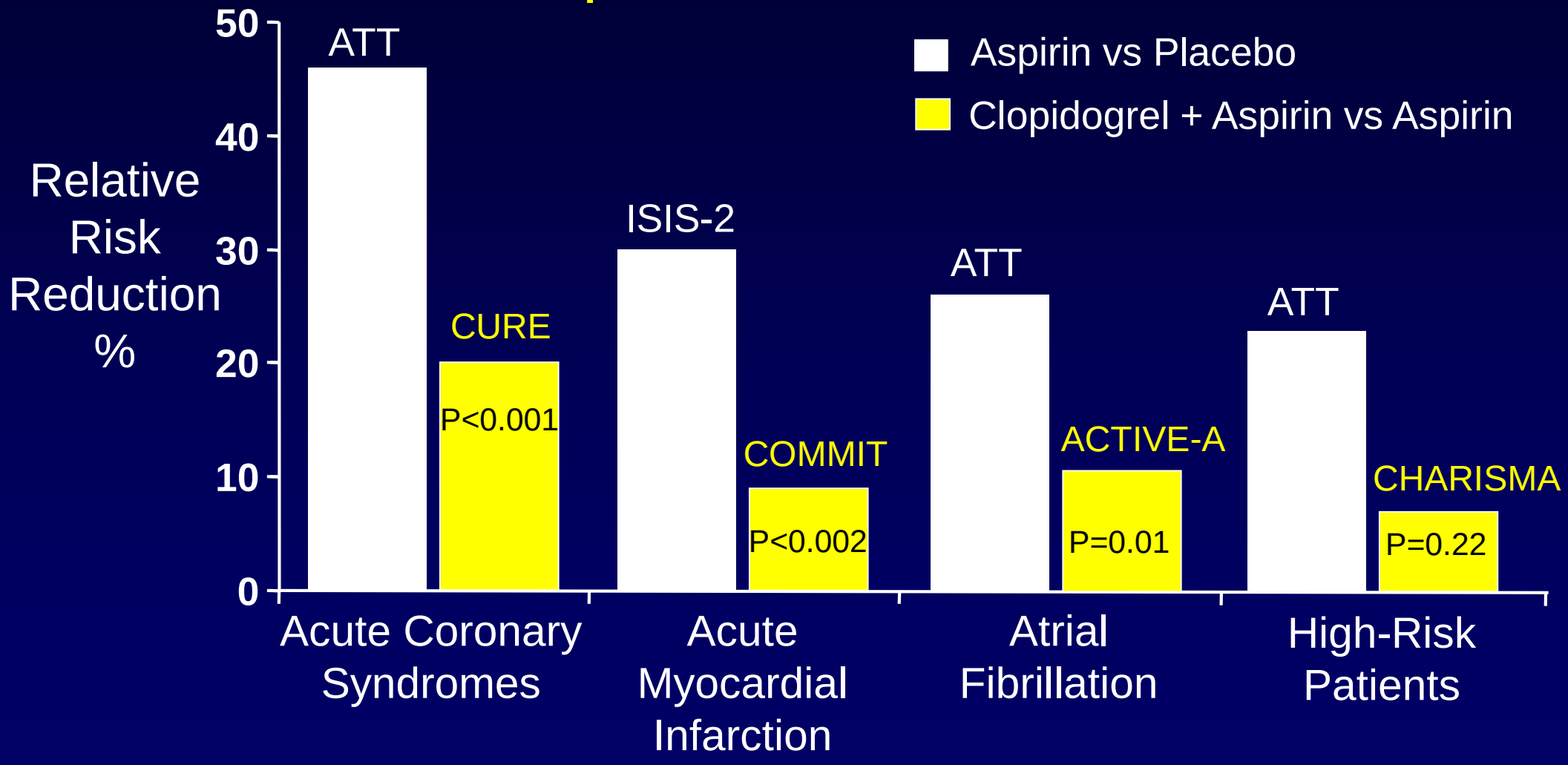


ATT Collaboration, Lancet 2009; 373:1849-60

Increasing Benefit of Dual Antiplatelet Therapy is a Constant Finding in Clinical Settings.

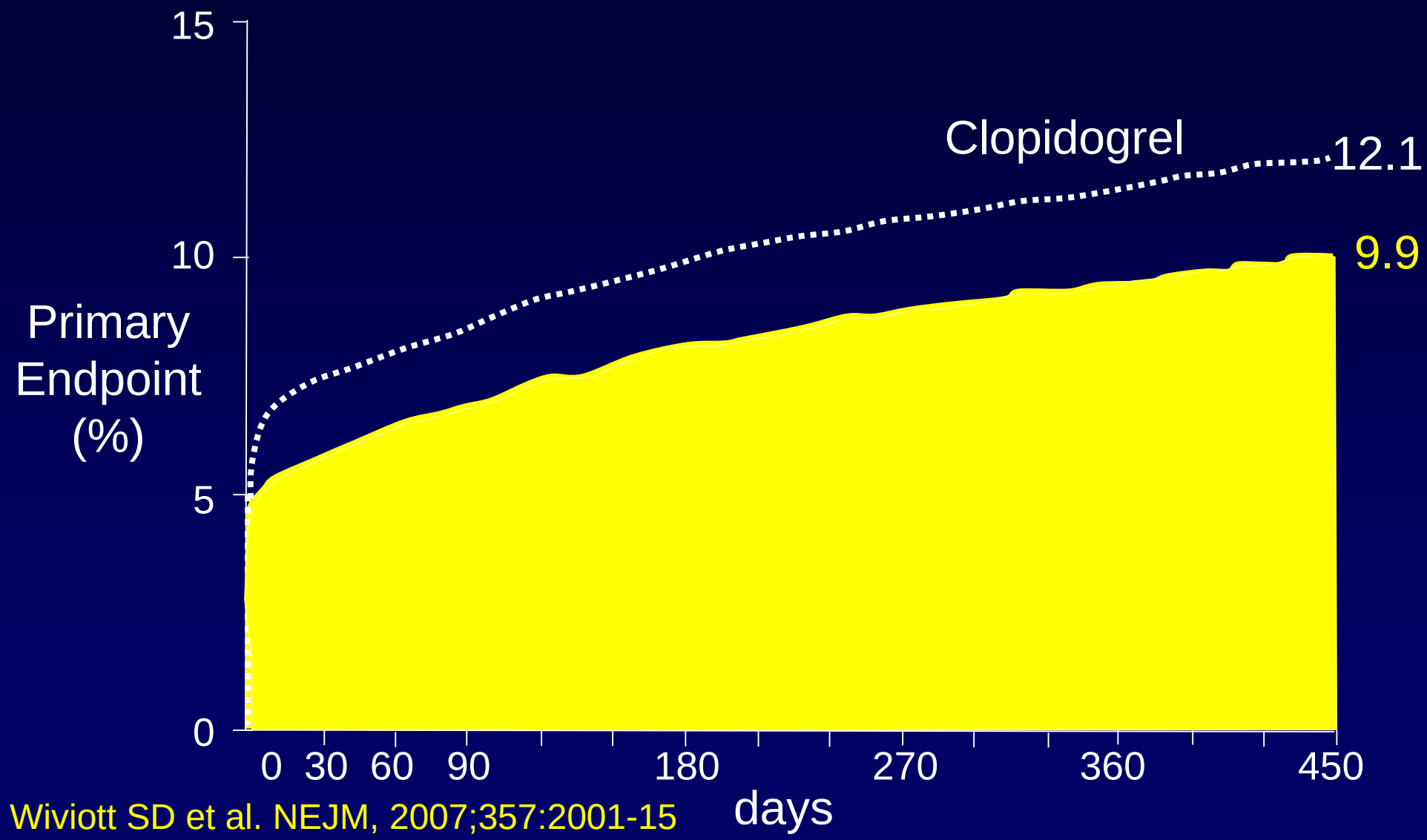
Clopidogrel Plus Aspirin vs Aspirin Alone in Different Clinical Settings.

Reduction of Events Achieved by Aspirin vs Placebo



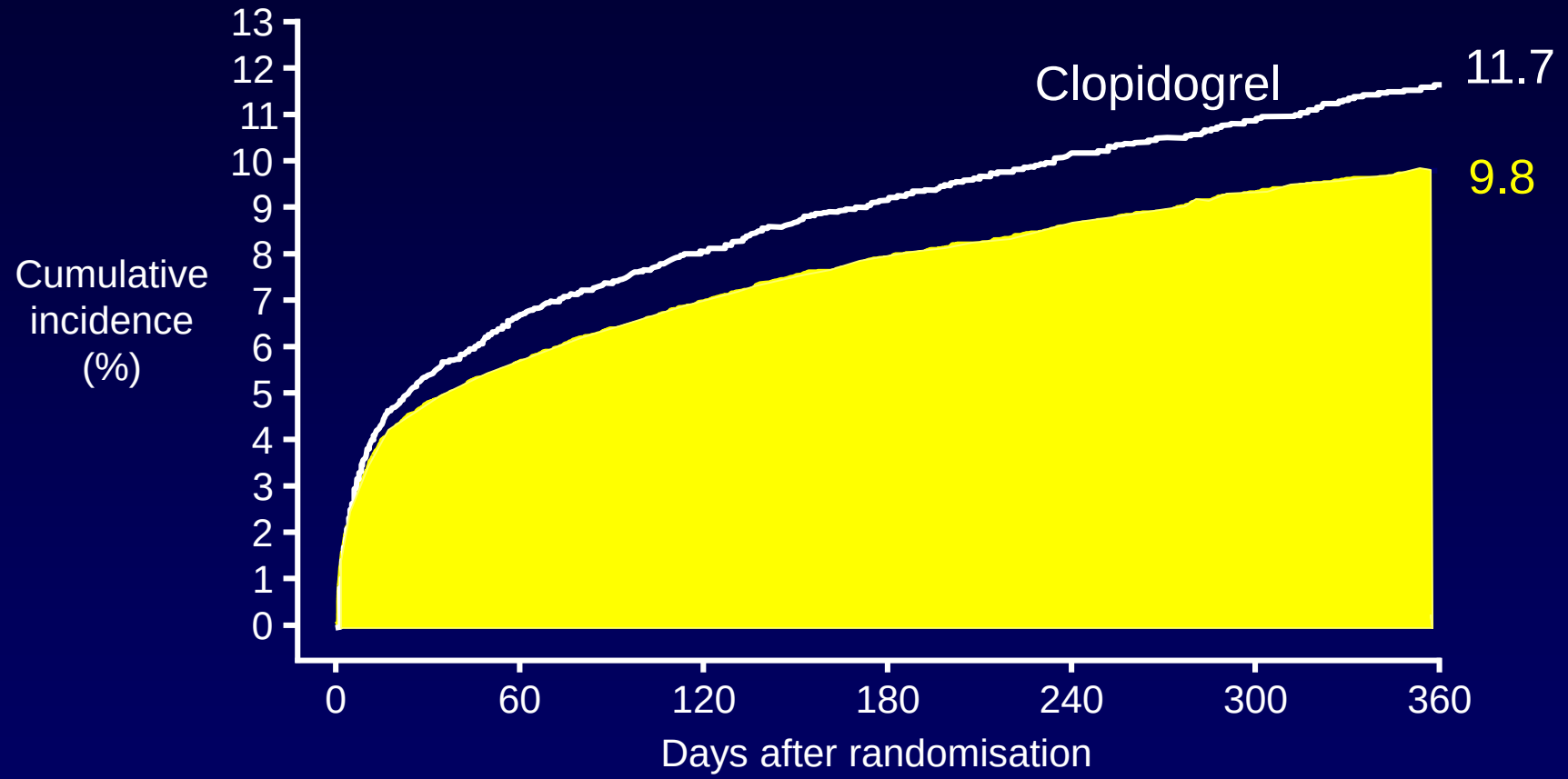
Updated from Patrono & Davì NEJM 2008; 358:1638-9

Cardiovascular Death, Myocardial Infarction or Stroke in TRITON-TIMI 38



Wiviott SD et al. NEJM, 2007;357:2001-15

K-M Estimate of Time to First Primary Efficacy Event (Composite of CV Death, MI or Stroke) in PLATO



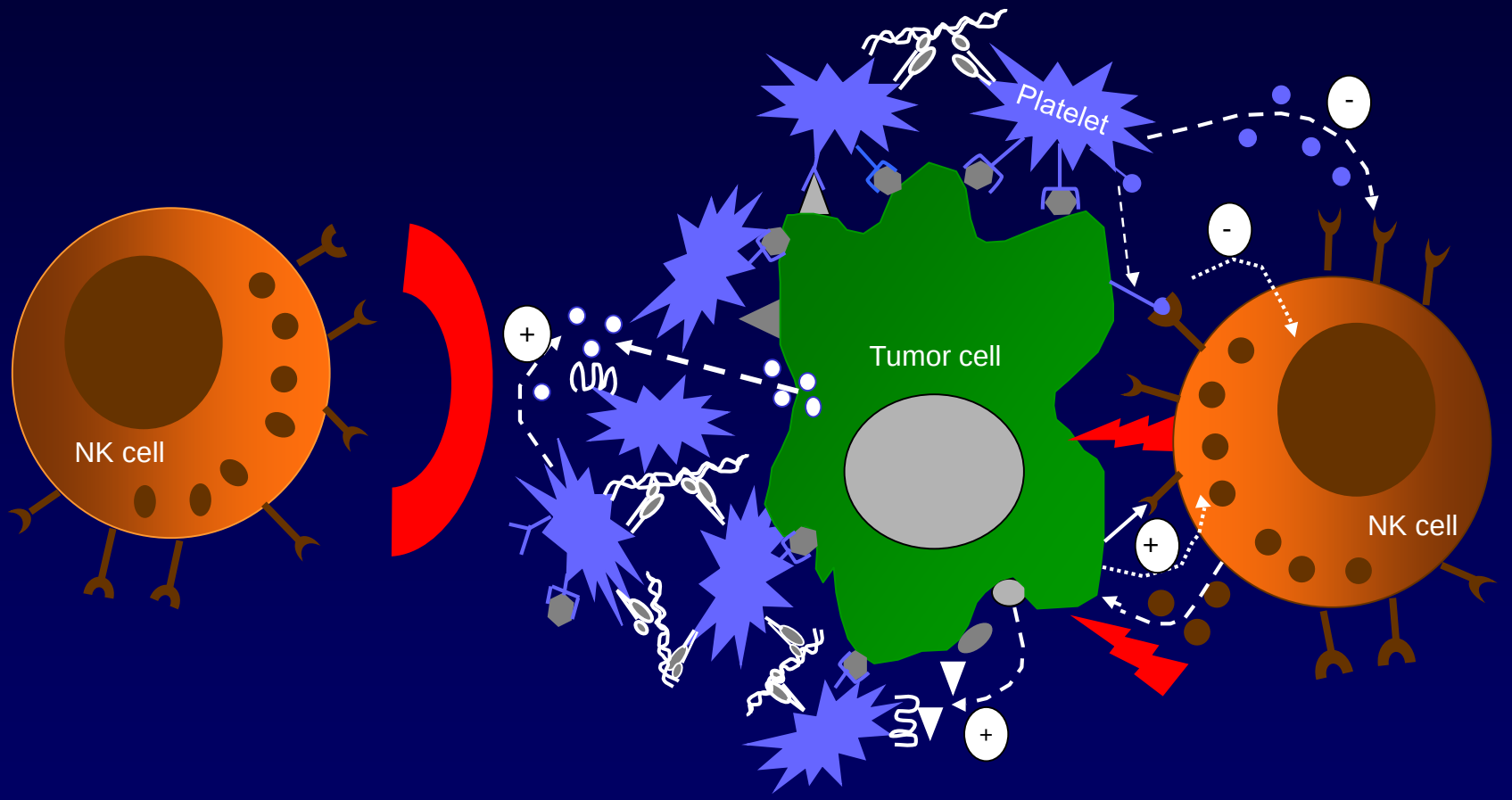
No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

Wallentin et al, N Engl J Med 2009; 361:1045-57

Sources of Evidence Supporting a Chemopreventive Effect of Aspirin Against Gastrointestinal Cancers

1. Over 40 observational case-control studies and their meta-analysis (Algra & Rothwell, Lancet Oncol 2012).
2. Four placebo-controlled RCTs in subjects with sporadic colorectal adenomas (Cole, JNCI 2009).
3. A placebo-controlled RCT in the Lynch syndrome with post-trial follow-up (CAPP2, NEJM 2008; Lancet 2011).
4. A post-hoc individual patient data (IPD) meta-analysis of 51 randomized controlled trials in prevention of vascular events (Rothwell et al, Lancet 2012).

Tumor Cell-Induced Platelet Aggregation Protects Tumor Cells from Natural Killer Cell-Mediated Lysis



Stegner D et al. Thromb Res 2014; 133 S2: S149-57

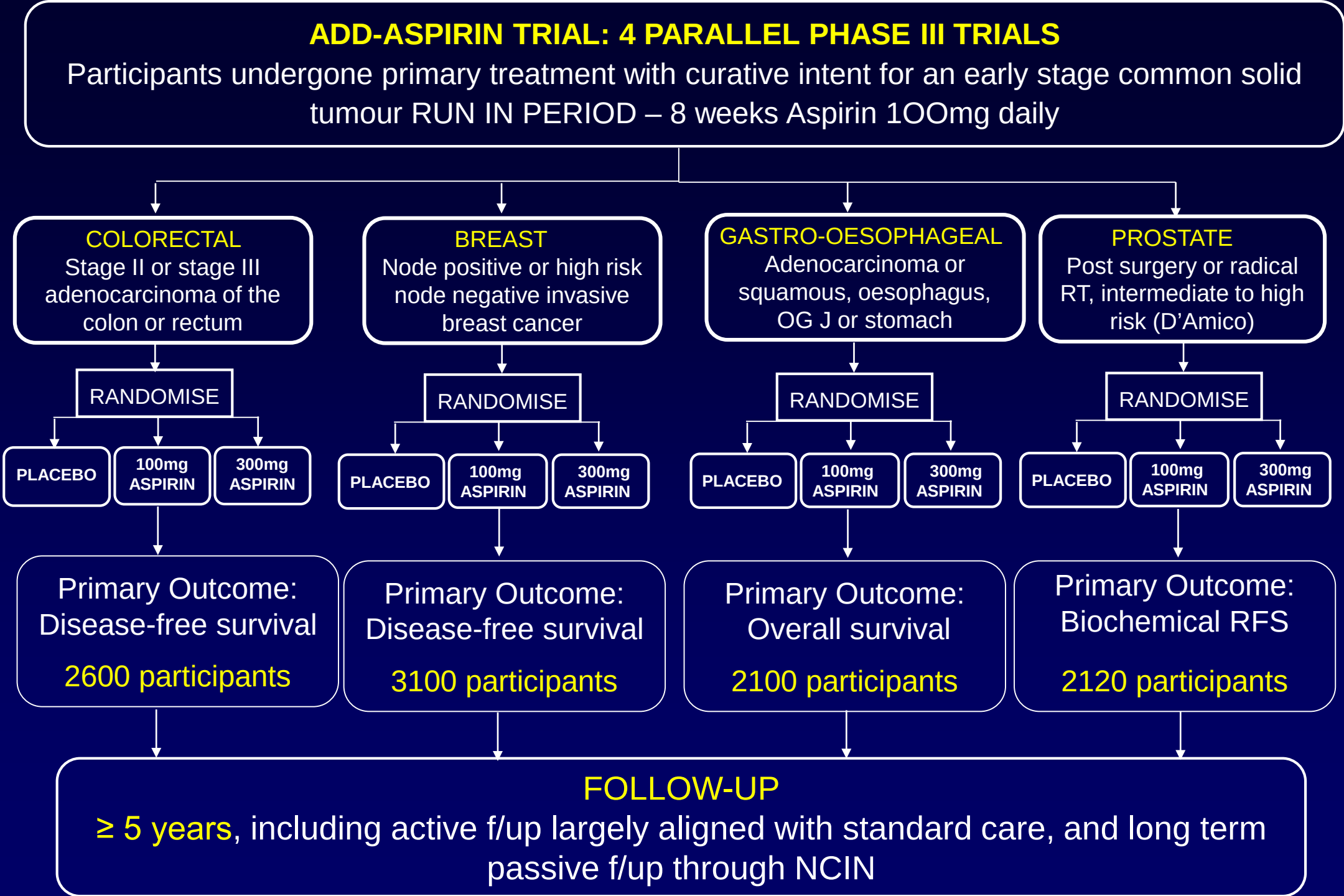
Ongoing Randomised Trials of Aspirin vs Placebo: Low-Risk Individuals

Study	Regimen(s)	Treatment duration	N	Eligibility	Primary endpoint	Estimated total of all cancers		End date
						≤5 years	>5 years	
ACCEPT-D	A100 vs open control; simvastatin for all	5 y	5170	Diabetes, no CVD	CV death, non-fatal stroke, nonfatal MI, other CV hospitalisation	~300	-	2015
ARRIVE	A100 enteric coated vs P	5y	12,000	10-20% estimated 10y risk of CHD	MI, stroke, CV death, unstable angina, TIA	~800	-	2016
ASPREE	A100 vs P	5 y	19,000	Elderly, no diabetes or CVD	Death, dementia or significant disability	~1000	-	2017
ASCEND	A100 vs P (ω3FA vs P)	7.5 y	15,000	Diabetes, no CVD	MI, stroke or TIA, or CV death	~900	~500 in trial, then registry)	2018

Ongoing Randomised Trials of Aspirin vs Placebo: High-Risk Cancer Patients

Study	Regimen(s)	Treatment duration	N	Eligibility	Primary endpoint	Estimated total of all cancers		End date
						≤5 years	>5 years	
AspECT	A300 vs P	8 y	2500	Barrett's oesophagus	Death/adeno-carcinoma or high-grade metaplasia	~120	~100	2017
seAFOod	A300 vs P (EPA vs P)	1 y	904	Multiple adenomas at BCSP	≥1 adenoma at 1 year screen	<10	-	NA
ASCOLT	A200 vs P	3y	2660	Dukes C or high-risk Dukes B cancer	3 year disease-free survival	900	-	NA
ADD-Aspirin	A100 vs A300 vs P	5y	~9,920	CRC, breast, gastro-oesophageal, prostate ca	Disease-free survival (death for gastro-oesophageal)	3400	>1000	2025

Abbreviations: BCSP = Bowel Cancer Screening Programme; CRC = colorectal cancer


ADD-ASPIRIN TRIAL: 4 PARALLEL PHASE III TRIALS
Participants undergone primary treatment with curative intent for an early stage common solid tumour RUN IN PERIOD – 8 weeks Aspirin 1OOmg daily
COLORECTAL
Stage II or stage III adenocarcinoma of the colon or rectum
BREAST
Node positive or high risk node negative invasive breast cancer
GASTRO-OESOPHAGEAL
Adenocarcinoma or squamous, oesophagus, OG J or stomach
PROSTATE
Post surgery or radical RT, intermediate to high risk (D'Amico)
RANDOMISE
RANDOMISE
RANDOMISE
RANDOMISE
PLACEBO
100mg ASPIRIN
300mg ASPIRIN
PLACEBO
100mg ASPIRIN
300mg ASPIRIN
PLACEBO
100mg ASPIRIN
300mg ASPIRIN
PLACEBO
100mg ASPIRIN
300mg ASPIRIN
Primary Outcome: Disease-free survival
2600 participants
Primary Outcome: Disease-free survival
3100 participants
Primary Outcome: Overall survival
2100 participants
Primary Outcome: Biochemical RFS
2120 participants
FOLLOW-UP
≥ 5 years, including active f/up largely aligned with standard care, and long term passive f/up through NCIN