EVIDENZE E NUOVE PROSPETTIVE NEL TRATTAMENTO DELLE PATOLOGIE TROMBOEMBOLICHE

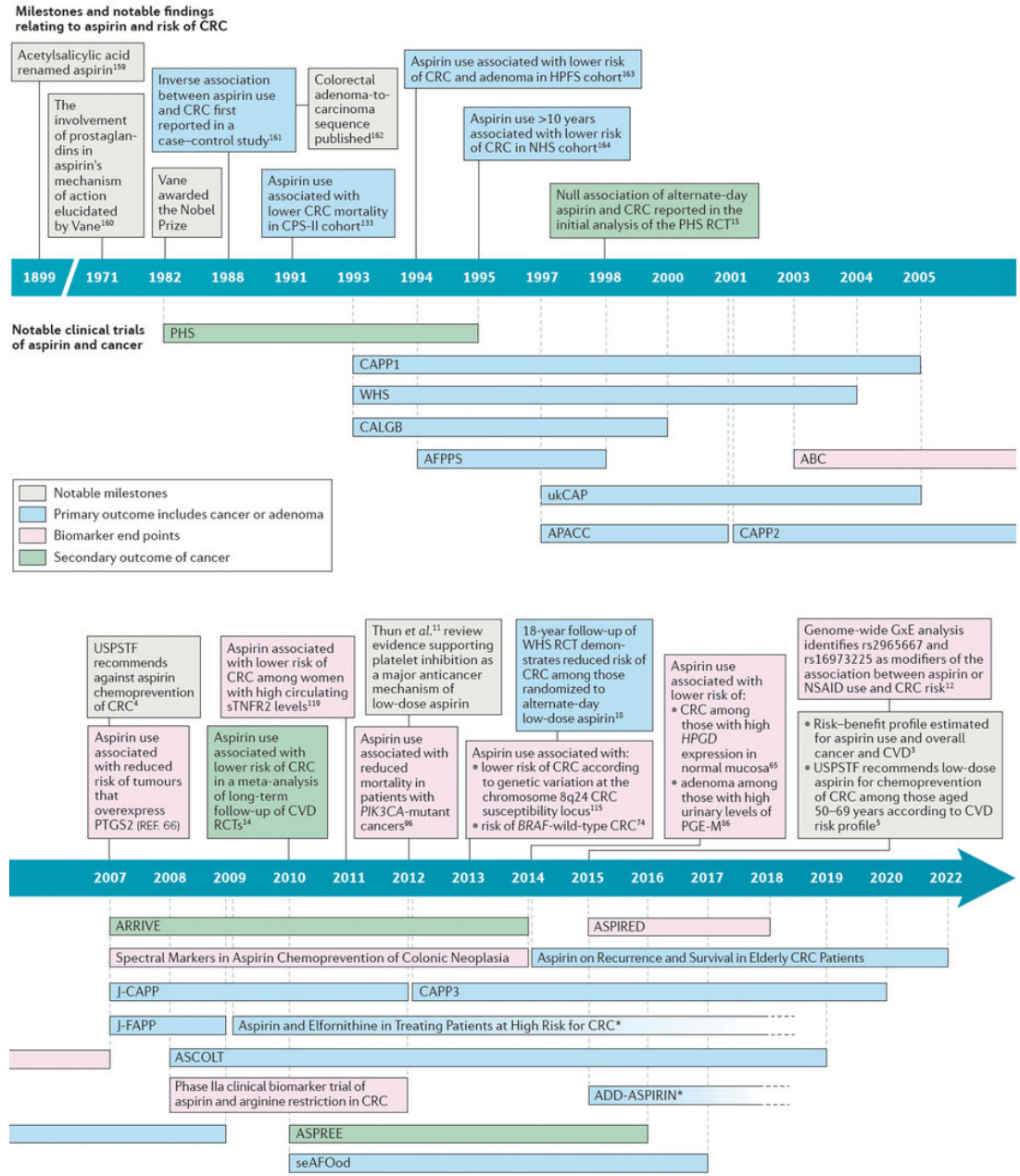
Varese, 16 Marzo 2018

Acido acetilsalicilico e Tumori

Francesca Santilli

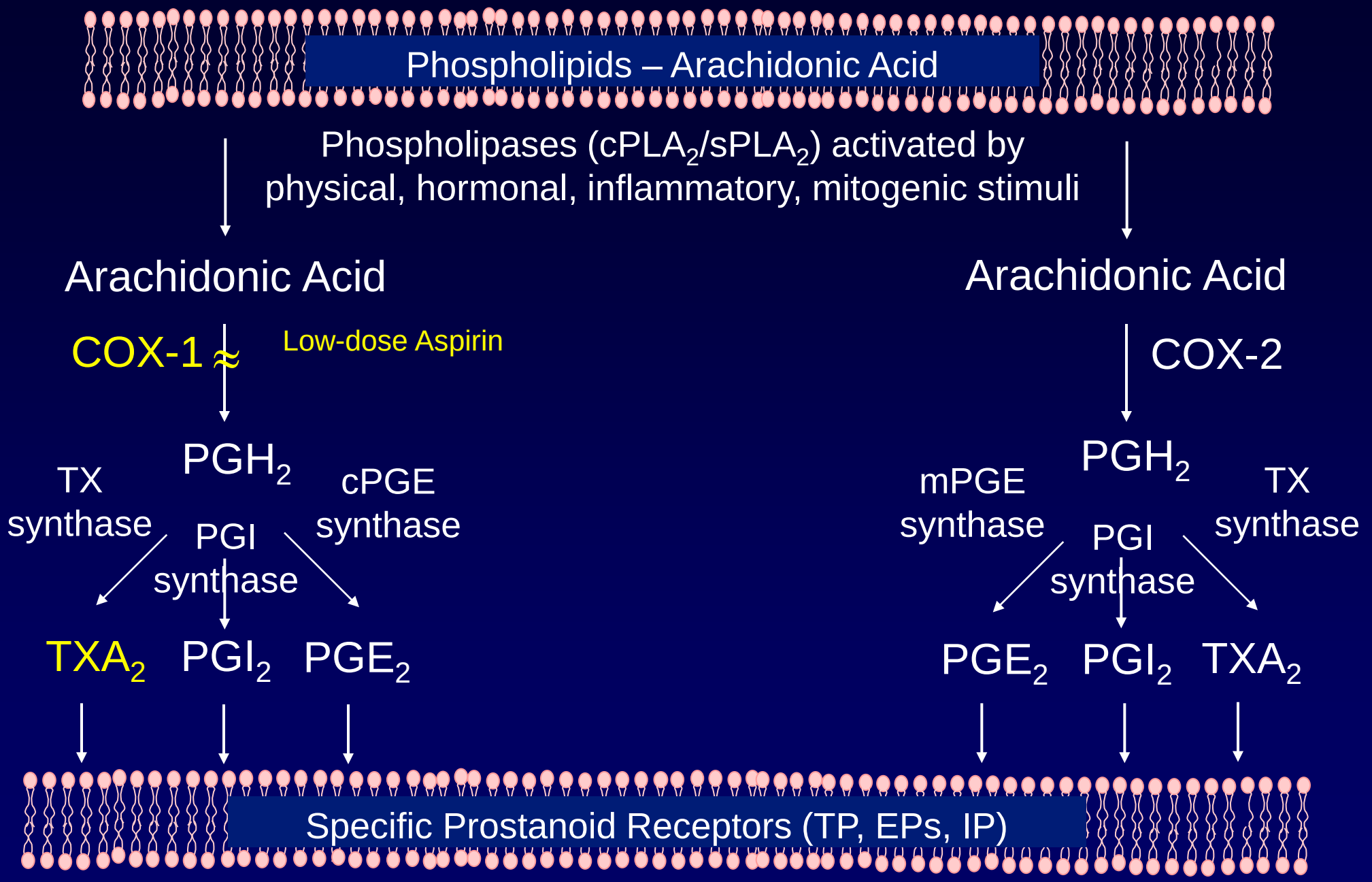
Medicina Interna

Università di Chieti


Milestones and notable findings relating to aspirin and risk of CRC
Acetylsalicylic acid renamed aspirin[159]
The involvement of prostaglandins in aspirin's mechanism of action elucidated by Vane[160]
Inverse association between aspirin use and CRC first reported in a case–control study[161]
Vane awarded the Nobel Prize
Colorectal adenoma-to-carcinoma sequence published[162]
Aspirin use associated with lower CRC mortality in CPS-II cohort[133]
Aspirin use associated with lower risk of CRC and adenoma in HPFS cohort[163]
Aspirin use >10 years associated with lower risk of CRC in NHS cohort[164]
Null association of alternate-day aspirin and CRC reported in the initial analysis of the PHS RCT[15]
1899
1971
1982
1988
1991
1993
1994
1995
1997
1998
2000
2001
2003
2004
2005
Notable clinical trials of aspirin and cancer
PHS
CAPP1
WHS
CALGB
AFPPS
ABC
ukCAP
APACC
CAPP2
Notable milestones
Primary outcome includes cancer or adenoma
Biomarker end points
Secondary outcome of cancer
USPSTF recommends against aspirin chemoprevention of CRC[4]
Aspirin use associated with reduced risk of tumours that overexpress PTGS2 (REF. 66)
Aspirin associated with lower risk of CRC among women with high circulating sTNFR2 levels[119]
Aspirin use associated with lower risk of CRC in a meta-analysis of long-term follow-up of CVD RCTs[14]
Thun et al.[11] review evidence supporting platelet inhibition as a major anticancer mechanism of low-dose aspirin
Aspirin use associated with reduced mortality in patients with PIK3CA-mutant cancers[96]
18-year follow-up of WHS RCT demonstrates reduced risk of CRC among those randomized to alternate-day low-dose aspirin[18]
Aspirin use associated with:
• lower risk of CRC according to genetic variation at the chromosome 8q24 CRC susceptibility locus[115]
• risk of BRAF-wild-type CRC[74]
Aspirin use associated with lower risk of:
• CRC among those with high HPGD expression in normal mucosa[65]
• adenoma among those with high urinary levels of PGE-M[86]
Genome-wide GxE analysis identifies rs2965667 and rs16973225 as modifiers of the association between aspirin or NSAID use and CRC risk[12]
• Risk–benefit profile estimated for aspirin use and overall cancer and CVD[3]
• USPSTF recommends low-dose aspirin for chemoprevention of CRC among those aged 50–69 years according to CVD risk profile[5]
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2022
ARRIVE
ASPIRED
Spectral Markers in Aspirin Chemoprevention of Colonic Neoplasia
Aspirin on Recurrence and Survival in Elderly CRC Patients
J-CAPP
CAPP3
J-FAPP
Aspirin and Elfornithine in Treating Patients at High Risk for CRC*
ASCOLT
Phase IIa clinical biomarker trial of aspirin and arginine restriction in CRC
ADD-ASPIRIN*
ASPREE
seAFOod

OUTLINE

- SOURCES OF EVIDENCE FOR A CHEMOPREVENTIVE EFFECT OF ASPIRIN
- IS THERE A BIOLOGICALLY PLAUSIBLE MECHANISM OF ACTION?
- WHAT IS THE SIZE OF THE APPARENT CHEMOPREVENTIVE EFFECT, AND CAN IT POSSIBLY CHANGE THE BENEFIT/RISK PROFILE OF ASPIRIN IN PRIMARY PREVENTION?
- IS THE CURRENT EVIDENCE SUFFICIENT TO ISSUE CHEMOPREVENTIVE TREATMENT GUIDELINES?
- WHERE DO WE GO FROM HERE?


Phospholipids – Arachidonic Acid
Phospholipases (cPLA2/sPLA2) activated by physical, hormonal, inflammatory, mitogenic stimuli
Arachidonic Acid
Arachidonic Acid
COX-1
Low-dose Aspirin
COX-2
PGH2
PGH2
TX synthase
cPGE synthase
PGI synthase
mPGE synthase
PGI synthase
TX synthase
TXA2
PGI2
PGE2
PGE2
PGI2
TXA2
Specific Prostanoid Receptors (TP, EPs, IP)

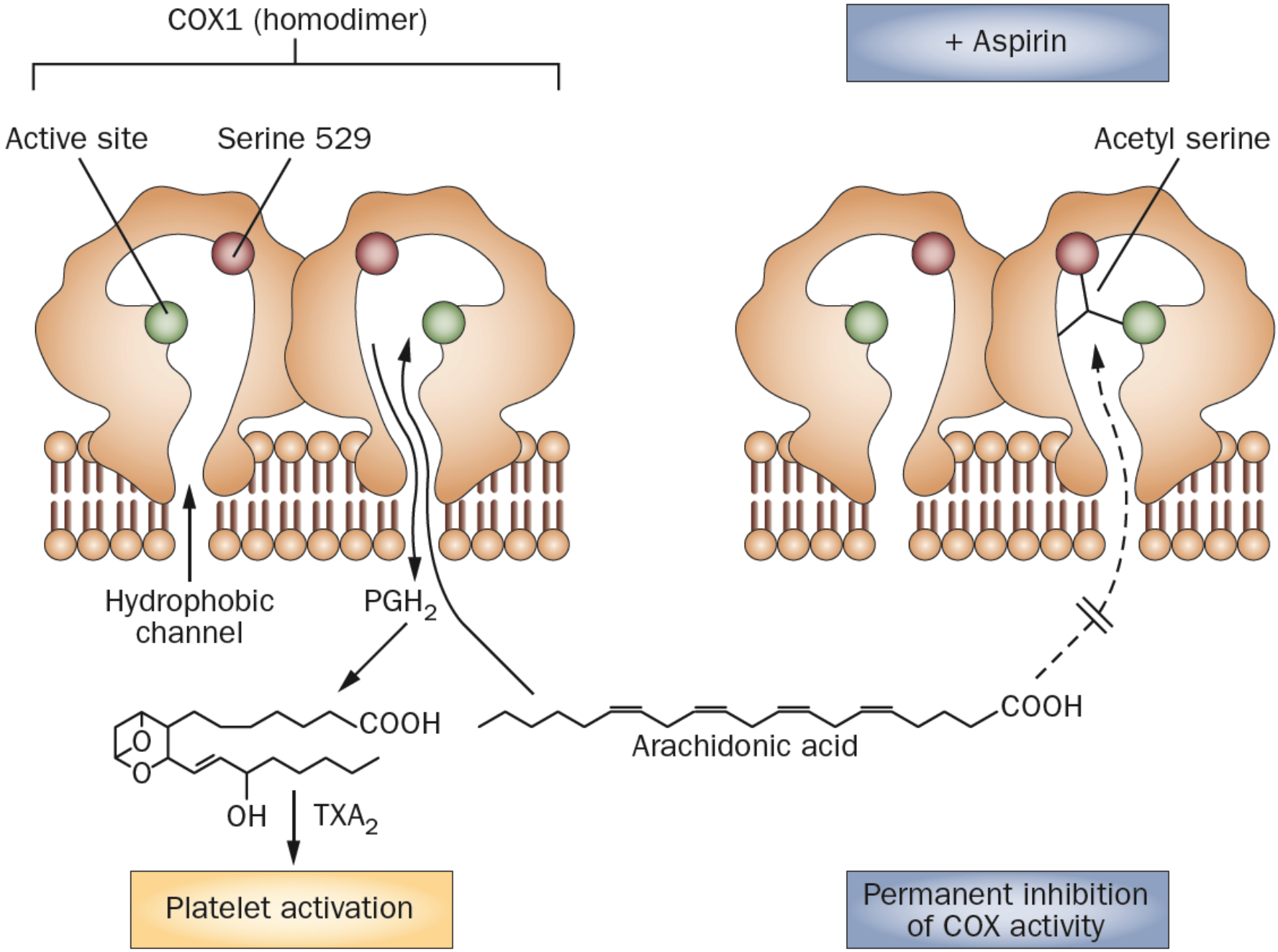
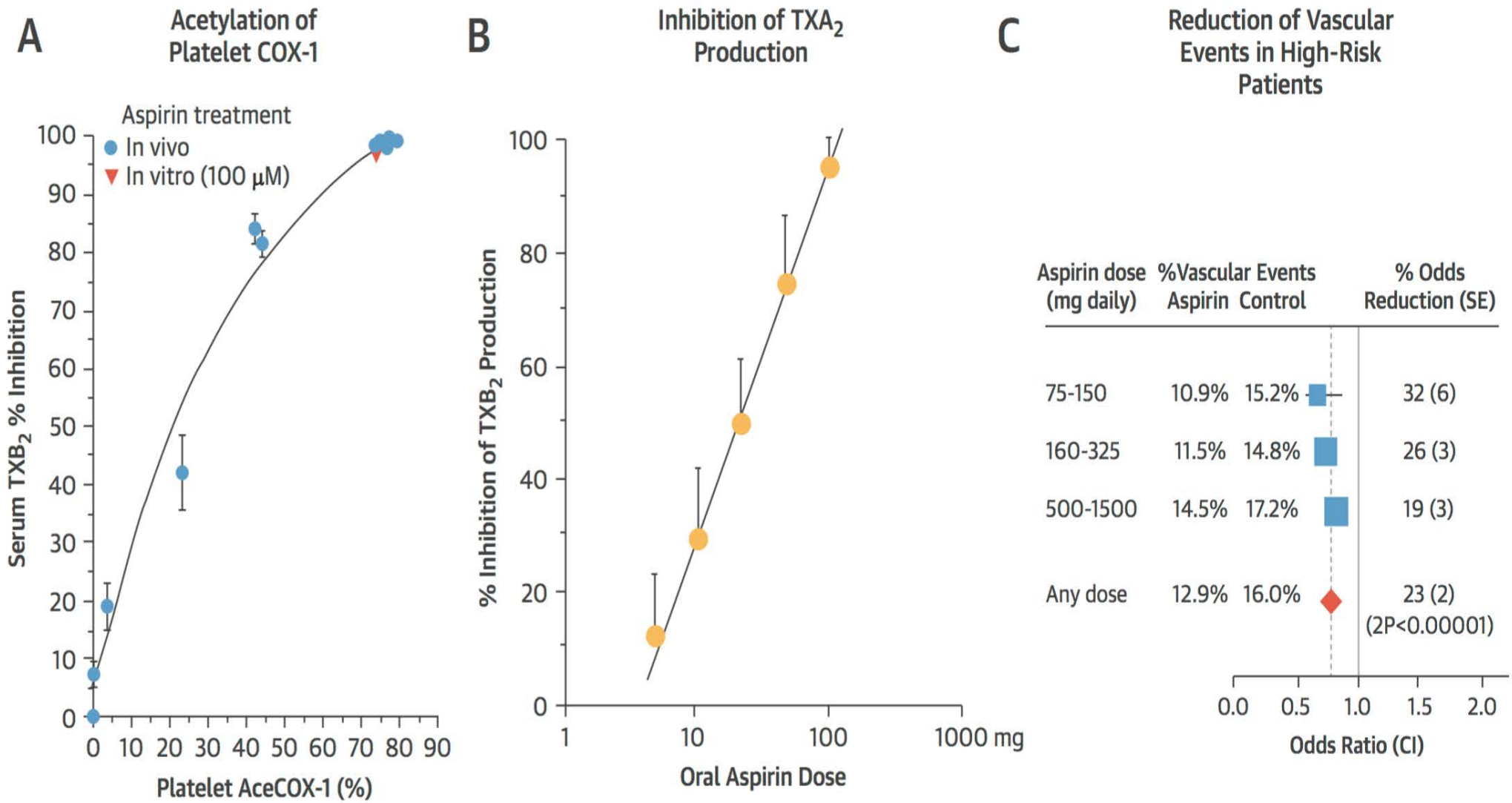
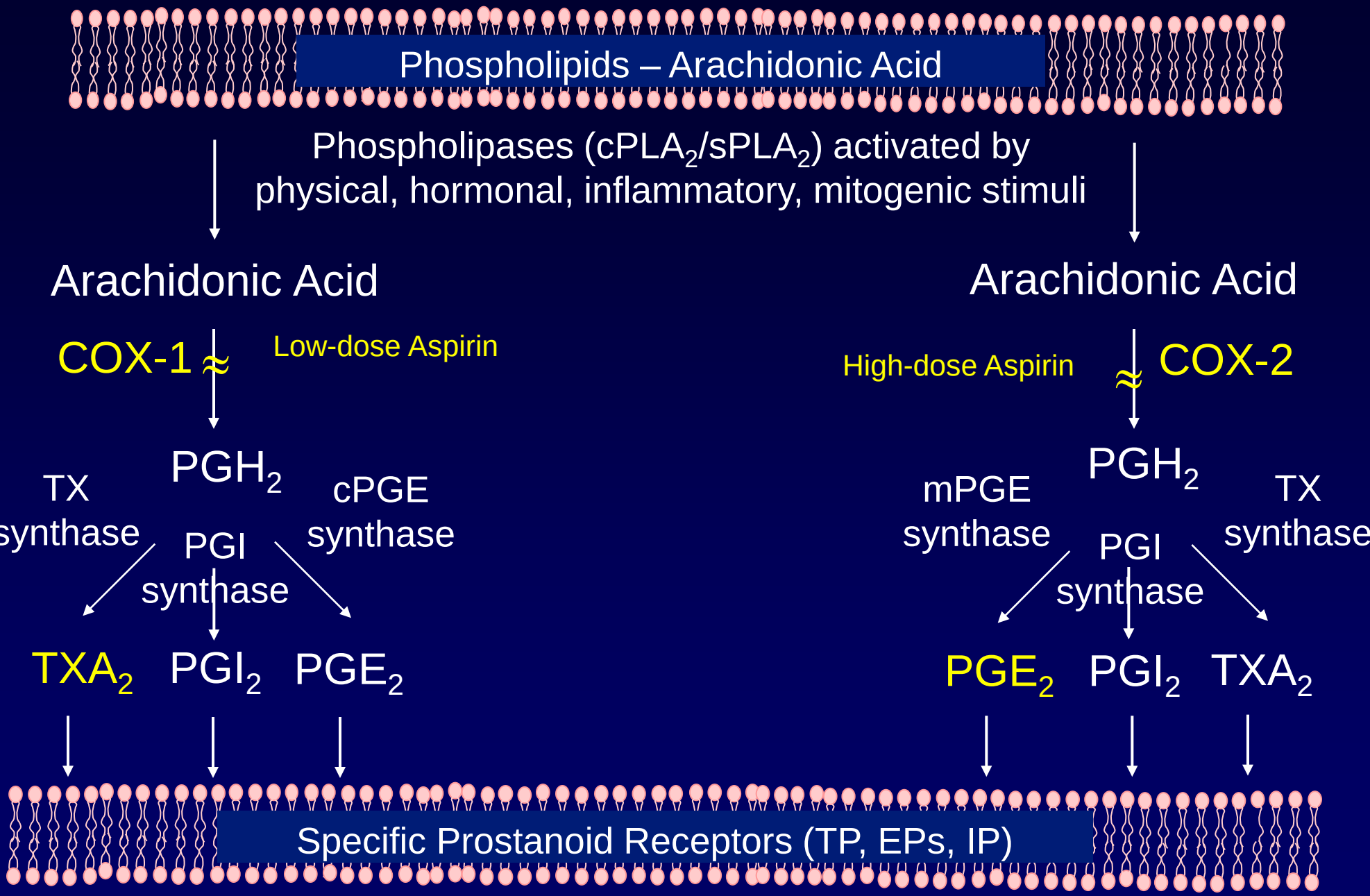

COX1 (homodimer)
+ Aspirin
Active site
Serine 529
Acetyl serine
Hydrophobic channel
PGH2
COOH
O
O
OH
TXA2
Arachidonic acid
COOH
Platelet activation
Permanent inhibition of COX activity

FIGURE 1 Acetylation of Platelet Cyclooxygenase-1, Inhibition of Platelet Thromboxane Production, and Cardioprotection by Aspirin Are Saturable at Low Doses



Patrignani P and Patrono C, JACC 2016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Phospholipases (cPLA2/sPLA2) activated by physical, hormonal, inflammatory, mitogenic stimuli
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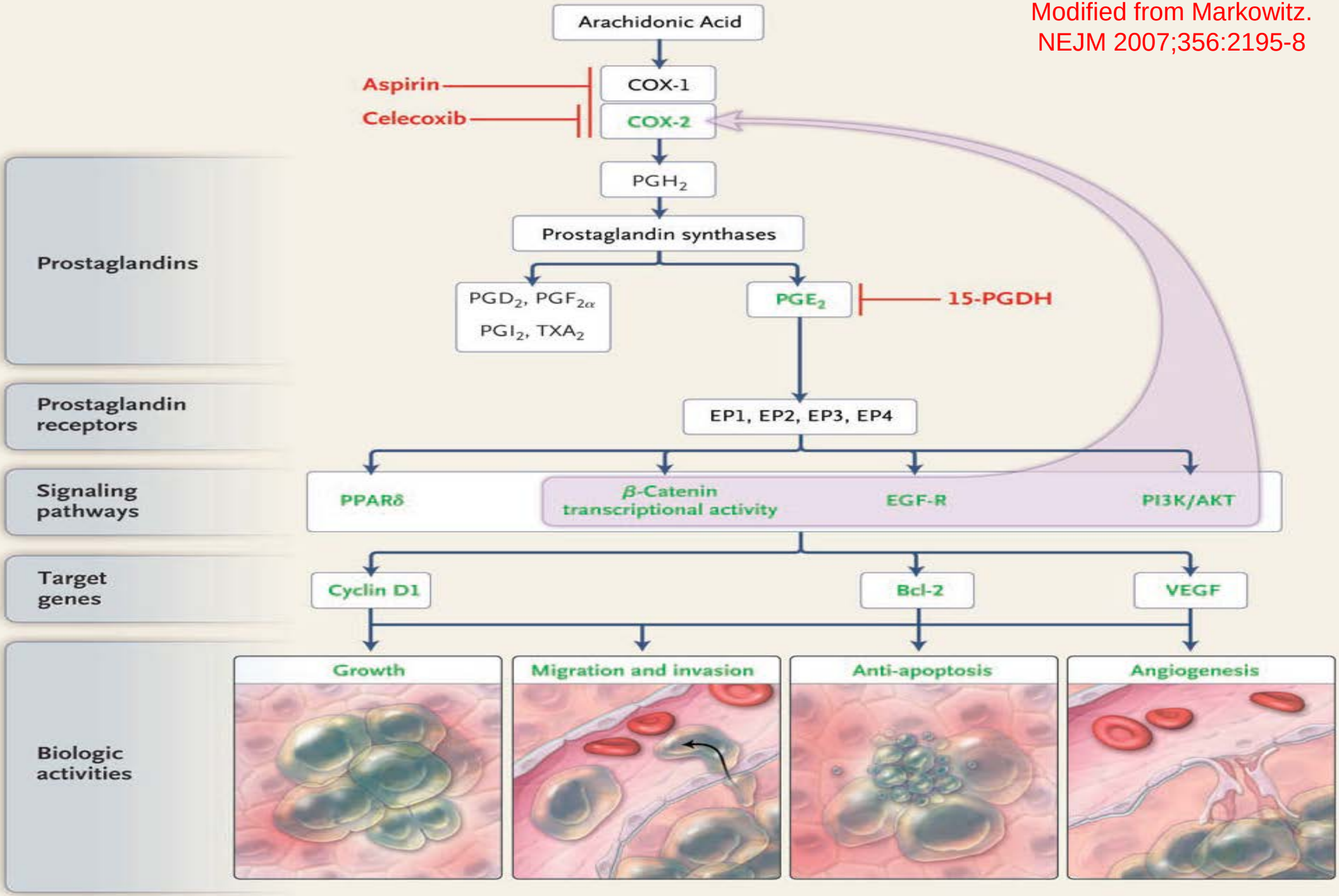
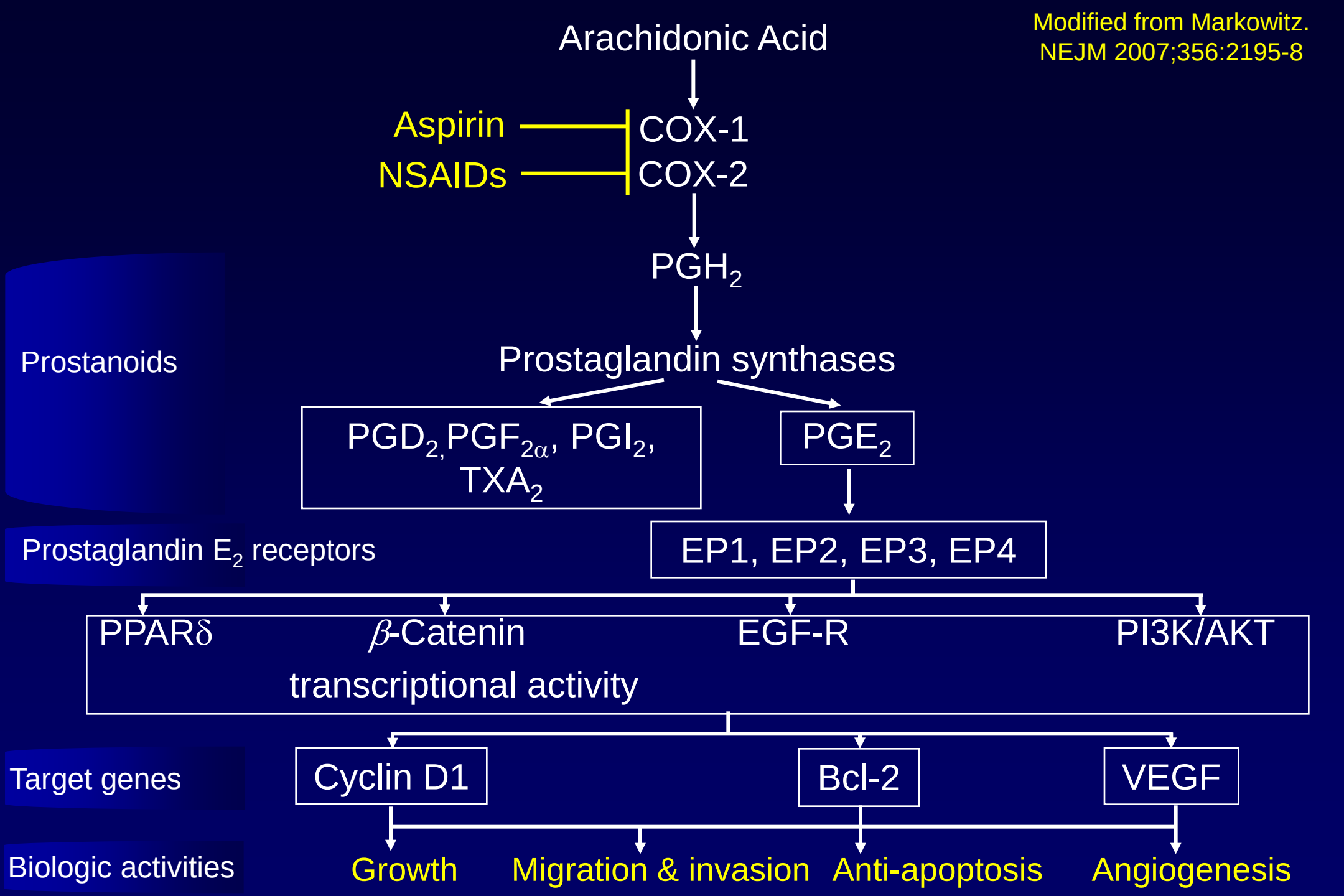
PGI synthase
cPGE synthase
mPGE synthase
PGI synthase
TX synthase
TXA2
PGI2
PGE2
PGE2
PGI2
TXA2
Specific Prostanoid Receptors (TP, EPs, IP)

Modified from Markowitz.
NEJM 2007;356:2195-8

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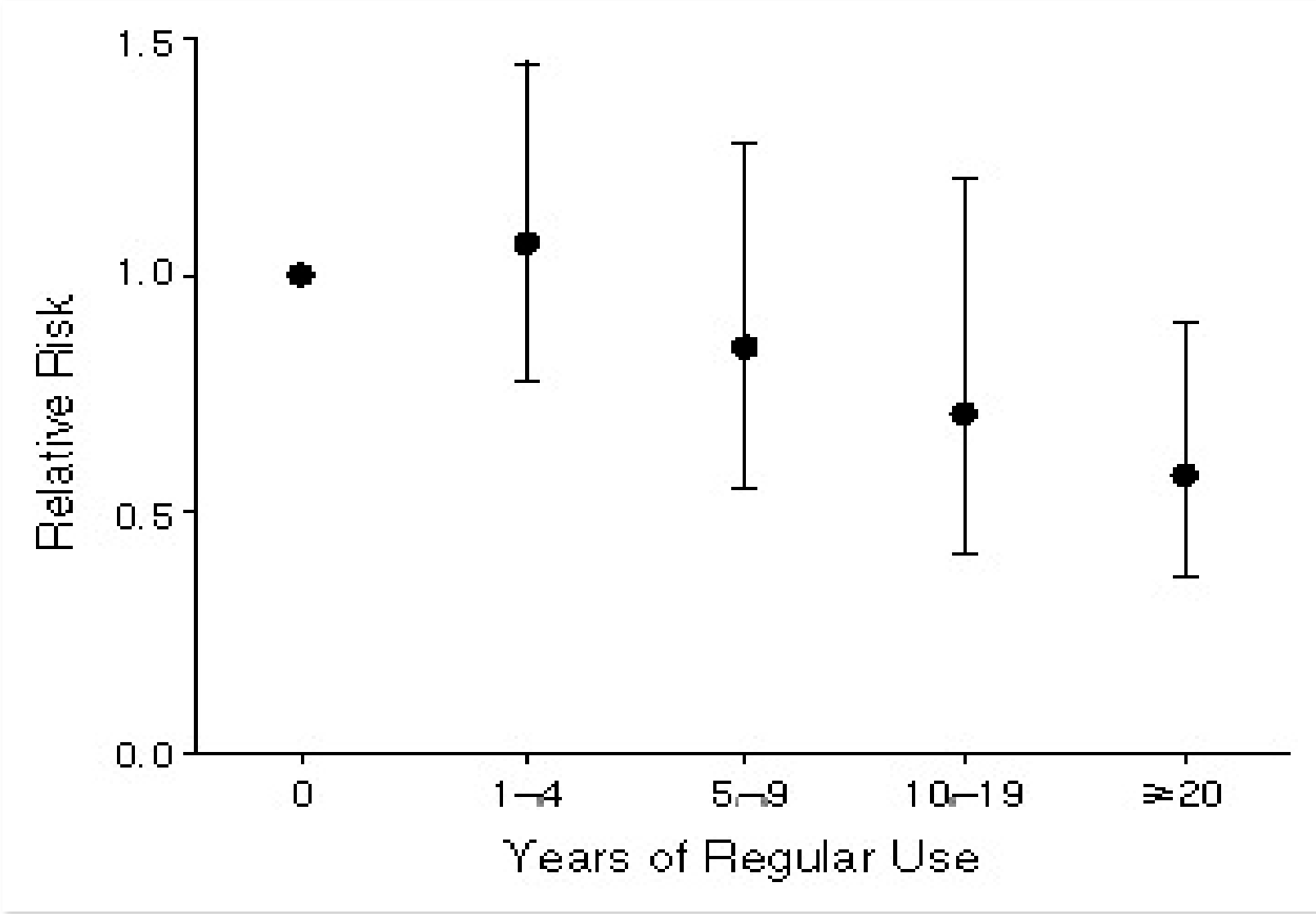
Arachidonic Acid
Aspirin
NSAIDs
COX-1
COX-2
PGH2
Prostanoids
Prostaglandin synthases
PGD2, PGF2α, PGI2, TXA2
PGE2
Prostaglandin E2 receptors
EP1, EP2, EP3, EP4
PPARδ
β-Catenin
EGF-R
PI3K/AKT
transcriptional activity
Target genes
Cyclin D1
Bcl-2
VEGF
Biologic activities
Growth
Migration & invasion
Anti-apoptosis
Angiogenesis

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 randomized, placebo-controlled clinical trials 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).

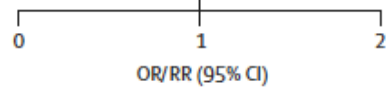
Age-Adjusted Relative Risks of Colorectal Cancer According to the Number of Consecutive Years of Regular Aspirin Use among Users as Compared with Nonusers of Aspirin



Nurses' Health Study
Giovannucci E et al. N Engl J Med 1995;333:609-614

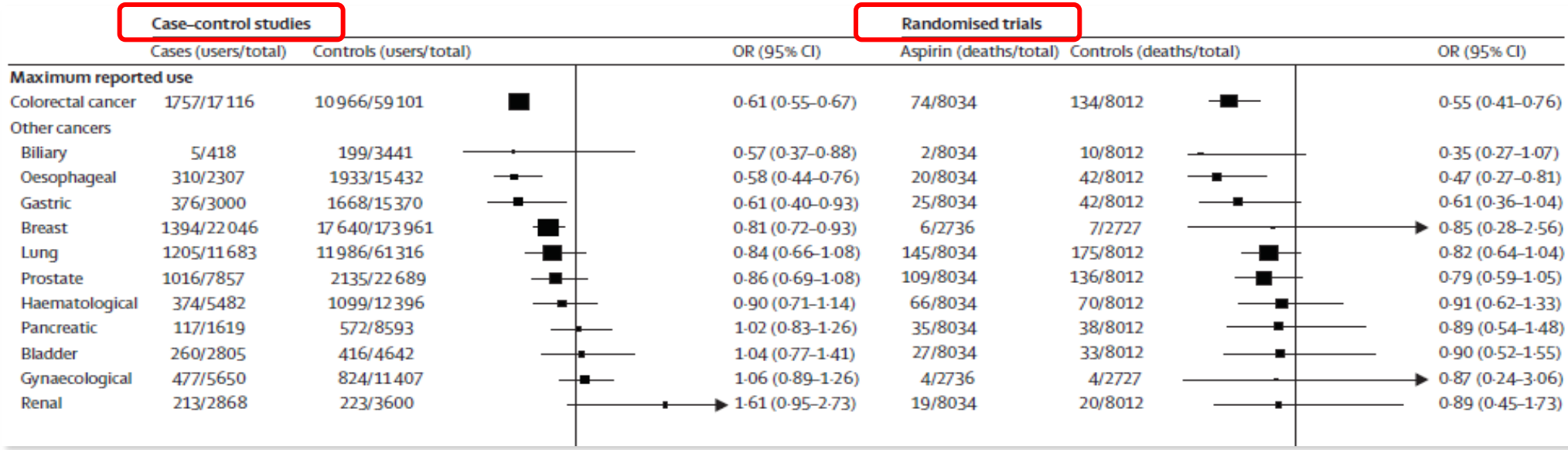
Associations between regular use of aspirin and risk of colorectal cancer in case–control and cohort studies compared with estimates from randomised controlled trials

Study type	N	Aspirin	Controls	OR (95% CI)	Significance	Heterogeneity
Randomised trials						
Daily aspirin	6	91/9833	154/9859	0·58 (0·44–0·78)	p=0·0002	p=0·45
Daily aspirin ≥5 years	6	74/8034	134/8012	0·55 (0·41–0·76)	p=0·0002	p=0·26
	N	**Cases**	**Controls**	**OR (95% CI)**	**Significance**	**Heterogeneity**
Case–control						
Any aspirin	26	10 464/25 618	28 300/47 834	0·67 (0·60–0·74)	p<0·0001	p<0·0001
Maximum reported aspirin	17	1551/12 659	2664/18 153	0·62 (0·58–0·67)	p<0·0001	p=0·13
Aspirin ≥5 years	10	971/7682	1534/10 029	0·68 (0·63–0·75)	p<0·0001	p=0·82
Daily aspirin	4	165/1254	349/1523	0·49 (0·40–0·60)	p<0·0001	p=0·65
Daily aspirin ≥5 years	1	66/1668	121/1973	0·63 (0·46–0·86)	p=0·004	NA
	N	**Aspirin**	**Controls**	**RR (95% CI)**	**Significance**	**Heterogeneity**
Standard cohort						
Any aspirin	11	3791/2 764 414	3623/2 514 652	0·85 (0·82–0·89)	p<0·0001	p=0·12
Maximum reported aspirin	8	661/664 475	1858/1 374 905	0·78 (0·71–0·84)	p<0·0001	p=0·02
Aspirin ≥5 years	4	889/1 022 192	1311/1 304 760	0·76 (0·70–0·82)	p<0·0001	p=0·32
Daily aspirin	5	741/658 536	1115/819 288	0·80 (0·73–0·88)	p<0·0001	p=0·01
Daily aspirin ≥5 years	1	60/38 302	420/232 116	0·68 (0·52–0·90)	p=0·006	NA
	N	**Cases**	**Controls**	**OR (95% CI)**	**Significance**	**Heterogeneity**
Nested case–control						
Any aspirin	6	2215/8926	65 099/109 526	0·87 (0·75–1·00)	p=0·07	p=0·005
Maximum reported aspirin	5	206/4457	8302/40 948	0·67 (0·58–0·77)	p<0·0001	p=0·10
Aspirin ≥5 years	1	116/228	23 704/37 935	0·62 (0·48–0·81)	p<0·0001	NA
Daily aspirin	1	53/165	8744/22 975	0·77 (0·55–1·07)	p=0·14	NA
Daily aspirin ≥5 years	1	29/141	7274/21 505	0·51 (0·34–0·76)	p=0·012	NA



Algra AM & Rothwell P. Lancet Oncol. 2012;13:518-27

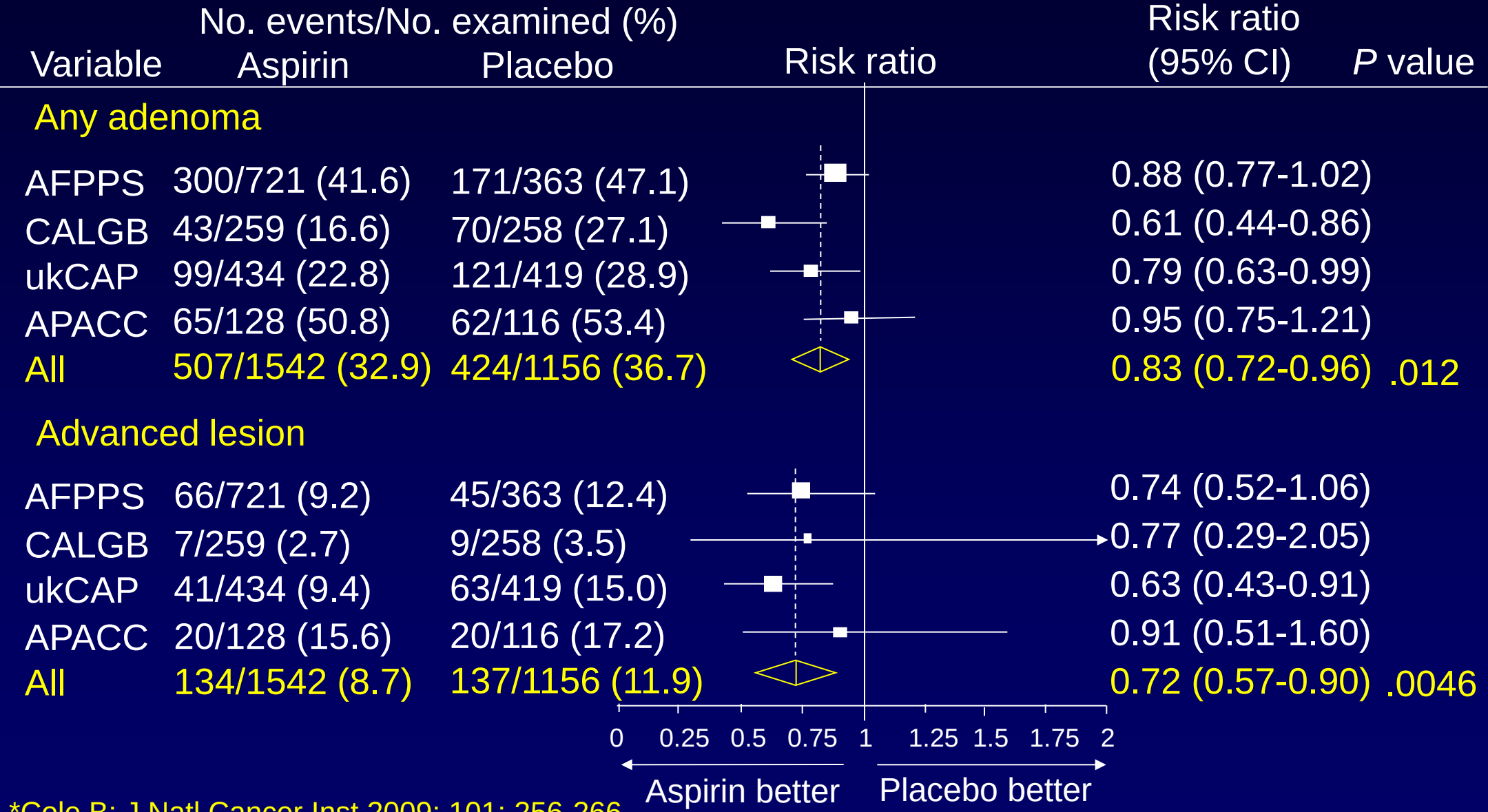
Evidence from case-control studies vs evidence from meta-analysis of trials of aspirin versus control, by tumor site



	Case–control studies			Randomised trials		
	Cases (users/total)	Controls (users/total)	OR (95% CI)	Aspirin (deaths/total)	Controls (deaths/total)	OR (95% CI)
Maximum reported use						
Colorectal cancer	1757/17 116	10 966/59 101	0·61 (0·55–0·67)	74/8034	134/8012	0·55 (0·41–0·76)
Other cancers						
Biliary	5/418	199/3441	0·57 (0·37–0·88)	2/8034	10/8012	0·35 (0·27–1·07)
Oesophageal	310/2307	1933/15 432	0·58 (0·44–0·76)	20/8034	42/8012	0·47 (0·27–0·81)
Gastric	376/3000	1668/15 370	0·61 (0·40–0·93)	25/8034	42/8012	0·61 (0·36–1·04)
Breast	1394/22 046	17 640/173 961	0·81 (0·72–0·93)	6/2736	7/2727	0·85 (0·28–2·56)
Lung	1205/11 683	11 986/61 316	0·84 (0·66–1·08)	145/8034	175/8012	0·82 (0·64–1·04)
Prostate	1016/7857	2135/22 689	0·86 (0·69–1·08)	109/8034	136/8012	0·79 (0·59–1·05)
Haematological	374/5482	1099/12 396	0·90 (0·71–1·14)	66/8034	70/8012	0·91 (0·62–1·33)
Pancreatic	117/1619	572/8593	1·02 (0·83–1·26)	35/8034	38/8012	0·89 (0·54–1·48)
Bladder	260/2805	416/4642	1·04 (0·77–1·41)	27/8034	33/8012	0·90 (0·52–1·55)
Gynaecological	477/5650	824/11 407	1·06 (0·89–1·26)	4/2736	4/2727	0·87 (0·24–3·06)
Renal	213/2868	223/3600	1·61 (0·95–2·73)	19/8034	20/8012	0·89 (0·45–1·73)

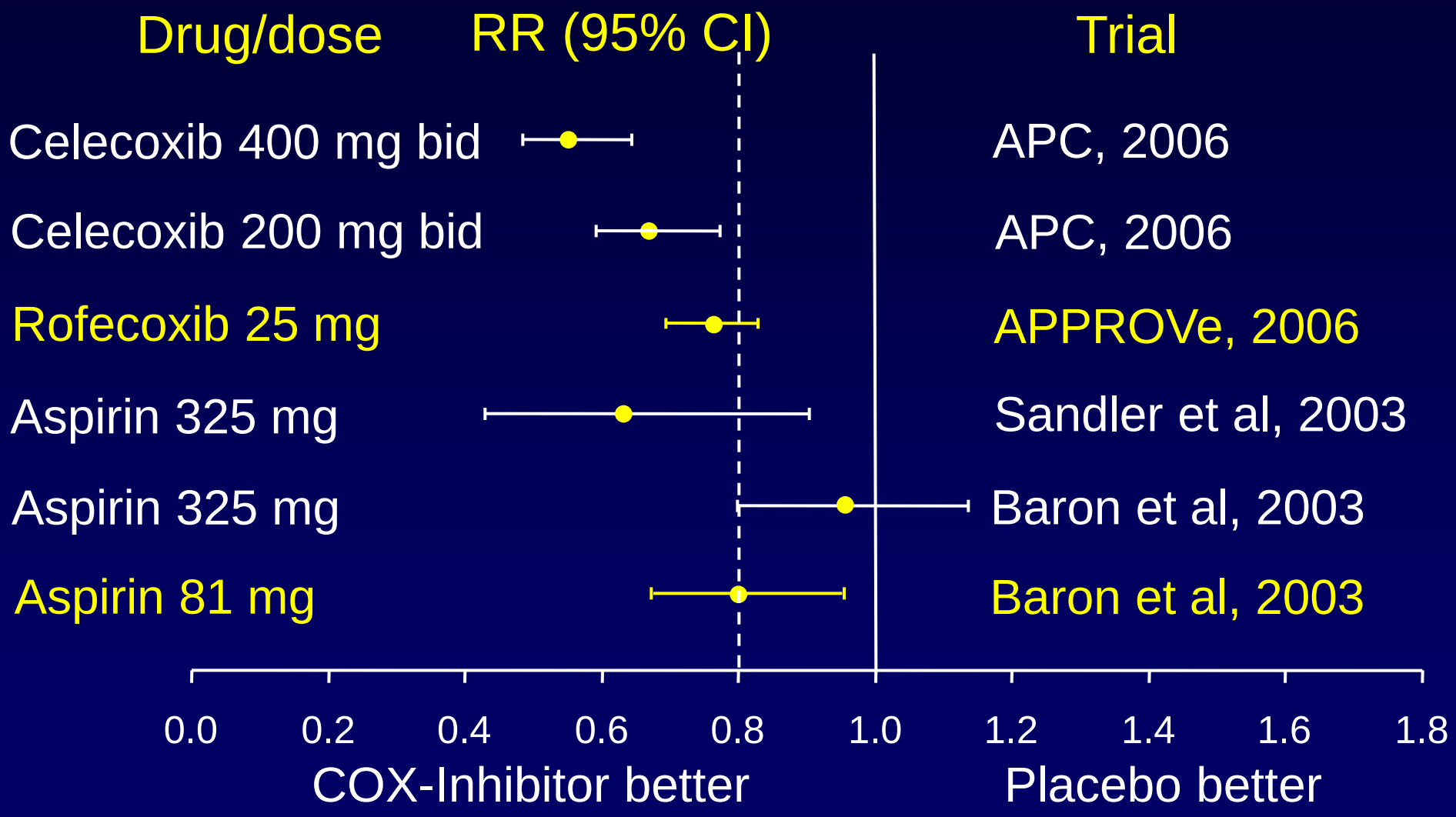
Algra AM & Rothwell P. Lancet Oncol. 2012;13:518-27

Meta-Analysis of RCTs of Aspirin vs Placebo for the Secondary Prevention of Colorectal Adenomas*



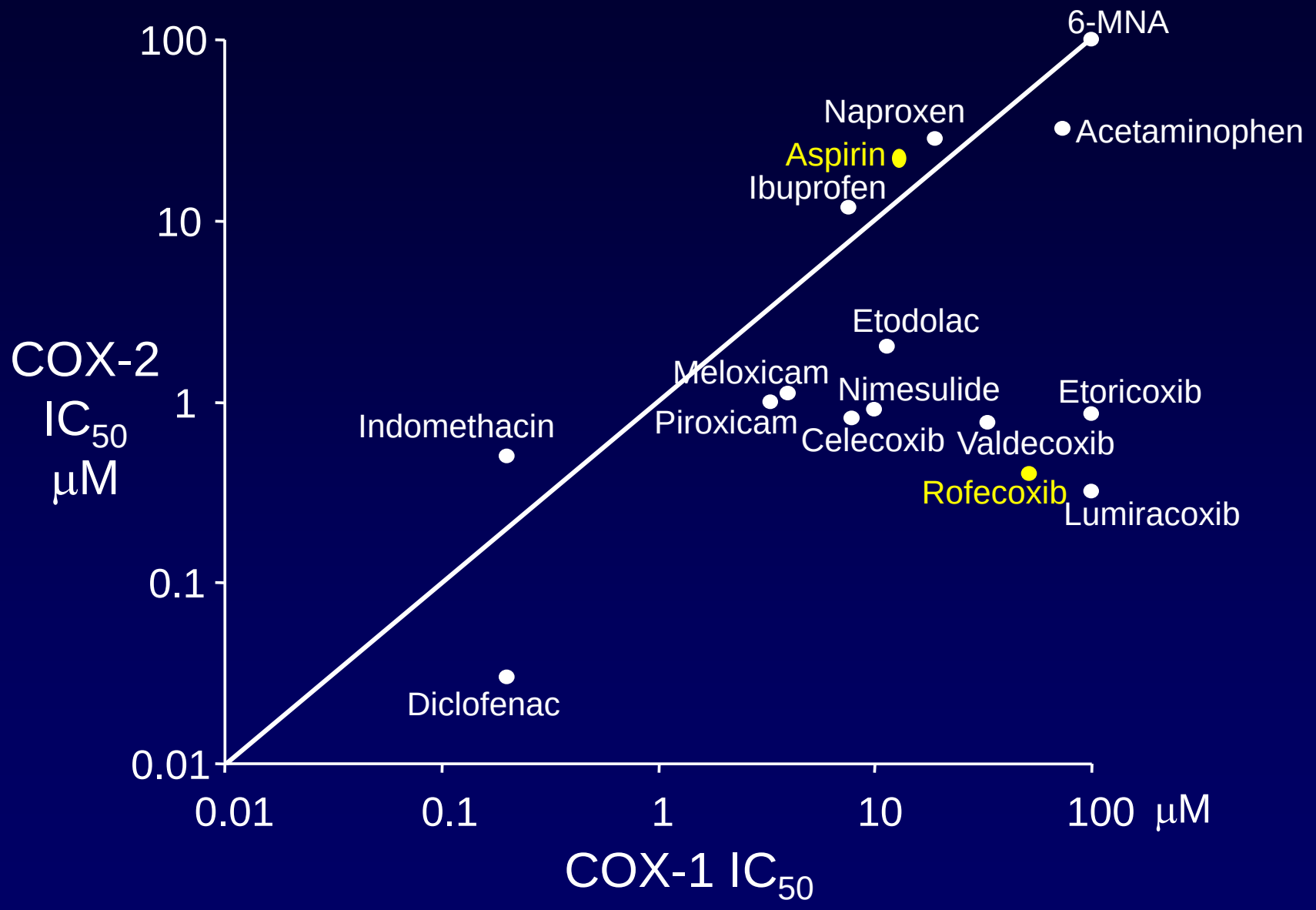
*Cole B; J Natl Cancer Inst 2009; 101: 256-266

Relative Risk of Any Colorectal Adenoma at Follow-up Endoscopic Examination



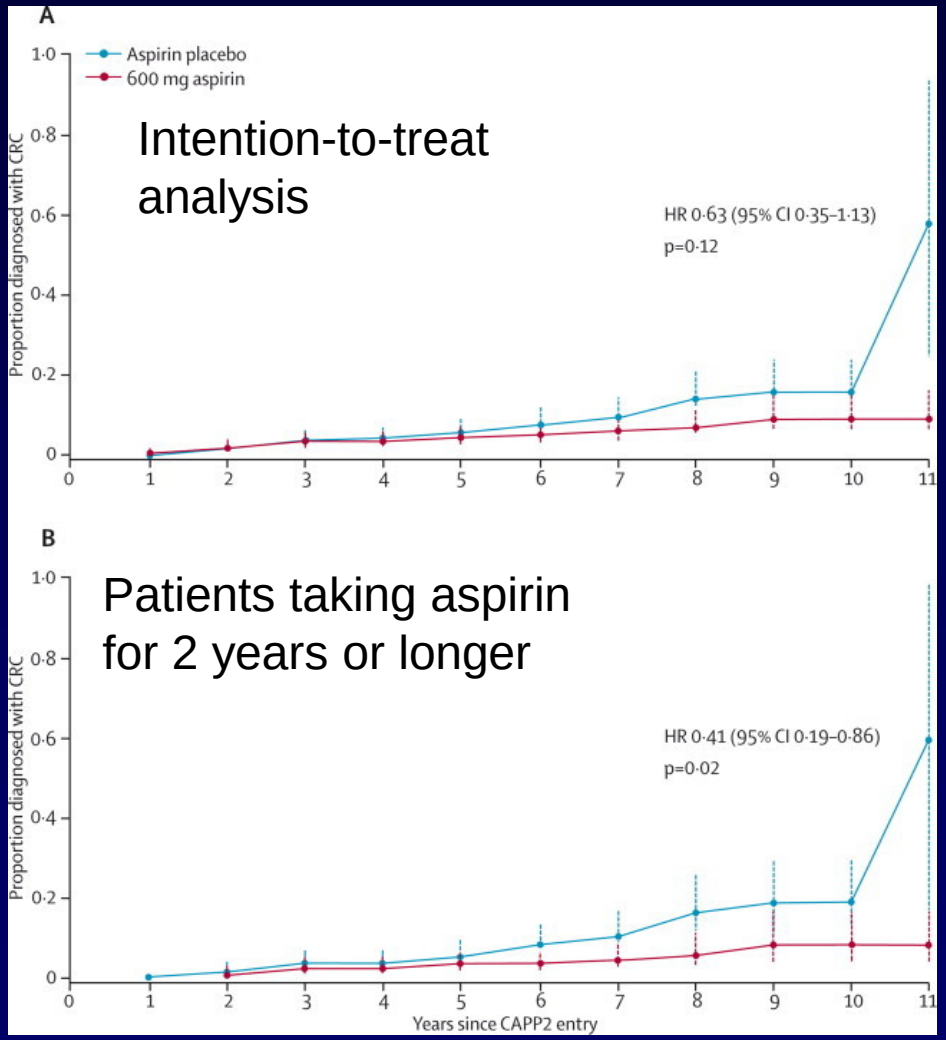
Patrono & Rocca, ATVB 2008;28:25S-32S

COX-2 Selectivity as a Continuous Variable



Updated from FitzGerald & Patrono, N Engl J Med 2001; 345:433-442

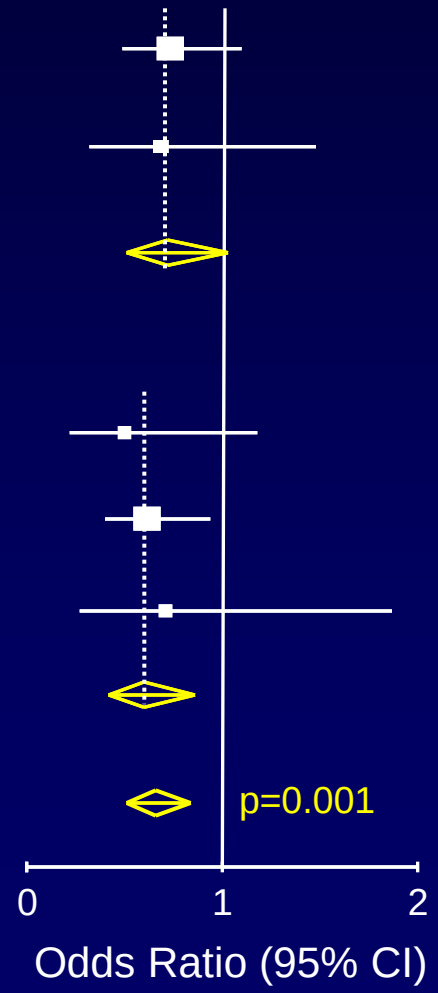
Death due to CRC in patients with Linch Syndrome randomly assigned to aspirin 600 mg compared with those assigned to aspirin placebo



Burn J. Lancet. 2011;378:2081-7

Death Due to Colorectal Cancer on Long-Term Follow-Up After Randomization in Trials of Aspirin vs Control

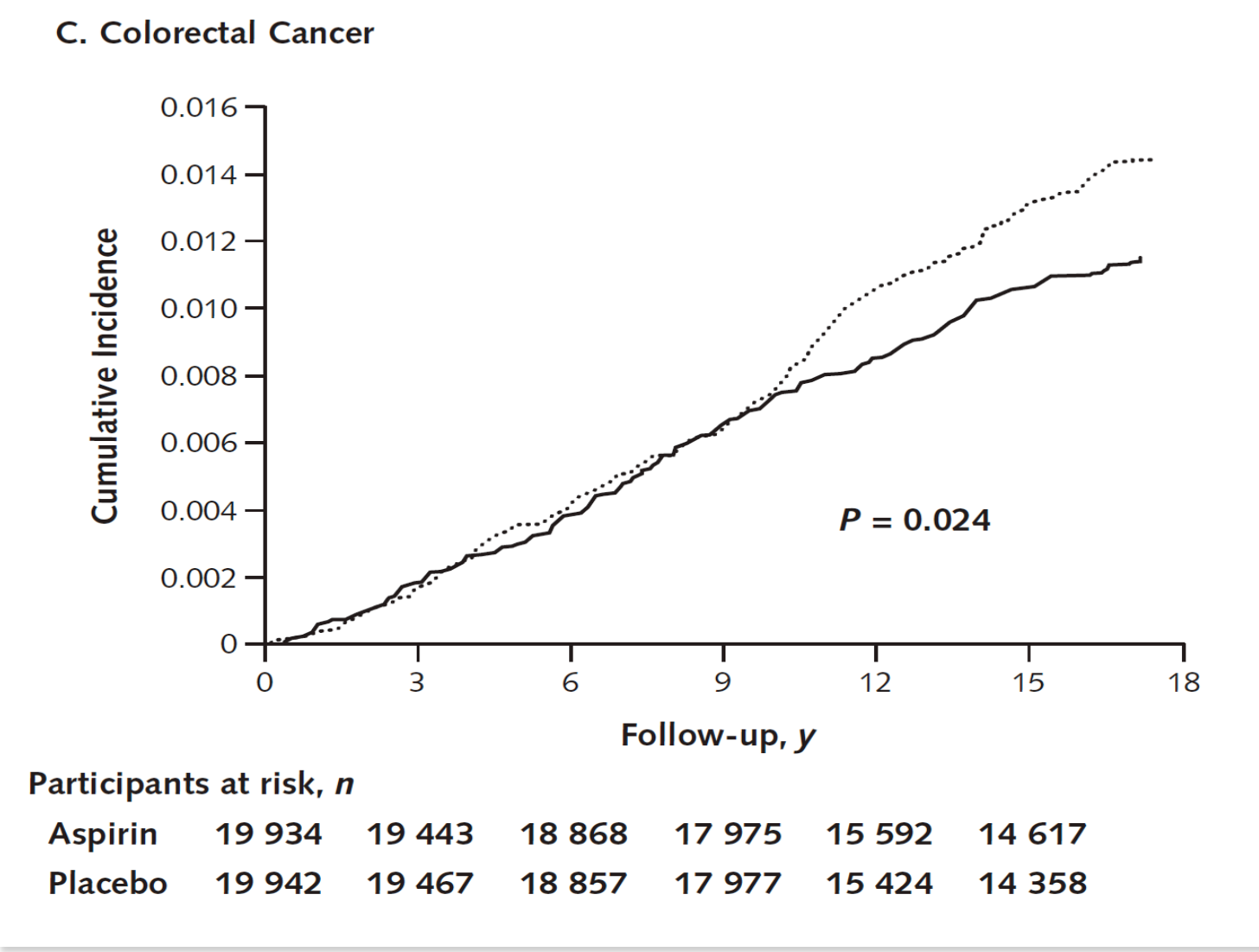
	Deaths due to cancer Aspirin	Control	Odds Ratio	95% CI
500-1200mg daily				
British Doctors Study (500mg)	59/3429	40/1710	0.73	0.49-1.10
UK-TIA (1200mg)	11/821	16/817	0.68	0.31-1.47
SUBTOTAL	70/4250	56/2527	0.72	0.50-1.03
75 - 300mg daily				
UK-TIA (300mg)	8/811	16/817	0.50	0.21-1.17
TPT (75mg)	34/2545	55/2540	0.61	0.40-0.94
SALT (75mg)	7/676	10/684	0.71	0.27-1.86
SUBTOTAL	49/4032	81/4041	0.60	0.42-0.86
TOTAL	119/8282	137/6568	0.66	0.51-0.84



Heterogeneity: p=0.84

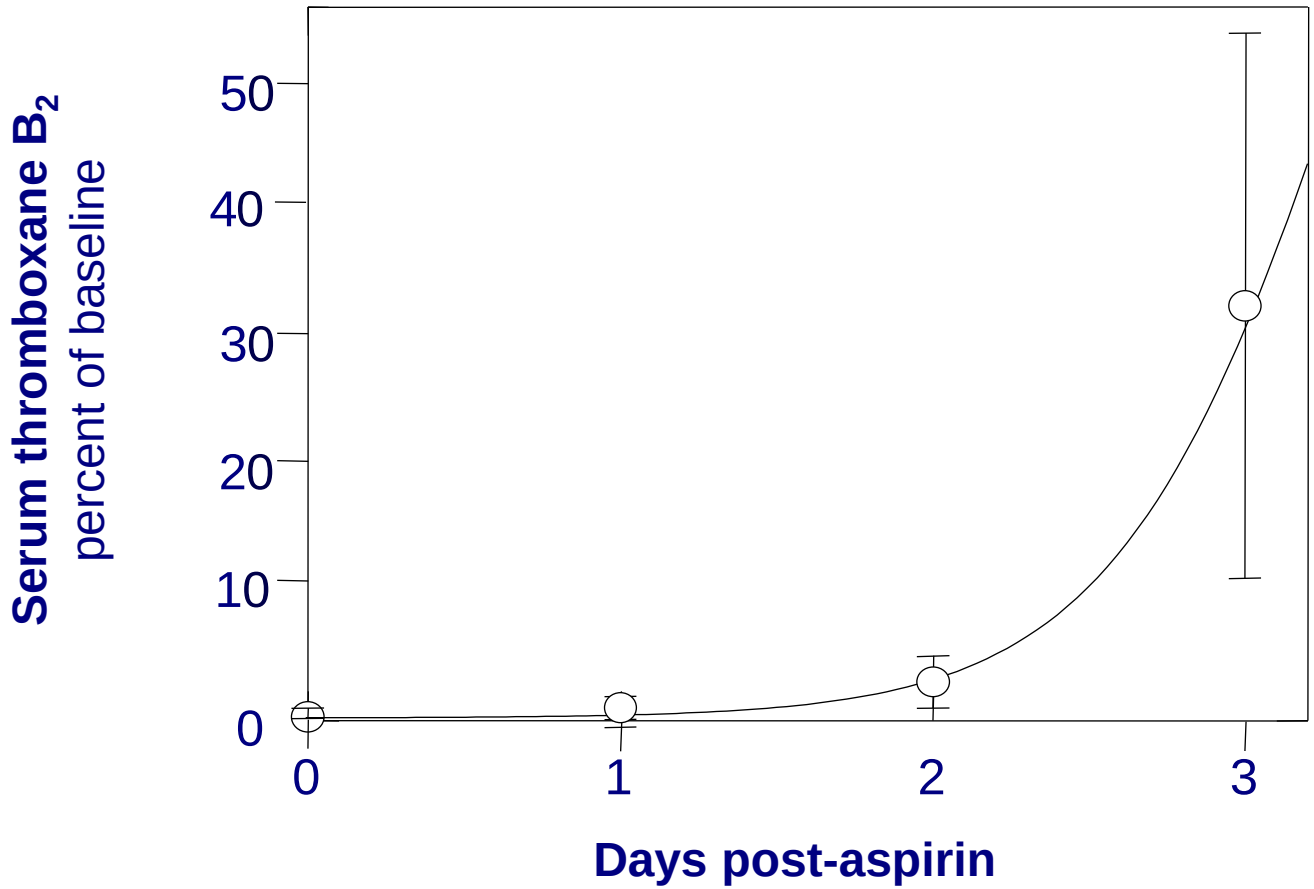
Rothwell PM et al, Lancet 2010; 376:1741-50

Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of Women's Health Study



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

Lag in recovery of serum TXB_2 after aspirin withdrawal in healthy volunteers



Santilli, Rocca et al JACC 2009;53:677-77

Some Features of the Chemopreventive Effect of Aspirin Against Colorectal Cancer in Cardiovascular Trials

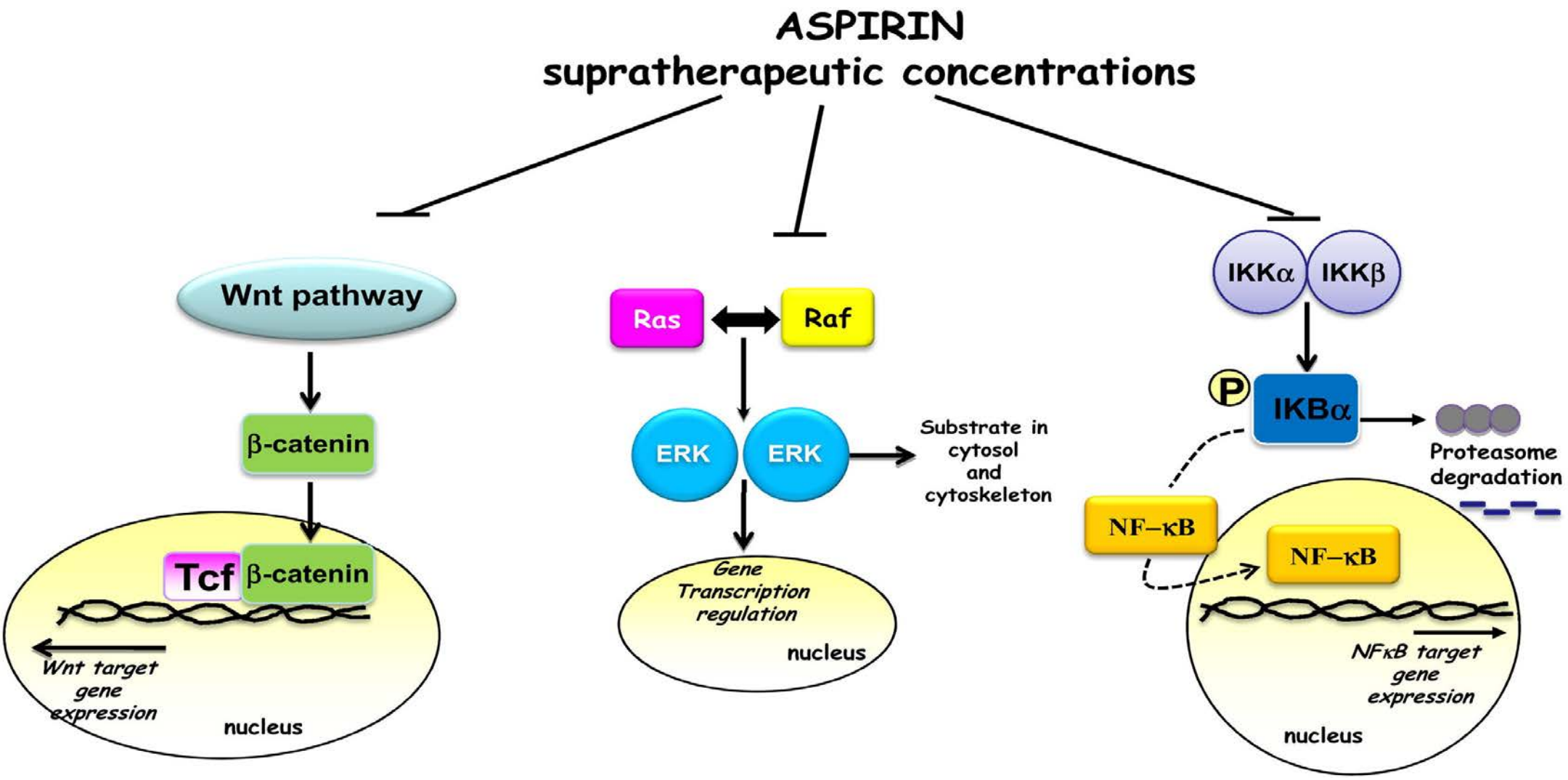
- Detectable benefits at daily doses as low as 75 mg (SALT, TPT);
- No convincing evidence that higher doses (up to 1200 mg daily) are more effective (Rothwell et al 2010, 2011);
- Chemoprevention detectable with alternate day 100 mg dosing in healthy women (Cook et al, Ann Intern Med 2013);
- Chemoprevention detectable with a low-dose (75 mg) controlled-release formulation developed to maximize cumulative inhibition of platelet COX-1 in the prehepatic circulation and minimize inhibition of COX-2 in the systemic vascular endothelium (FitzGerald et al; TPT).

Patrono C. Eur Heart J 2013;34:3403-11

Any effects of low-dose aspirin administered once daily or every other day on nucleated cellular targets would be more difficult to reconcile with its pharmacokinetics (very short half-life) and pharmacodynamics (relatively selective inhibition of platelet COX-1)

None of these features are compatible with a direct inhibitory effect of low-dose aspirin on COX-2 or with various COX-independent mechanisms that have been proposed.

COX-independent mechanisms of the antitumoural effects of aspirin



Bruno A et al. Best Pract Res Clin Gastroenterol 2012;26:e1-e13

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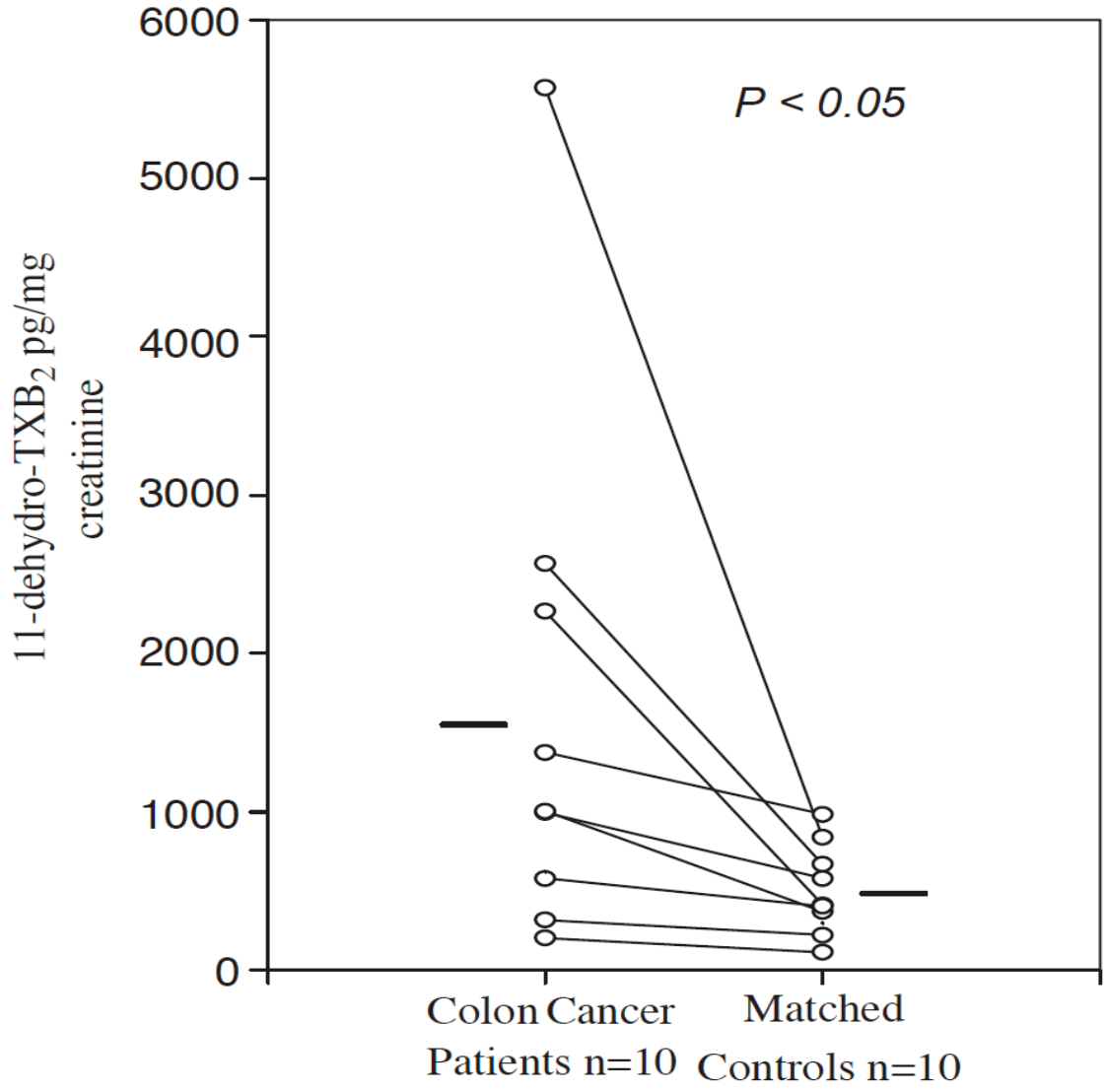
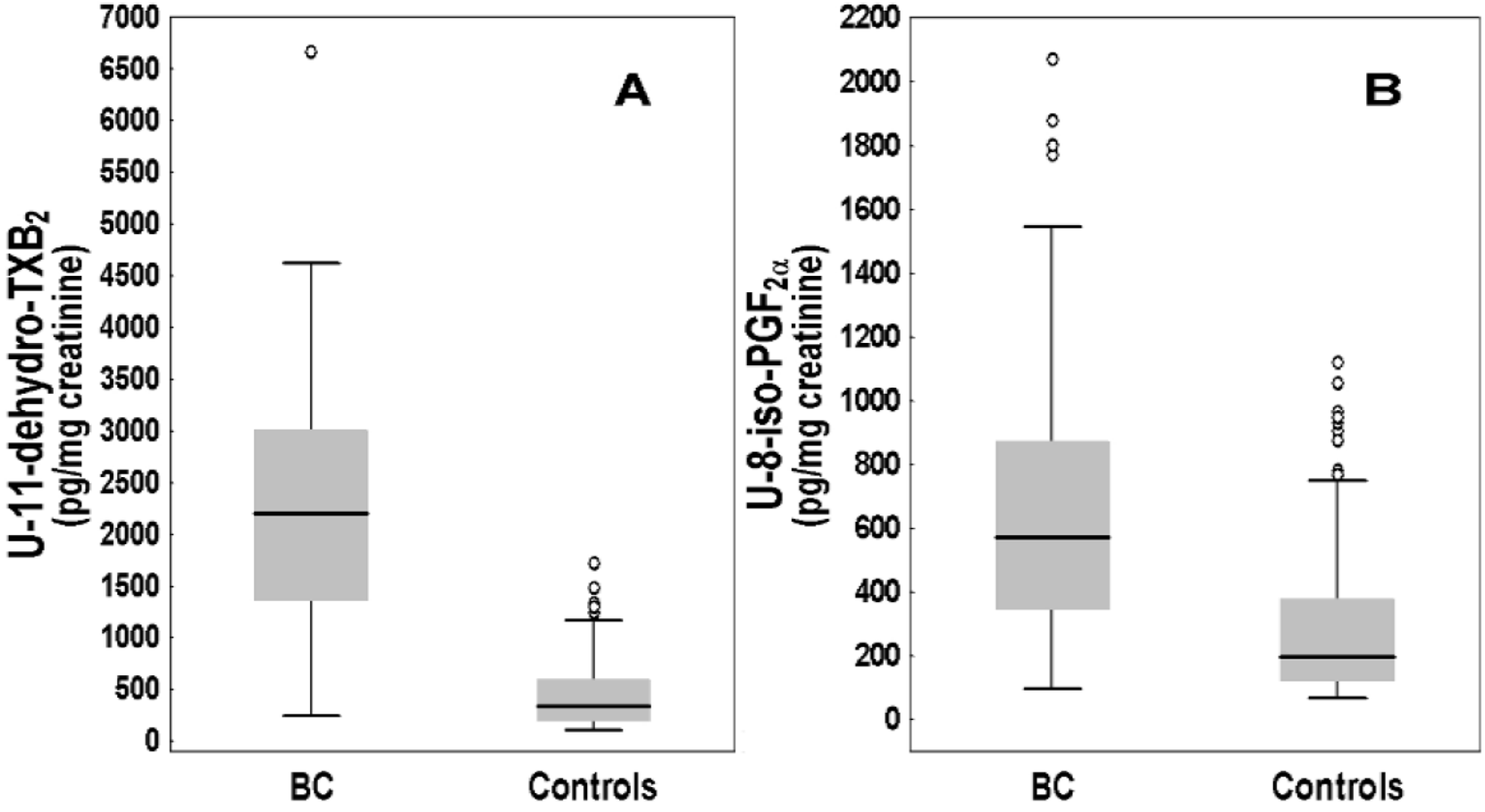
Platelet activation in patients with colorectal cancer



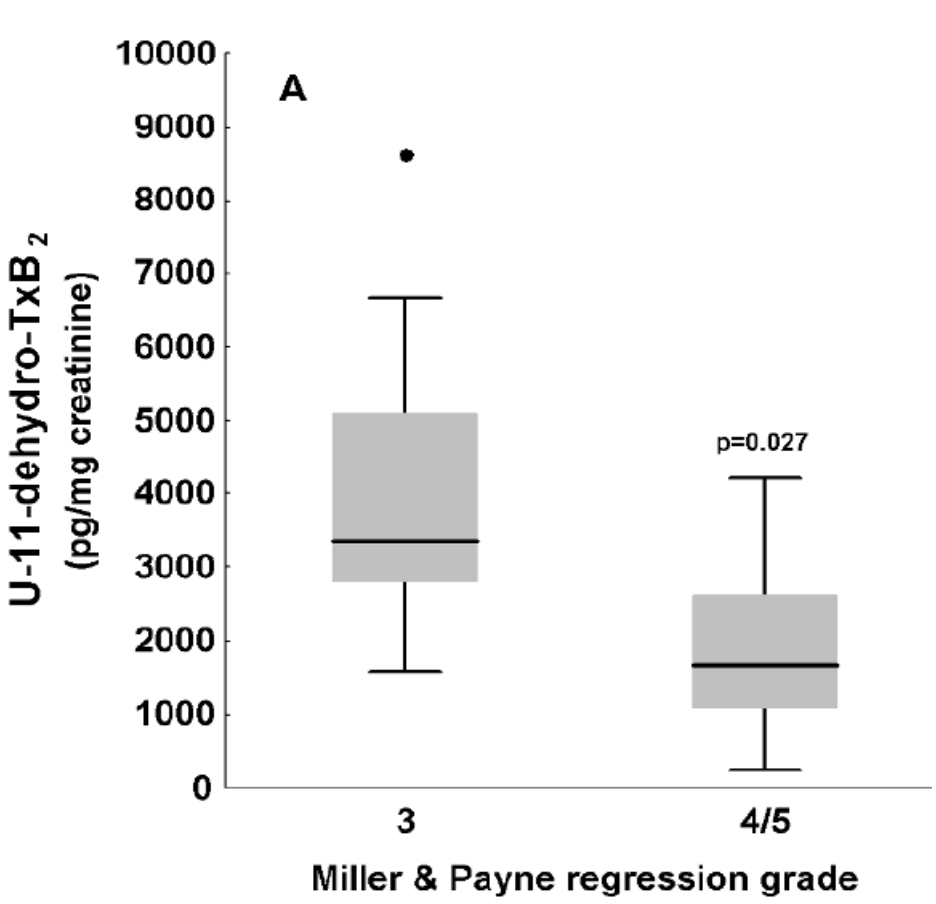
Sciulli MG et al. Prostaglandins Leukot Essent Fatty Acids 2005;72:79-83

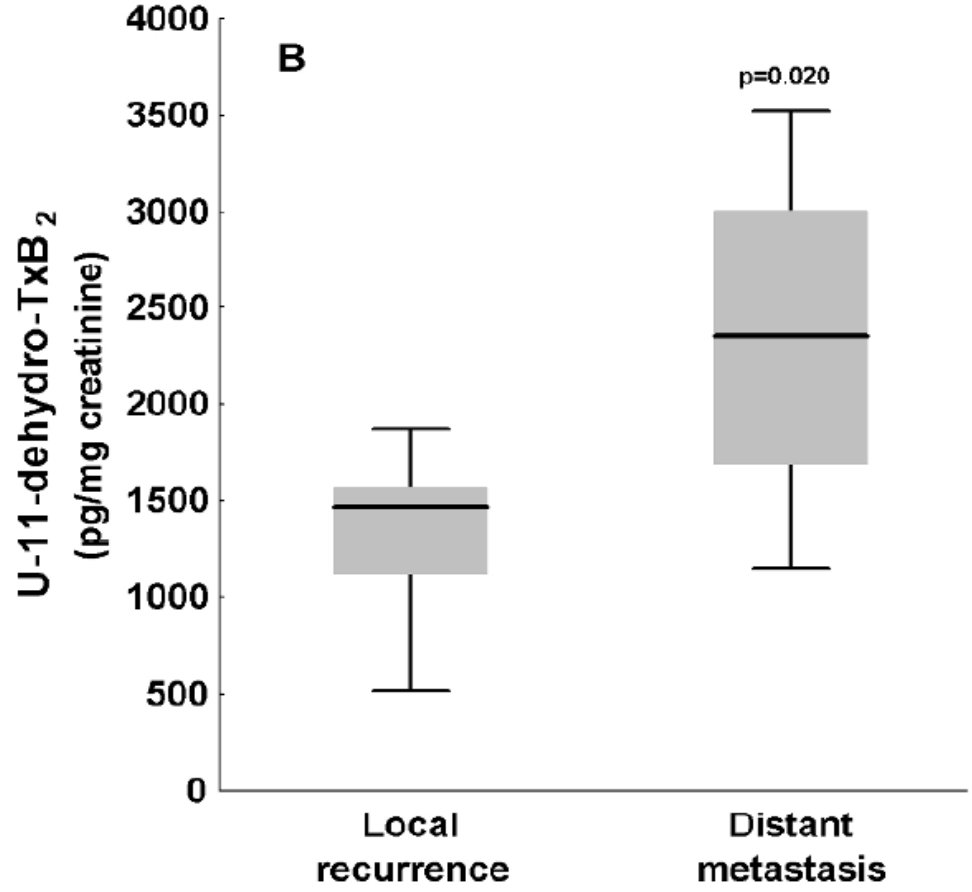
Oxidant stress as a major determinant of platelet activation in invasive breast cancer



Ferroni P, Santilli F, Davì G, et al. Int J Cancer 2016.

U-11-dehydro-TXB_2 excretion levels measured at time of surgery predicted poor pathological response to neoadjuvant chemotherapy and distant metastasis





Ferroni P, Santilli F, Davì G, et al. Int J Cancer 2016.

Activated Platelets at Sites of Intestinal Mucosal Injury

Low-dose Aspirin

Pro-angiogenic

TXA_2
PDGF
TGFβ

PGE_2
IL-1β

Pro-inflammatory

Endothelial cells

Stromal cells

COX-2

COX-2

t-NSAIDs
Coxibs

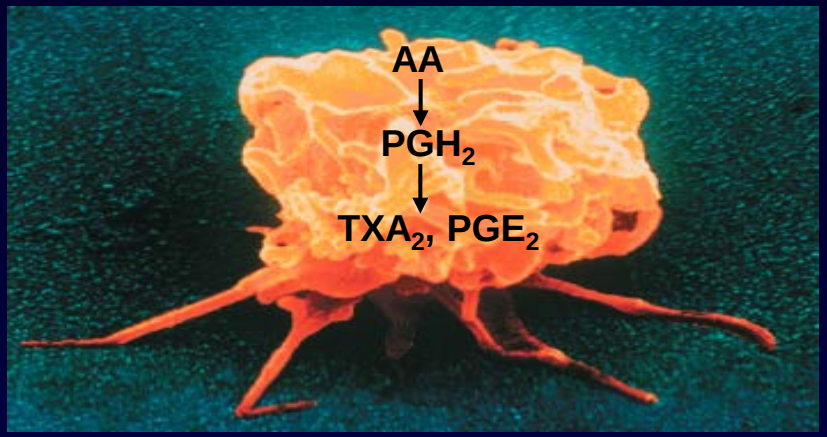
PGE_2

PGE_2

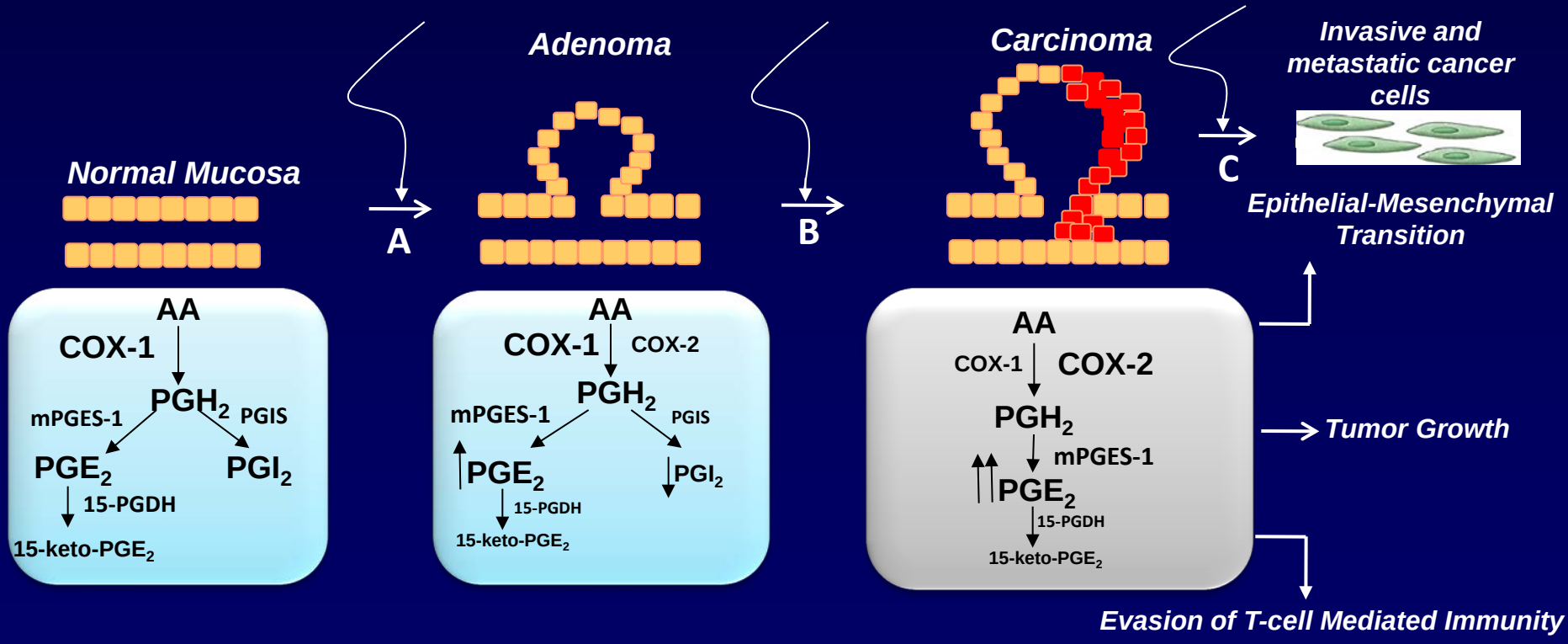
Patrono, Patrignani & Garcìa Rodrìguez, JCI 2001;Thun, Jacobs & Patrono, Nature Rev Clin Oncol 2012

↑ Angiogenesis

↓ Apoptosis ↑ Cellular proliferation



Lipid and protein mediators, and microvescicles (rich in microRNAs) are released from activated platelets and interact with adjacent resident cells and circulating cancer cells

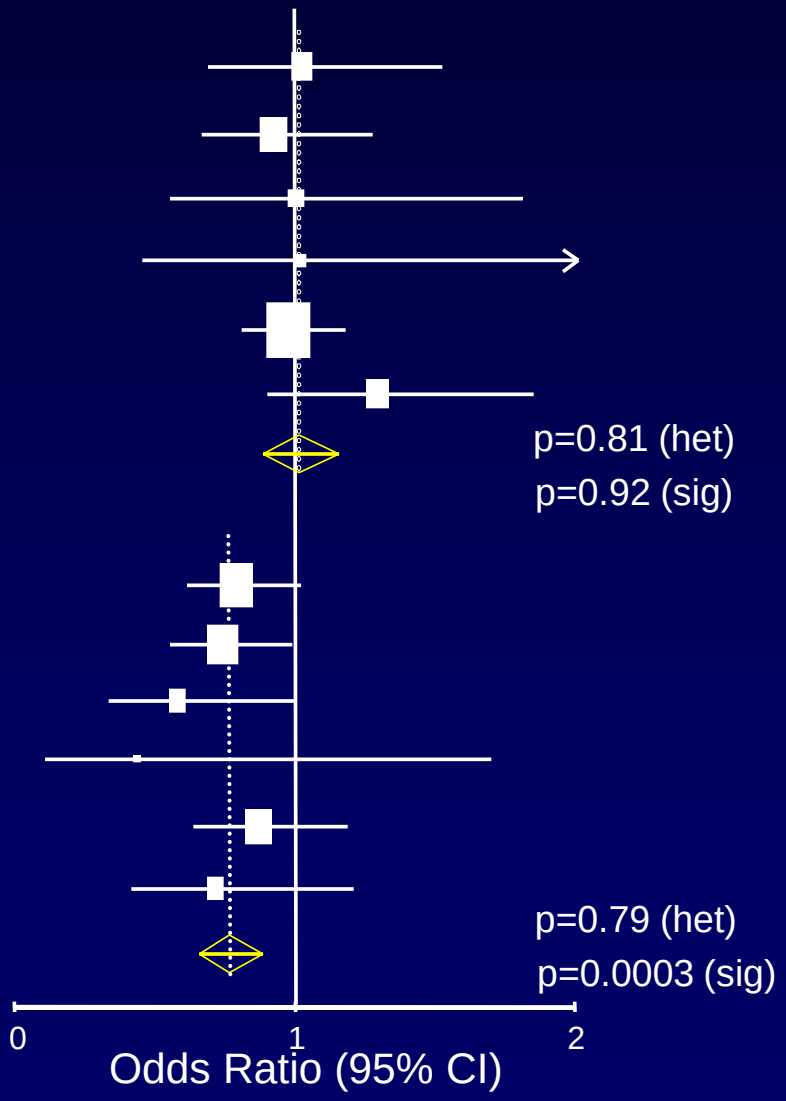


Patrignani & Patrono, J Am Coll Cardiol 2016;68:967-76.

What is the time course of the chemopreventive effect?

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

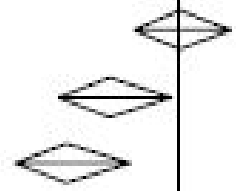


Rothwell et al, Lancet 2012;379:1602–1612

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

	Events/participants		ARR per 1000 patients per year	Odds ratio (95% CI)	$p_{interaction}$
	Aspirin	Control			
Cancers					
0–2·9 years	445/17745	442/17790	−0·06	1·01 (0·88–1·15)	
3·0–4·9 years	193/16463	237/16484	2·19	0·81 (0·67–0·98)	0·04
≥5 years	131/4444	184/4460	4·80	0·70 (0·56–0·88)	



Rothwell PM et al. Lancet 2012;379:1602-12

Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials

Peter M Rothwell, Michelle Wilson, Jacqueline F Price, Jill F F Belch, Tom W Meade, Ziyah Mehta

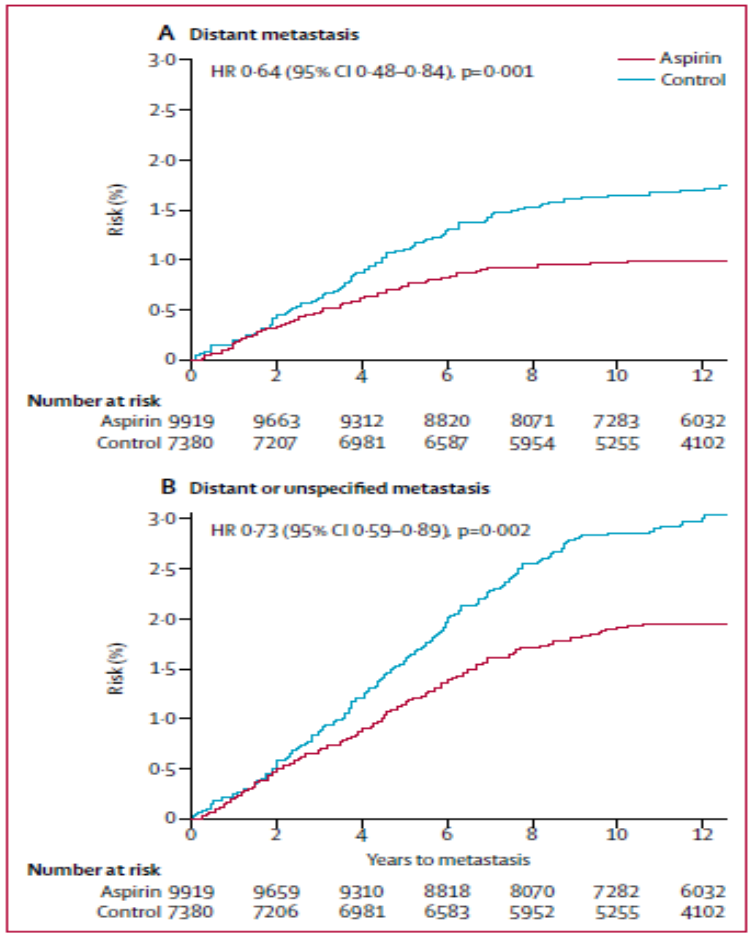


Figure 1: **The effect of aspirin on risk of metastasis due to any incident cancer diagnosed during five trials of aspirin versus control**
Analysis is based on time from randomisation to diagnosis of metastasis during or after the trials. Part A shows definite site-specific distant metastasis and part B also includes metastatic cancers in which the site of the metastasis was not specified. HR=hazard ratio from a Cox regression stratified by trial.

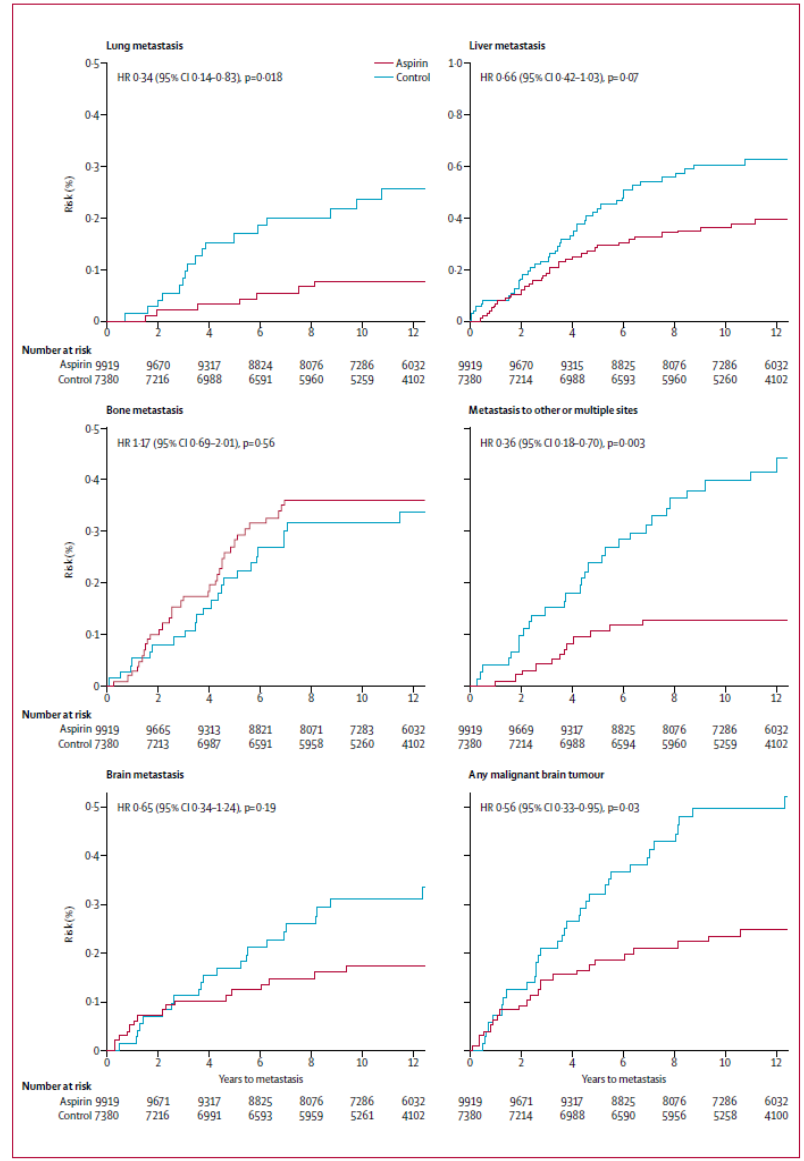
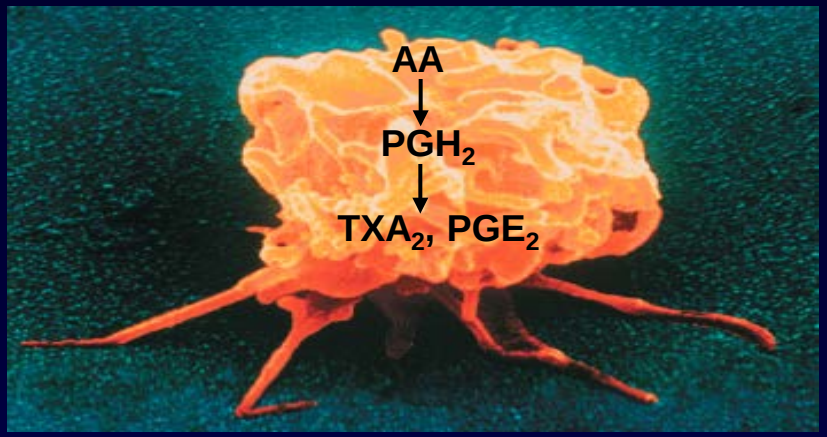


Figure 2: **The effect of aspirin on risk of definite distant metastasis due to any incident cancer diagnosed during five trials of aspirin versus control, stratified by site of metastasis**
Analysis is based on time from randomisation to diagnosis of metastasis during or after the trials. The sensitivity analysis of the effect of aspirin on risk of all malignant brain tumours is included because of the clinical inaccuracy in differentiating between a primary brain tumour and a solitary metastasis, particularly if a biopsy was not undertaken. 29 patients in the analysis of other or multiple metastasis are also included in analyses of site-specific metastasis. HR=hazard ratio from a Cox regression stratified by trial.



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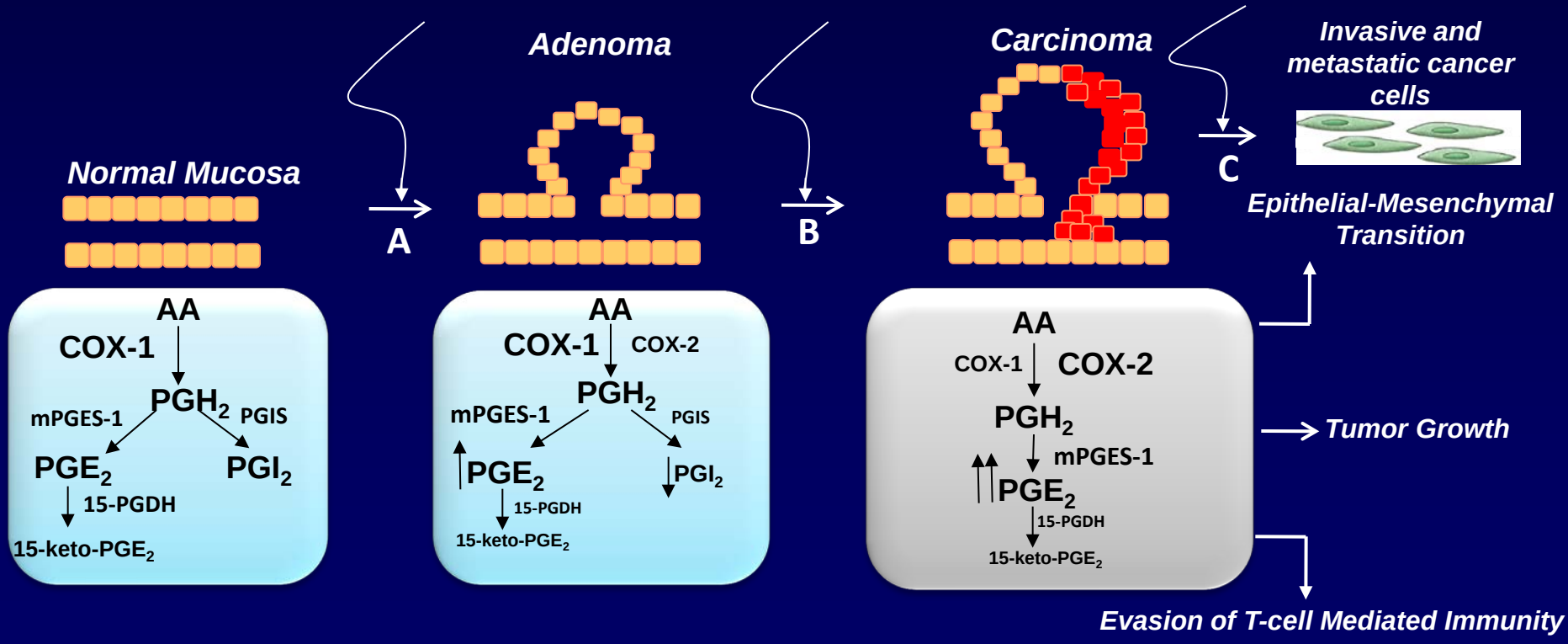


Patrignani & Patrono, J Am Coll Cardiol 2016;68:967-76.

Santilli et al. Eur J Intern Med 2016

TUMOR GROWTH

- Growth factors
- Angiogenesis
- Granulocytes reclutation

IMMUNE ESCAPE

- Platelet-cancer cell aggregates
- Platelet-fibrin deposition
- Blocking NK cell-mediated cytolysis

EXTRAVASATION

- MMP production
- MMP-mediated matrix degradation
- Vessel permeability
- EMT induction

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

IMMUNOTHERAPY

Platelets subvert T cell immunity against cancer via GARP-TGFβ axis

Saleh Rachidi,[1,2]* Alessandra Metelli,[1,2]* Brian Riesenberg,[1,2] Bill X. Wu,[1,2] Michelle H. Nelson,[1,2] Caroline Wallace,[1,2] Chrystal M. Paulos,[1,2,3] Mark P. Rubinstein,[1,2,3] Elizabeth Garrett-Mayer,[2,4] Mirko Hennig,[5] Daniel W. Bearden,[6] Yi Yang,[1,2] Bei Liu,[1,2] Zihai Li[1,2,7]†

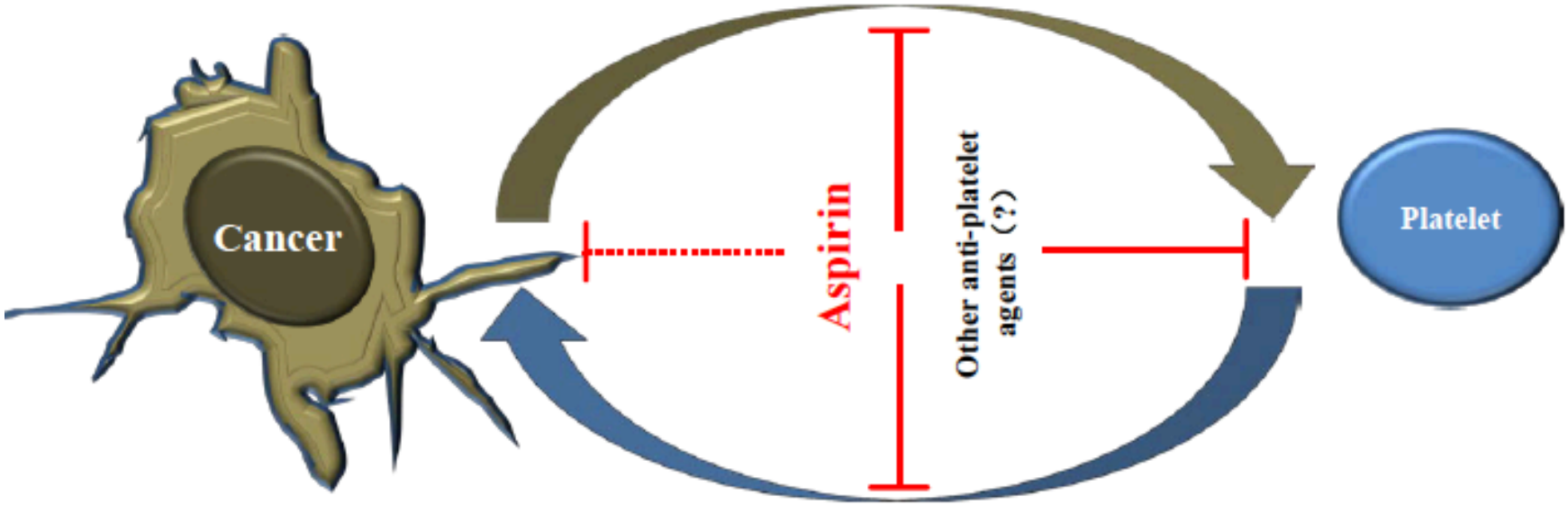
Cancer-associated thrombocytosis has long been linked to poor clinical outcome, but the underlying mechanism is enigmatic. We hypothesized that platelets promote malignancy and resistance to therapy by dampening host immunity. We show that genetic targeting of platelets enhances adoptive T cell therapy of cancer. An unbiased biochemical and structural biology approach established transforming growth factor β (TGFβ) and lactate as major platelet-derived soluble factors to obliterate $CD4^+$ and $CD8^+$ T cell functions. Moreover, we found that platelets are the dominant source of functional TGFβ systemically as well as in the tumor microenvironment through constitutive expression of the TGFβ-docking receptor glycoprotein A repetitions predominant (GARP) rather than secretion of TGFβ per se. Platelet-specific deletion of the GARP-encoding gene *Lrrc32* blunted TGFβ activity at the tumor site and potentiated protective immunity against both melanoma and colon cancer. Last, this study shows that T cell therapy of cancer can be substantially improved by concurrent treatment with readily available anti-platelet agents. We conclude that platelets constrain T cell immunity through a GARP-TGFβ axis and suggest a combination of immunotherapy and platelet inhibitors as a therapeutic strategy against cancer.

Rachidi et al. Sci Immunol 2017

Cancer and Platelet Crosstalk

Tumor cells

- induce platelet activation and aggregation;
- cause platelet extracellular vesicles and granule contents release;
- alter platelet phenotypes and platelet RNA profiles;
- enhance thrombopoiesis, etc.



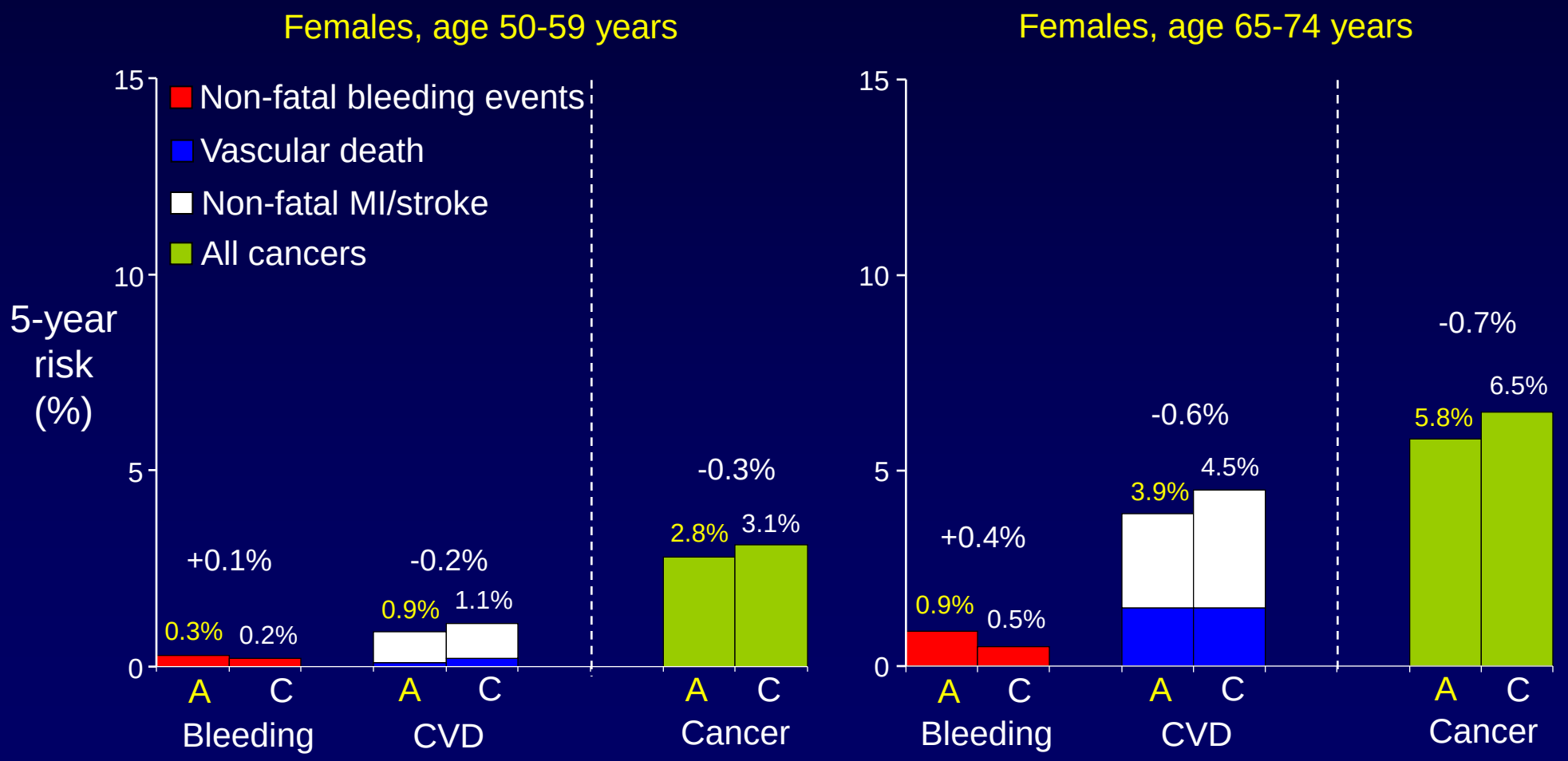
Platelets

- facilitate cancer to sustain proliferative signaling, resist cell death and induce angiogenesis;
- activate tumor cell invasion and support metastasis;
  a) induce an invasive epithelial-mesenchymal transition phenotype of tumor cells
  b) promote tumor cell survival in blood circulation
  c) facilitate tumor arrest at the vascular endothelium, extravasation and seeding
- promote tumor to evade immune destruction, etc.

Xu XR. Blood 2018 Mar 8

- SOURCES OF EVIDENCE FOR A CHEMOPREVENTIVE EFFECT OF ASPIRIN
- IS THERE A BIOLOGICALLY PLAUSIBLE MECHANISM OF ACTION?
- WHAT IS THE SIZE OF THE APPARENT CHEMOPREVENTIVE EFFECT, AND CAN IT POSSIBLY CHANGE THE BENEFIT/RISK PROFILE OF ASPIRIN IN PRIMARY PREVENTION?
- IS THE CURRENT EVIDENCE SUFFICIENT TO ISSUE CHEMOPREVENTIVE TREATMENT GUIDELINES?
- WHERE DO WE GO FROM HERE?

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

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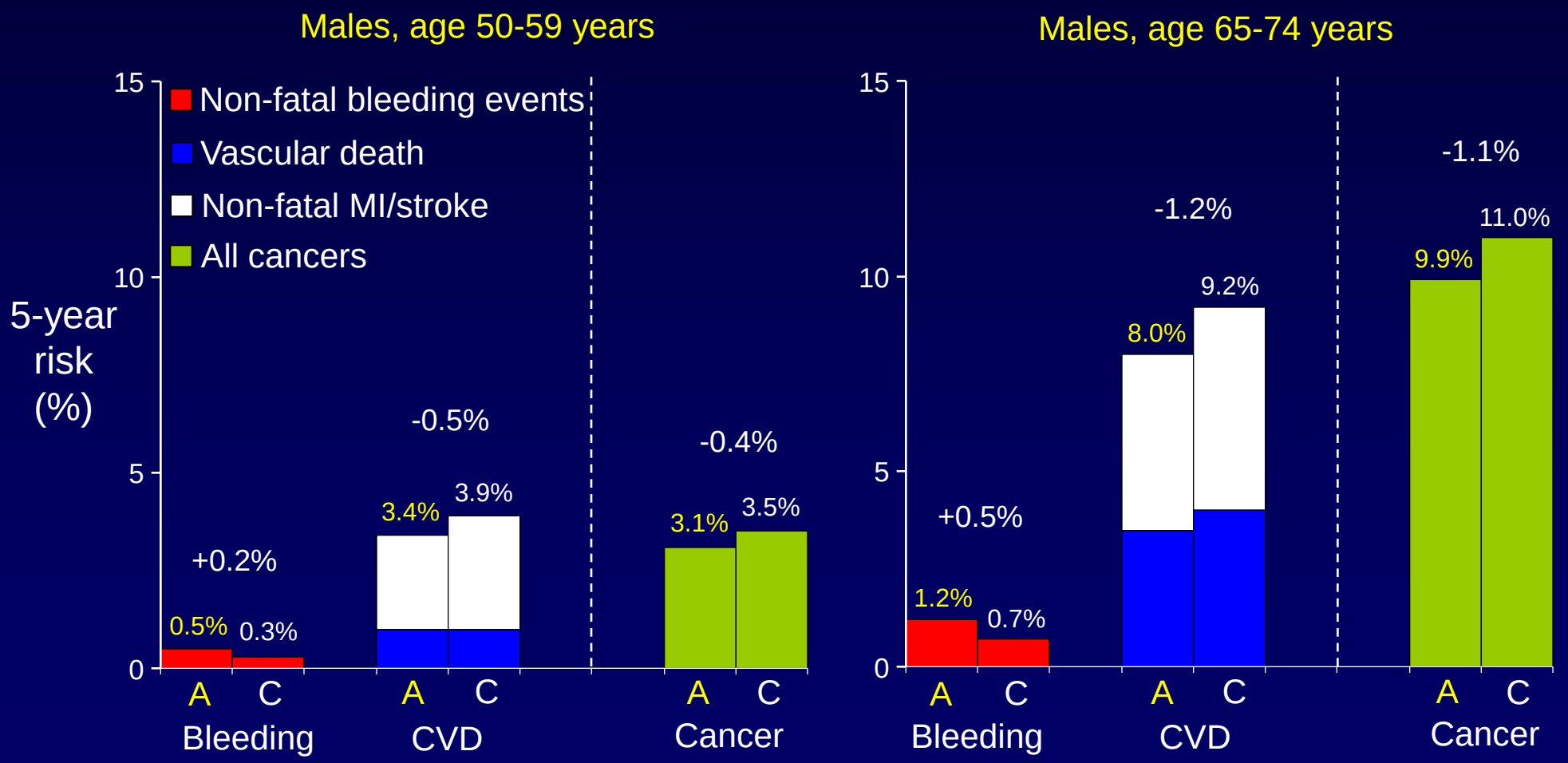
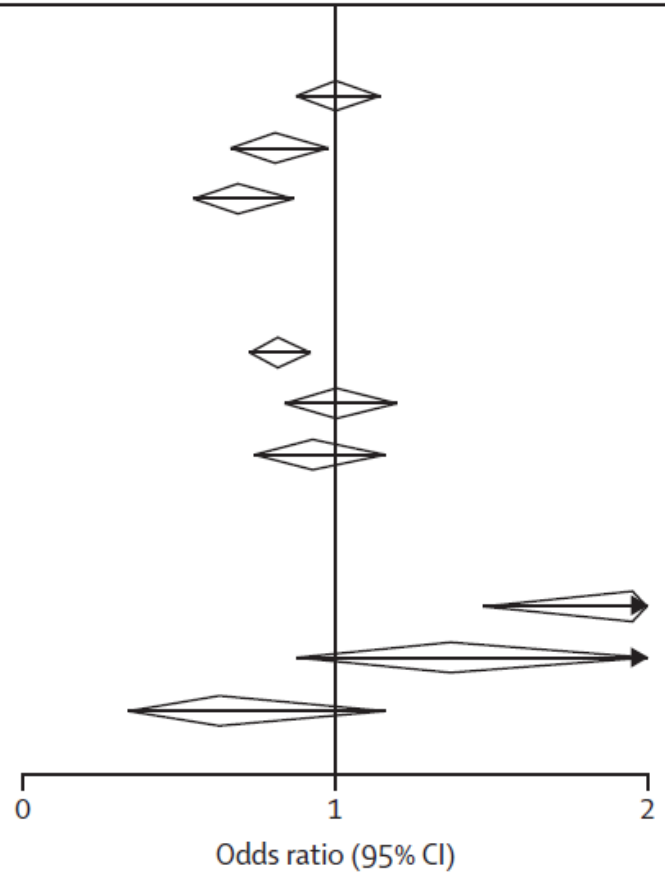


Thun, Jacobs, Patrono *Nature Rev Clin Oncol* 2012;9:259-67

Summary of primary prevention meta-analyses of the effect of aspirin on risks of incident cancer, major vascular events, and major extracranial bleeds

	Events/participants		ARR per 1000 patients per year	Odds ratio (95% CI)	$p_{interaction}$
	Aspirin	Control			
Cancers					
0–2·9 years	445/17745	442/17790	–0·06	1·01 (0·88–1·15)	
3·0–4·9 years	193/16463	237/16484	2·19	0·81 (0·67–0·98)	0·04
≥5 years	131/4444	184/4460	4·80	0·70 (0·56–0·88)	
Major vascular events					
0–2·9 years	481/17745	586/17790	2·04	0·82 (0·72–0·92)	
3·0–4·9 years	241/16477	239/16402	–0·10	1·00 (0·84–1·20)	0·07
≥5 years	153/4404	164/4393	0·99	0·93 (0·74–1·16)	
Major extracranial bleeds					
0–2·9 years	142/17745	73/17790	–1·33	1·95 (1·47–2·59)	
3·0–4·9 years	45/16655	33/16733	–0·59	1·37 (0·87–2·14)	0·003
≥5 years	16/4595	26/4648	0·96	0·63 (0·34–1·16)	



***Rothwell PM. Lancet* 2012; 379: 1602–12**

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

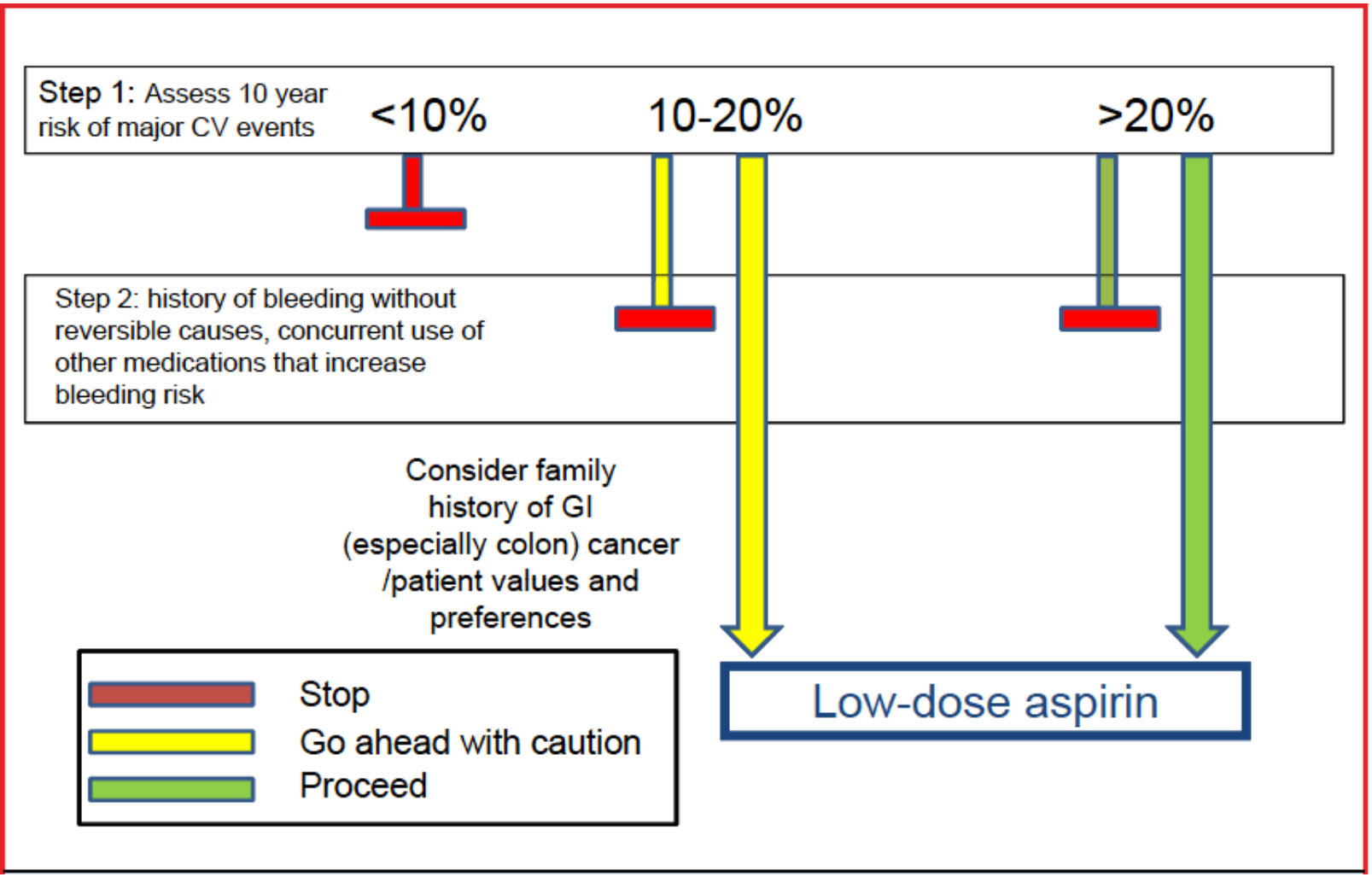
Population	Recommendation	Grade
Adults aged 50 to 59 years	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C

Bibbins-Domingo et al. Ann Intern Med 2016;164:836-45

Aspirin Therapy in Primary Cardiovascular Disease Prevention

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

J Am Coll Cardiol 2014



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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

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 100 mg daily

COLORECTAL

Stage II or stage III adenocarcinoma of the colon or rectum

RANDOMISE

- PLACEBO
- 100mg ASPIRIN
- 300mg ASPIRIN

Primary Outcome: Disease-free survival

2600 participants

BREAST

Node positive or high risk node negative invasive breast cancer

RANDOMISE

- PLACEBO
- 100mg ASPIRIN
- 300mg ASPIRIN

Primary Outcome: Disease-free survival

3100 participants

GASTRO-OESOPHAGEAL

Adenocarcinoma or squamous, oesophagus, OG J or stomach

RANDOMISE

- PLACEBO
- 100mg ASPIRIN
- 300mg ASPIRIN

Primary Outcome: Overall survival

2100 participants

PROSTATE

Post surgery or radical RT, intermediate to high risk (D'Amico)

RANDOMISE

- PLACEBO
- 100mg ASPIRIN
- 300mg ASPIRIN

Primary Outcome: Biochemical RFS

2120 participants

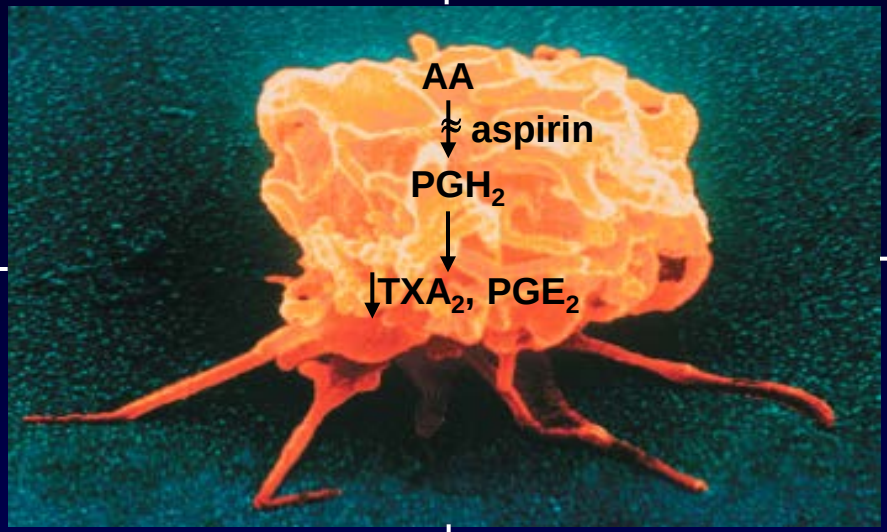
FOLLOW-UP

≥ 5 years, including active f/up largely aligned with standard care, and long term passive f/up through NCIN

Patrignani & Patrono, J Am Coll Cardiol 2016;68:967-76.

Release of microparticles

Patrono, JACC 2015;66:74-85



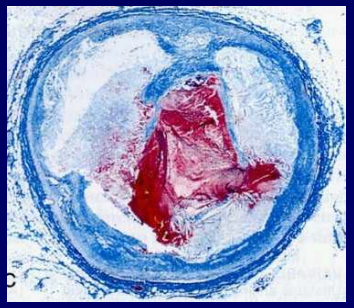
Platelet surface for clotting factors assembly

Release of pro-thrombotic prostanoids

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

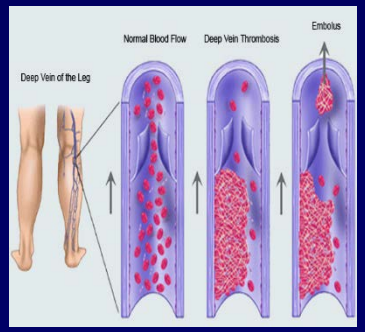
Coronary Atherothrombosis

- Evidence from >50 RCTs and meta-analyses



Venous Thromboembolism

- Evidence from several RCTs and meta-analyses

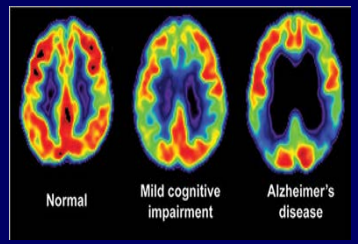


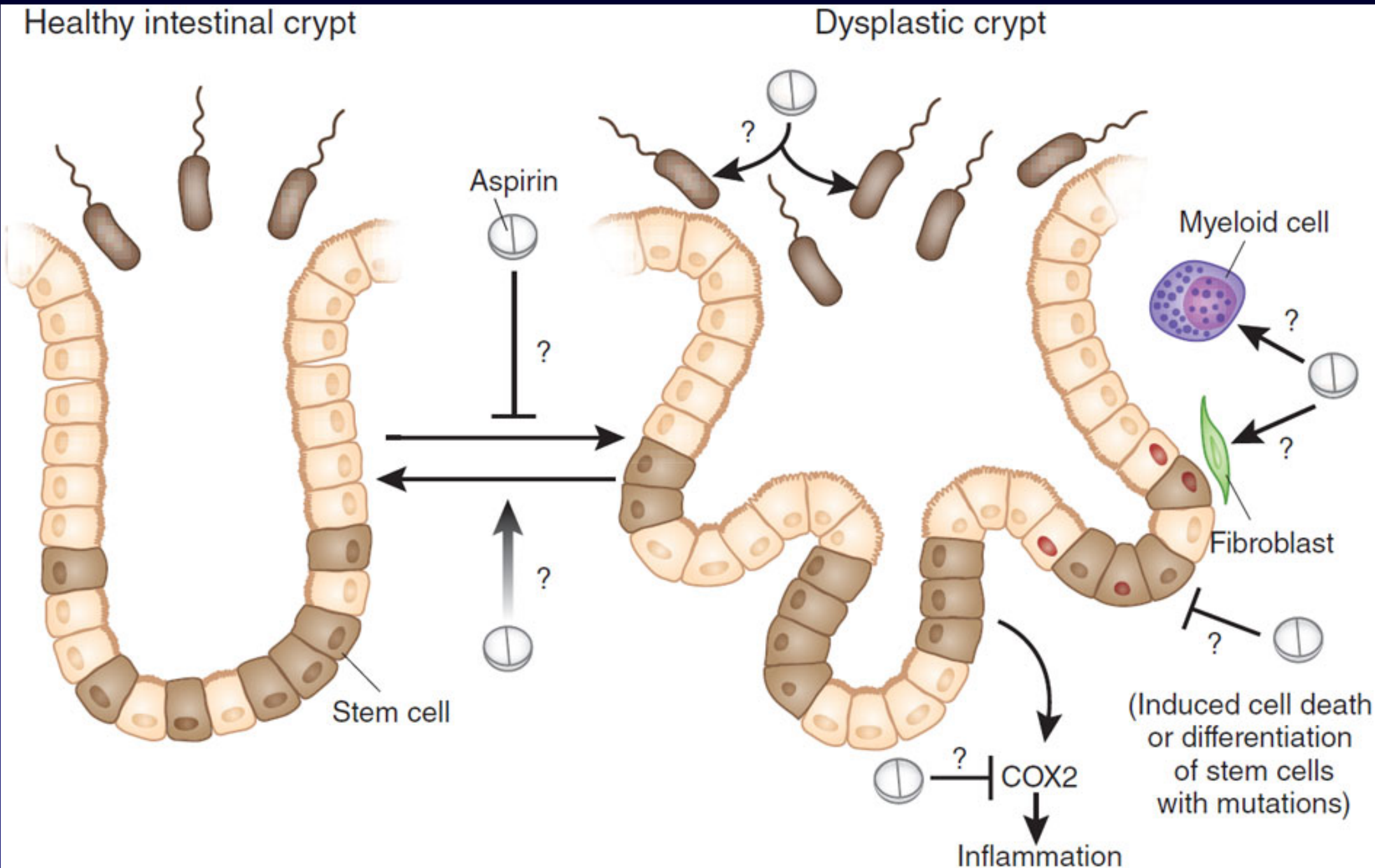
Colorectal Cancer

- 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

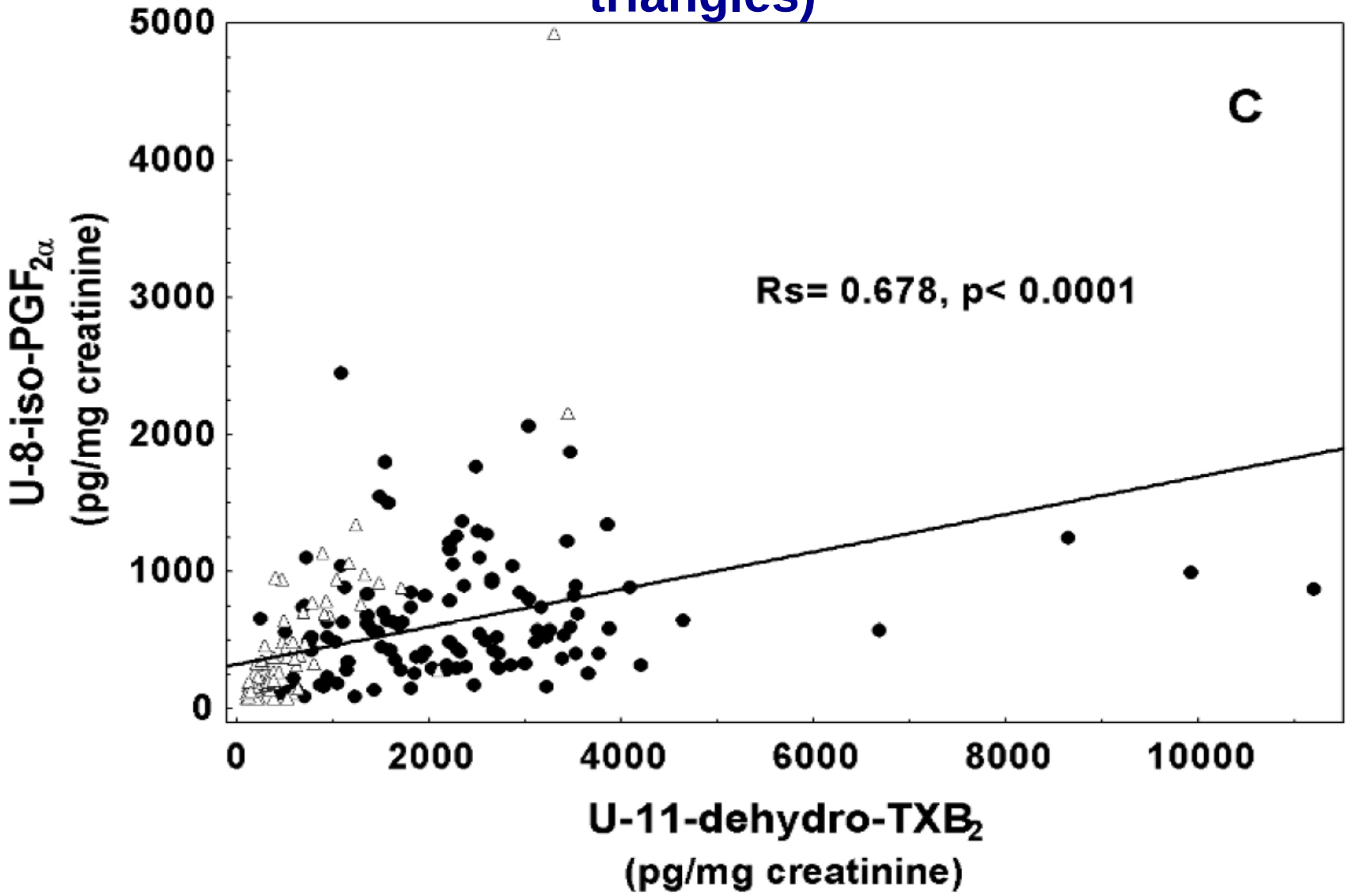



Healthy intestinal crypt
Dysplastic crypt
Aspirin
?
?
?
?
Myeloid cell
?
?
Fibroblast
?
Stem cell
?
COX2
Inflammation
(Induced cell death
or differentiation
of stem cells
with mutations)

COX-2-Dependent Clinical Read-Outs: Are They Modulated by Aspirin *In Vivo*?

Clinical Read-Out	Effect of 75-100 mg	Effect of 300-325 mg	Effect of 650-1,300 mg
PGI_2 biosynthesis	⇄	↓	↓↓
PD interaction with ACE-inhibitors	⇄	+	++
Pain & inflammation in OA/RA	?	↓	↓↓

Correlation between urinary levels of U-11-dehydro-TXB_2 and U-8-iso-$PGF_{2\alpha}$ in breast cancer (closed circles) and control women (open triangles)



Ferroni P, Santilli F, Davì G, et al. Int J Cancer 2010.

Position Paper SIMG-FADOI-AMD sull'utilizzo di ASA a basse dosi in prevenzione cardiovascolare

TABELLA III.

Fattori di rischio CV extra SCOREE ISS e danno d'organo considerati.

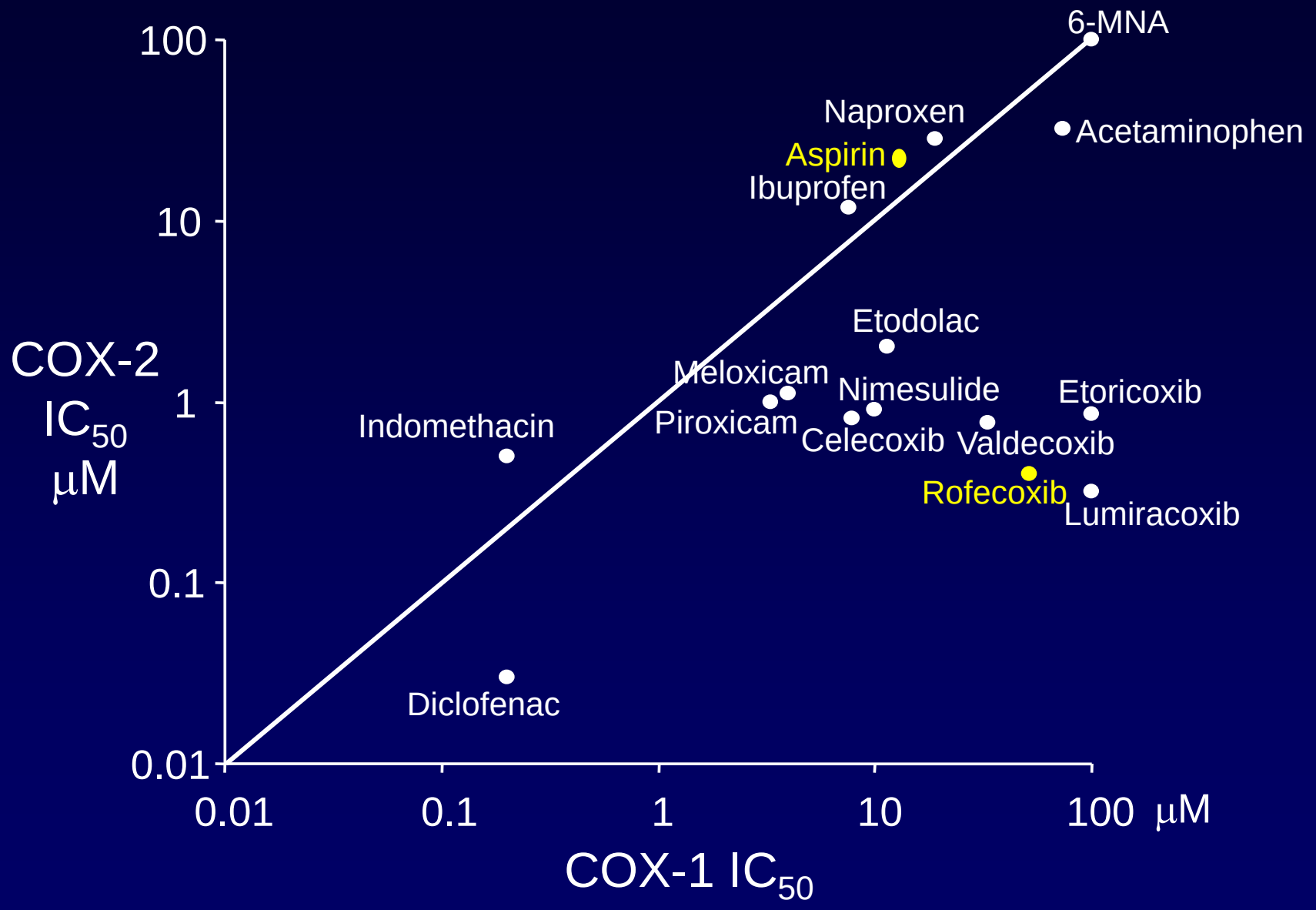
•	Familiarità di 1° per malattie CV in età precoce (< 55 anni per l'uomo e < 60 anni per la donna)
•	Obesità (BMI > 29)
•	Ipertrofia ventricolare sinistra
•	Ateromasia carotidea non emodinamicamente significativa e/o ispessimento mio intimale
•	Danno renale (micro-macroalbuminuria o FG < 60 ml/min)

Queste condizioni conferiscono un rischio CV elevato, superiore a quanto stratificabile con la carta di rischio.

Ongoing…

1. Mechanistic studies to test the “platelet hypothesis” in animal models of intestinal cancer
2. RCTs to assess prospectively the efficacy and safety of low-dose aspirin as a chemopreventive agent: adjuvant therapy *vs* primary prevention
3. Adequate knowledge of the available clinical trial evidence to inform patients, physicians and guideline writing committees about the quality and interpretation of the evidence

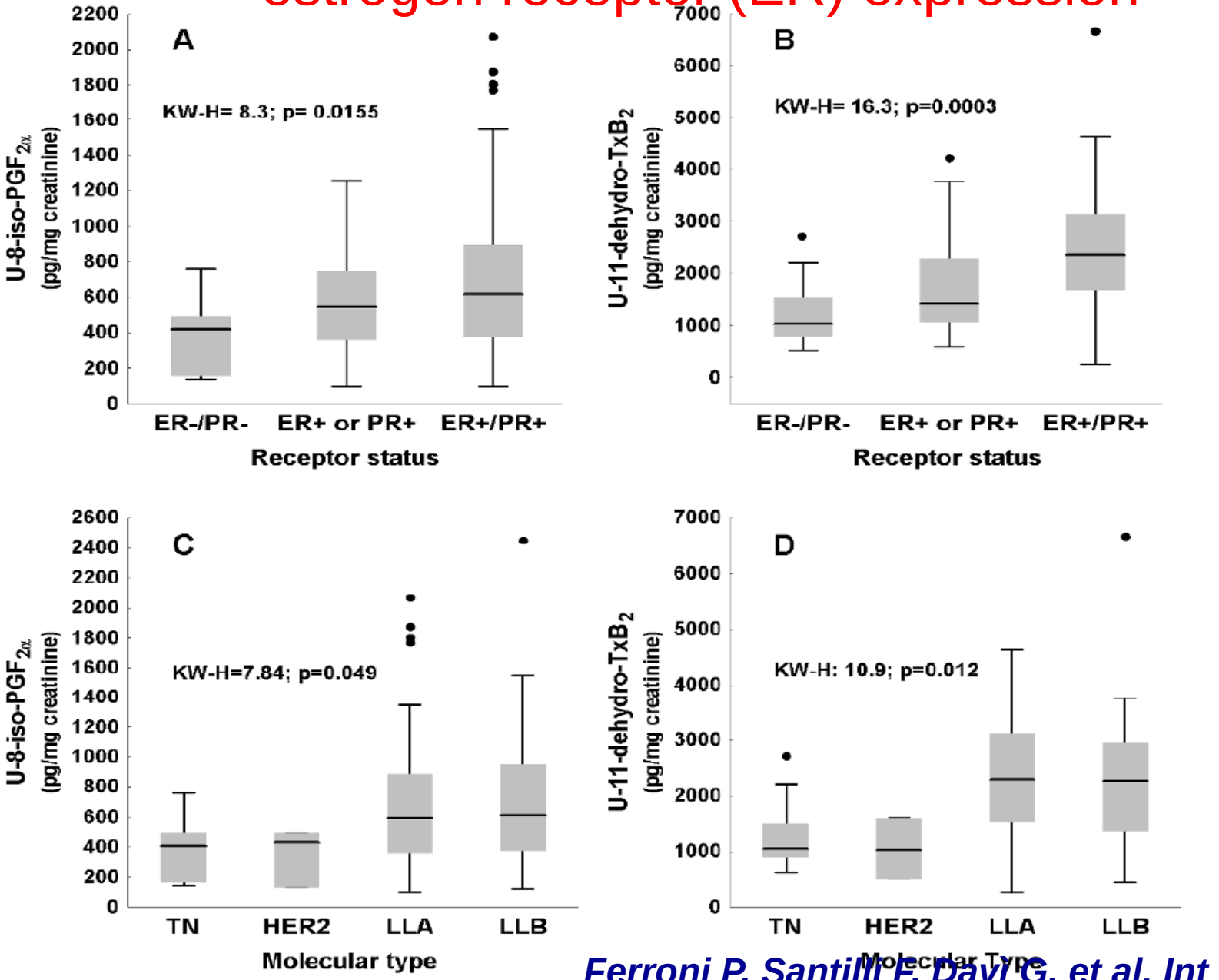
COX-2 Selectivity as a Continuous Variable



Updated from FitzGerald & Patrono, N Engl J Med 2001; 345:433-442

Whether we hypothesize a direct effect of aspirin on nucleated cellular targets (cancer or inflammatory cells), the chemopreventive effects of low-dose aspirin administered once daily do not fit with its pharmacokinetics (very short half-life) and pharmacodynamics (the relatively selective inhibition of platelet COX-1)

Both urinary biomarkers directly correlated with BC patients' estrogen receptor (ER) expression



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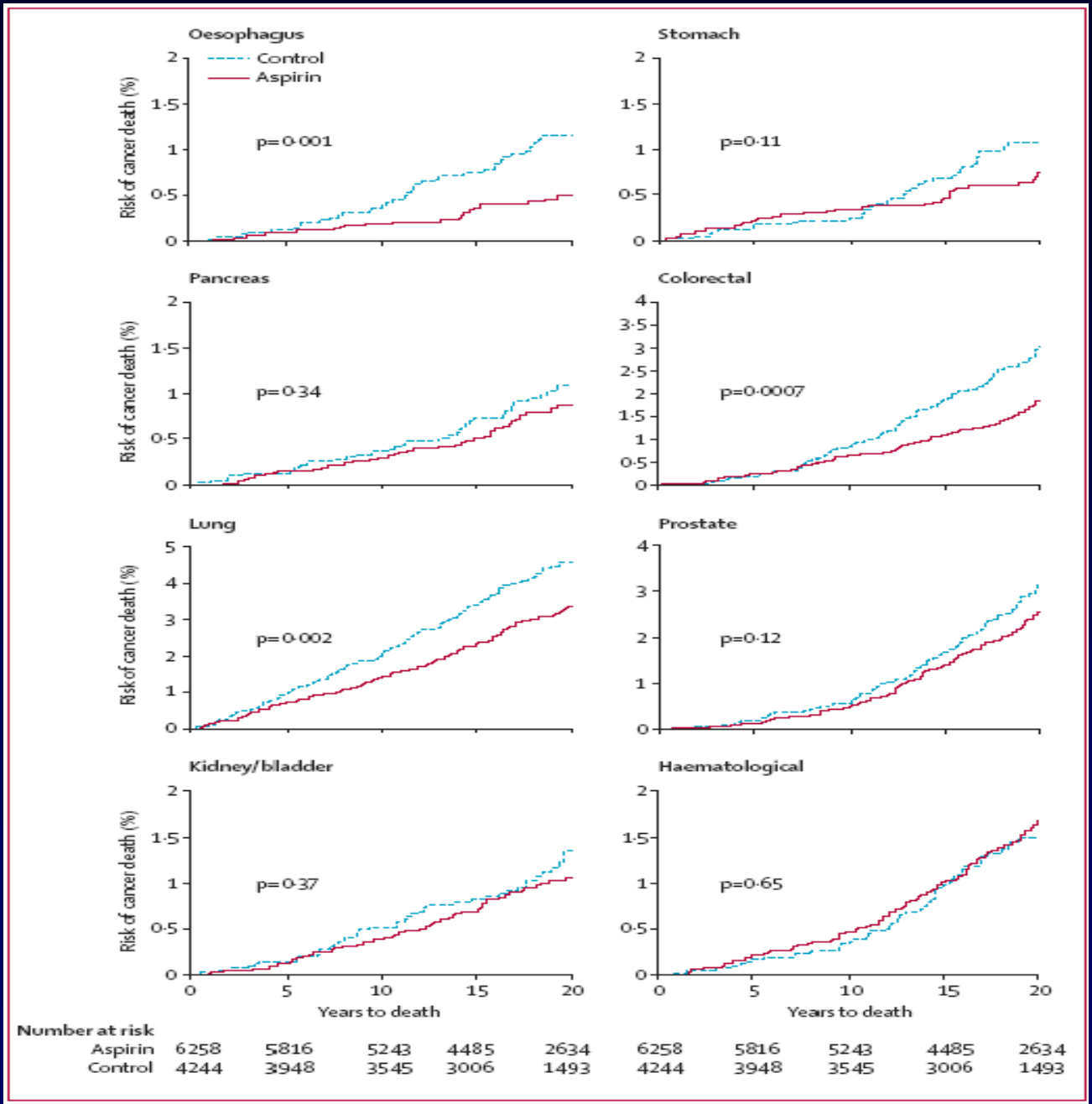
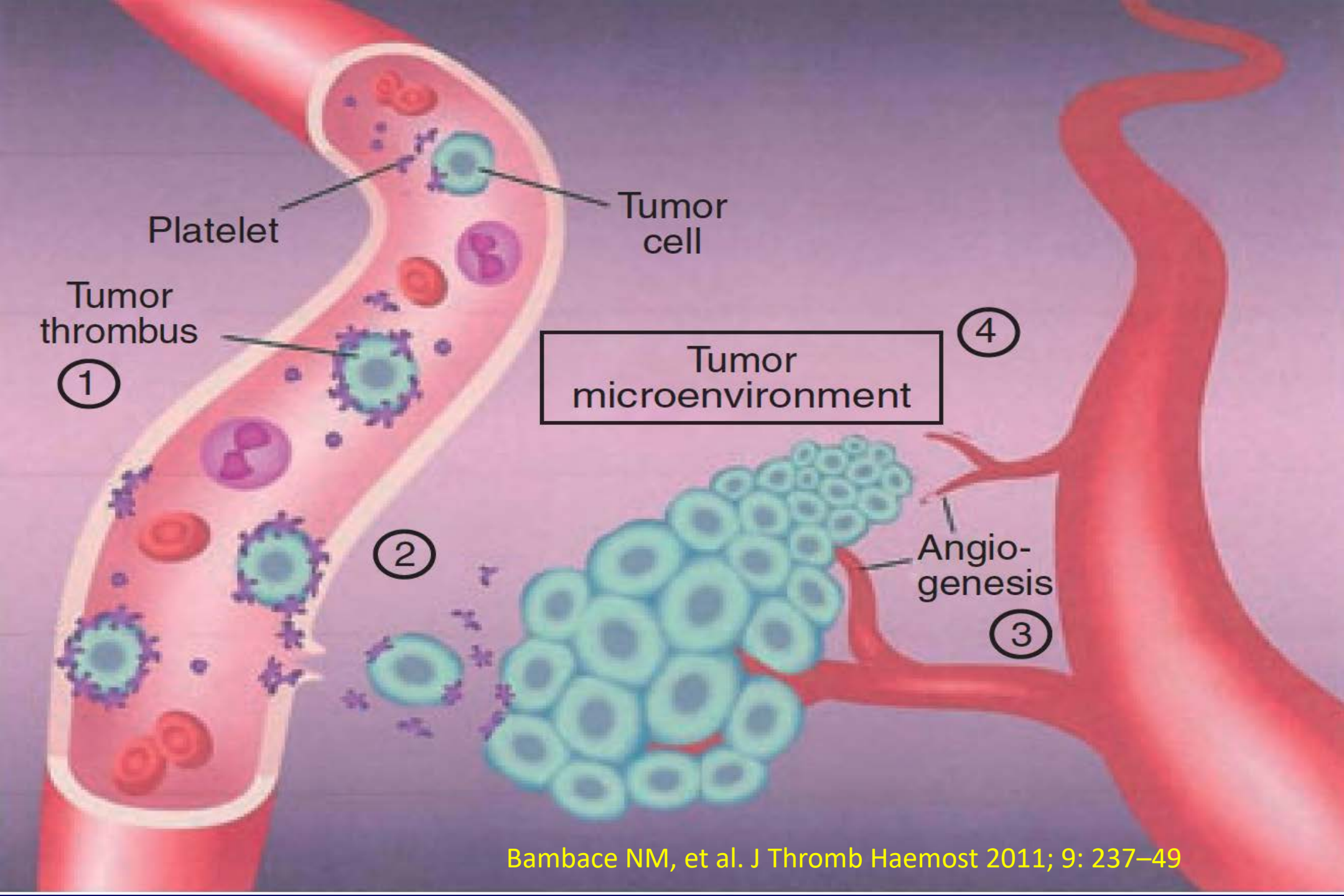
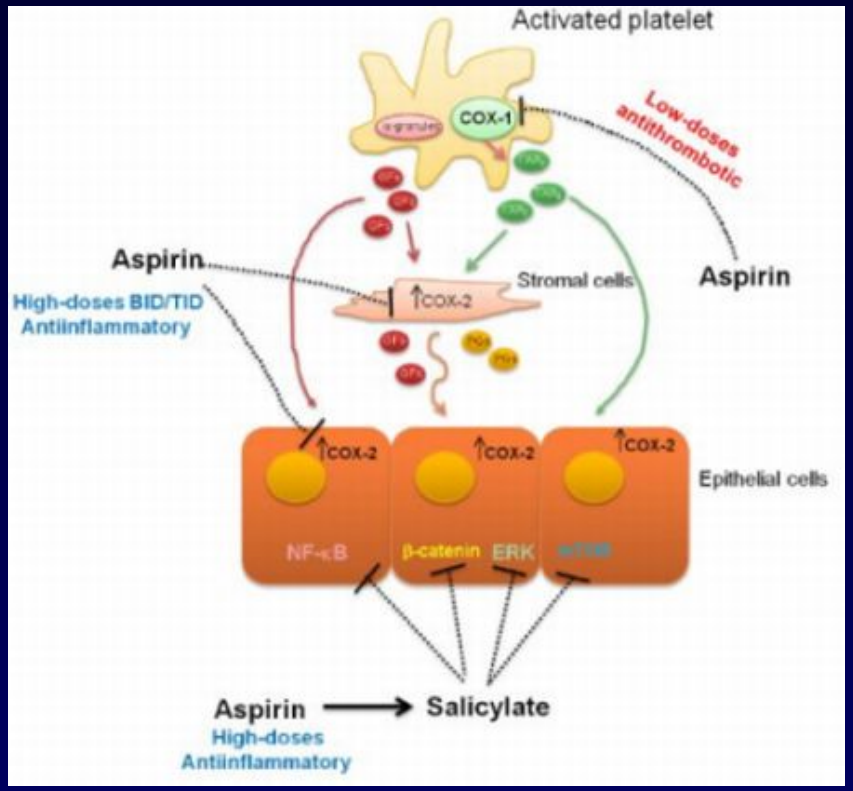


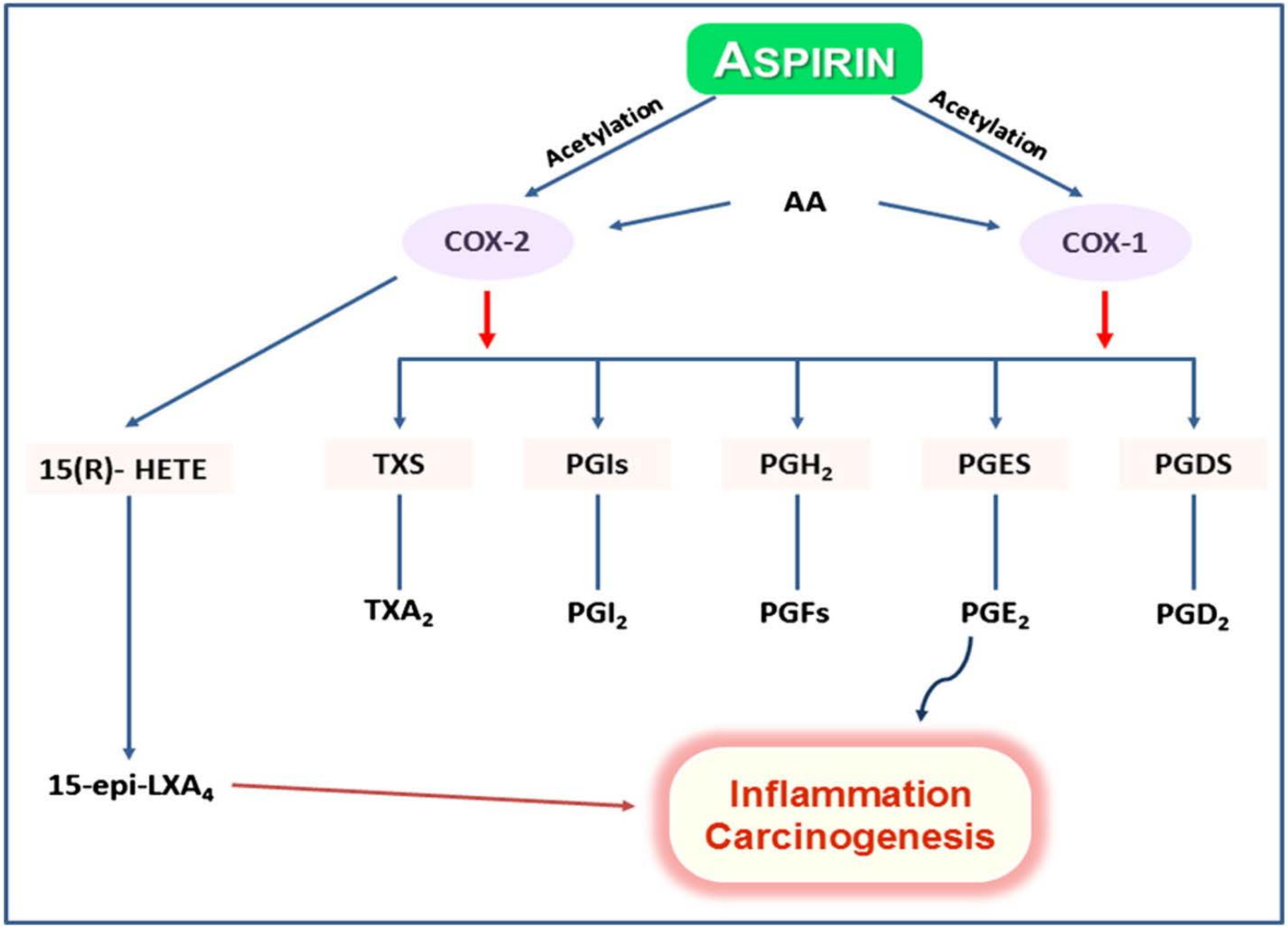
Figure 4: Effect of allocation to aspirin versus control on the 20-year risk of death due to the most common fatal cancers in the 10 502 patients with scheduled treatment duration of 5 years or longer in the three trials with long-term follow-up[37–39]

Effect by Tumor Site



Bambace NM, et al. J Thromb Haemost 2011; 9: 237–49


Activated platelet
COX-1
Low-doses
antithrombotic
Aspirin
Aspirin
Stromal cells
COX-2
High-doses BID/TID
Antiinflammatory
COX-2
COX-2
COX-2
Epithelial cells
NF-κB
β-catenin
ERK
mTOR
Aspirin
Salicylate
High-doses
Antiinflammatory


ASPIRIN
Acetylation
Acetylation
AA
COX-2
COX-1
15(R)- HETE
TXS
PGIs
PGH2
PGES
PGDS
TXA2
PGI2
PGFs
PGE2
PGD2
15-epi-LXA4
Inflammation
Carcinogenesis