Chemoprevention of Colorectal Cancer: Aspirin? NSAIDS? or Nothing?

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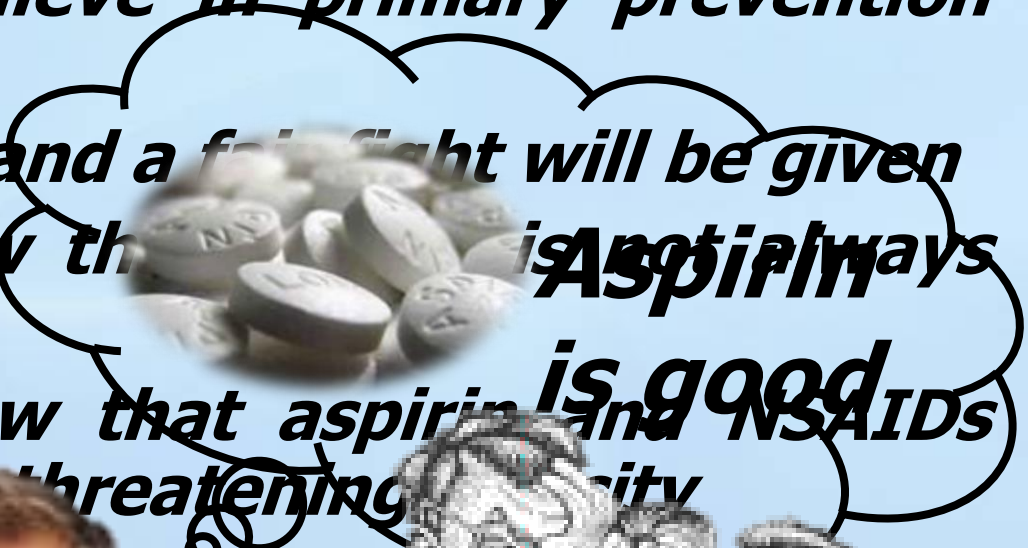
ESMO 2012

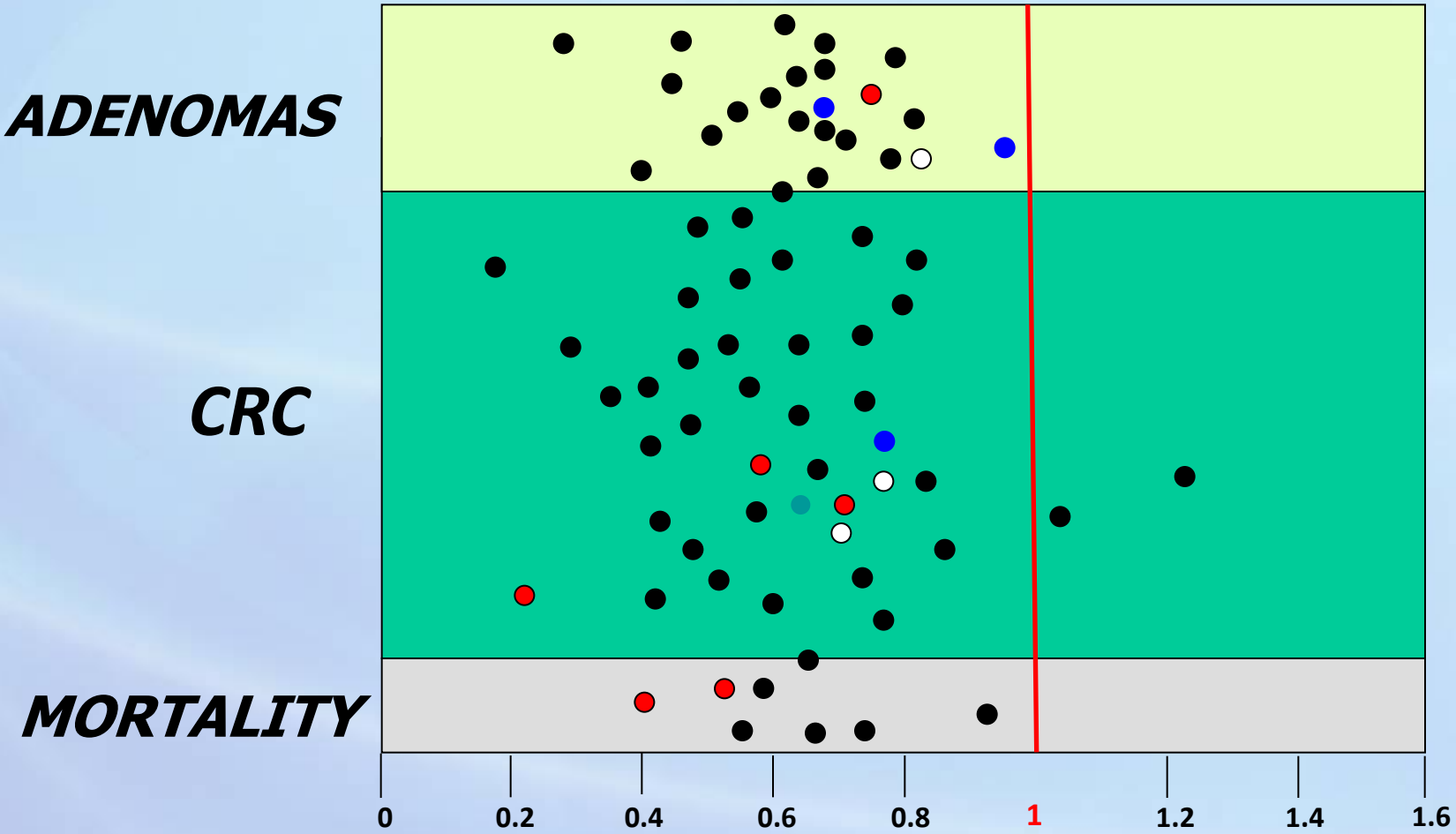
Vienna 1.10.2012

NO Routine Use of Aspirin/ NSAIDs for CRC Prevention

- *Personally I do believe in primary prevention with aspirin*
- *But it is a debate….and a fair fight will be given*
- *I am going to show that aspirin is not always beneficial*
- *I am going to show that aspirin and NSAIDs have significant life threatening toxicity*
- *I am going to propose that only some at risk may benefit at risk may benef*
- *Most importantly the guidelines do not recommend it*



NSAIDs and Aspirin Decrease the Incidence and the Mortality from CRC



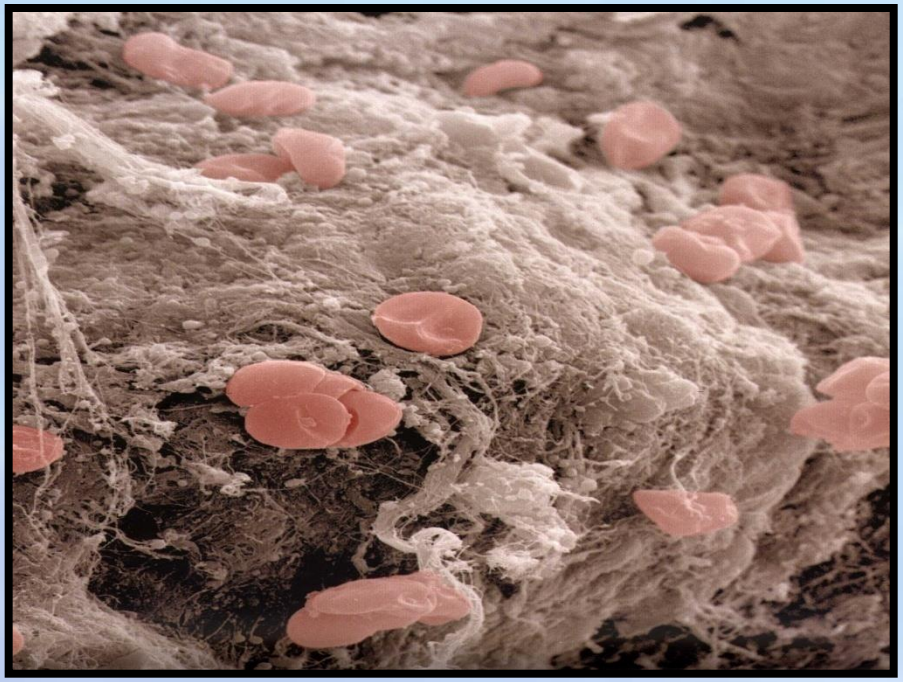
**72 Epidemiological Studies, 1988-2012*

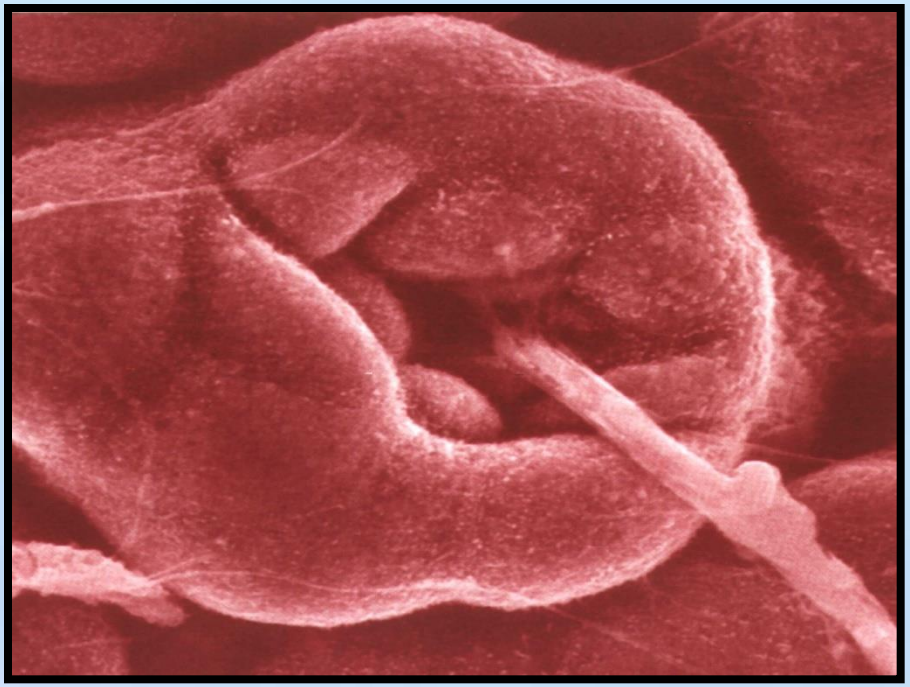
Modified from Arber and Levin, Gastro 2008

NSAIDs and Aspirin are Toxic!

- Headache
- Dizziness
- Hearing impairment
- Dim vision
- Confusion
- Drowziness
- Sweating
- Hyperventilation
- Nausea
- Vomiting
- Acid-base disturbances
- Hyperpyrexia
- Dehydration
- Renal failure
- Exacerbation of IBD
- Hallucinations
- Depression
- Seizures
- Aplastic anemia

A Bleeding Ulcer



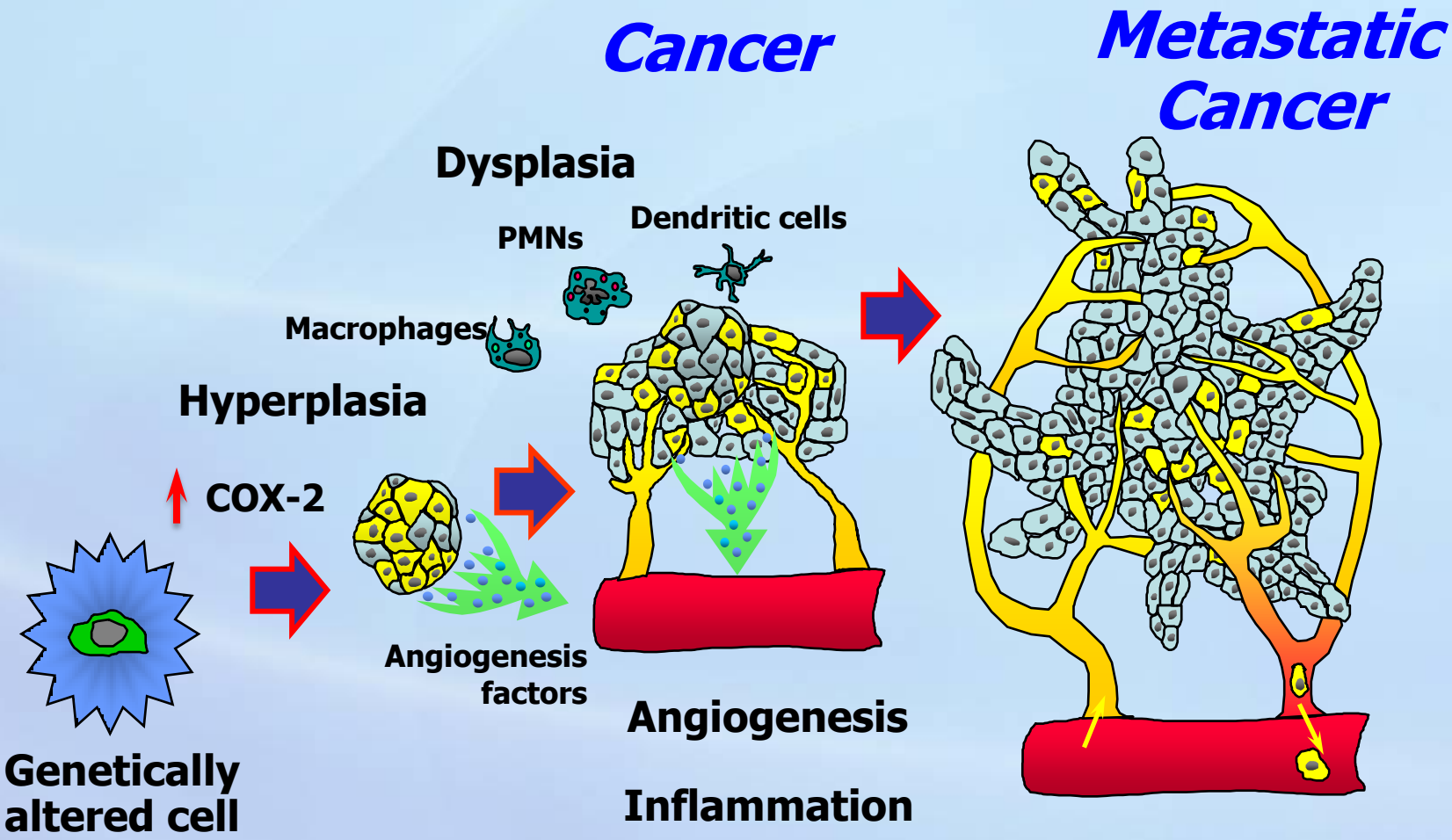


NSAIDs May Hike Long-Term CV Risk Post-MI

(Circulation 2012)

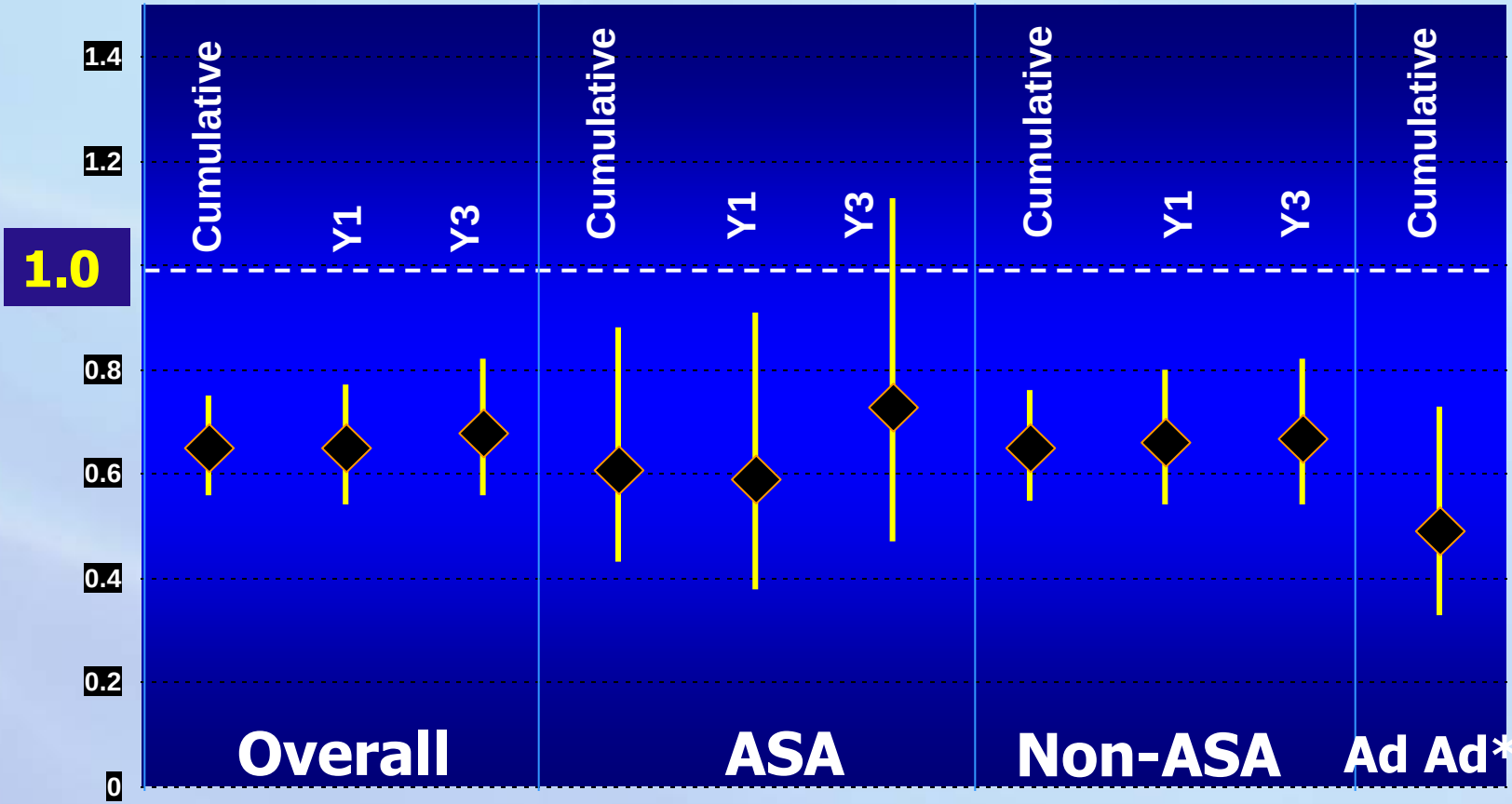
- ***Study in Copenhagen***
- ***Nearly 100,000 patients***
- ***First-time MI***
- ***NSAIDs users HR 1.59 at 1 year (95% CI 1.49 to 1.69) and HR 1.63 (95% CI 1.52 to 1.74) at 5 years***
- ***41% increased risk of a second MI***
- ***30% increased risk of coronary death during the 5-year follow-up***

COX-2: Involved in All Stages of Carcinogenesis



PreSAP Study: 1561

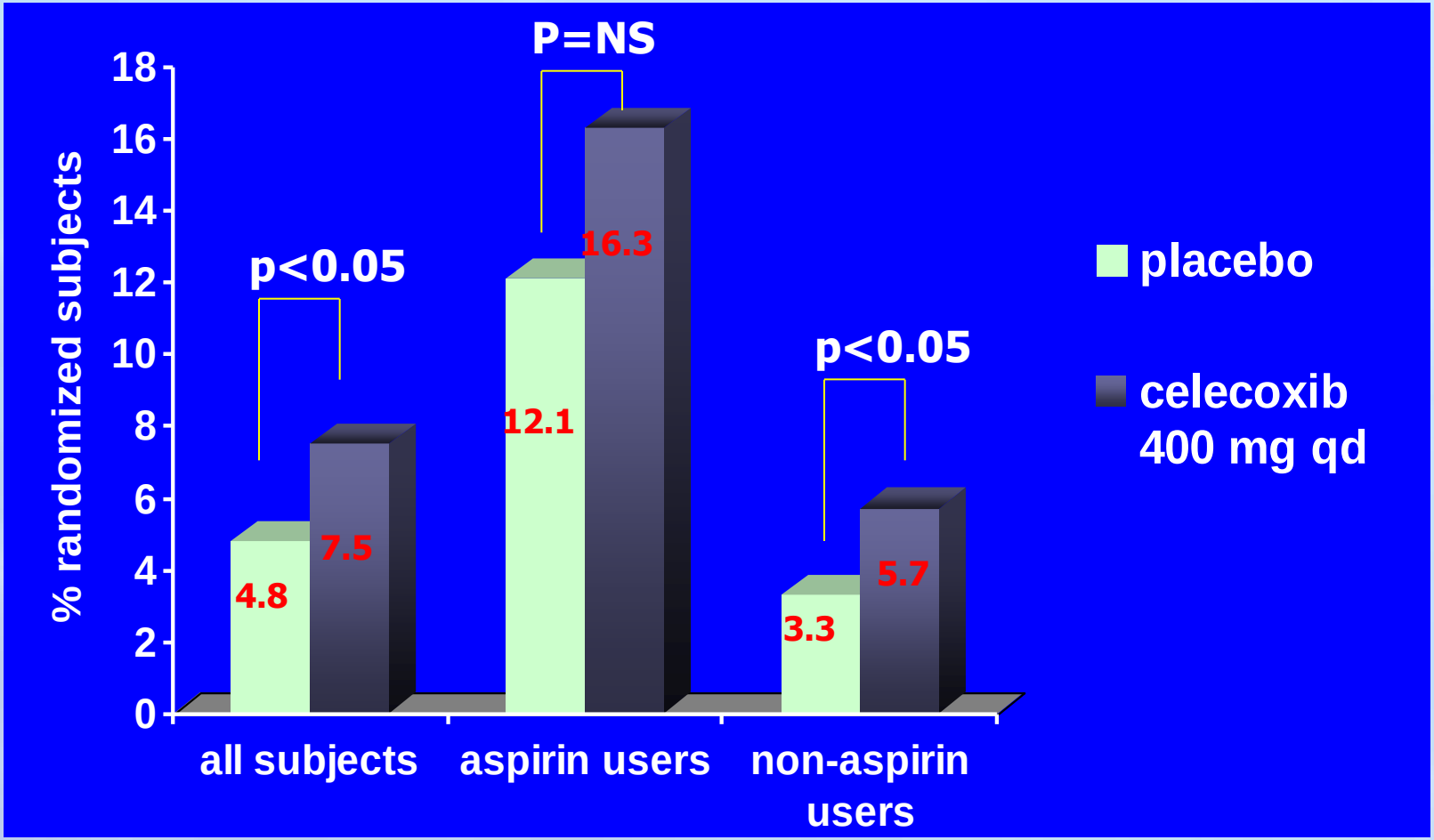
106 clinical sites in 32 countries



**Advanced adenoma ≥1 cm diameter, villous or tubulovillous, high grade dysplasia, intramucosal or invasive carcinoma*

Arber et al NEJM 31.8.2006

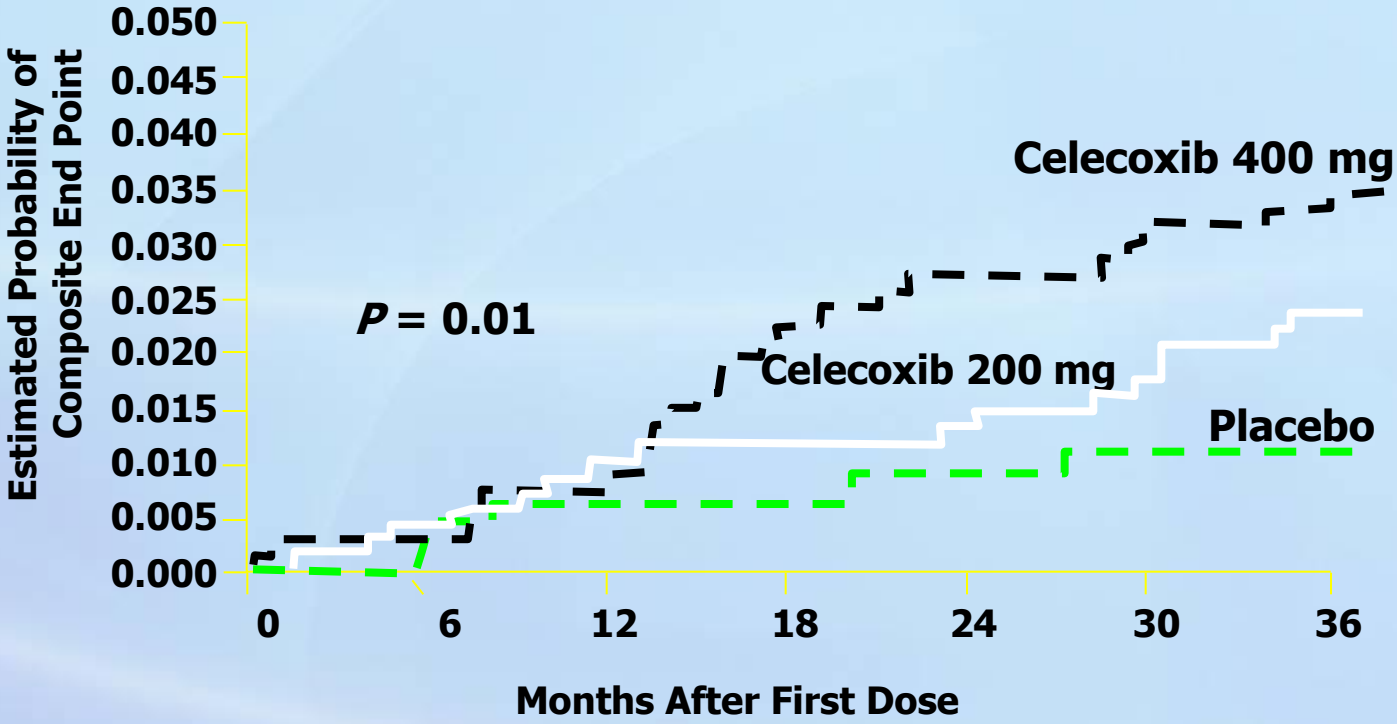
Cardiovascular AEs



Arber, et al NEJM 2006
Arber et al AJG 2011

Time to CV Death, MI, Stroke, or Heart Failure

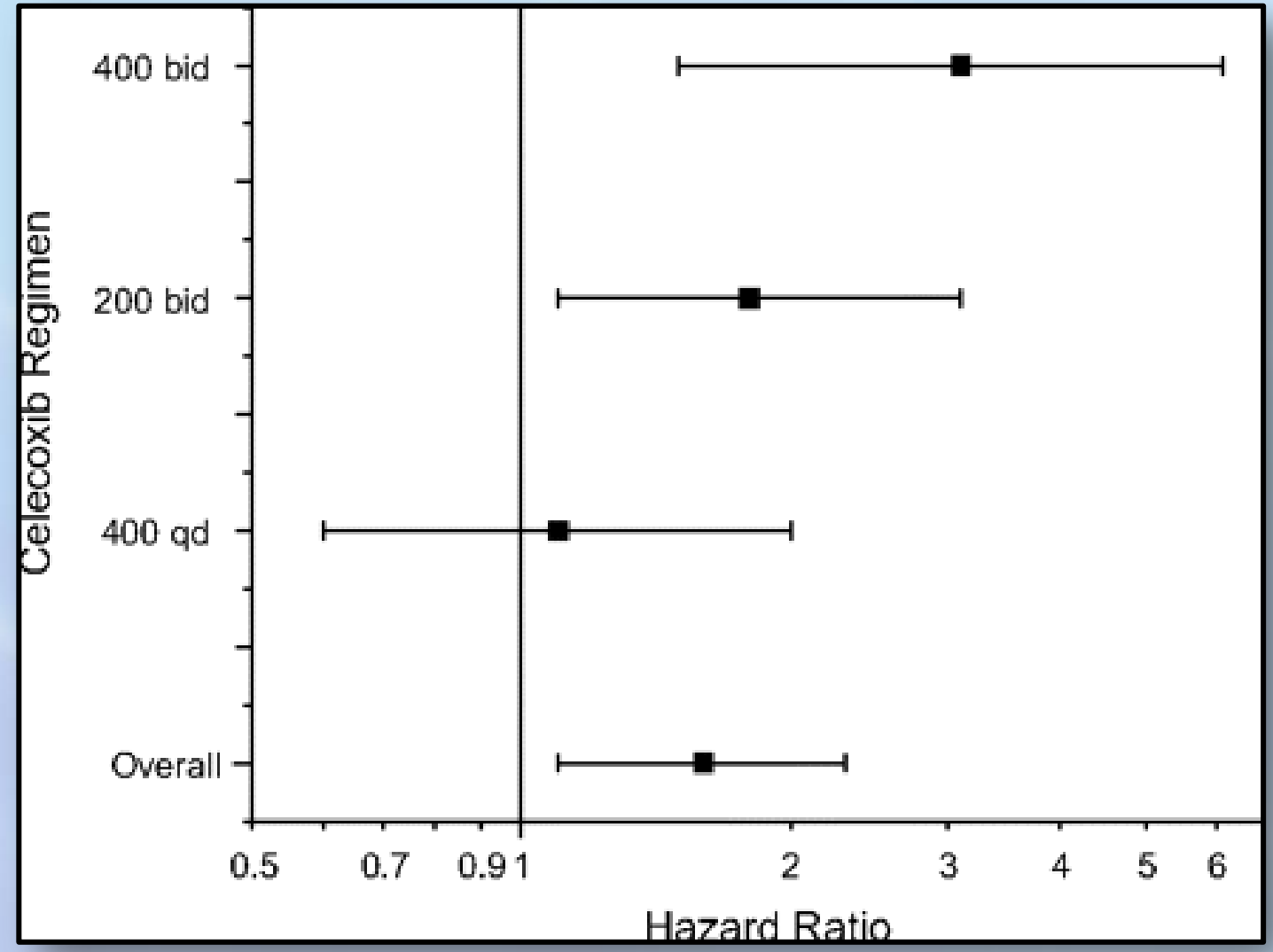
(APC Study)



No. at Risk							
Celecoxib 400 mg	617	669	665	655	651	648	576
Celecoxib 200 mg	685	681	676	675	673	670	595
Placebo	679	677	675	672	668	667	585

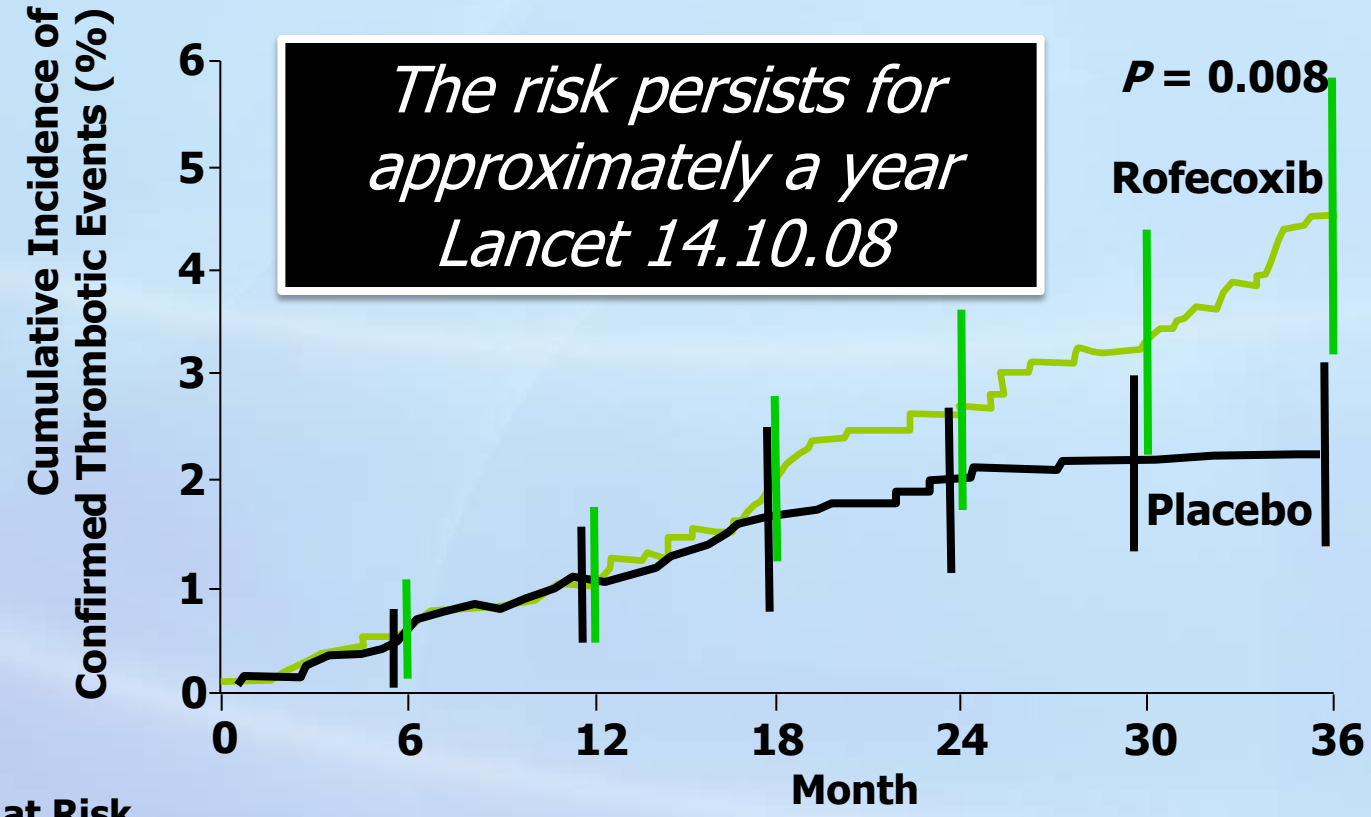
Solomon et al. N Engl J Med. 2005;352:1071-1080.

Cardiovascular Risk of Celecoxib in Six Randomized Placebo-Controlled Trials



Solomon et al, Circulation 2008

Rofecoxib: Cardiovascular Toxicity in the APPROVe Study



No. at Risk

Rofecoxib	n = 1287	1129	1057	939	938	896	727
Placebo	n = 1299	1195	1156	1079	1042	1001	835

Bresalier et al. *N Engl J Med*. 2005;352:1092-1102.

DEMAND

BAYER

ASPIRIN

Unless you see the "Bayer Cross" on package or on tablets you are not getting the genuine Bayer Aspirin proved safe by millions and prescribed by physicians over twenty-seven years for

Colds	Headache
Neuritis	Lumbago
Toothache	Rheumatism
Neuralgia	Pain, Pain

DOES NOT AFFECT THE HEART

Each unbroken "Bayer" package contains proven directions. Handy boxes of twelve tablets cost few cents. Druggists also sell bottles of 24 and 100.

Aspirin is the trade mark of Bayer Manufacture of Monoaceticacidester of Salicylicacid

No Effect of Aspirin on Vascular and Nonvascular Outcomes: Meta-analysis of RCTs

Conclusions: Despite important reductions in nonfatal MI, aspirin prophylaxis in people without prior CVD does not lead to reductions in either cardiovascular death or cancer mortality……treatment decisions need to be considered on a case-by-case basis

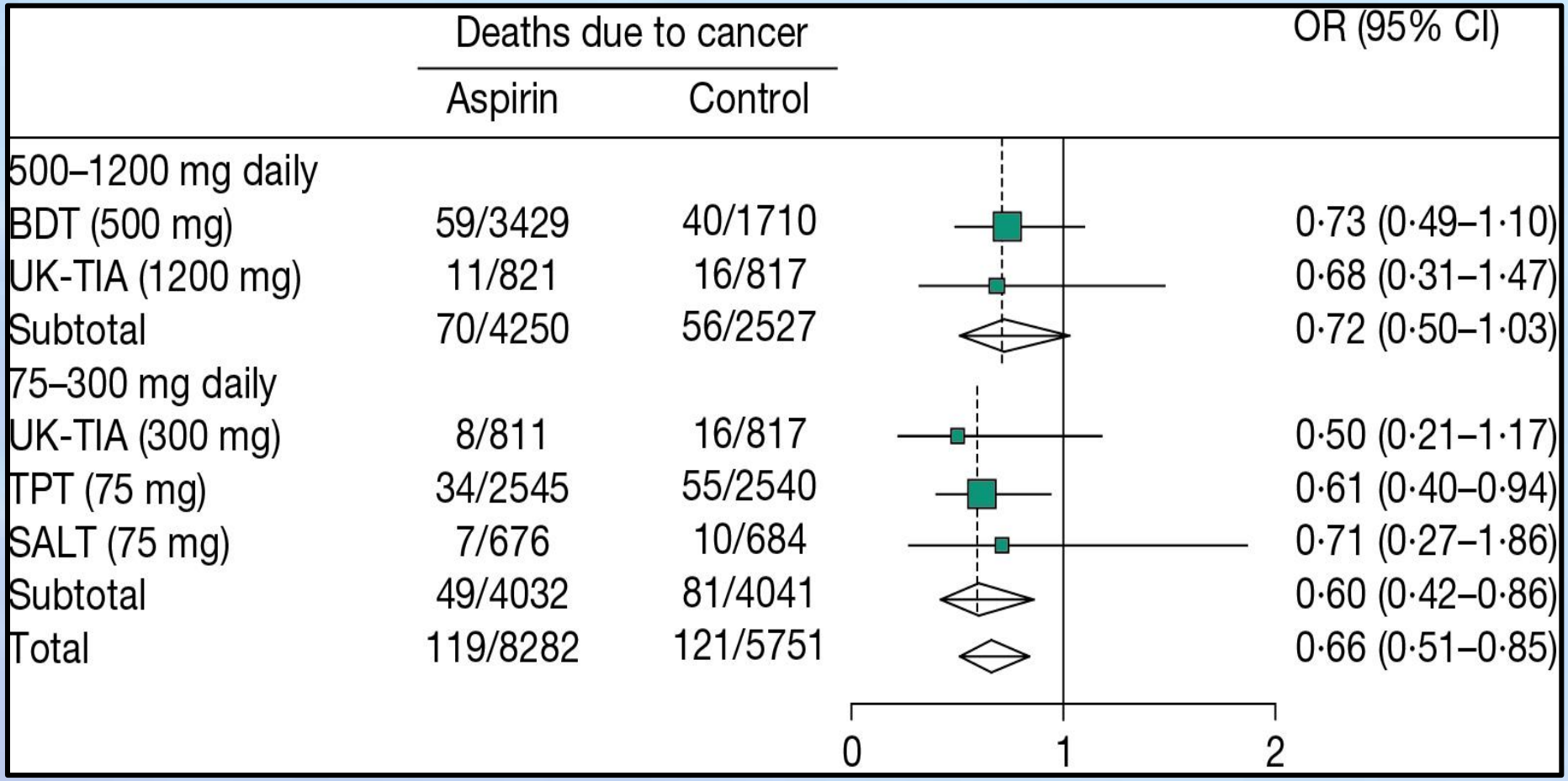
Arch Intern Med. 2012;172(3):209-216

Time to Rethink Aspirin's CV Benefits

Our study demonstrated that the incidence of major bleeding events is much higher than that recorded in randomized, prospective clinical trials…the use of aspirin was associated with a 55% increase relative risk in major bleeding…

(JAMA. 2012;307(21):2286-2294.)

Aspirin Reduces Long-term CRC Mortality*



*Pooled analysis of SALT, TPT, UK-TIA and BDT. Rothwell PM, et al. Lancet 2010;376:1741-50.

Aspirin and NSAIDs Should Not be Used for Cancer Prevention: The St. Galen Consensus:

(The Lancet Oncology 2009, Vol 10, Issue 5, P. 501 - 507)

Evidence clearly shows a chemopreventive effect for aspirin and NSAIDs on CRC and probably other cancer types; **however,** data on the risk–benefit profile for cancer prevention are insufficient and

no definitive recommendations can be made…..

Dose Long Term Aspirin Prevent Cancer?

(Moayyedi & Jankowski)

If most of the population started taking aspirin our gastrointestinal services might be overwhelmed. Until further evidence from RCTs is accrued, aspirin should NOT be recommended for everyone

BMJ 2010;340:c7326

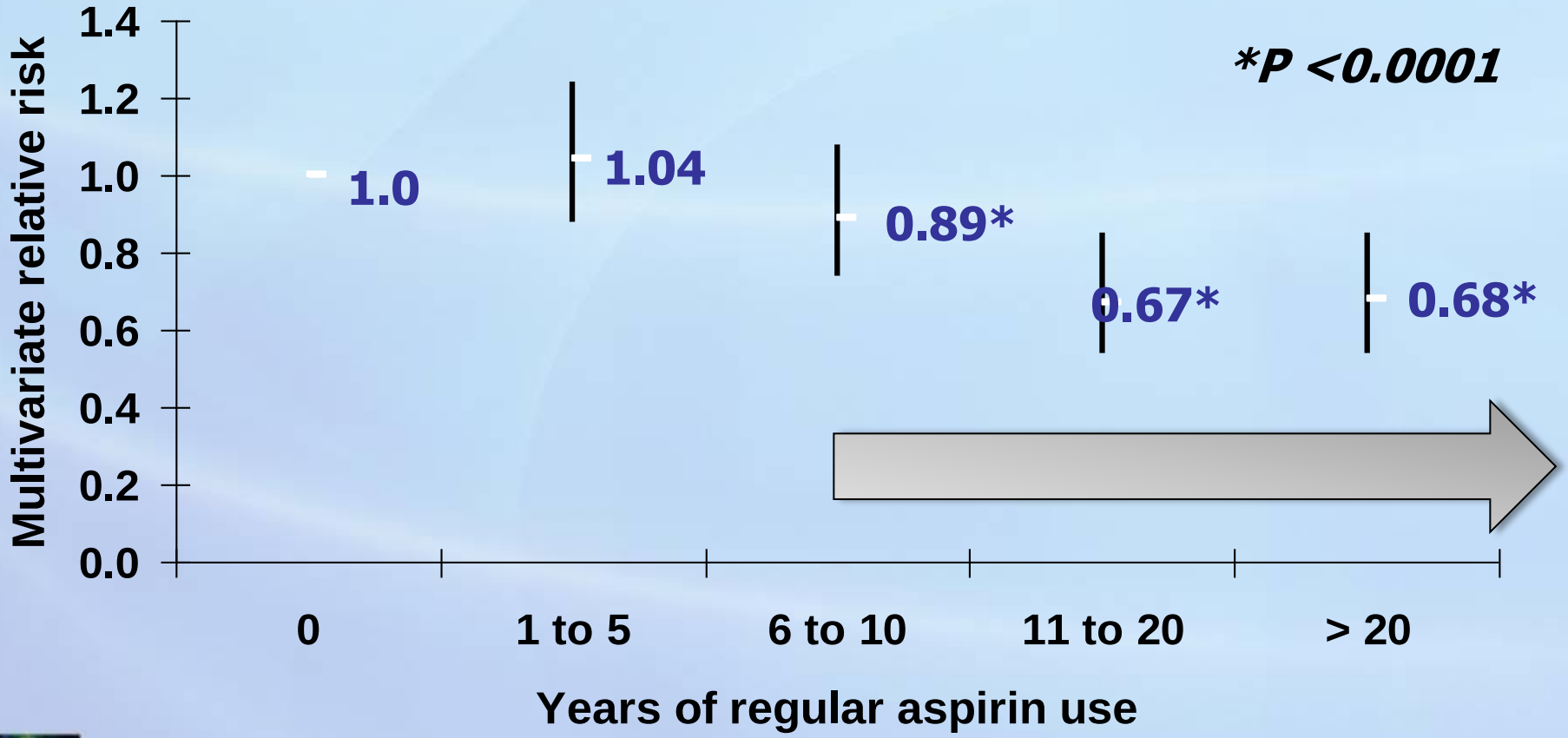
No Role of Aspirin in Primary CRC Prevention

Michael J. Thun, Eric J. Jacobs and Carlo Patrono

.....in average-risk populations, these benefits alone do not outweigh harms from aspirin-induced bleeding.....

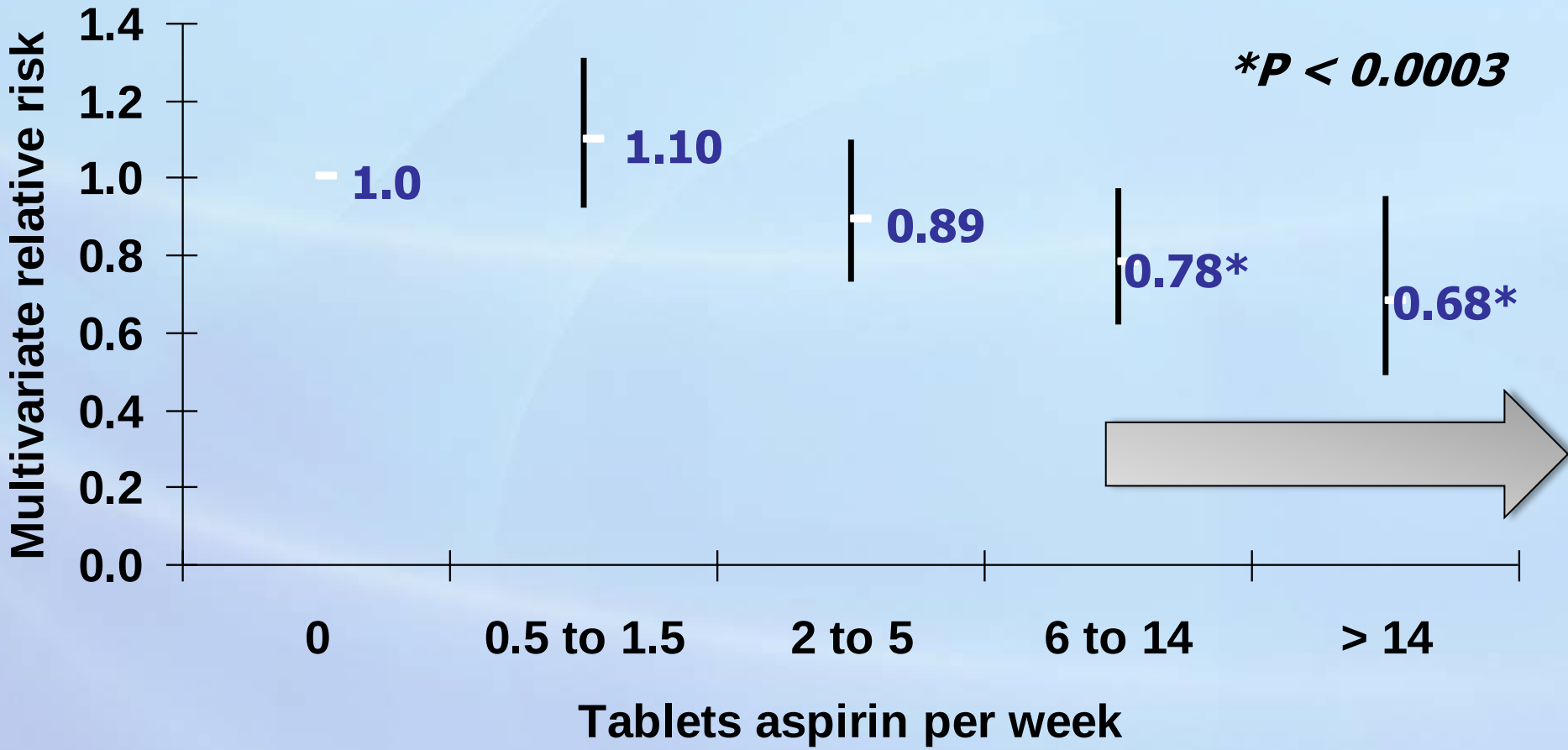
(Nat. Rev. Clin. Oncol. 9, 259–267, 2012)

Aspirin is NOT Effective Until a Decade of Use



Chan, JAMA 2005

Aspirin is NOT Effective Unless You Take it Everyday



Chan, JAMA 2005

Aspirin is NOT Effective Unless the Adenoma Express COX-2

	Non-Users	Regular Users
All colorectal cancer	1.0	0.73 (0.62-0.86)
COX-2 positive	1.0	0.64 (0.52-0.78)
COX-2 negative	1.0	0.96 (0.73-1.26)

P=0.02

Chan, JAMA 2005

Aspirin Prevents ONLY Proximal CRC

	Any aspirin treatment duration[1]		Scheduled aspirin treatment ≥5 years[1]	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Total CRC	0.76 (0.63-0.94)	0.01	0.68 (0.54-0.87)	0.002
Proximal	0.45 (0.28-0.74)	0.001	0.35 (0.20-0.63)	<0.0001
Distal	1.10 (0.73-1.64)	0.66	1.14 (0.69-1.86)	0.61
Rectum	0.74 (0.51-1.07)	0.11	0.81 (0.52-1.25)	0.34

Chan et al, 2007

NSAIDs and Aspirin

American Cancer Society Website on CRC

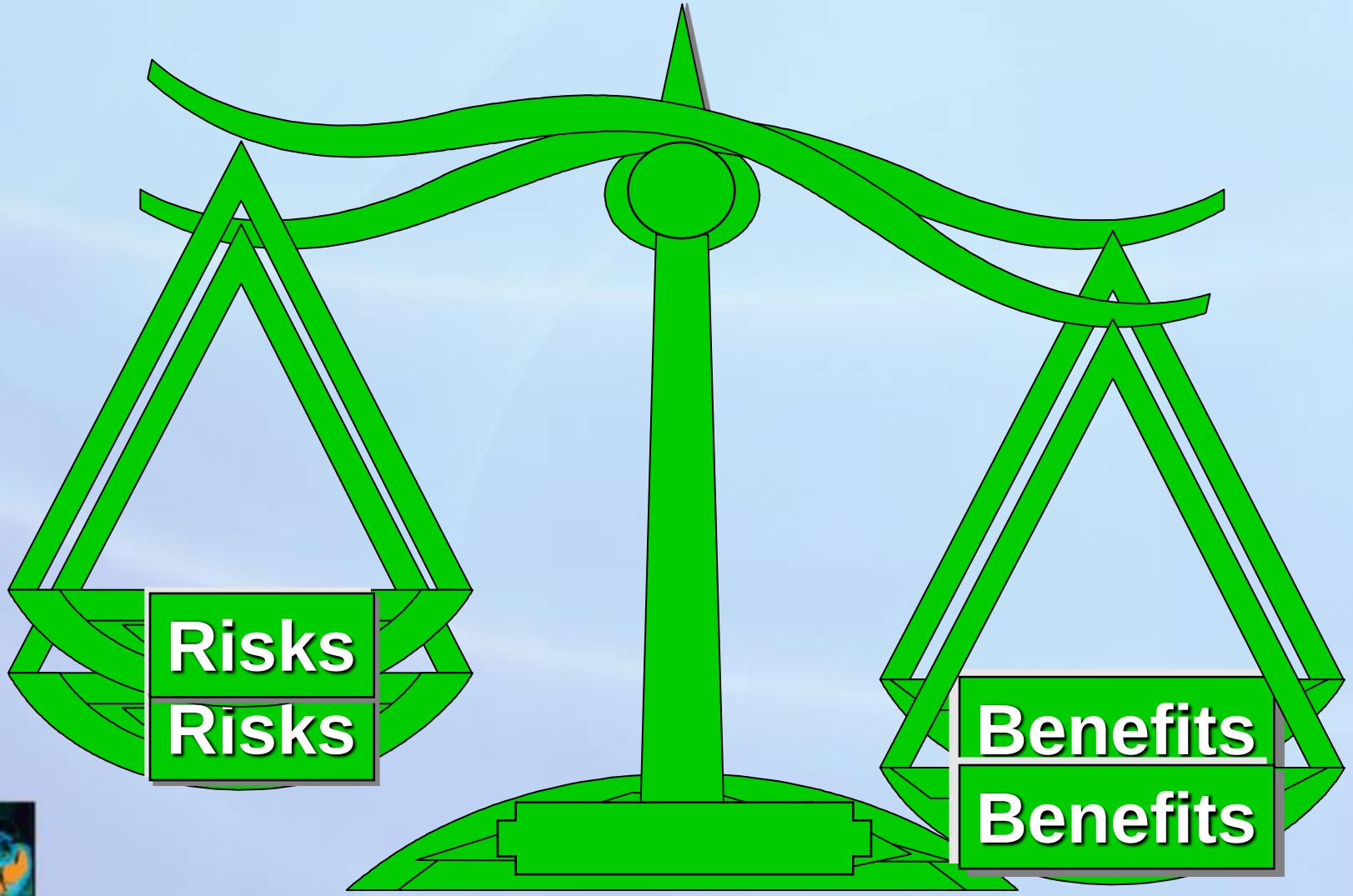
- People who regularly use aspirin and NSAIDs have a lower risk of CR neoplasia
- Primary (IHD) and secondary (adenomas, cancer) prevention or therapy (arthritis)

But they can cause serious life-threatening side effects (e.g. bleeding, MI) which may outweigh the benefits of these medicines for the general public

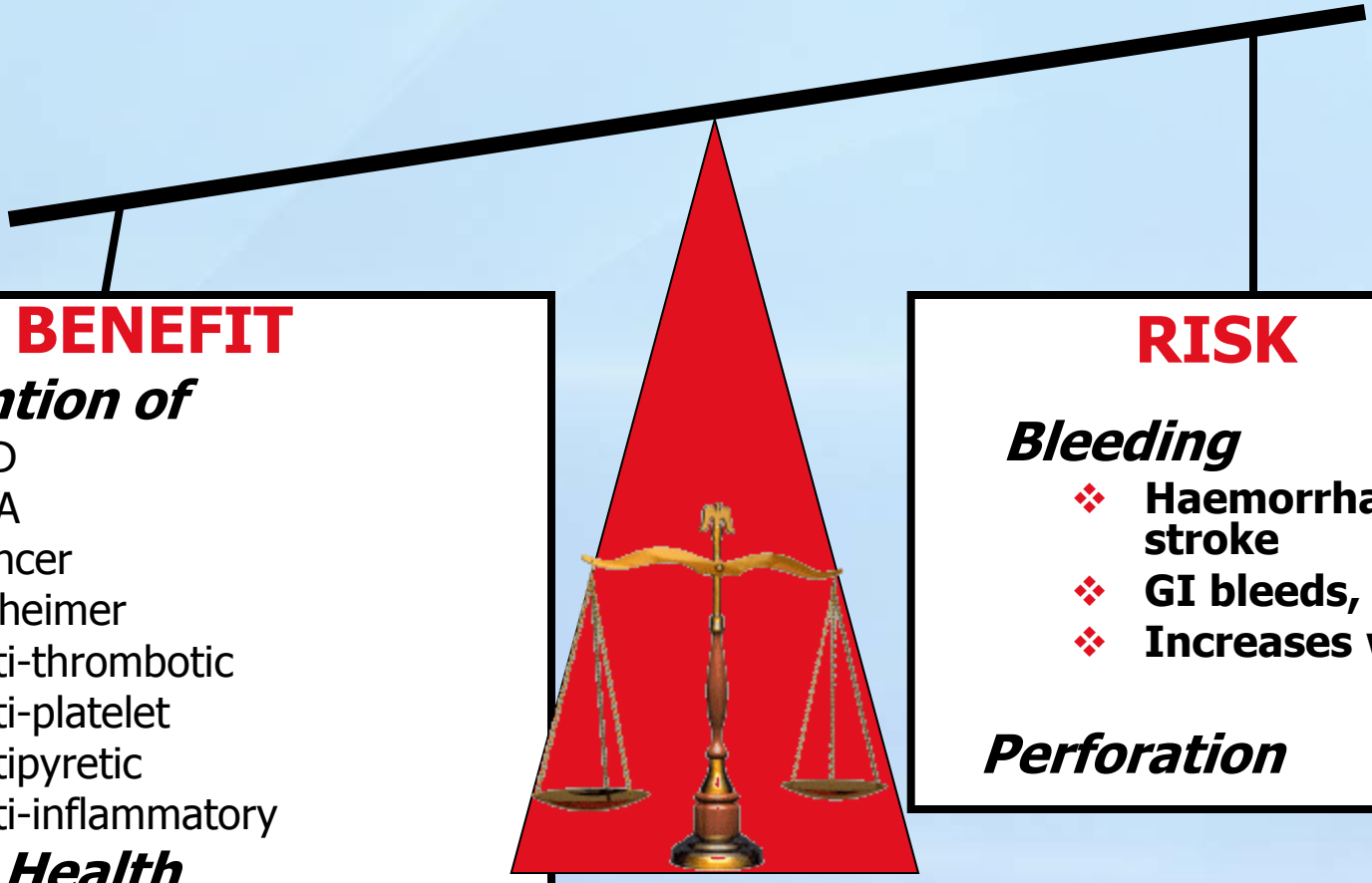
- COX 2 inhibitors reduce polyp formation in high risk groups, it causes less GI toxicity but may increase the risk of heart attacks and strokes

One should takes no risks

Weighing Tradeoffs of Chemoprevention



Benefit:Risk Balance for Aspirin Use



BENEFIT

Prevention of

- IHD
- CVA
- Cancer
- Alzheimer
- Anti-thrombotic
- Anti-platelet
- Antipyretic
- Anti-inflammatory

Public Health

- Inexpensive
- Widely available
- High compliance

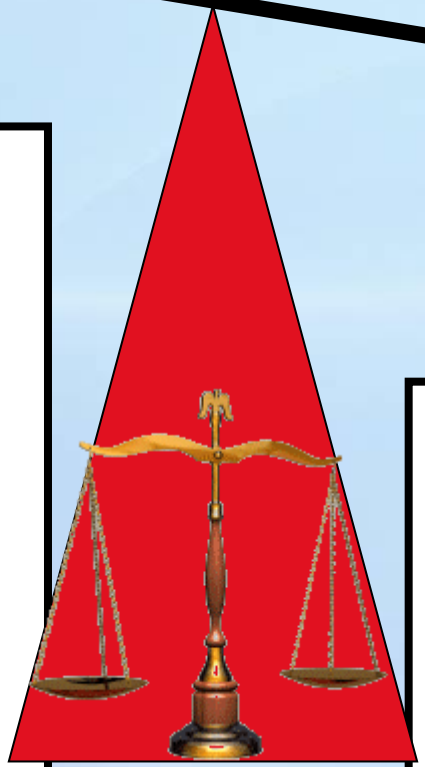
RISK

Bleeding

- **Haemorrhagic stroke**
- **GI bleeds, ulcers**
- **Increases with age**

Perforation

Oops...Risk:Benefit Balance for Aspirin Use



BENEFIT

Prevention of

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Public Health

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RISK

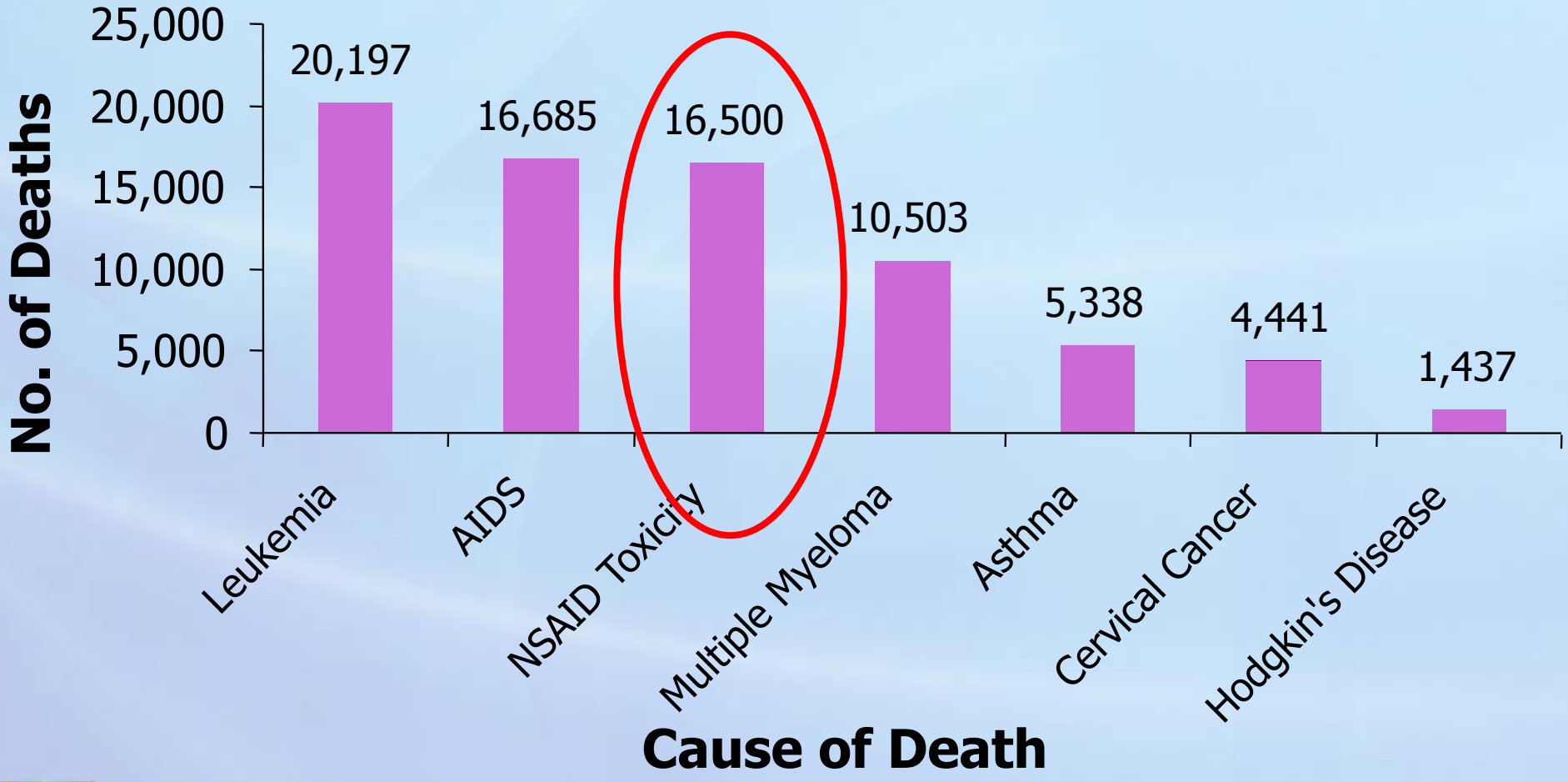
Bleeding

- **Haemorrhagic stroke**
- **GI bleeds, ulcers**
- **Increases with age**

Perforation

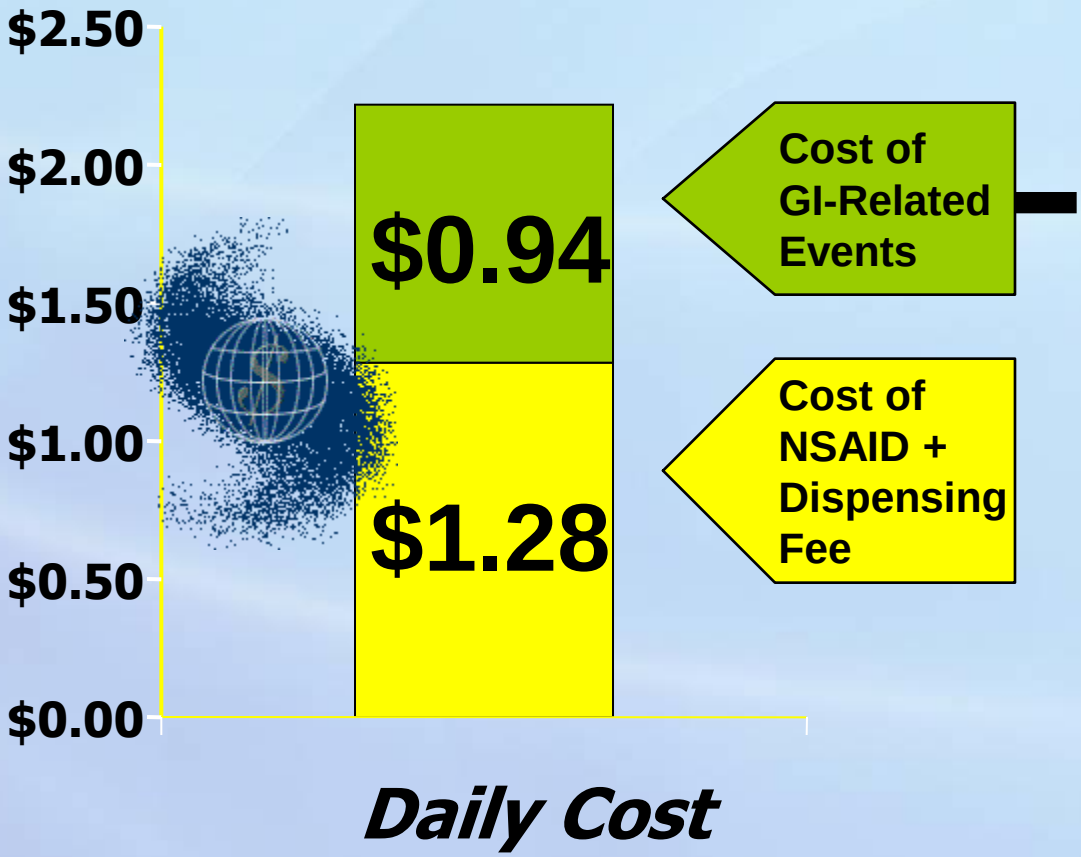
Obstruction

U.S. Mortality Data for Several Selected Disorders in 1997



Wolfe et al.
N Engl J Med 1999;340:1888-1899

Approximately One Dollar is Added to a Day of NSAID Therapy for GI Problems



$1.34: Daily cost of GI events when patient was on NSAIDs

$0.40: Daily costs of GI events when patient was not on NSAIDs

$1.34 - $0.40 = $0.94
Cost of GI events attributable to NSAIDs

Chemoprevention in Populations at Risk for Colorectal Cancer?

High Risk: **YES, in all subjects**

Familial Adenomatous Polyposis (FAP)

Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

Lifetime risk ~ 80-100%

Moderate Risk: **YES, in some carefully chosen subjects Patients preference**

Personal history of adenoma or CRC

Lifetime risk ~ 10-20%

Approaches in the General Population

30-50% incidence of adenomas

> 1,200,000 CRC cases/year

Lifetime risk = 6%

- **Diet**
- **Exercise**
- **Tobacco avoidance**
- **Limitation of alcohol**
- **Screening**
- **Aspirin? Curcumin?**

Targeting Chemoprevention to Persons with Risky Phenotypes and/or Behaviors

Current smoking	**RR 1.9**
Current Smoking and > 25 pack years	**RR 3.0**
Alcohol, > 14 units per week	**RR 2.2**
Obesity, BMI > 27	**RR 1.5**
sedentarians	**RR 1.7**
Red meat, > 4 times per week	**RR 2.7**
Specific genetic profile	**?**

Development of a Risk Score for Colorectal Cancer in Men

Jane A. Driver, MD, MPH,[a] J. Michael Gaziano MD, MPH,[a,b,e] Rebecca P. Gelber, MD, MPH,[e] I-Min Lee, MBBS, ScD,[b,c]
Julie E. Buring, ScD,[a,b,c,d] Tobias Kurth, MD, ScD[a,b,c]

Development of a simple scoring system for CRC in a cohort of >21.000 men

Predictor	*Odds ratio (95%CI)*	*Prediction Score Points*
Age (y)		
>30 kg/m²	**1.62** (1.09-2.42)	**2**
Alcohol use (>once/week)	**1.36** (1.08-1.71)	**1**
APC polymorphisms (I1307K)		**1**
APC polymorphisms (E1317Q)		**4**

Those in the highest risk group (9-10 points) had an OR of 15.3 for CRC compared with those with the lowest risk (0-3 points)

Driver et al. Am J Med 2007; 120: 257-263.

Impact of Genetic Polymorphisms on Adenoma Recurrence and Toxicity in a COX-2 Inhibitor (Celecoxib) Trial:

Ulrich and Arber groups *Submitted for publication*

Candidate Genes

Most promising genes for tailored Coxib chemoprevention are genotypes in:

- **COX-1, COX-2**
- **Prostacyclin synthase (PGIS)**
- **Thromboxane synthase (TBXAS)**
- **Arachidonate 15-Lipoxygenase (ALOX15)**
- **5-Lipoxygenase activating protein (FLAP)**
- **Prostaglandin EP4/E2 receptor genes**

COX Polymorphisms (1)

	Adenoma Recurrence =YES	Adenoma Recurrence= NO
COX1_ rs6478565	19 (32.8%)	12 (20.7%)
	39 (67.2%)	46 (79.3%)

Chi-square p-value
Crude OR and 95% CI: 1.9 (0.8-4.3

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
COX1_ rs10306164	19 (32.2%)	10 (17.2%)
	40 (67.8%)	48 (82.8%)

Chi-square p-value=0.06
Crude OR and 95% CI: 2.3 (0.95-5.5)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
COX1_ rs10306194	15 (25.0%)	23 (39.7%)
	45 (75.0%)	35 (60.3%)

Chi-square p-value=0.09
Crude OR and 95% CI: 0.5 (0.2-1.1)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
COX2_ rs5275	45 (77.6%)	33 (57.9%)
	13 (22.4%)	24 (42.1%)

Chi-square p-value=0.02
Crude OR and 95% CI: 2.5 (1.1-5.7)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
COX2_ rs5277	9 (15.3%)	15 (25.9%)
	50 (84.8%)	43 (74.1%)

Fisher's p-value=0.18
Crude OR and 95% CI: 0.5 (0.2-1.3)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
COX2_ rs2066826	30 (50.9%)	20 (35.1%)
	29 (49.2%)	37 (64.9%)

Chi-square p-value=0.09
Crude OR and 95% CI: 1.9 (0.9-4.0)

COX Polymorphisms (2)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
COX2_ rs2206593	3 (5.1%)	9 (15.5%)
	56 (94.9%)	49 (84.5%)

Fisher's p-value=0.07
Crude OR and 95% CI: 0.3 (0.07-1.1)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
COX2_ rs2745557	13 (22.4%)	24 (41.4%)
	45 (77.6%)	34 (58.6%)

Chi-square p-value=0.03
Crude OR and 95% CI: 0.4 (0.2-0.9)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
COX2_ rs4648276	32 (52.5%)	20 (35.1%)
	29 (47.5%)	37 (64.9%)

Chi-square p-value=0.06
Crude OR and 95% CI: 2.0 (0.91-4.3)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
COX2_ rs4648308	33 (55.9%)	22 (38.6%)
	26 (44.1%)	35 (61.4%)

Chi-square p-value=0.06
Crude OR and 95% CI: 2.0 (0.91-4.3)

Other Polymorphisms

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
ALOX15_ rs4796535	17 (28.8%)	7 (12.1%)
	42 (71.2%)	51 (87.9%)

Fisher's p-value=0.04
Crude OR and 95% CI: 2.9 (1.1-7.8)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
EP2_3779	5 (8.3%)	11 (19.0%)
	55 (91.7%)	47 (81.0%)

Fisher's p-value=0.11
Crude OR and 95% CI: 0.4 (0.1-1.2)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
EP2_7039	4 (6.8%)	9 (15.5%)
	55 (93.2%)	49 (84.5%)

Fisher's p-value=0.15
Crude OR and 95% CI: 0.4 (0.1-1.4)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
EP4_2876	17 (28.8%)	6 (10.3%)
	42 (71.2%)	52 (89.7%)

Fisher's p-value=0.02
Crude OR and 95% CI: 3.5 (1.3-9.7)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
FLAP_ rs3803278	25 (43.1%)	34 (58.6%)
	33 (56.9%)	24 (41.4%)

Chi-square p-value=0.09
Crude OR and 95% CI: 0.5 (0.3-1.1)

	Adenoma Recurrence =YES	Adenoma Recurrence =NO
FLAP_ rs12019512	23 (39.7%)	14 (24.1%)
	35 (60.3%)	44 (75.9%)

Polymorphisms Significantly Associated with GI Toxicity

SNP	Location	Gastrointestinal toxicity					
		Both treatments		Celecoxib		Placebo	
		OR (95% CI)	p-value[2]	OR (95% CI)	p-value[2]	OR (95% CI)	p-value[2]
Primary genes of interest							
EGFR rs2072454	Cds-synon	2.48 (1.10-5.61)	**0.03**	2.51 (0.84-7.51)	0.10	1.86 (0.45-7.71)	0.39
EGFR rs4947984	Intron	0.46 (0.17-1.21)	0.12	0.20 (0.04-1.01)	0.051	0.83 (0.19-3.58)	0.80
Secondary genes of interest							
ALOX15 rs2255888	nearGene-5	2.04 (0.94-4.44)	**0.07**	3.49 (1.20-10.16)	**0.02**	1.20 (0.33-4.36)	0.79
EP4 rs4133101	-1529G>A	1.35 (0.56-3.29)	0.50	5.52 (1.13-27.06)	**0.04**	0.20 (0.04-1.01)	0.052
EP4 rs13186505	-1408G>A	2.61 (1.17-5.81)	**0.02**	3.35 (1.11-10.10)	**0.03**	1.86 (0.53-6.61)	0.34
FLAP rs4254165	Intron	0.37 (0.17-0.80)	**0.01**	0.55 (0.20-1.55)	0.26	0.12 (0.03-0.50)	**<0.01**
PGDH rs9312555	UTR-3	0.38 (0.17-0.89)	**0.03**	0.39 (0.12-1.22)	0.11	0.57 (0.15-2.18)	0.41
SRC rs7269342	Intron	0.49 (0.22-1.06)	0.07	0.59 (0.20-1.74)	0.34	0.26 (0.07-0.96)	**0.04**
Tertiary genes of interest							
GPX3 rs3828599	Intron	0.43 (0.20-0.93)	**0.03**	1.09 (0.40-3.02)	0.87	0.11 (0.03-0.48)	**<0.01**
GPX3 rs736775	nearGene-3	0.30 (0.13-0.70)	**<0.01**	0.50 (0.17-1.46)	0.20	0.14 (0.03-0.64)	**0.01**
GPX4 rs8178977	Intron	0.46 (0.22-0.99)	**0.046**	0.52 (0.18-1.51)	0.23	0.44 (0.13-1.50)	0.19
SEPP1 rs13168440	Intron	2.00 (0.71-5.61)	0.19	0.61 (0.11-3.40)	0.57	7.30 (1.19-44.85)	**0.03**
SEPP1 rs28919899	Intron	2.00 (0.71-5.61)	0.19	0.61 (0.11-3.40)	0.57	7.30 (1.19-44.85)	**0.03**

[1] **Most frequent gastrointestinal toxicities (n>5): abdominal pain, heartburn, diarrhea, reflux, constipation, vomiting**

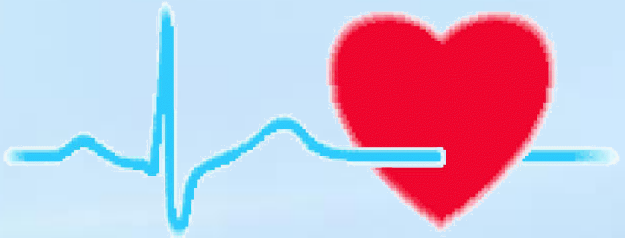
[2] **All polymorphisms with p-values≤0.05 in any one group are shown here**

Kraus et al., submitted for publication

All Drugs Do Not Fit All

The Three Major Killing Diseases

- Cardiovascular disease



- Cancer

- Alzheimer's disease

Personalized Therapy

Calculate absolute 10-year risk of IHD, CRC and Alzheimr

High risk

Cardiov[illegible]ular Disease
([illegible]gham

[illegible]MYH

Alzheimer Disease (>15%
Strong family history,
known mutations)

Low risk

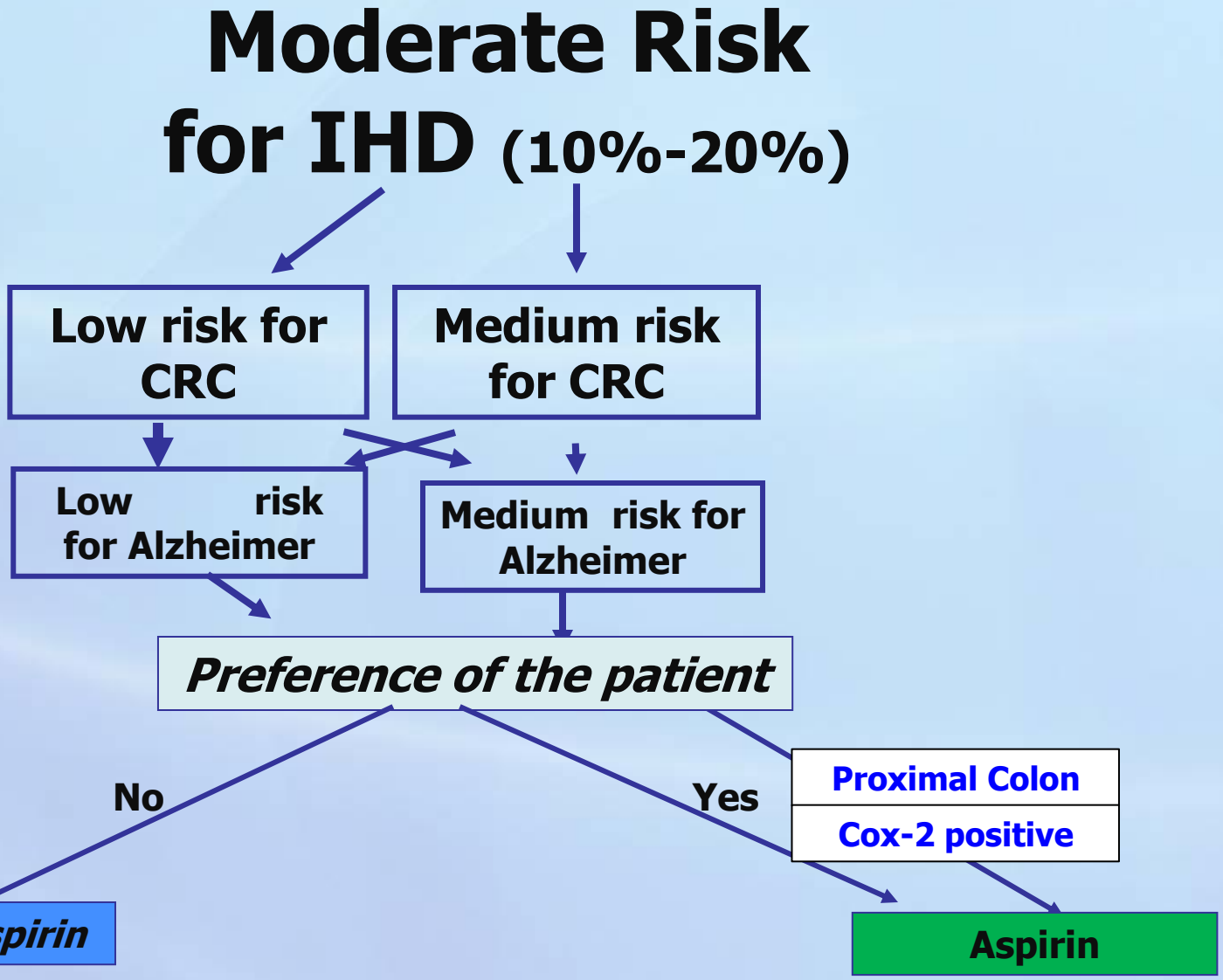
Cardiovascular
Disease(<10%
Framingham Study)

CRC- No symptoms, no
family history and
negative colonoscopy

Alzheimer <10%

Personalized Therapy

Calculate absolute 10-year risk of IHD, CRC and Alzheimr



Personalized Therapy

Calculate absolute 10-year risk of IHD, CRC and Alzheimr

High risk

Cardiovascular Disease

Aspirin

CRC (FAP, HNPCC, MYH polyposis*)*

Aspirin/NSAIDs

Alzheimer Disease

Aspirin?

Moderate Risk for IHD (10%-20%)

Low risk for CRC

Medium risk for CRC

Low risk for Alzheimer

Medium risk for Alzheimer

Preference of the patient

No

No aspirin

Yes

Proximal Colon

Cox-2 positive

Aspirin

Low risk

Cardiovascular Disease

CRC (FAP, HNPCC, MYH polyposis*)*

Alzheimer Disease

"An aspirin a day will help prevent a heart attack if you have it for lunch instead of a cheeseburger."