New York Cardiovascular Symposium

New York, December 11-13 2015

New York Hilton Midtown

Session IV: Trends and Challenges of Prevention

December 11 2015 – 15:15-17:30

Aspirin Therapy in Primary Cardiovascular Disease Prevention Only for Those at High Cardiovascular Risk, the Dose Under Trials

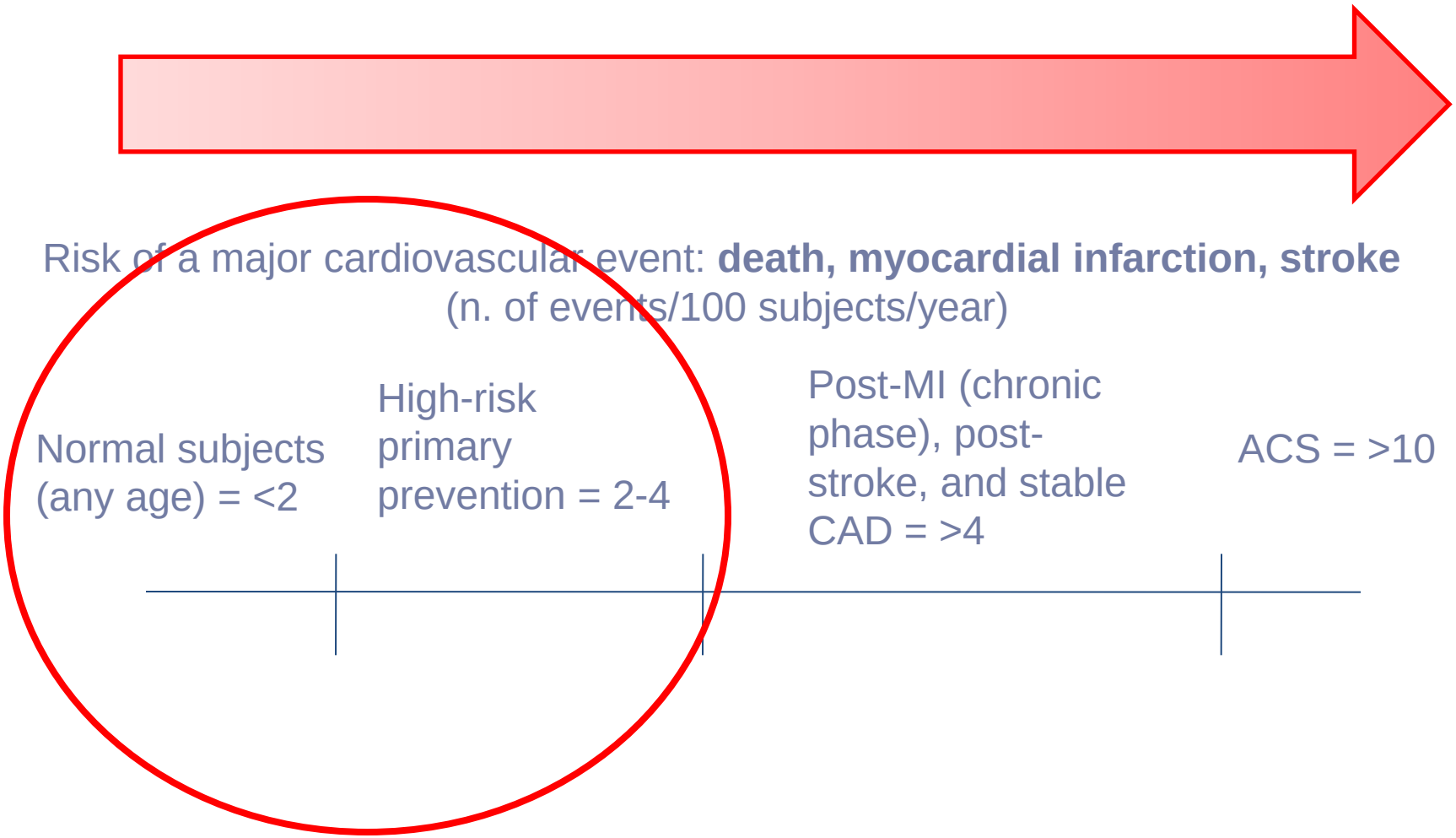
Raffaele De Caterina

December 11, 2015 – 16:15-16:35, 20 min. + 35 min. disc.

Prof. Raffaele De Caterina
Conflicts of Interest

- Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
- Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI
- Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck. Lilly
- None related to this topic

The spectrum of cardiovascular risk



EFFICACY and EFFICIENCY of aspirin at different levels of CV risk in secondary and primary prevention

Condition	CV risk level No. events % pts/year	Relative RR	Absolute RR (No. Events)	NNT
ACS (high risk)	15	- 30%	4.5	22
Stable angina (medium risk)	4	- 30%	1.2	
Primary prevention (low risk)	1	-30% (?)	0.30	

De Caterina, Coccheri et al, G Ital Card 2012

Nota: However, as primary prevention could be extended to whole populations, the small absolute reduction could translate into exceedingly high numbers.

4 recent meta-analyses of trials of primary CV prevention with aspirin

	Berger JS et al. 2011 RR	Bartolucci AA et al 2011 OR	Raju N et al 2011 RR	Seshasai SRK et al 2012 OR
Non fatal MI	0.84 n	0.81*	0.83*	0.80*
Stroke (all)	0.94 n	0.92 n	0.93 n	0.94 n
Composite endpoint°	0.90*	0.86*	0.88*	0.90*
Vascular mortality	0.99 n	0.96 n	0.96 n	0.99 n
Total mortality	0.94 n	0.94 n	0.94 n	0.94 n

°Composite endpoint= nf MI + nf Stroke + Vasc Death; *= significant; n=non-significant

Comment

Across the 4 meta-analyses, there is total concordance on the composite endpoint (always significant). Negative concordance for vascular and total mortality (claimed significant by Raju). Accord in non-fatal AMI (significant in 3 out of 4).

NET BENEFIT OF ASPIRIN IN PRIMARY PREVENTION ?

In fact

- ***In 1000 persons treated for 5 years there were:***
  - **About 3 ischemic events avoided**
  - **About 3 major bleeds caused**

} **poor net benefit**

From Berger JS, Am Heart J, 2011

Benefit and harms (absolute risk figures per 100,000 patient-years of follow-up) in primary prevention with aspirin

Benefits (events averted) Number and (NNT)	
Total mortality	33-46 (250)
Major CV events	60-84 (138)
CHD events	47-64 (182)
Cancer mortality	17-85 (n.c.)
Colorectal cancer mortality	34-36 (285)

Source: Sutcliffe P et al. Health Techn Ass 2013 S ep

NEWS 2013-2014
ON PRIMARY PREVENTION OF CV EVENTS

- **The use of aspirin seems no longer justifiable in primary prevention in patients with or without diabetes**

  Mathys E et al. Eur J Prev Cardiol 2014

- **Low dose aspirin can cause upper gastro-intestinal bleeding (UGIB): RR 1.90 in primary vs RR 1.40 in secondary prevention: however because of higher baseline risk incidence of UGIB is higher in secondary (NNH 391) than in primary prevention (NNH 601)**

  Lin KJ et al. Circulation CQO 2014

Thus, an important shift in advice, as only 5 years before the statement was that «a baby aspirin should be used in every male American >50 years of age»

AND IN PEOPLE WITH DIABETES?

A meta-analysis

- **20 studies including 17,522 pts of which 13 of secondary prevention and 7 of primary prevention**
- **Aspirin use in secondary prevention associated with lower mortality RR= 0.82; p = 0.03**
- **Aspirin use in primary prevention : RR = 1.01; n.s.**
- **Results highly heterogeneous among trials**

Simpson SH et al. J Gen Int Med 2011

And in asymptomatic PAD patients?

POPADAD (with diabetes) and AAA

All cause mortality	HR 0.93-0.95 (ns)
Non fatal AMI	HR 0-91-0.98 (ns)
Non fatal stroke	HR 0.71-0.87 (ns)
Cardiovascular mortality	HR 0.95-1.23 (ns)
Composite vascular events	HR 0.98-1.00 (ns)
Safety concerns	Inconclusive results

There was HIGH STRENGTH OF EVIDENCE for all efficacy endpoints

Source: Jones WS et al.
Agency for Healthcare Res and Quality, Review 118, Rockville 2013

Leading to statements like this:

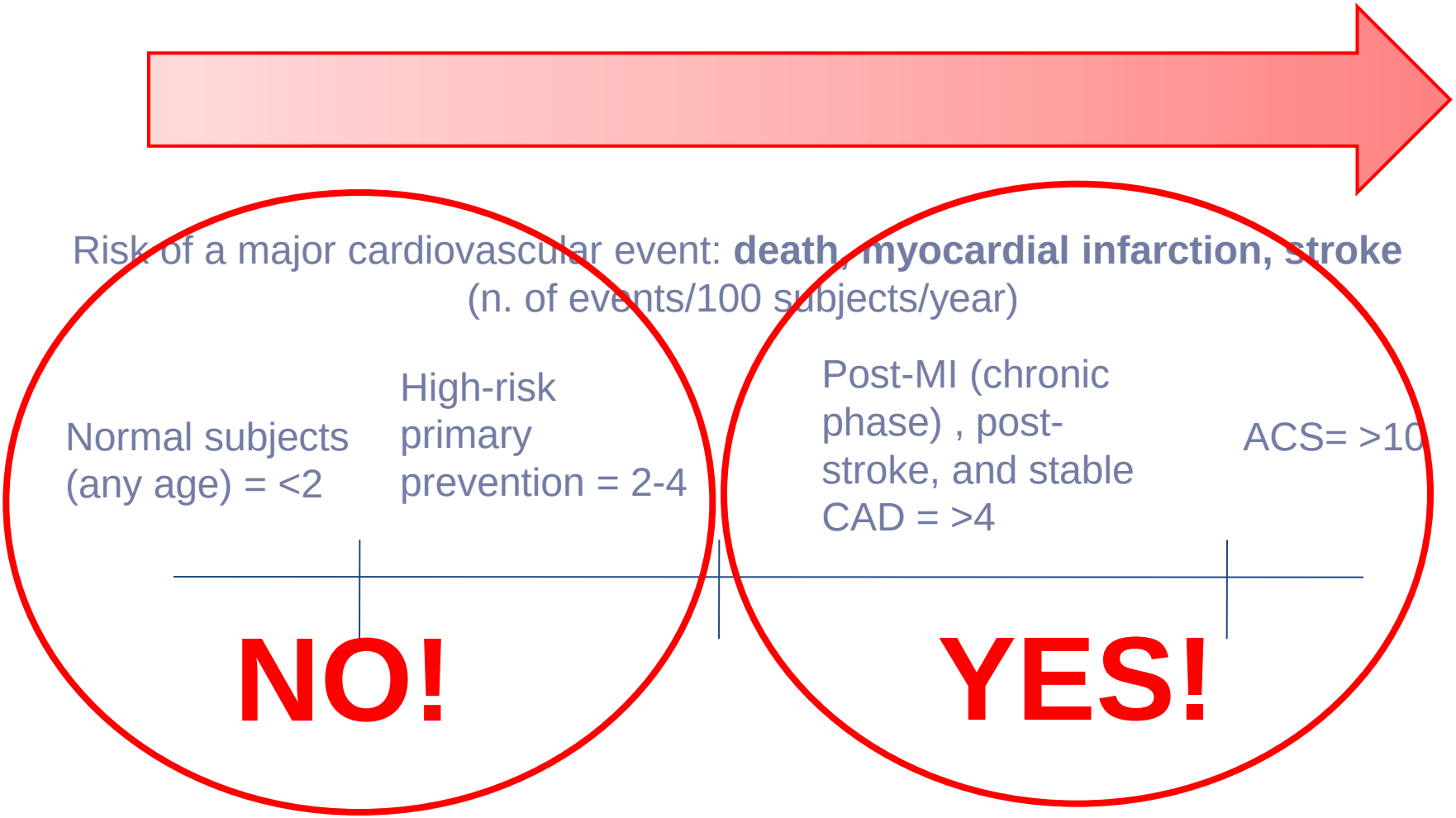
- «… doctors should select on an individual basis after careful discussion with the patient…»

or

- «aspirin cannot be recommended in primary prevention due to its increased risk of major bleeding” *

*2012 European Society of Cardiology (ESC) Guidelines on Cardiovascular Disease Prevention in Clinical Practice

But if cardiovascular risk is a spectrum, how can we dicothomize recommendations?



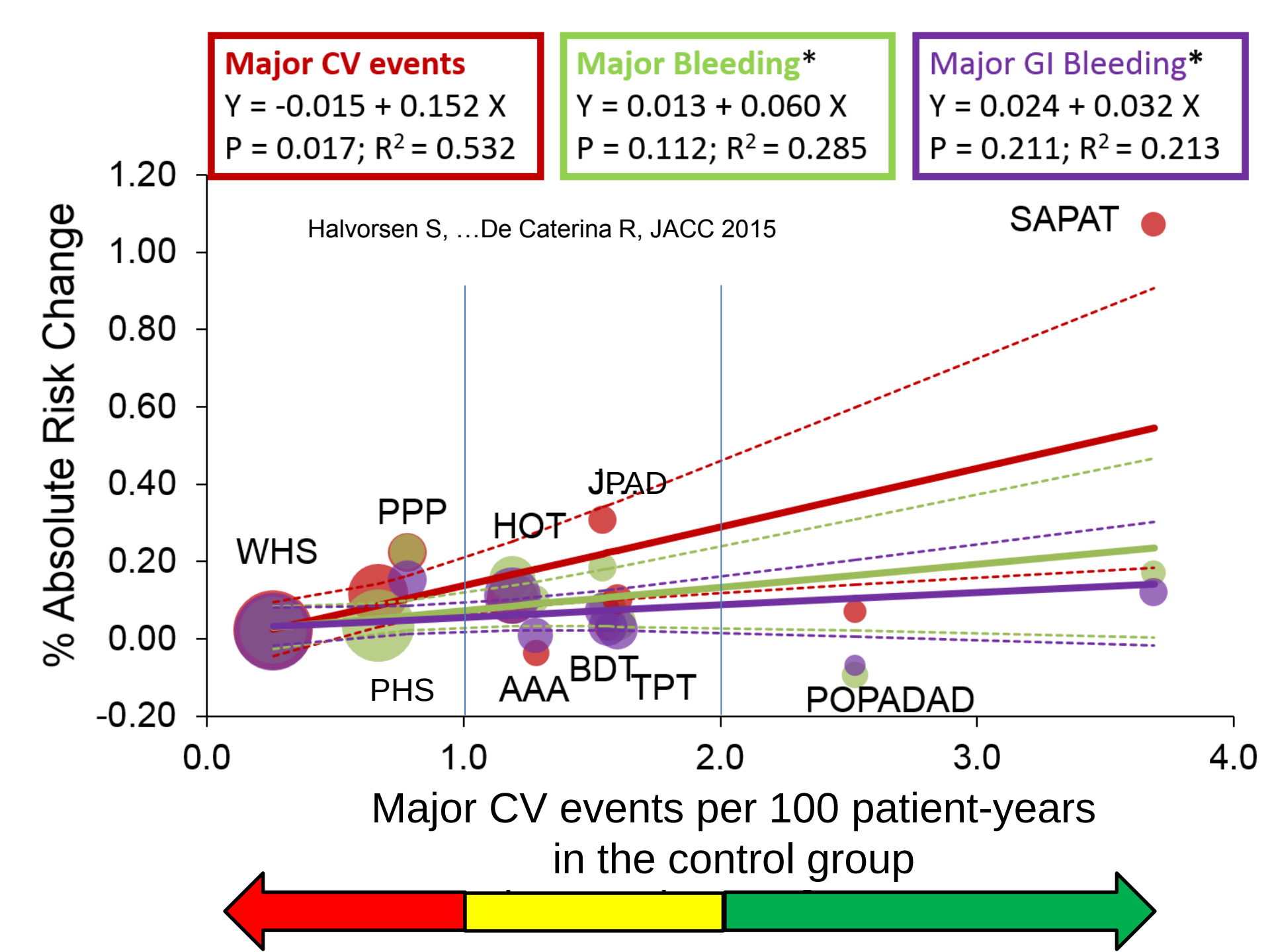
"Natura non facit saltus."
(Nature does not make jumps)
Gottfried Leibniz

REVIEW TOPIC OF THE WEEK

Aspirin Therapy in Primary Cardiovascular Disease Prevention

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

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


Major CV events
Y = -0.015 + 0.152 X
P = 0.017; R2 = 0.532
Major Bleeding*
Y = 0.013 + 0.060 X
P = 0.112; R2 = 0.285
Major GI Bleeding*
Y = 0.024 + 0.032 X
P = 0.211; R2 = 0.213
Halvorsen S, …De Caterina R, JACC 2015
% Absolute Risk Change
1.20
1.00
0.80
0.60
0.40
0.20
0.00
-0.20
0.0
1.0
2.0
3.0
4.0
SAPAT
JPAD
PPP
HOT
WHS
PHS
AAA
BDT
TPT
POPADAD
Major CV events per 100 patient-years
in the control group

Low-dose aspirin and cancer mortality - a new element in decision-making

- A meta-analysis of 23 randomized trials of low dose aspirin, primary or secondary prevention, any duration
- All trials reported that **non-vascular mortality** was reduced by aspirin: RR 0.88 (0.81-0.96)
- 11 trials reported that **cancer mortality** was even *more reduced: RR 0.77 (0.63-0.95)
- Effects became statistically significant after 4y follow up

Mills EJ et al. Am J Med 2012

Effect of aspirin on cancer incidence and mortality

From an analysis of 51 randomized trials

- **In six trials of primary CV prevention low dose aspirin reduced cancer incidence from 3y onwards in men and women (OR 0.76/0.77, p significant)**
- **With increasing follow up effect on CVE and bleeding declined leaving alone the reduced risk of cancers**
- **The absolute reduction in cancer incidence was 3.13 cases per 1000 pts/year from 3y onwards**

Rothwell PM et al. Lancet 2012

Aspirin prevention of cancer

- **Strength of evidence of long-term prophylactic effect of low-dose aspirin towards cancer is higher for:**
  - **Long duration (> 5 y)**
  - **Colorectal versus other types of cancer**
  - **Daily administration and compliance**
- **However, results are based on trials of several types: and especially on groups nested in studies "post hoc" rather than "ad hoc"**
- **And still some groups deny primary prevention of cancer by aspirin (*Hollestein LM et al. Int J Cancer 2014*)**

Ongoing randomized trials of low-dose aspirin for primary CVD prevention

TABLE 2 Ongoing Randomized Trials of Low-Dose Aspirin for Primary Prevention

Study (Ref. #)	Regimen(s)	Treatment Duration	N	Eligibility	Primary Endpoint	End Date
ACCEPT-D (23)	Aspirin 100 mg versus open control; simvastatin for all	5 yrs	5,170	Diabetes, no CVD	CV death, nonfatal stroke, nonfatal MI, other CV hospitalization	2015
ARRIVE (25)	Aspirin 100 mg versus placebo	5 yrs	~12,000	10-20% estimated 10-yr risk of CHD	MI, stroke, CV death, unstable angina, TIA	2016
ASPREE (24)	Aspirin 100 mg versus placebo	5 yrs	~19,000	Elderly, no diabetes or CVD	Death, dementia or significant disability	2017
ASCEND (22)	Aspirin 100 mg versus placebo (ω3FA vs. placebo)	7.5 yrs	~15,000	Diabetes, no CVD	MI, stroke or TIA, or CV death	2018

ACCEPT-D = Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trials in Diabetes; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = ASPirin in Reducing Events in the Elderly; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; FA = fatty acids; MI = myocardial infarction; TIA = transient ischemic attack.

Patrono C, 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

CONCLUSIONS
AND PROPOSED RECOMMENDATIONS

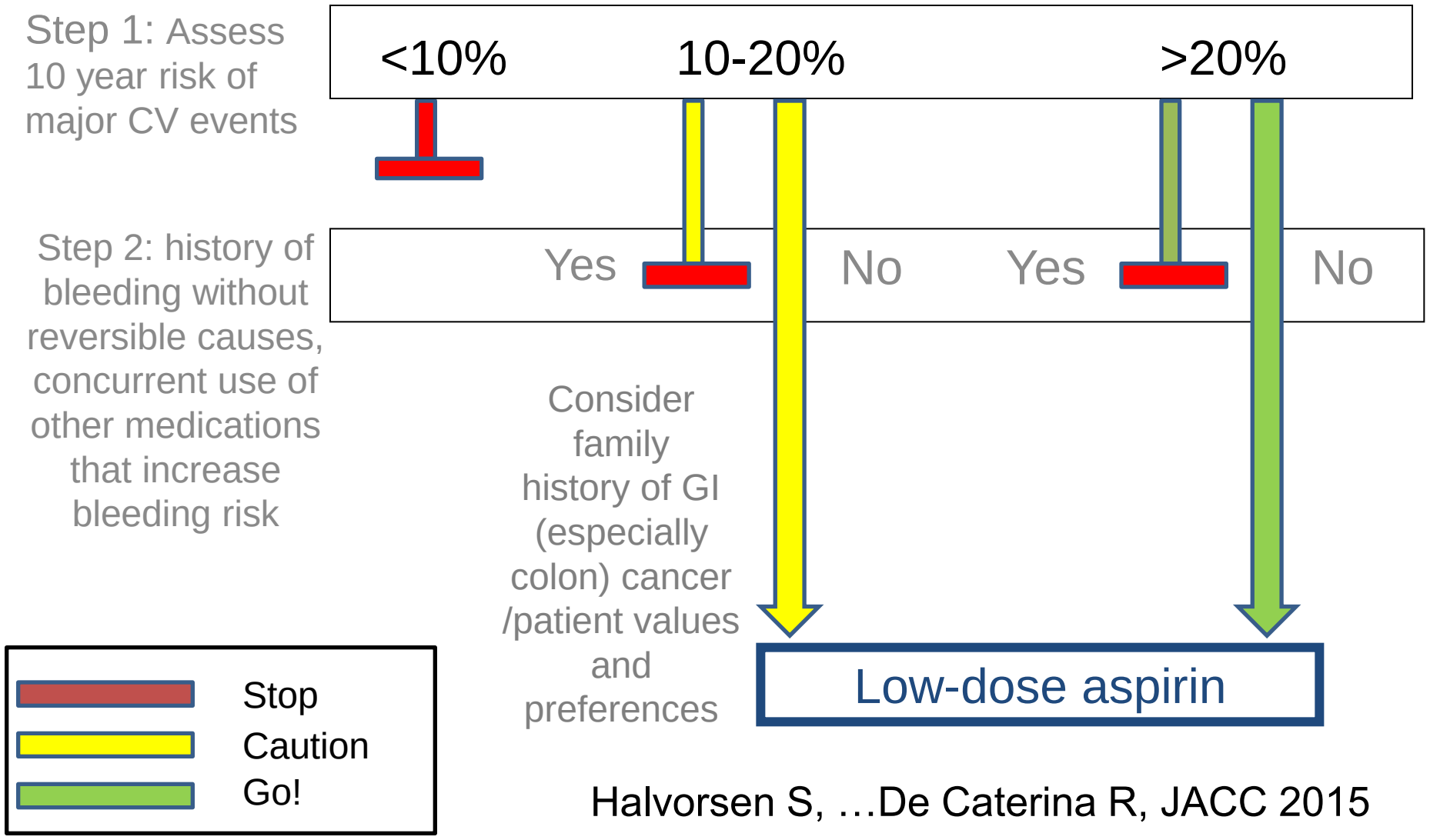
- **Aspirin use in primary prevention of MCE should be guided by an assessment of the global cardiovascular risk. Risk of colorectal cancer may support long term duration of treatment.**

- **Aspirin is expected to be benefcial at the level of risk of MCE > 2/100 person-years, in absence of an increased risk of bleeding**

Source: Halvorsen S…De Caterina R. JACC, 2014

Collaborative group:
S. Halvorsen (Oslo); F. Andreotti (Rome); J.M. Ten Berg (Nieuwegein); M. Cattaneo (Milan); S. Coccheri (Bologna); R. Marchioli (Chieti); J. Morais (Leiria); F.W.A. Verheugt (Amsterdam); R. De Caterina (Chieti).

Low-dose aspirin in primary CVD prevention



Halvorsen S, …De Caterina R, JACC 2015

- We are aware of the lack of data in the high-risk primary prevention category
- But lack of evidence is NOT evidence against
- Decisions in the meantime will have to be taken
- And logic should here help

At the end, we don’t put hands on fire, despite having no RCT to support this

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J Am Coll Cardiol 2014;64:319–27

DOCUMENTO DI CONSENSO

La terapia con aspirina nella prevenzione cardiovascolare primaria. Documento di consenso intersocietario italiano

Massimo Volpe[1], Maurizio Giuseppe Abrignani[2], Claudio Borghi[3], Sergio Coccheri[4], Paolo Gresele[5], Giuseppe Patti[6], Bruno Trimarco[7], Raffaele De Caterina[8]

[1]Sapienza Università di Roma, e IRCCS Neuromed di Pozzilli (IS)
in rappresentanza di: Società Italiana dell'Ipertensione Arteriosa (SIIA)
[2]Ospedale S. Antonio Abate di Trapani
in rappresentanza di: Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO)
[3]Università degli Studi di Bologna
in rappresentanza di: Società Italiana dell'Ipertensione Arteriosa (SIIA)
[4]Università degli Studi di Bologna
in rappresentanza di: Società Italiana di Angiologia e Patologia Vascolare (SIAPAV)
[5]Università degli Studi di Perugia
in rappresentanza di: Società Italiana per lo Studio dell'Emostasi e della Trombosi (SISET)
[6]Università Campus Bio-Medico di Roma
in rappresentanza di: Società Italiana di Cardiologia (SIC)
[7]Università degli Studi "Federico II" di Napoli
in rappresentanza di: Società Italiana per la Prevenzione Cardiovascolare (SIPREC)
[8]Università degli Studi "G. d'Annunzio" di Chieti
in rappresentanza di: European Society of Cardiology Working Group on Thrombosis

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Thank you!