Peripheral Arterial Disease - antiplatelet therapy

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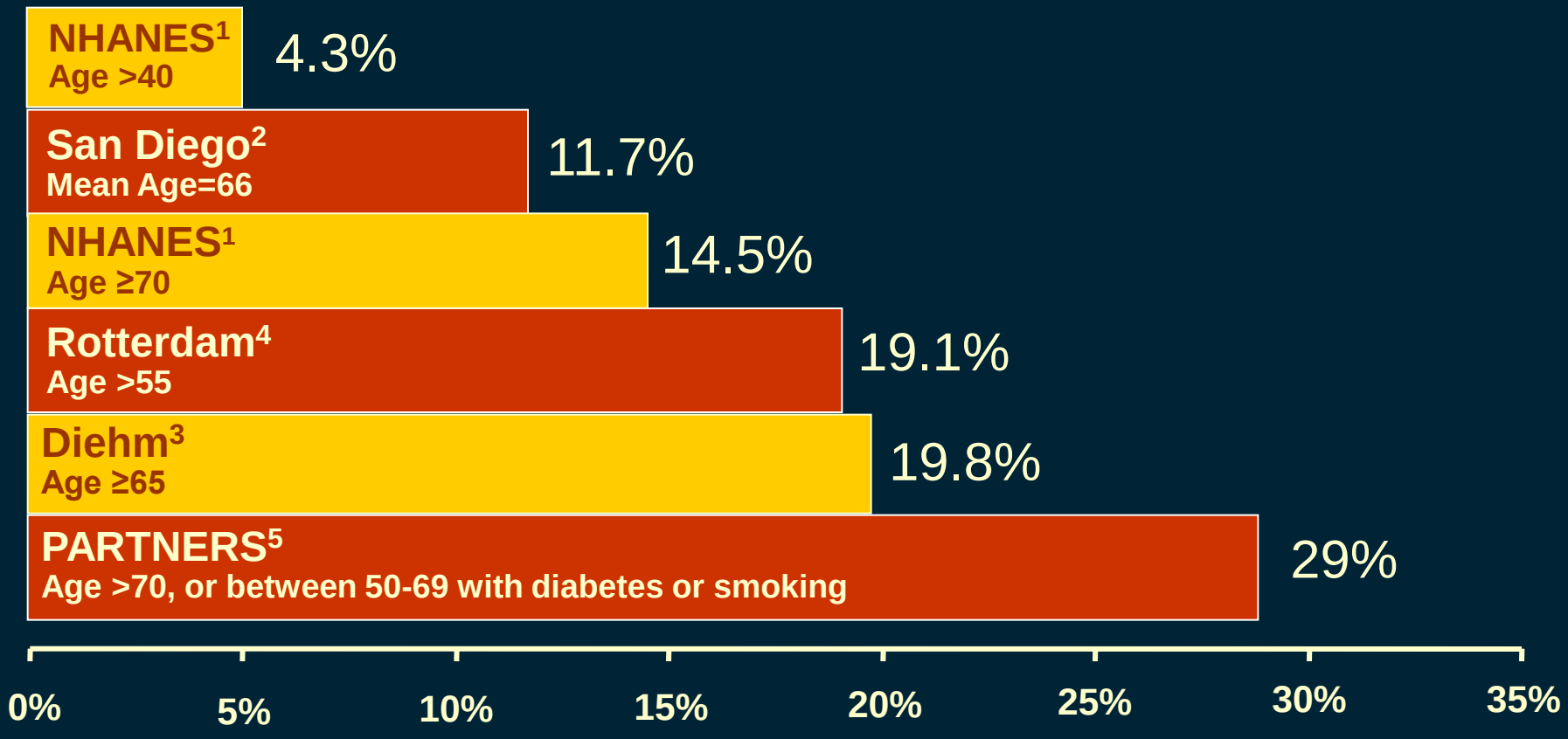
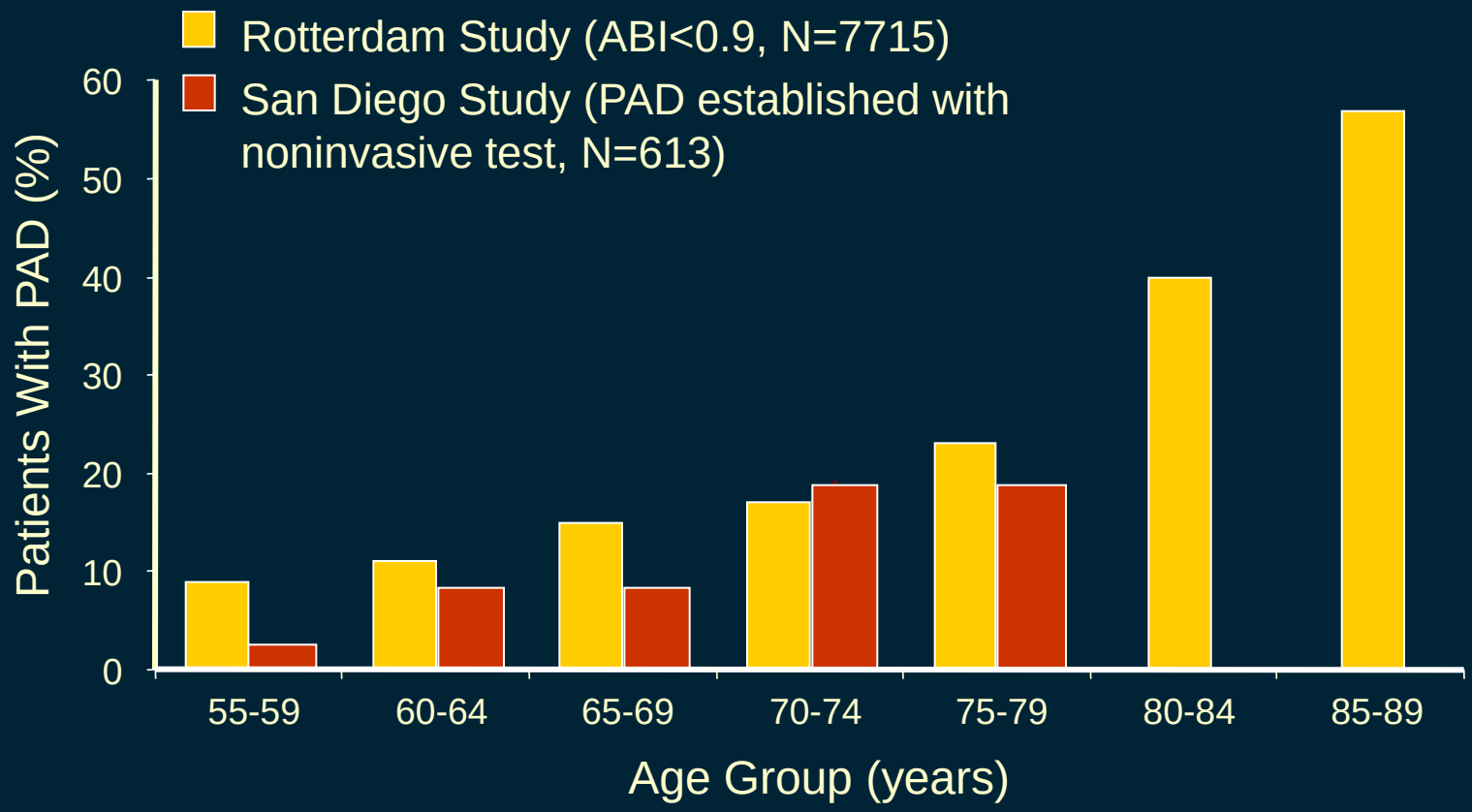
CARDIONALE
PRAGUE 2010

Documented Presence of PAD



1. Selvin E, Erlinger TP. NHANES. *Circulation.* 2004;110:738-743.
2. Criqui MH, et al. *Circulation.* 1985;71:510-515.
3. Diehm C, et al. *Atherosclerosis.* 2004;172:95–105.
4. Meijer WT, et al. *Arterioscler Thromb Vasc Biol*. 1998;18:185-192.
5. Hirsch AT, et al. *JAMA.* 2001;286:1317-1324.

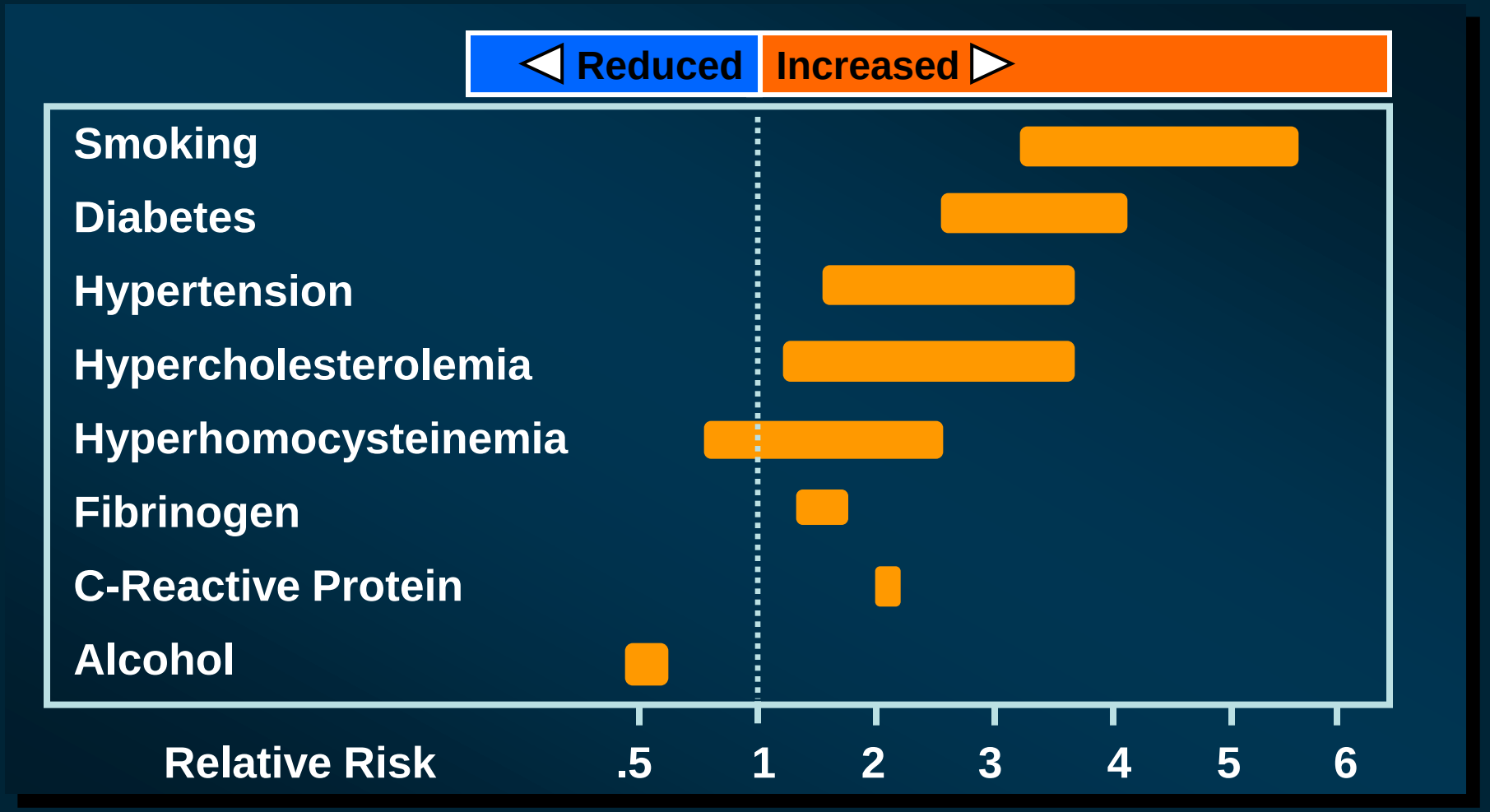
Prevalence of PAD Increases With Age



Adapted from Golomb BA, et al. In: Creager MA, ed. *Management of Peripheral Arterial Disease: Medical, Surgical and Interventional Aspects*; 2000:1-18.
Meijer WT, et al. *Arterioscler Thromb Vasc Biol*. 1998;18:185-192.
Criqui MH, et al. *Circulation*. 1985;71:510-515.

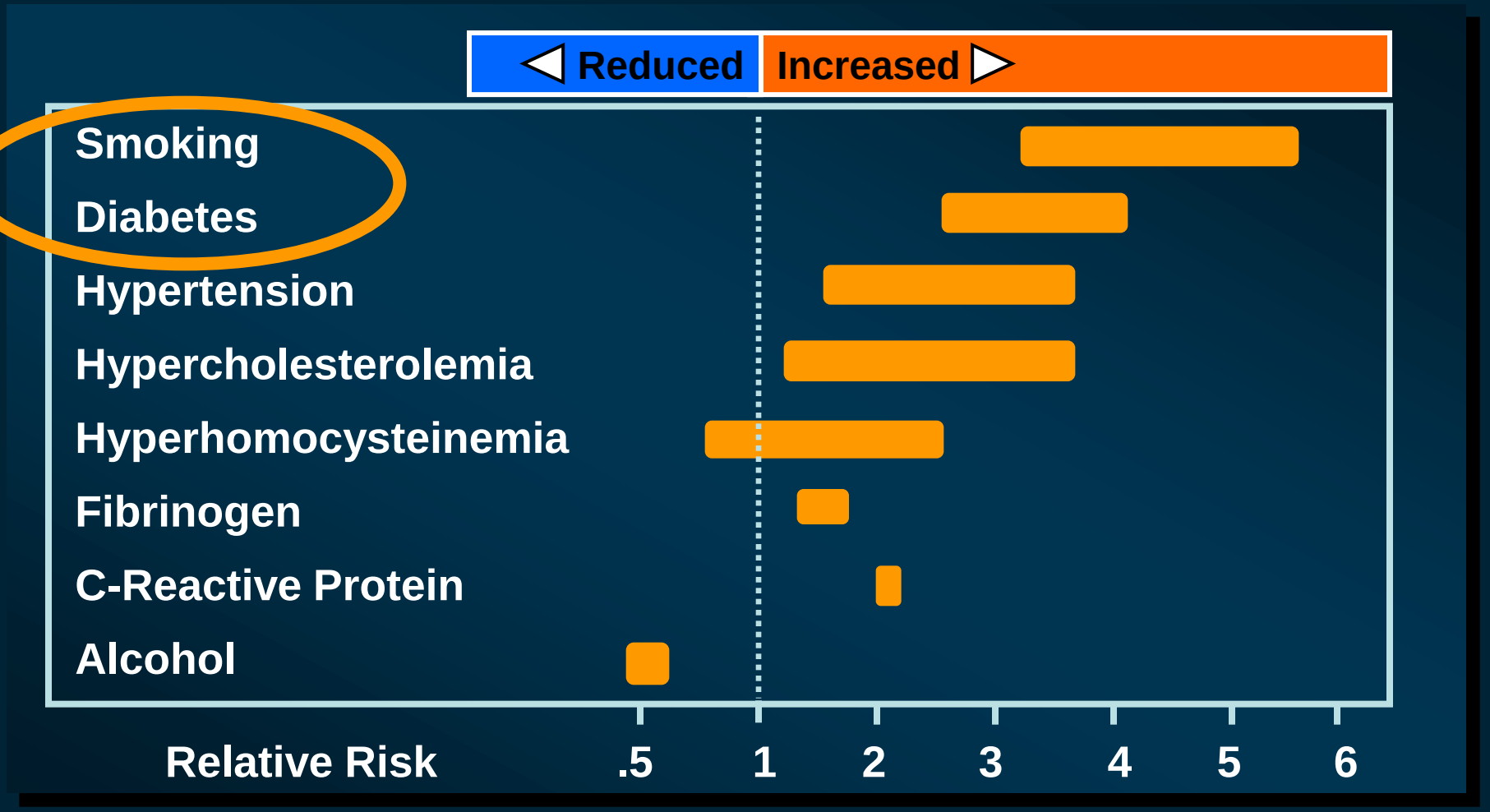
Risk Factors for PAD

PragueAngio 2008

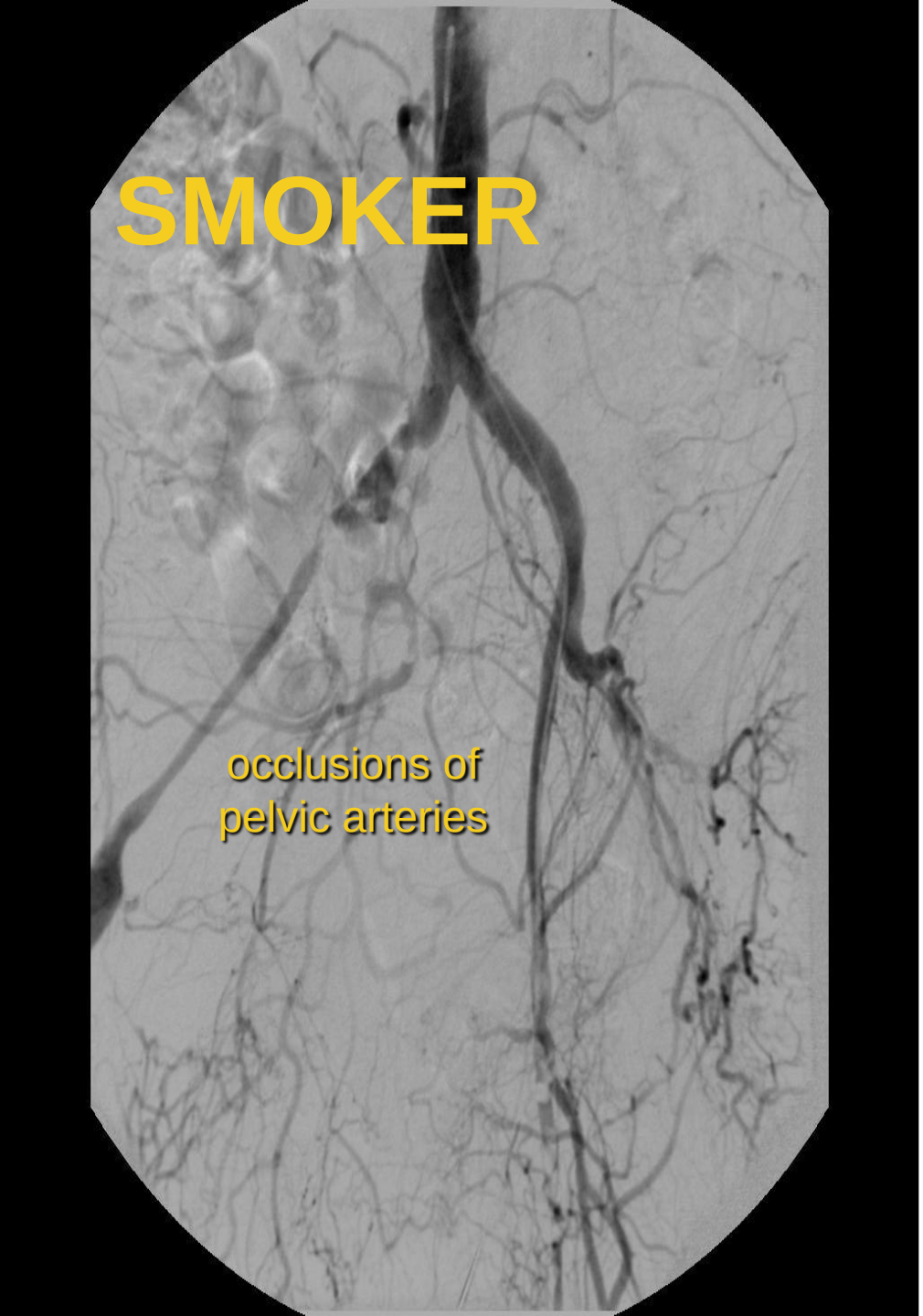


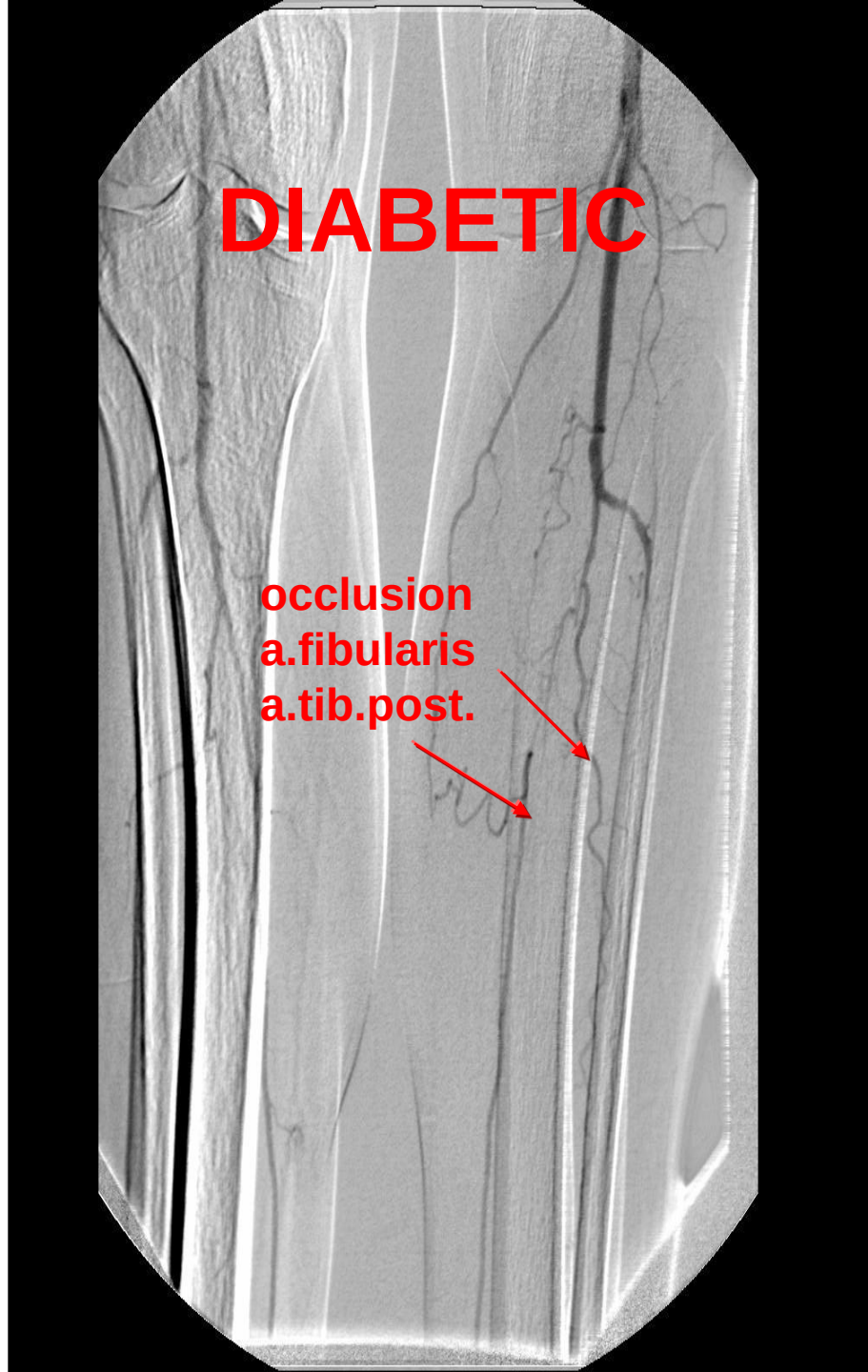
TASC II Working Group

Risk Factors for PAD

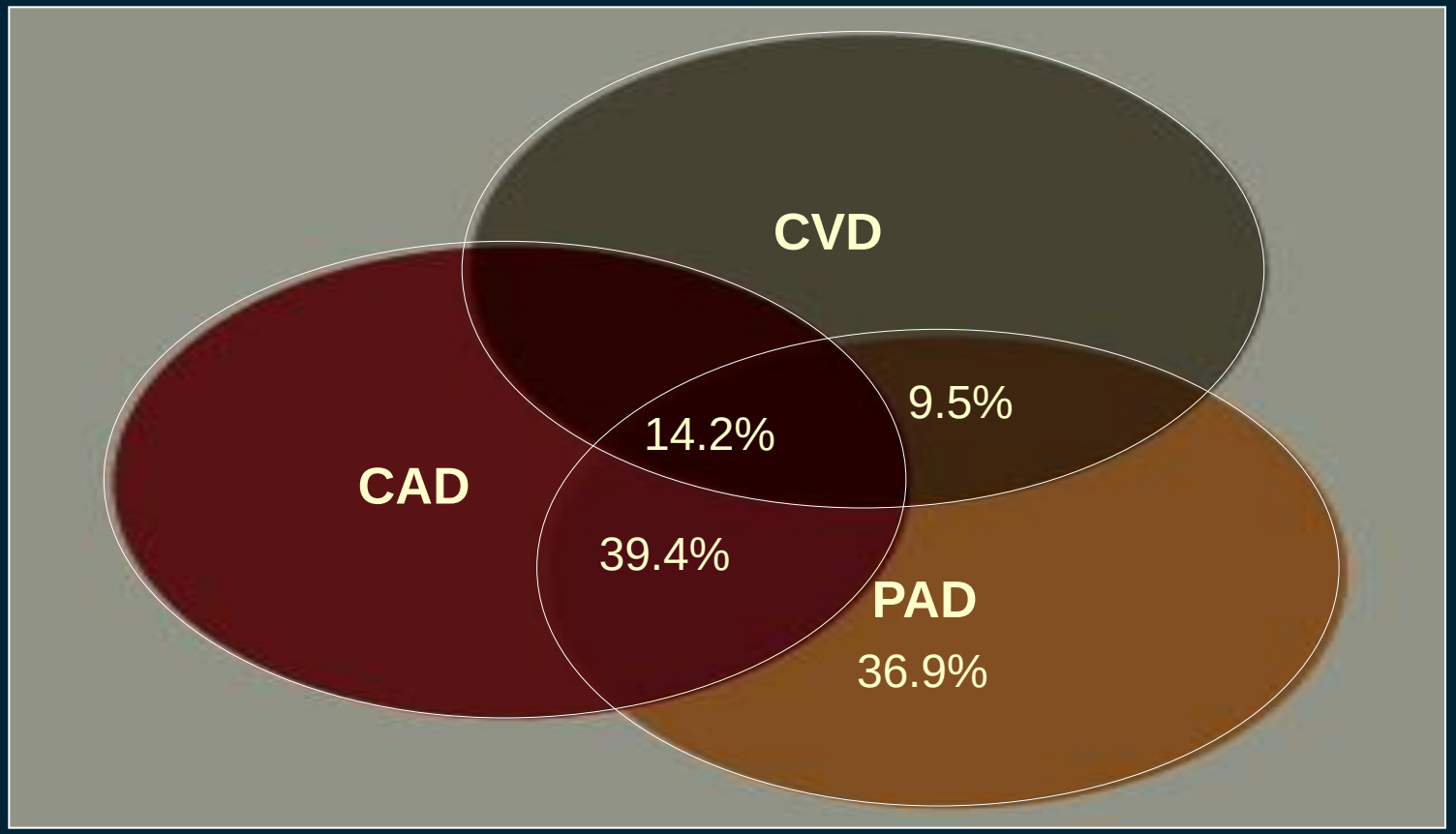


TASC II Working Group


SMOKER
occlusions of
pelvic arteries


DIABETIC
occlusion
a.fibularis
a.tib.post.

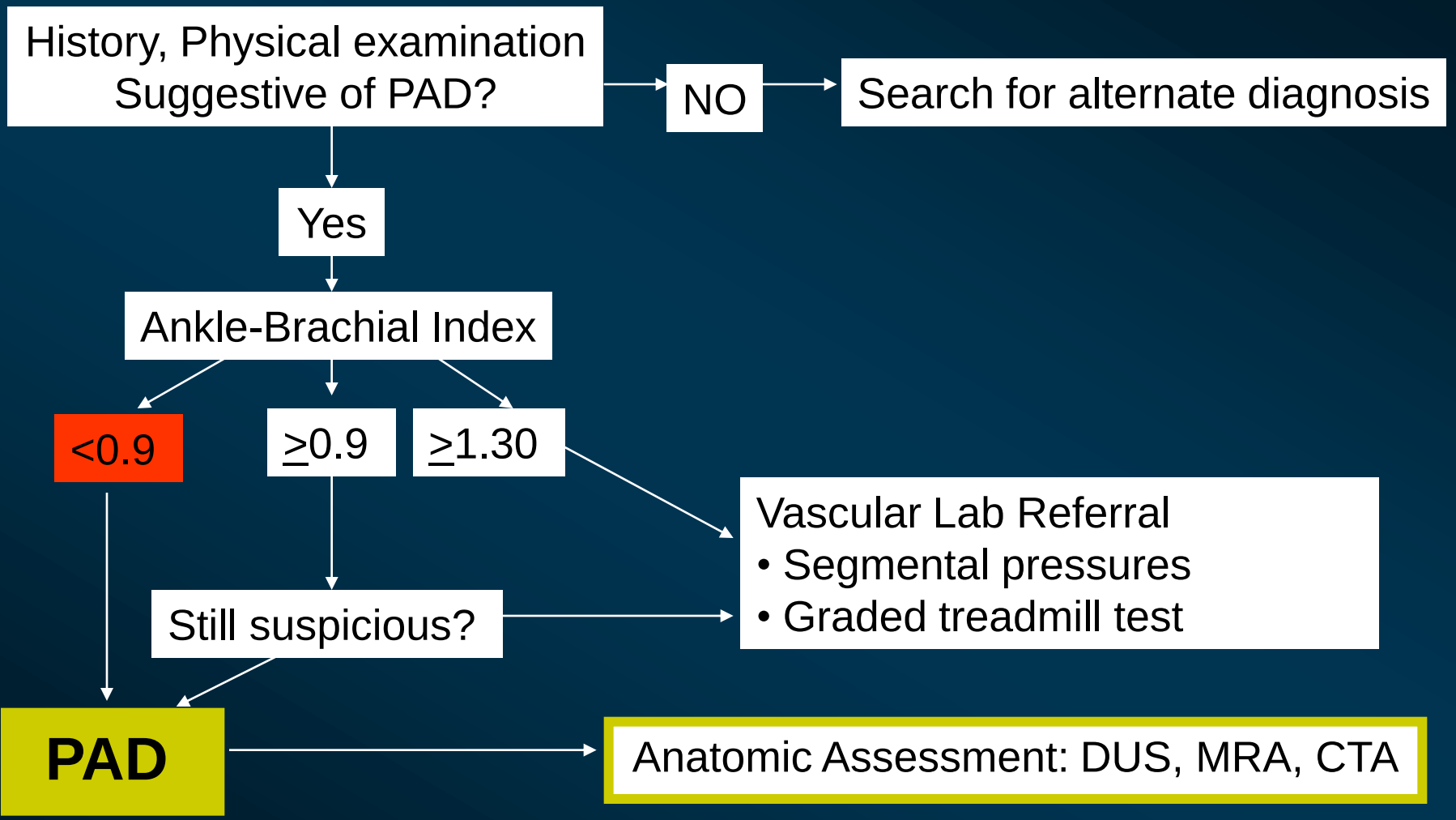
Overlap Between PAD, CAD, and CVD



Patients with one manifestation
often have coexistent disease in other vascular beds.

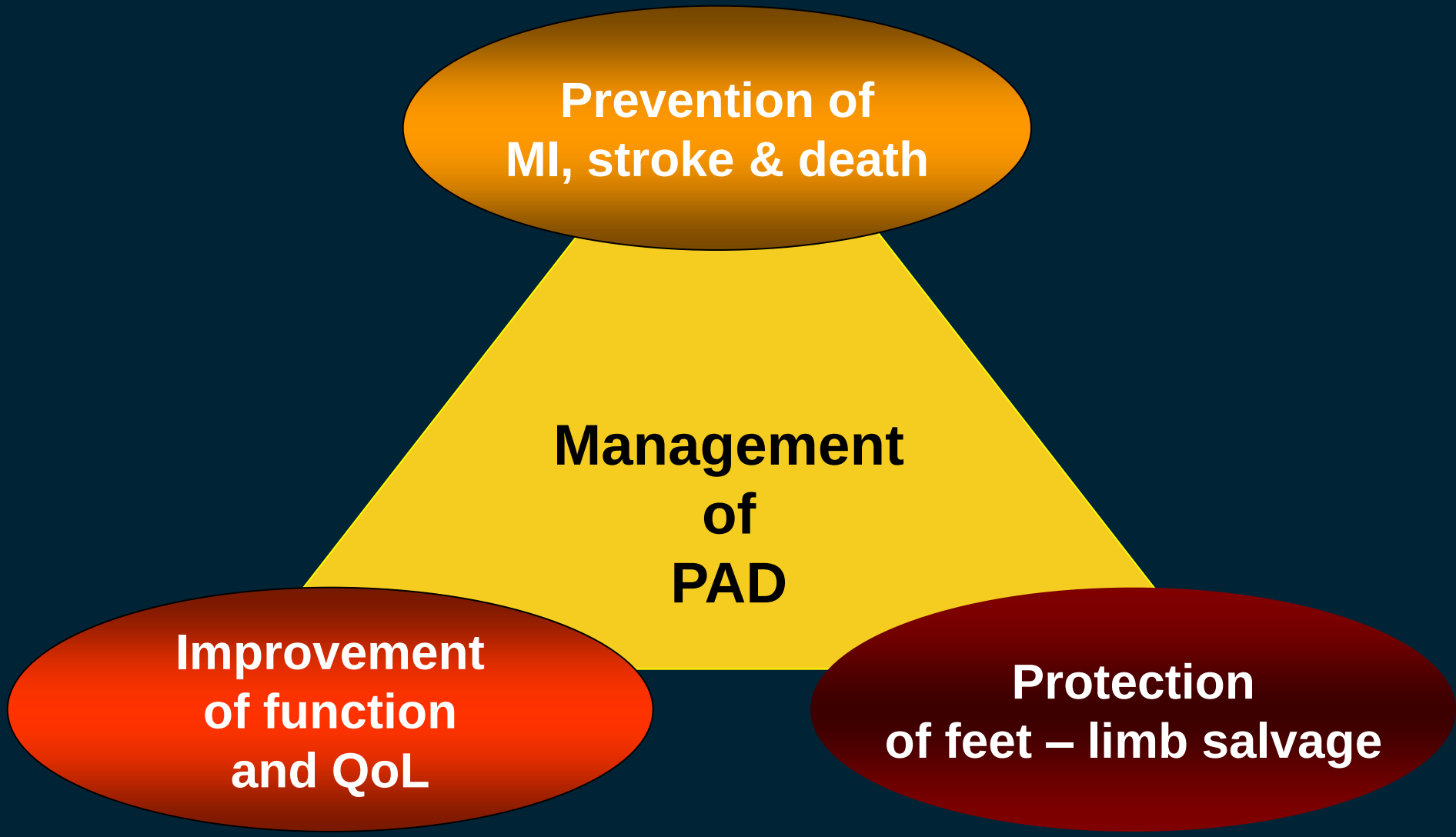
Bhatt DL, et al. REACH Investigation. Presented at: American College of Cardiology Annual Scientific Session; March 8, 2005; Orlando, FL. Abstract 1127-96.

Diagnostic Algorithm for PAD



The **5-year all-cause mortality** rates are as high as **30%** in patients with PAD,

PAD pts are **6 times more likely to die from CV disease within 10 yrs** than pts without PAD


Prevention of
MI, stroke & death
Management
of
PAD
Improvement
of function
and QoL
Protection
of feet – limb salvage

Treatment of All PAD Pts

Exercise programme

↓

Risk factor normalization:

- Immediate smoking cessation
- Treatment of hypertension
- Treatment of dyslipidemia to target levels
- Treatment of diabetes mellitus to HbA_{1c} < 7% (4,5%)

↓

Pharmacological treatment:

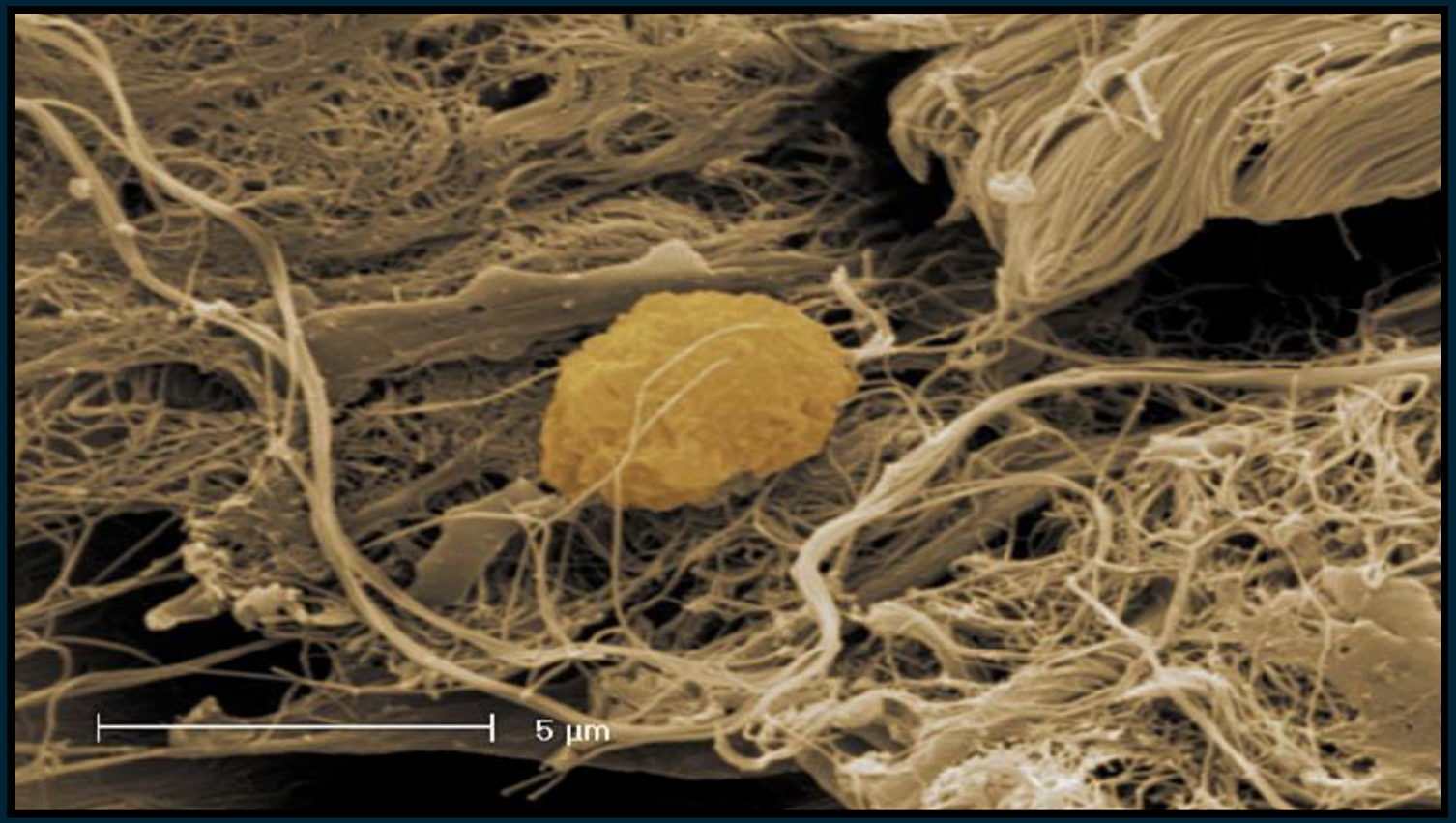
Antiplatelet therapy — cilostazol

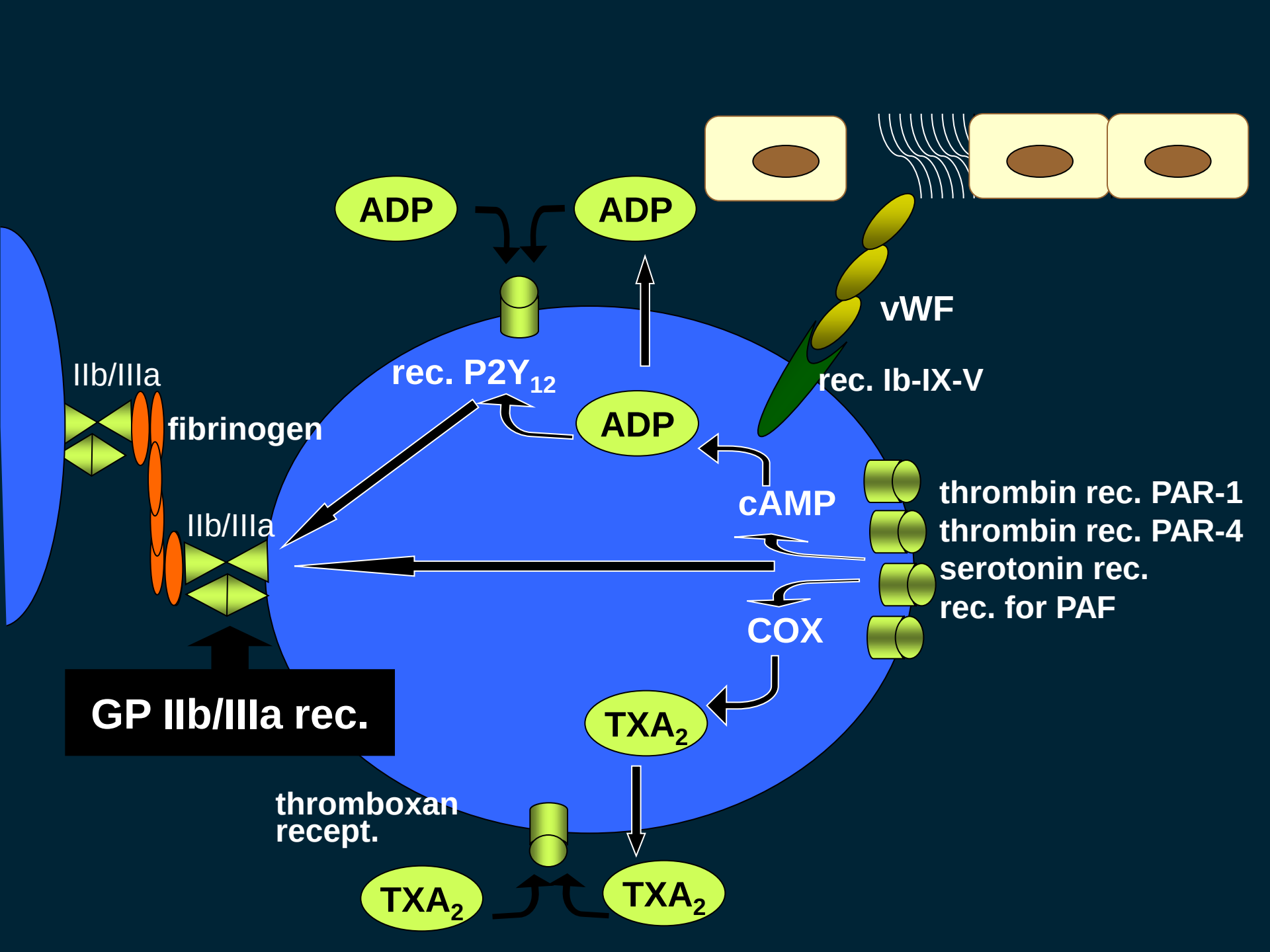
ACE inhibition / Sartans — naftidrofuryl

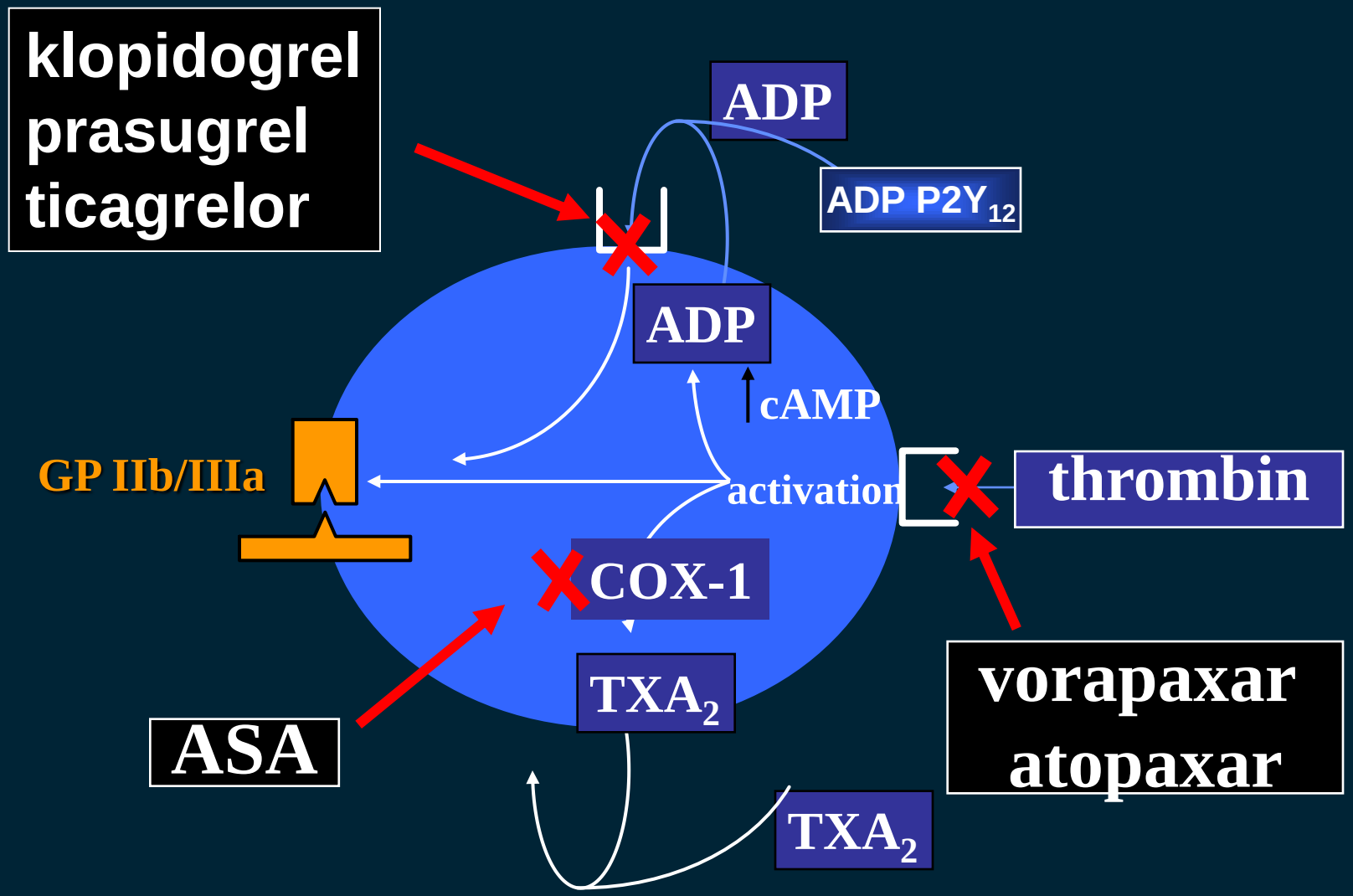
↓

Revascularization

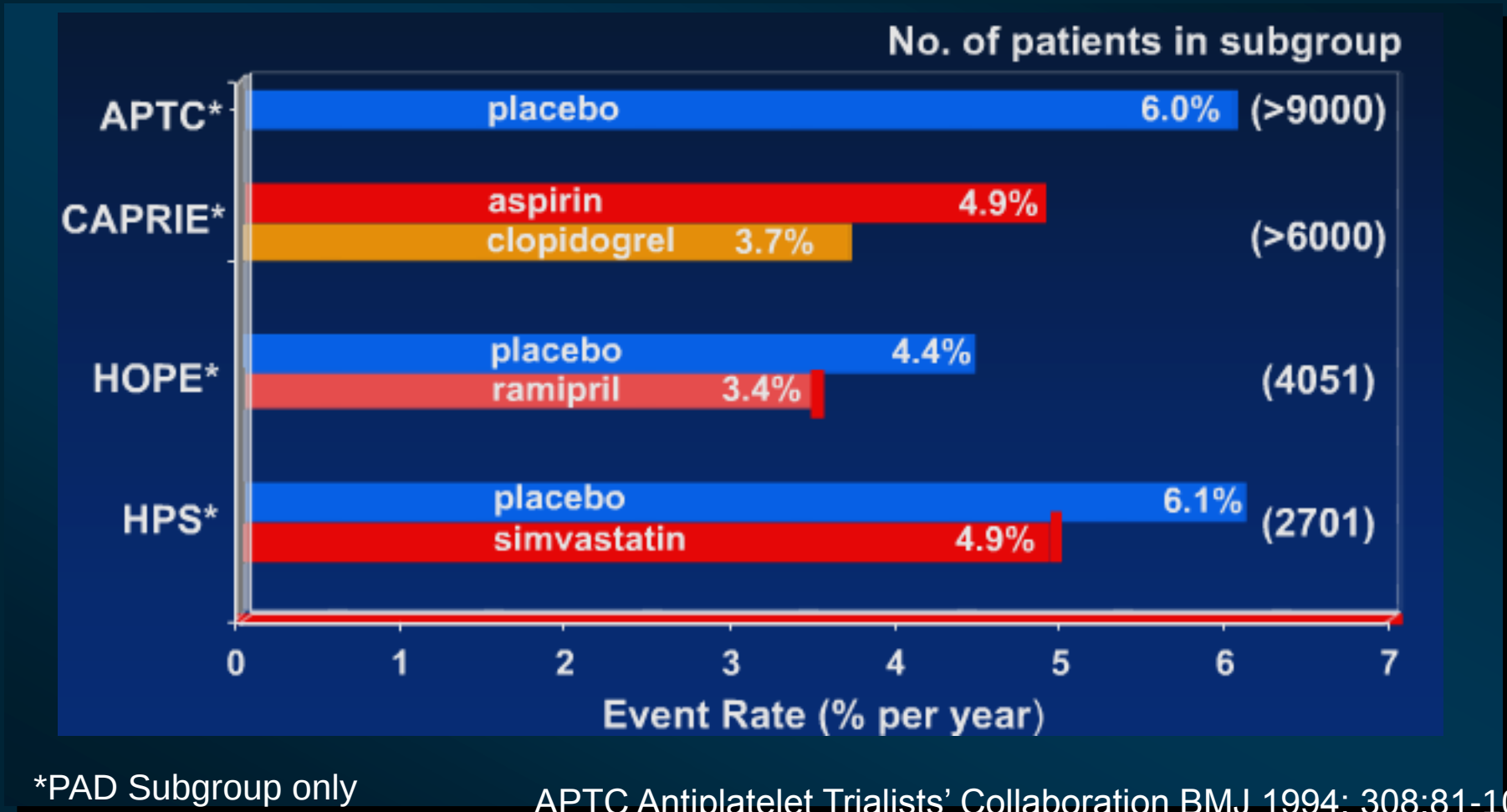
Antiplatelet therapy




ADP
ADP
vWF
rec. P2Y12
rec. Ib-IX-V
IIb/IIIa
fibrinogen
ADP
IIb/IIIa
cAMP
thrombin rec. PAR-1
thrombin rec. PAR-4
serotonin rec.
rec. for PAF
COX
GP IIb/IIIa rec.
TXA2
thromboxan
recept.
TXA2
TXA2


klopidogrel
prasugrel
ticagrelor
ADP
ADP P2Y12
ADP
cAMP
GP IIb/IIIa
activation
thrombin
COX-1
TXA2
vorapaxar
atopaxar
ASA
TXA2

Efficacy of Antiplatelet therapy, ACE-I, Statins in PAD



*PAD Subgroup only

APTC Antiplatelet Trialists' Collaboration BMJ 1994; 308:81-106
CAPRIE Steering Committee Lancet 1996; 348: 1329-1339
HOPE Study Investigators N Engl J Med 2000; 342:145-153
HPS Collaborative group Lancet; 2002; 360:7-22

Antithrombotic Trialists' Collaboration: PAD

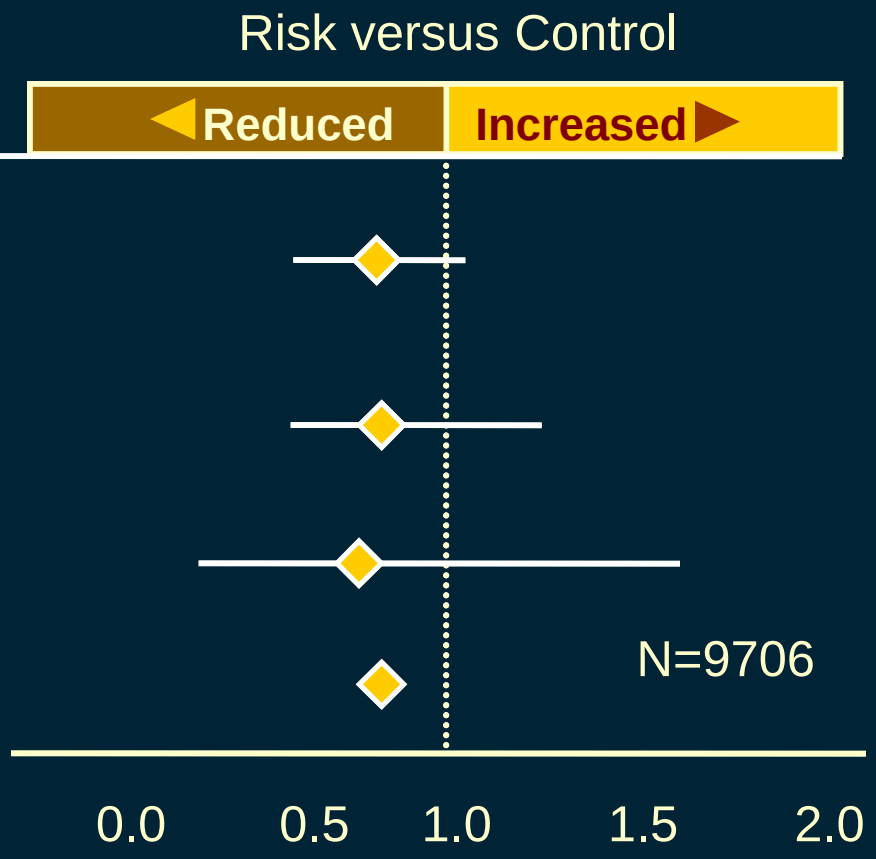
- 42 clinical trials
- 9,214 patients with PAD
- **23% reduction** of serious adverse vascular events (*P*=.004)
- Benefits similar among PAD subtypes (intermittent claudication, peripheral grafting, and peripheral angioplasty)

Antithrombotic Trialist's Collaboration. *BMJ.* 2002;324:71-86.

Antithrombotic Trialists' Collaboration

Risk of Vascular Events in High-Risk Patients

Risk Category (number of trials)	Patients with Event (%) APT	Control
Intermittent claudication (N=26)	6.4	7.9
Peripheral grafting (N=12)	5.4	6.5
Peripheral angioplasty (N=4)	2.5	3.6
All PAD trials (N=42)	5.8	7.1



APT=antiplatelet therapy with aspirin, clopidogrel, dipyridamide, or a glycoprotein IIb/IIIa antagonist

Antithrombotic Trialists' Collaboration. *BMJ*. 2002;324:71-86.

Is really the acetylsalicylic acid so beneficial drug for the patients with PAD ?

Aspirin for the Prevention of Cardiovascular Events in Patients With Peripheral Artery Disease: A Meta-analysis of Randomized Trials

Jeffrey S. Berger; Mori J. Krantz; John M. Kittelson; et al.

JAMA. 2009;301(18):1909-1919 (doi:10.1001/jama.2009.623)

- 18 trials involving 5 269 pts (1966-2008)
- CV events in 8,9% taking ASA and by 11% in the control group –nonsignificant 12% RR
- Reduction of nonfatal stroke but not associated with significant reduction in all-cause or cardiovascular mortality, MI
- 3 019 taking ASA alone (7 trials)– the same results

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JAMA. 2009;301(18):1909-1919 (doi:10.1001/jama.2009.623)

- 18 trials involving 5 269 pts (1966-2008)

Limitations:

- no evaluation of peripheral vascular events

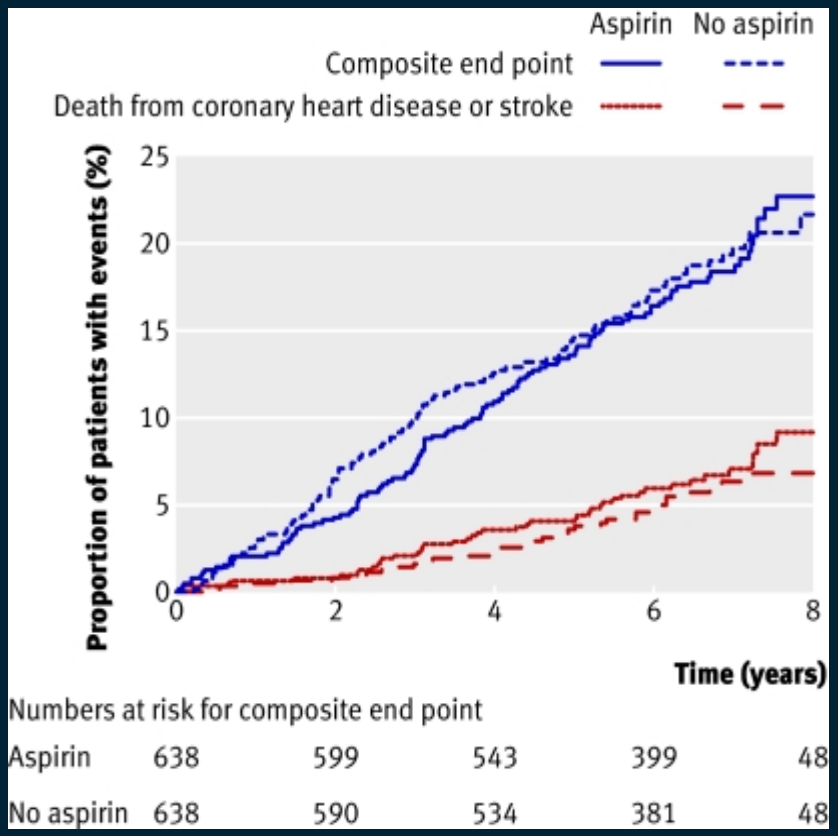
- the analysis is underpowered to detect a difference in primary outcome of less than 25%

Aspirin is efficacious in reducing vascular events with a benefit of less than 15%

60% of the data come from: POPADAD trial, VA-Cooperative trial

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

Jill Belch, professor of vascular medicine,[1] Angus MacCuish, consultant diabetologist,[2] Iain Campbell, professor of diabetic medicine,[3] Stuart Cobbe, Walton professor of cardiology,[4] Roy Taylor, professor of medicine and metabolism,[5] Robin Prescott, professor of health technology assessment,[6] Robert Lee, research associate,[6] Jean Bancroft, senior research nurse,[1] Shirley MacEwan, honorary senior research fellow,[1] James Shepherd, professor of pathological biochemistry,[6] Peter Macfarlane, professor of



BMJ 2008, 337: 1840

- ASA was not effective in the primary of CV events in pts with asymptomatic PAD
- Antioxidants showed no benefit as well

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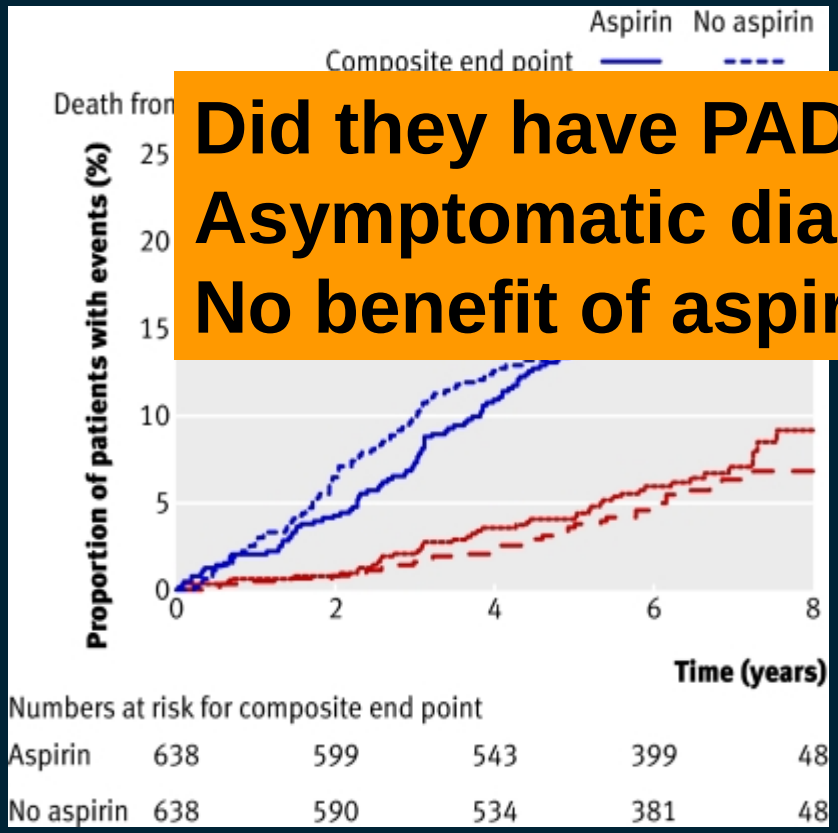


Did they have PAD? (ABI < 0,99)
Asymptomatic diabetics, aged > 40
No benefit of aspirin in this population

ctive
CV

asymptomatic PAD

- Antioxidants showed no benefit as well

BMJ 2008, 337: 1840

Aspirin for Prevention of Cardiovascular Events in a General Population Screened for a Low Ankle Brachial Index

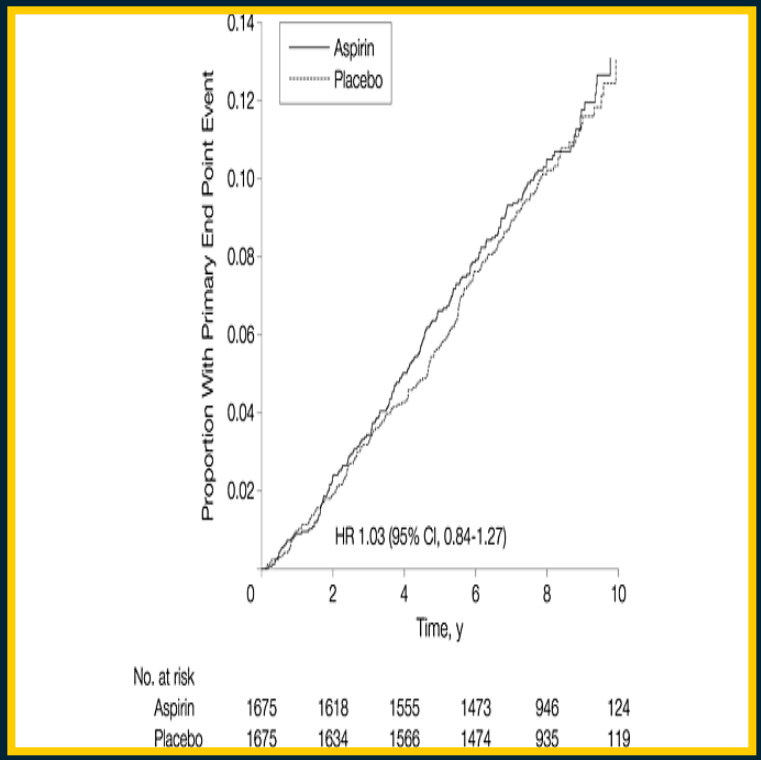
A Randomized Controlled Trial

F. Gerald R. Fowkes, FRCPE
Jacqueline F. Price, MD
Marlene C. W. Stewart, PhD
Isabella Butcher, PhD
Gillian C. Leng, MD
Alistair C. H. Pell, MD
Peter A. G. Sandercock, DM
Keith A. A. Fox, FRCP
Gordon D. O. Lowe, DSc
Gordon D. Murray, PhD
for the Aspirin for Asymptomatic Atherosclerosis Trialists

AAA trial

Aspirin for Asymptomatic Atherosclerosis

- among participants without clinical CV disease, identified with a low ABI based on screening a general population, the administration of ASA did not reduce vascular events



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for the
Athero

AAA trial

Aspirin for Asymptomatic Atherosclerosis

most pts with borderline ABI
70% of participants women
the rate of events lower than expected
- limited power of the study
enteric coated acetylsalicylic acid

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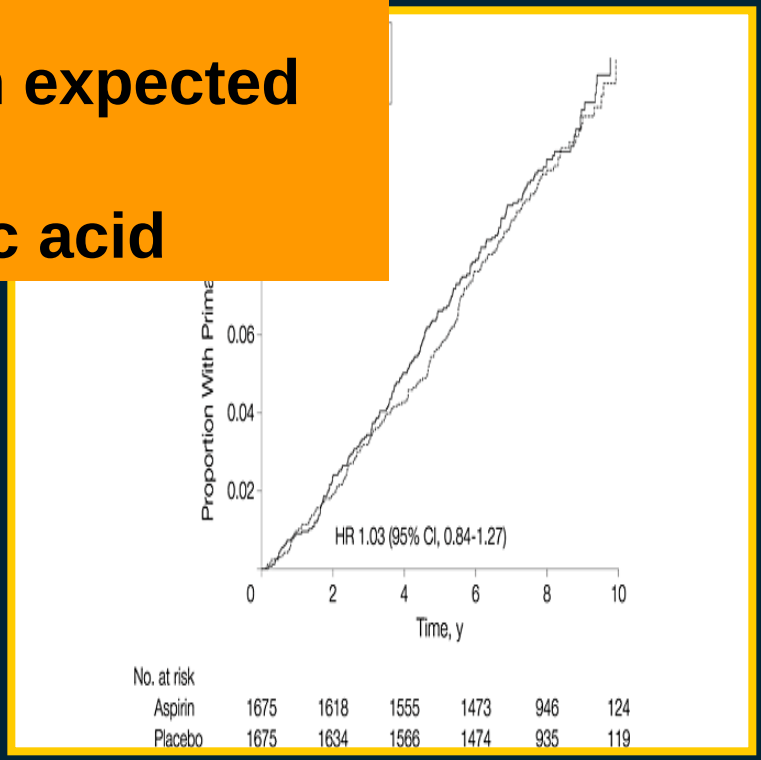
  on screening a general population, the administration of ASA did not reduce vascular events



Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial

Critical Leg Ischaemia Prevention Study (CLIPS) Group*

- Prevention of vascular events by aspirin amongst 366 pts with stage I-II (ABI < 0,85)
- Randomized, placebo-controlled
- 4 treatment groups: aspirin/vitE+C+betacarotene/both/neither
- 7/185 aspirin X 20/181 placebo suffered major CV event – reduction of 64%, 5 vs 8 cases of critical limb ischemia

Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial

Critical Leg Ischaemia Prevention Study (CLIPS) Group*

- Prevention of vascular events by aspirin among
- Rando
- 4 treatment groups: aspirin/vitE+C+betacarotene/both/neither
- 7/185 aspirin X 20/181 placebo suffered CVevent – reduction

Small study, small No of events
Antioxidants - no effect

Clopidogrel

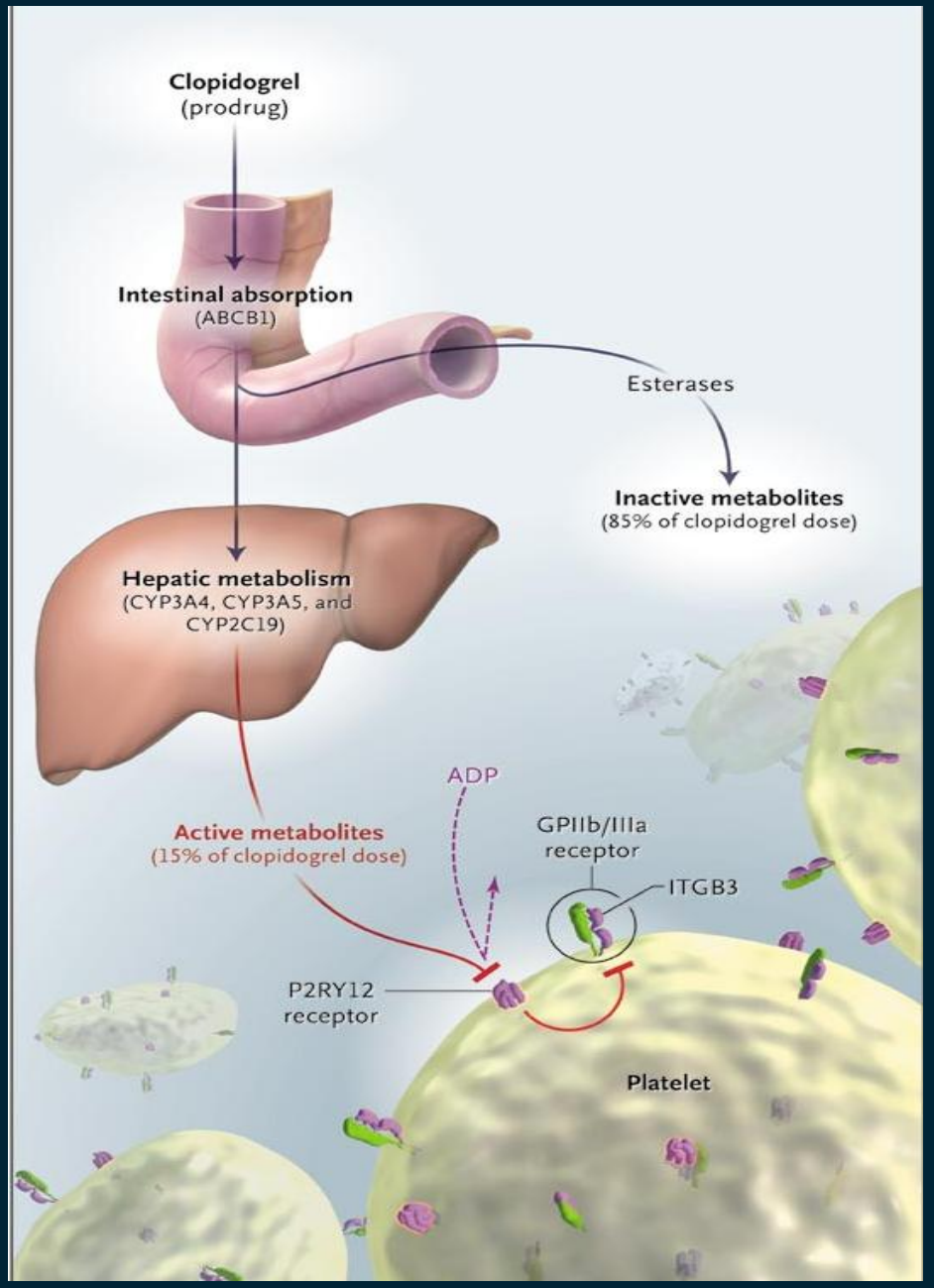
Clopidogrel is a prodrug

-> Metabolism through

the cytochrome P450

enzyme system

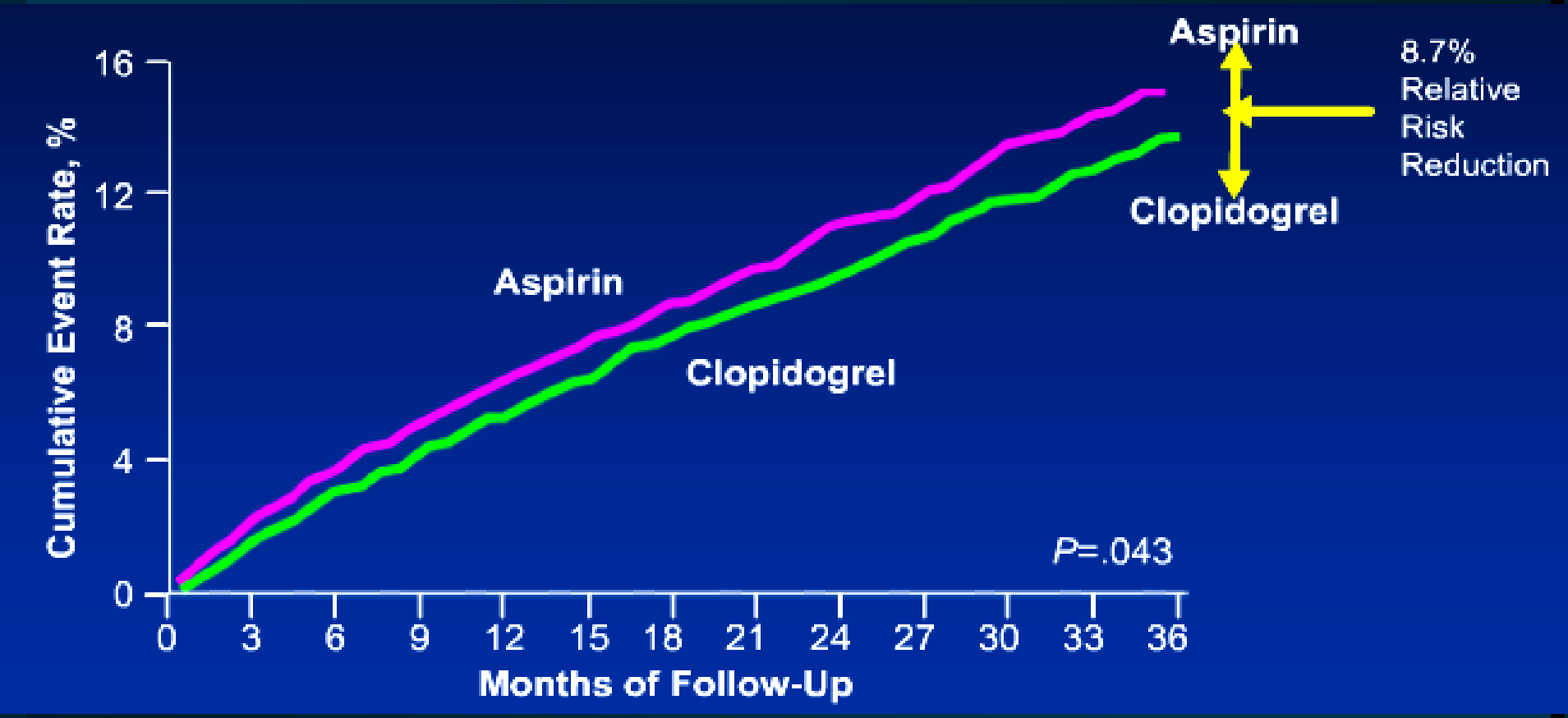
Active metabolite binds to platelet P2Y12 receptor and irreversibly blocks platelet activation by ADP



Simon et al., *NEJM* 2009;360:363-375.

CAPRIE Study

Efficacy of Clopidogrel in Primary Analysis of MI, Ischemic Stroke, or Vascular Death

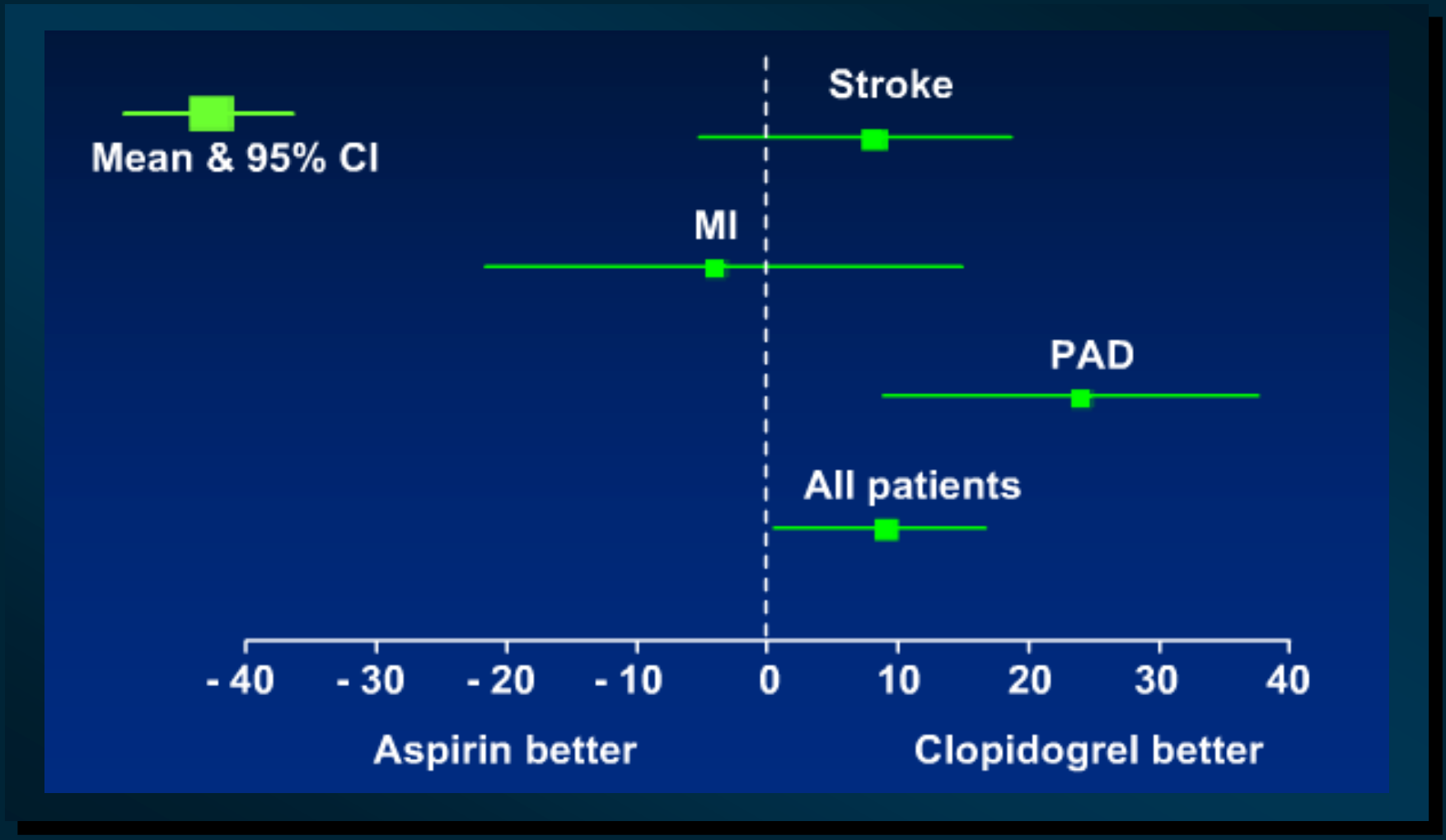


ITT Analysis

CAPRIE Steering Committee Lancet 1996; 348: 1329-1339

CAPRIE Study

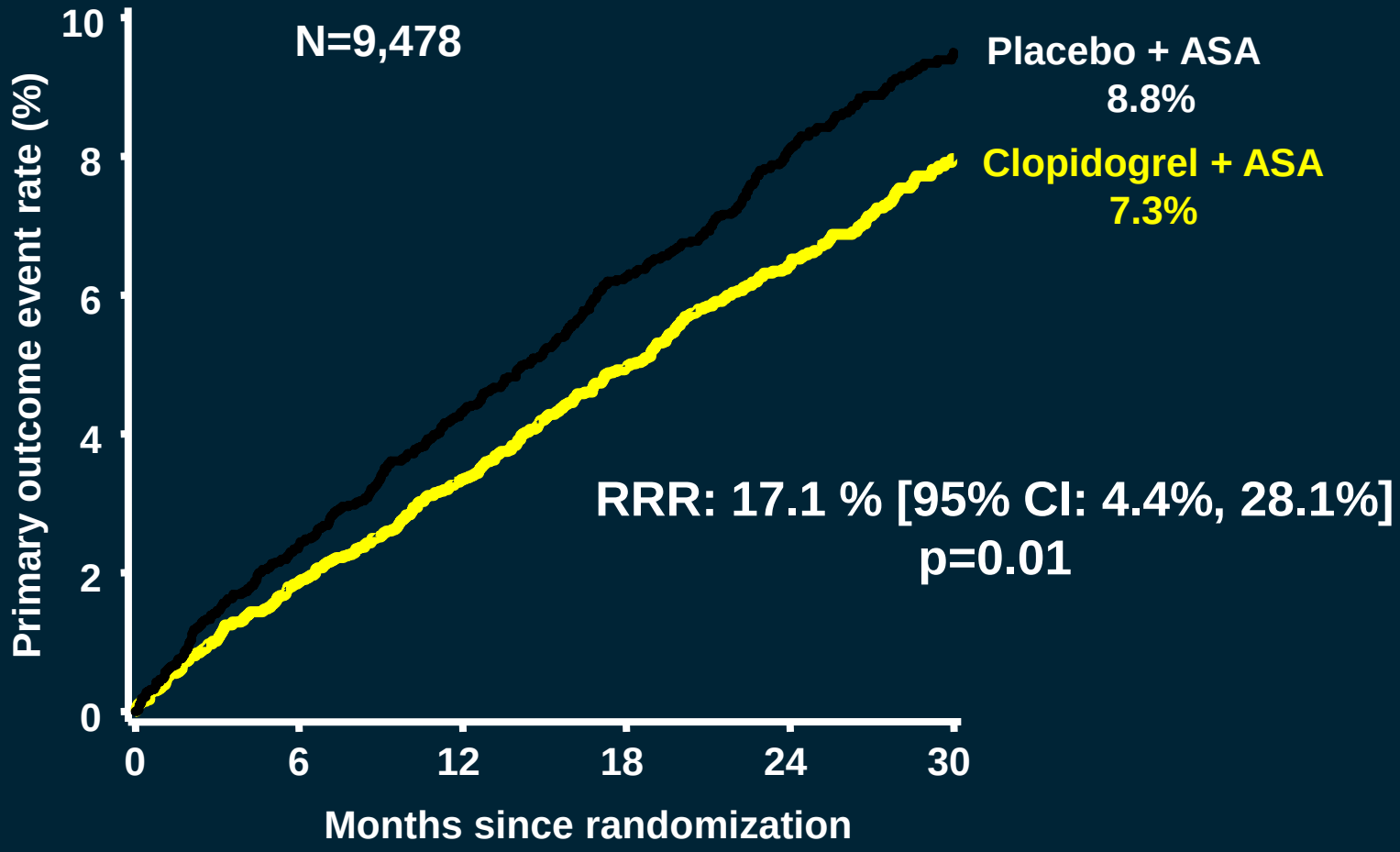
Outcome by Subgroup



CAPRIE Steering Committee Lancet 1996; 348: 1329-1339

CHARISMA

Primary Endpoint (MI/Stroke/CV Death) in Patients with Previous MI, IS, or PAD*



*** Post hoc analysis**

Bhatt DL. Presented at ACC 2006.

Summary

- PAD is a marker of atherosclerosis in the coronary and cerebral arteries
- PAD is often underestimated and underdiagnosed, and requires propper diagnosis
- Antiplatelet therapy reduces the risk of myocardial infarction, stroke and vascular death in patients with peripheral arterial disease, including patients with a history of angioplasty or bypass surgery[1,2]
- Most of the evidence with antiplatelet therapy in PAD is from ASA and ADP-receptor antagonists including clopidogrel[1,3]
- An ADP-receptor antagonist improves the long-term peripheral patency after revascularization procedures[2]

1. Robless P *et al*. *Br J Surg* 2001; 88: 787–800**. 2** Becquemin JP. *N Engl J Med* 1997; 337: 1726–31. 3. Girolami B *et al. Eur J Vasc Endovasc Surg* 2000; 19: 370–80. 4. Bhatt DL *et al*. *Am Heart J* 2000; 140: 67–73.

Summary

- The effect of aspirin in patients with PAD caused risk reduction of 20%, only 12% in primary prevention trials
- The benefit of aspirin in PAD pts is clear in reduction of nonfatal stroke
- Clopidogrel provides increased benefit over aspirin for secondary prevention in atherothrombotic patients, including those with diagnosed PAD
- Dual antiplatelet therapy may be beneficial in pts with extensive atherosclerotic disease

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of the International Union of

Angiology

July 1-5, 2012

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