Σιλοσταζόλη

Μια σύγχρονη καινοτόμος προσέγγιση στην αντιμετώπιση της συμπτωματικής περιφερικής αρτηριοπάθειας

Γεώργιος Ντάιος

Παθολογική Κλινική, Πανεπιστήμιο Θεσσαλίας

Disclosures

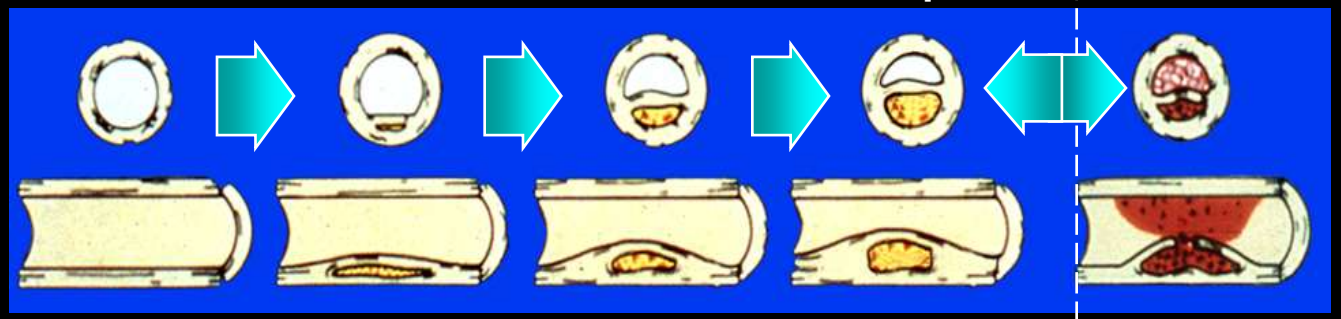
- Scholarships: European Stroke Organization; Hellenic Society of Atherosclerosis.
- Honoraria: Medtronic; Quintiles; CHUV; Belgian Stroke Council; Boehringer-Ingelheim.
- Speaker fees: Sanofi; Boehringer-Ingelheim; Galenica; Elpen; Bayer
- Support to attend conferences: Bayer; Sanofi-Aventis; Pfizer; Lundbeck; Boehringer-Ingelheim; Galenica; Elpen; Bristol Myers Squibb.
- Participation in trials:
  - NAVIGATE-ESUS / Steering Committee member, National Coordinator (Greece) & Principal Investigator (Larissa)
  - PRECIOUS / National Coordinator (Greece) & Executive Committee member.
  - ENOS / National Coordinator (Greece).
  - FOURIER / Principal investigator (Larissa).
  - GLORIA-AF / Sub-investigator (Larissa).
  - EBBINGHAUS / Principal Investigator (Larissa).
  - BIOSIGNAL / Principal Investigator (Larissa).
  - PREVISE / Principal investigator (Larissa).

Our patient .. and his wife

«Τρελάθηκες μωρέ;;
Τι θες στην ηλικία σου και σταματάς μπροστά από το sex shop ;;; »

- ✓ 75yrs
- ✓ DM, HbA1c: 8.2%
- ✓ 110 pack-years
- ✓ LDL: 135mg/dl
- ✓ Left carotid stenosis 70%
- ✓ Stable angina pectoris

Causes – atherosclerosis slide



Unstable Angina

Myocardial infarction

Stroke

Critical Leg Ischemia

Stable Angina

Intermittent claudication

Increasing Age

PAD demographics

ORIGINAL CONTRIBUTION

Peripheral Arterial Disease Detection, Awareness, and Treatment in Primary Care

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Context Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis that is common and is associated with an increased risk of death and ischemic events, yet may be underdiagnosed in primary care practice.

Objective To assess the feasibility of detecting PAD in primary care clinics, patient and physician awareness of PAD, and intensity of risk factor treatment and use of antiplatelet therapies in primary care clinics.

Design and Setting The PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, a multicenter, cross-sectional study conducted at 27 sites in 25 cities and 350 primary care practices throughout the United States in June-October 1999.

Patients A total of 6979 patients aged 70 years or older or aged 50 through 69 years with history of cigarette smoking or diabetes were evaluated by history and by measurement of the ankle-brachial index (ABI). PAD was considered present if the ABI was 0.90 or less, if it was documented in the medical record, or if there was a history of limb revascularization. Cardiovascular disease (CVD) was defined as a history of atherosclerotic coronary, cerebral, or abdominal aortic aneurysmal disease.

Main Outcome Measures Frequency of detection of PAD; physician and patient awareness of PAD diagnosis; treatment intensity in PAD patients compared with treatment of other forms of CVD and with patients without clinical evidence of atherosclerosis.

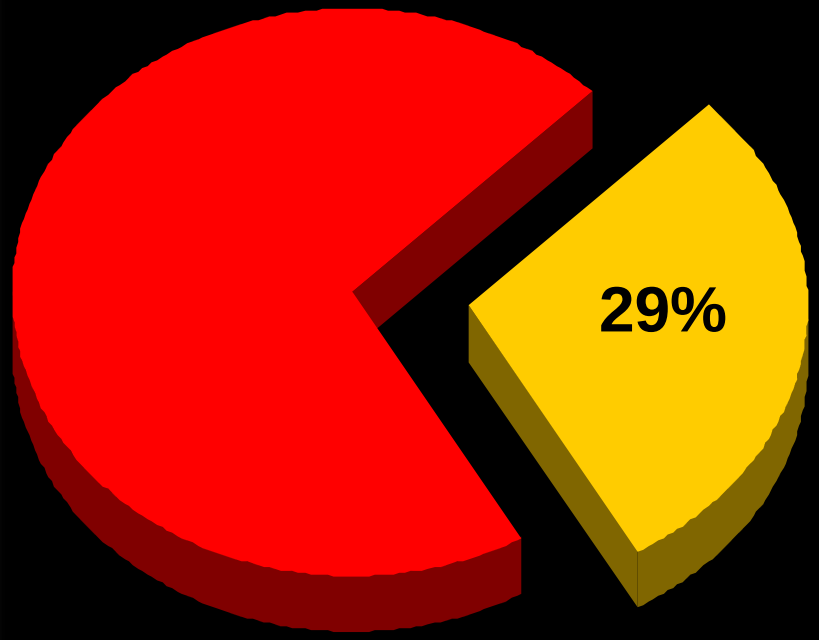
Results PAD was detected in 1865 patients (29%); 825 of these (44%) had PAD only, without evidence of CVD. Overall, 13% had PAD only, 16% had PAD and CVD, 24% had CVD only, and 47% had neither PAD nor CVD (the reference group). There were 457 patients (55%) with newly diagnosed PAD only and 366 (35%) with PAD and CVD who were newly diagnosed during the survey. Eighty-three percent of patients with prior PAD were aware of their diagnosis, but only 49% of physicians were aware of this diagnosis. Among patients with PAD, classic claudication was distinctly uncommon (11%). Patients with PAD had similar atherosclerosis risk factor profiles compared with those who had CVD. Smoking behavior was more frequently treated in patients with new (53%) and prior PAD (51%) only than in those with CVD only (35%; P <.001). Hypertension was treated less frequently in new (84%) and prior PAD (88%) only vs CVD only (95%; P <.001) and hyperlipidemia was treated less frequently in new (44%) and prior PAD (56%) only vs CVD only (73%, P<.001). Antiplatelet medications were prescribed less often in patients with new (33%) and prior PAD (54%) only vs CVD only (71%, P<.001). Treatment intensity for diabetes and use of hormone replacement therapy in women were similar across all groups.

Conclusions Prevalence of PAD in primary care practices is high, yet physician awareness of the PAD diagnosis is relatively low. A simple ABI measurement identified a large number of patients with previously unrecognized PAD. Atherosclerosis risk factors were very prevalent in PAD patients, but these patients received less intensive treatment for lipid disorders and hypertension and were prescribed antiplatelet therapy less frequently than were patients with CVD. These results demonstrate that underdiagnosis of PAD in primary care practice may be a barrier to effective secondary prevention of the high ischemic cardiovascular risk associated with PAD.

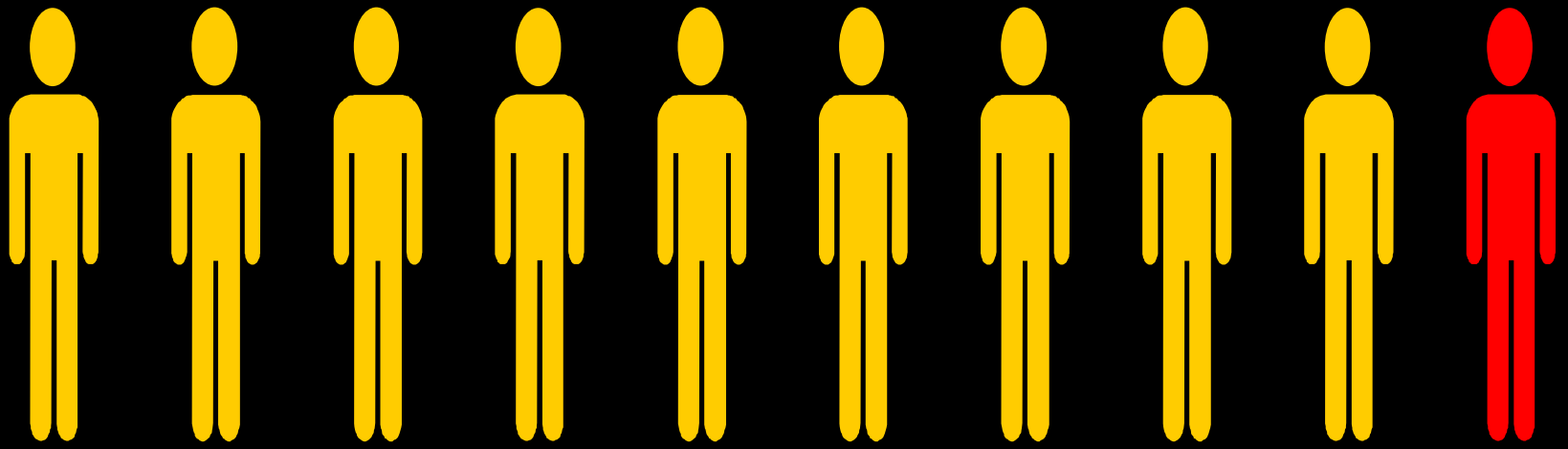
JAMA. 2001;286:1317-1324 www.jama.com

Author Affiliations, PARTNERS Investigators, and Financial Disclosure are listed at the end of this article. Corresponding Author and Reprints: Alan T. Hirsch, M.D., Vascular Medicine Program, Minnesota Vascular Diseases Center, Mayo Mail Code 508, University of Minnesota Medical School, 420 Delaware St, SE, Minneapolis, MN 55455 (e-mail: Hirsch001@umn.edu).

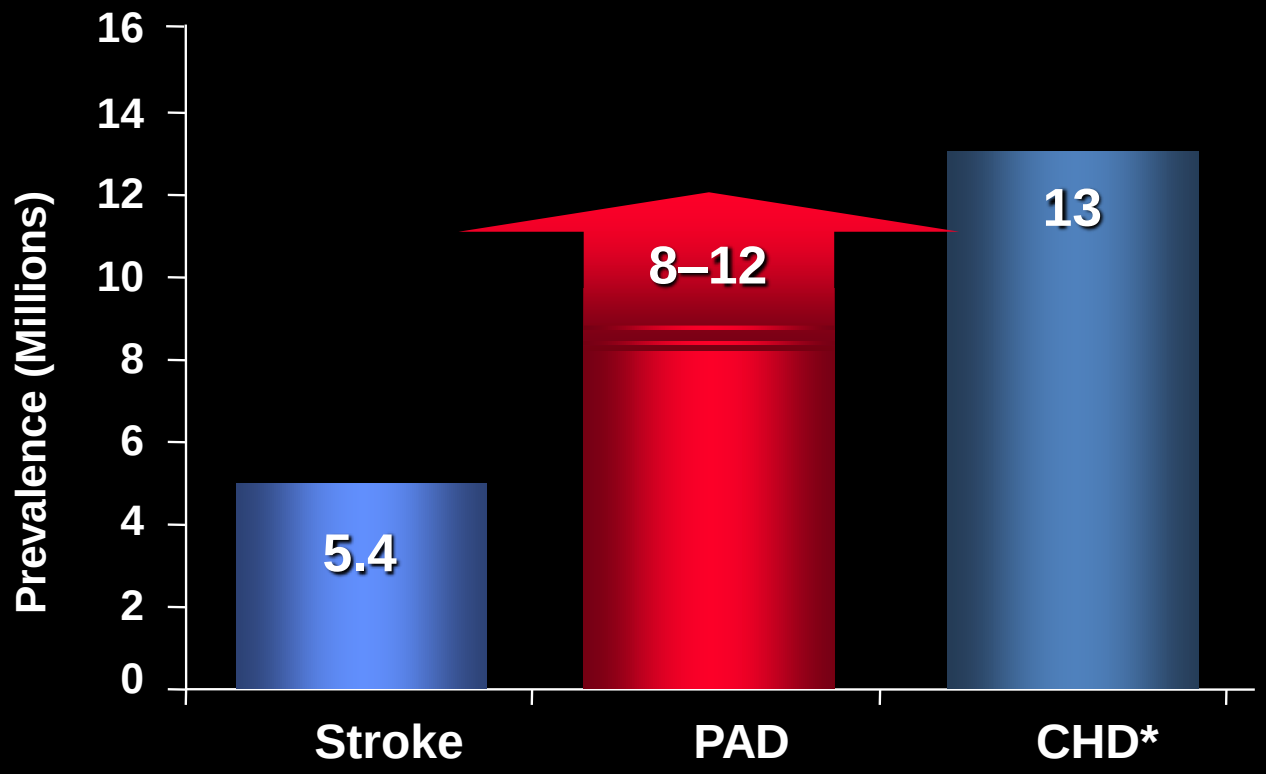
See also p 1380 and Patient Page.



PAD: mostly asymptomatic



PAD Prevalence

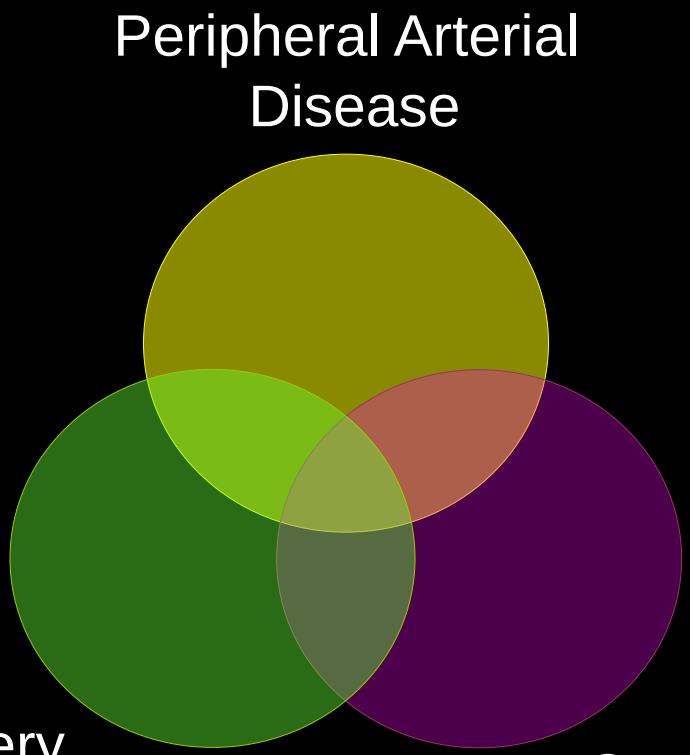


CHD = coronary heart disease. PAD = peripheral arterial disease.

* Includes myocardial infarction and angina pectoris.

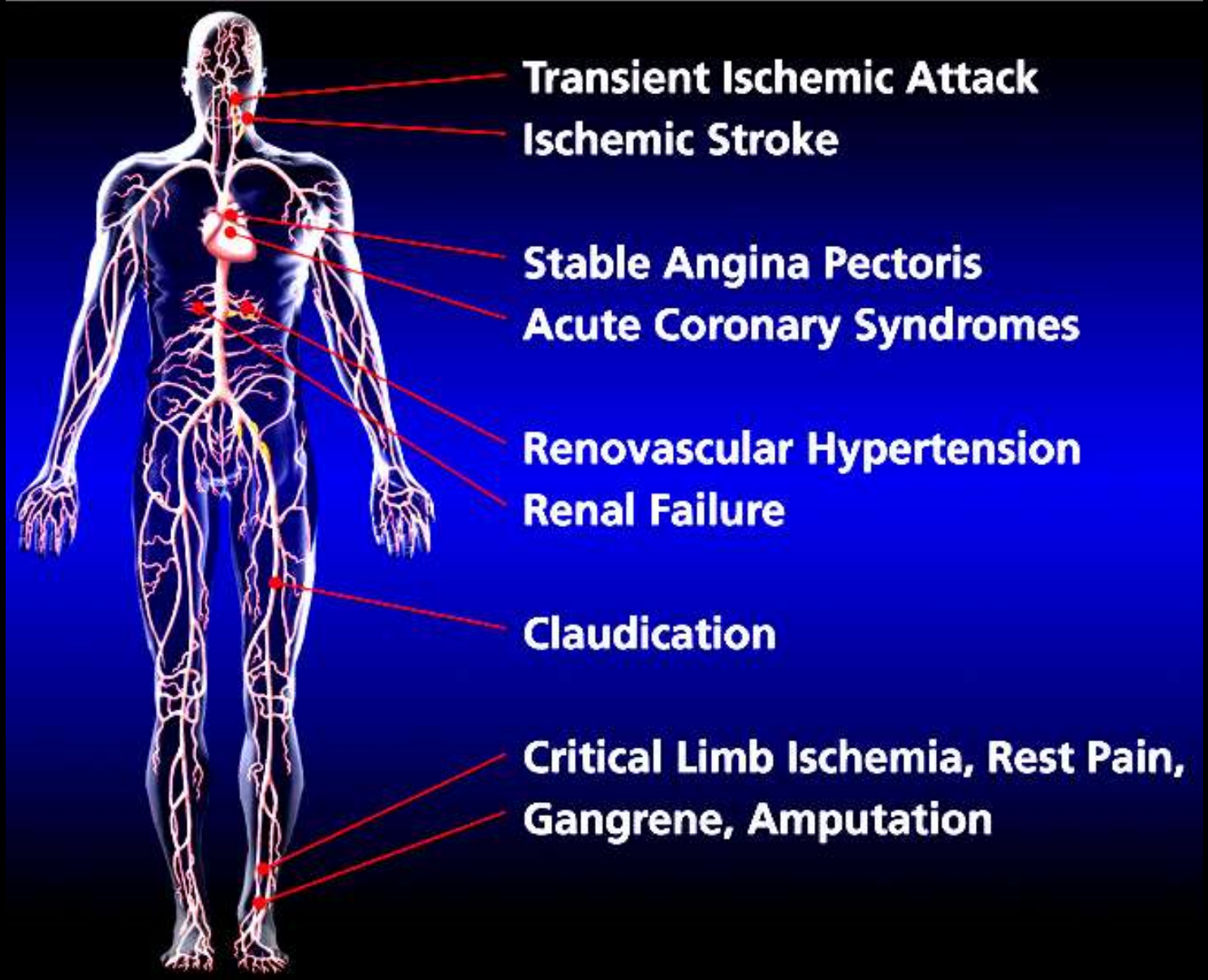
American Heart Association. *Heart Disease and Stroke Statistics—2005 Update*. 2005.

PAD: Overlap with other atheromatous diseases

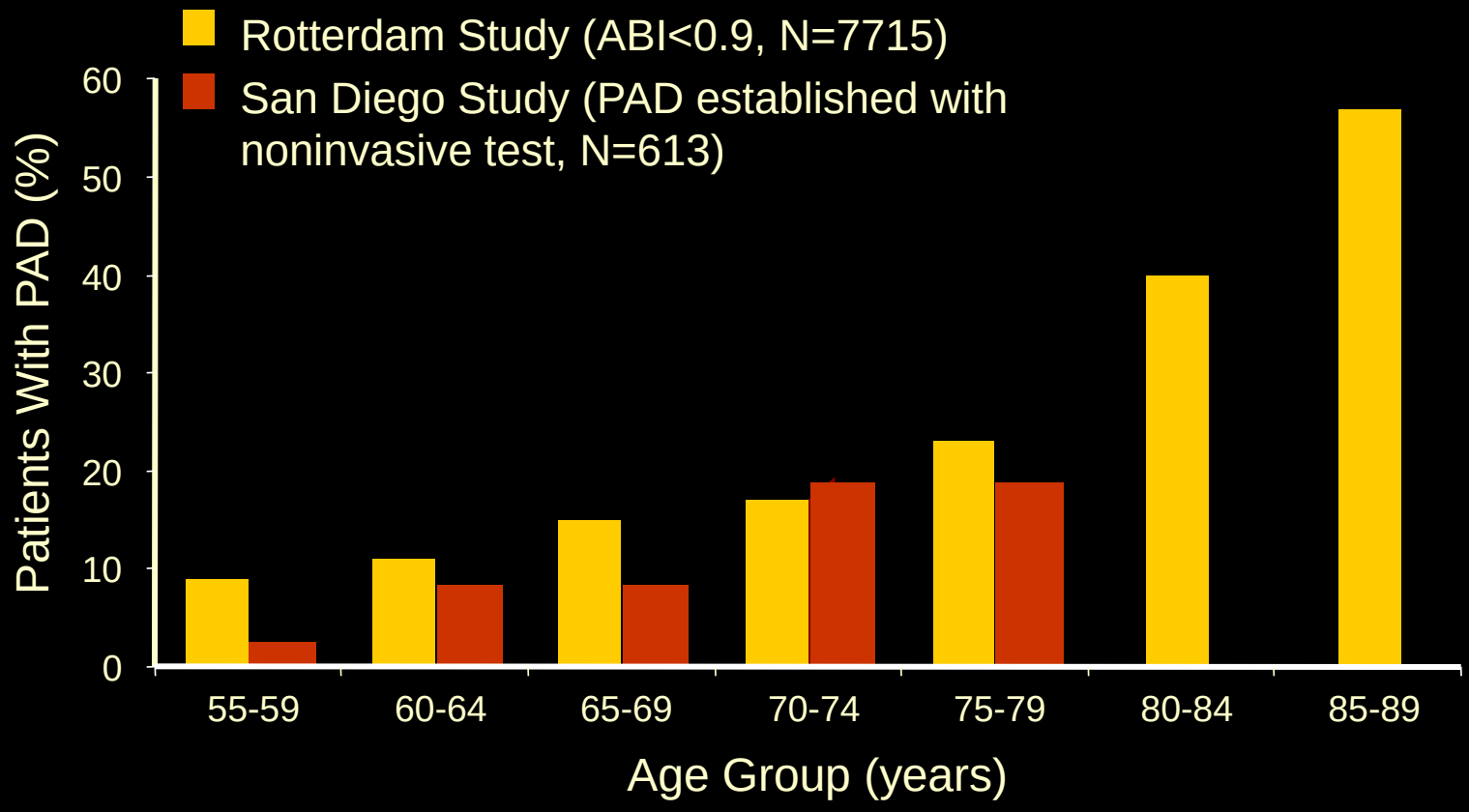


38% overlap
≥ 2 Vascular beds

Vessels are a continuum

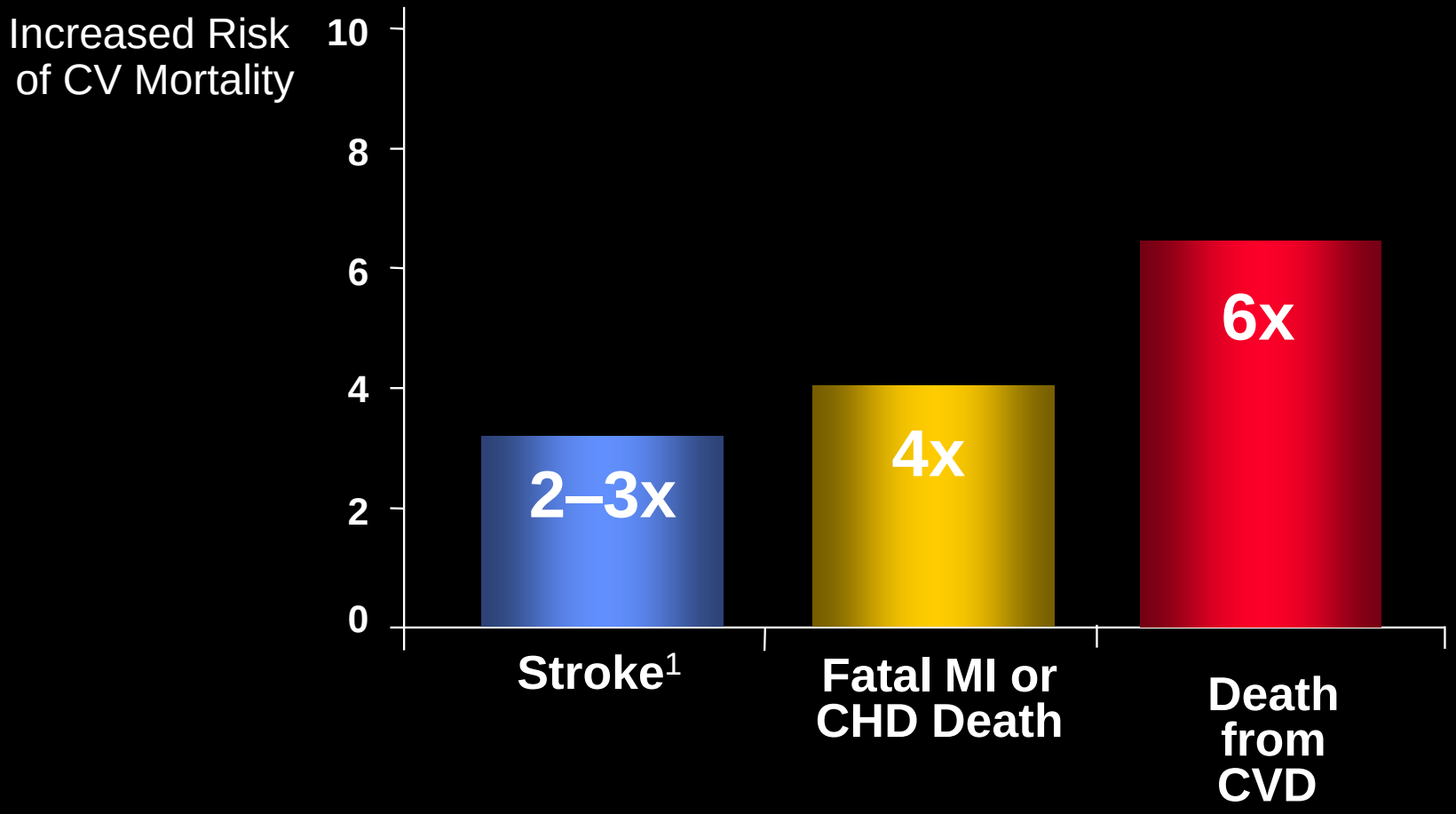


PAD Prevalence by age



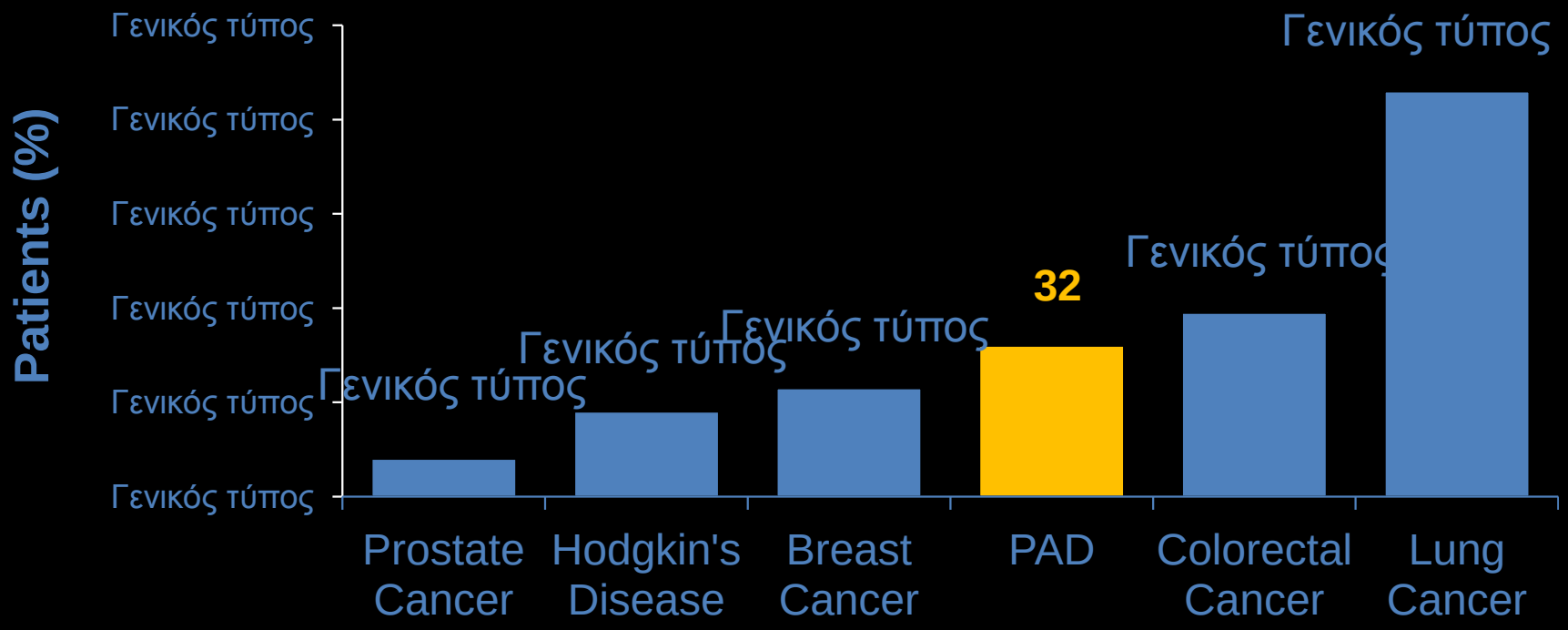
Adapted from Golomb BA, et al. In: Creager MA, ed. *Management of Peripheral Arterial Disease: Medical, Surgical and Interventional Aspects*; 2000:1-18.
Meijer WT, et al. *Arterioscler Thromb Vasc Biol*. 1998;18:185-192.
Criqui MH, et al. *Circulation*. 1985;71:510-515.

PAD & cardiovascular outcomes



Criqui et al N Engl J Med 1992; 326: 381-386

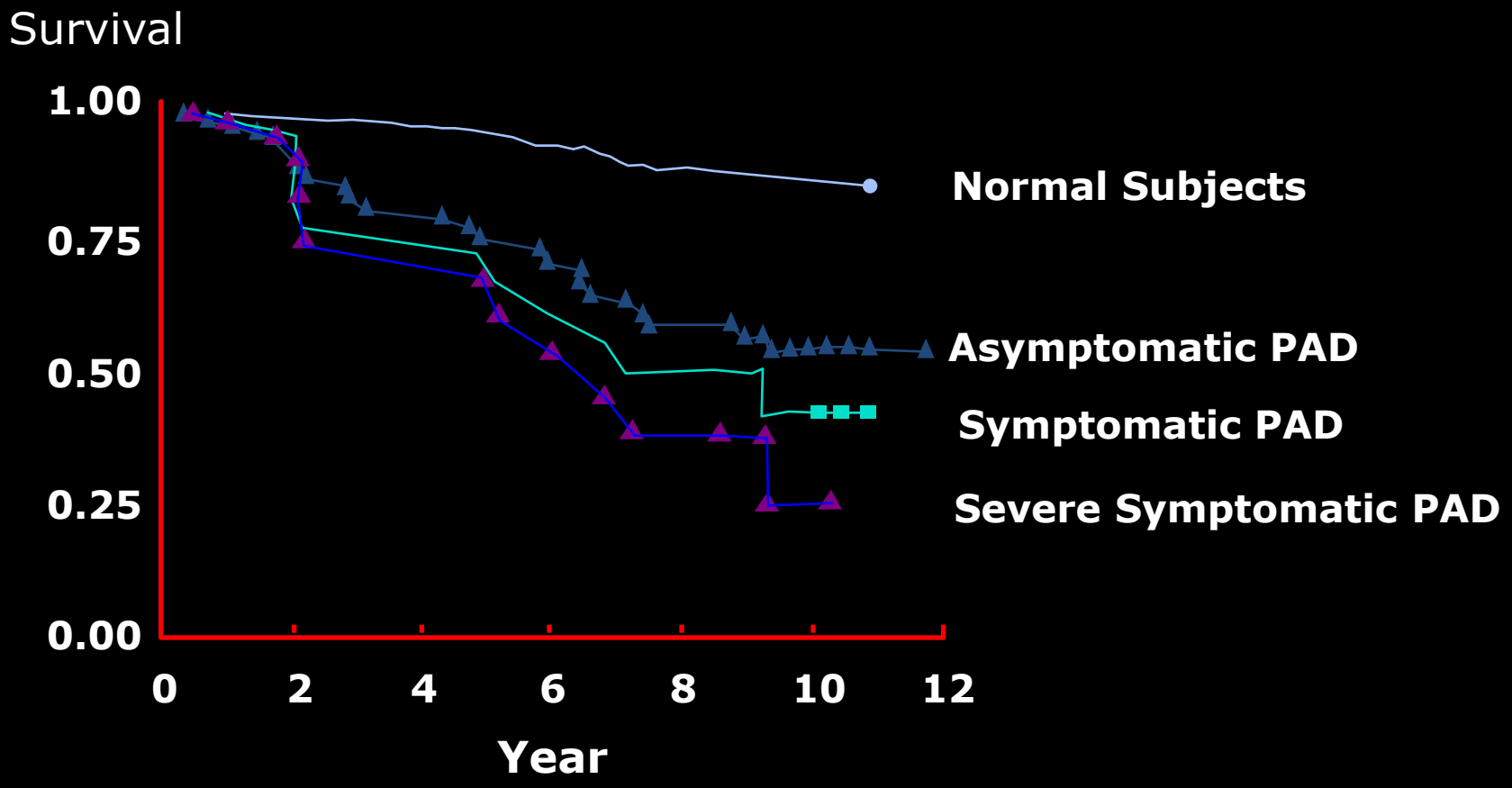
PAD & 5-Year Mortality



* American Cancer Society. Cancer Facts and Figures, 2000.

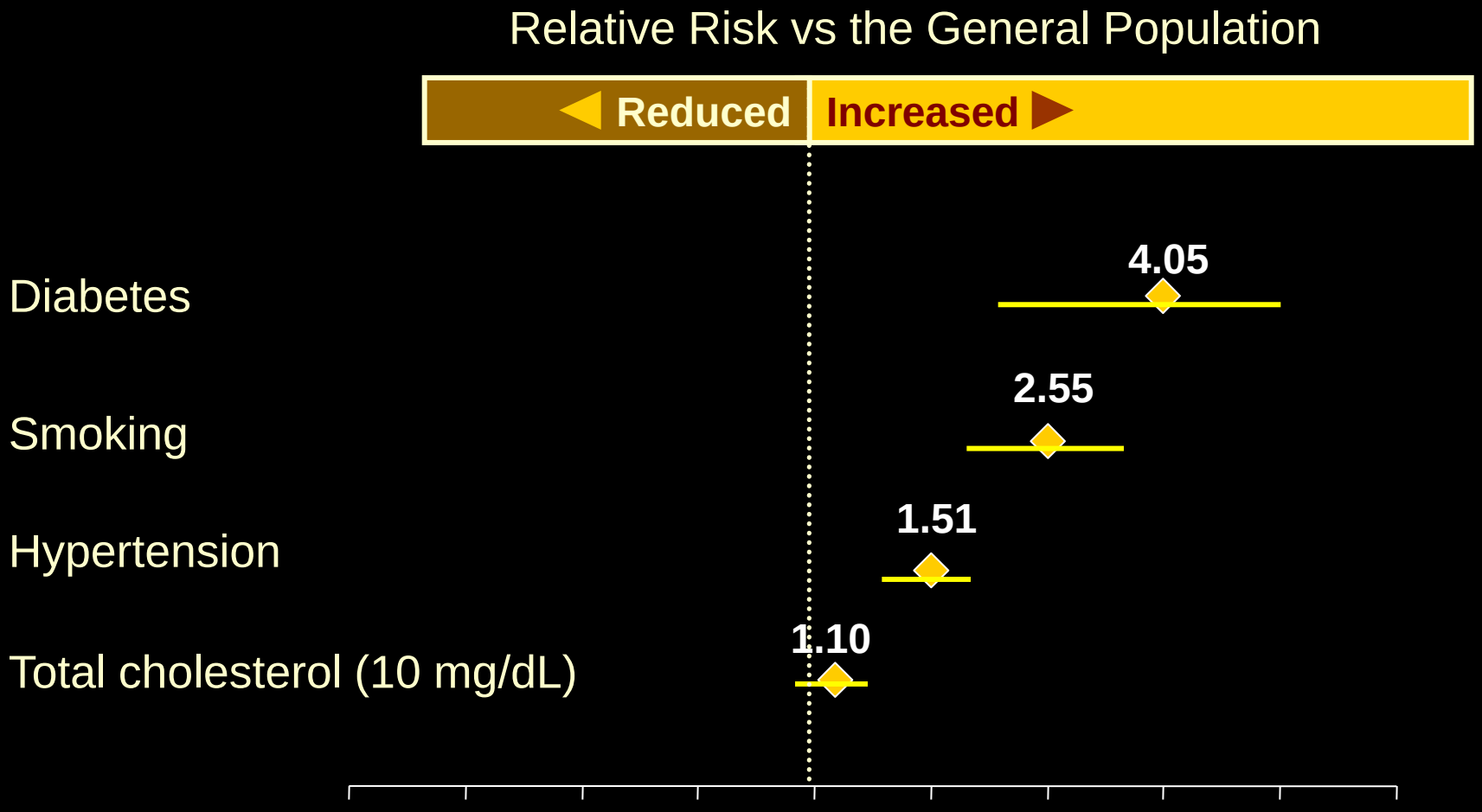
† Criqui MH, et al. N Engl J Med. 1992;326:381-386.

PAD severity and survival



Criqui et al N Engl J Med 1992; 326: 381-386

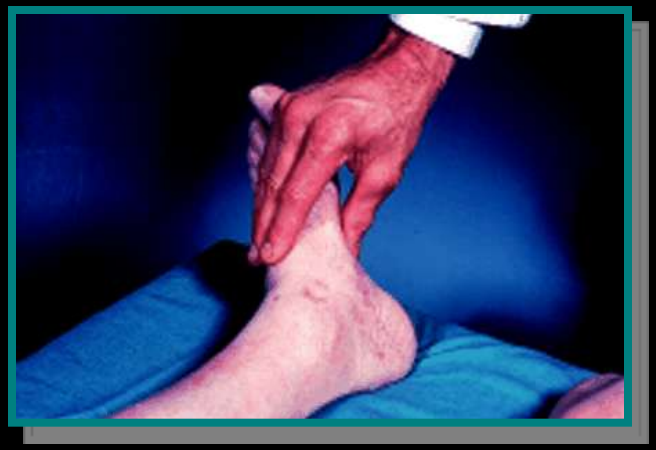
Risk Factors for PAD



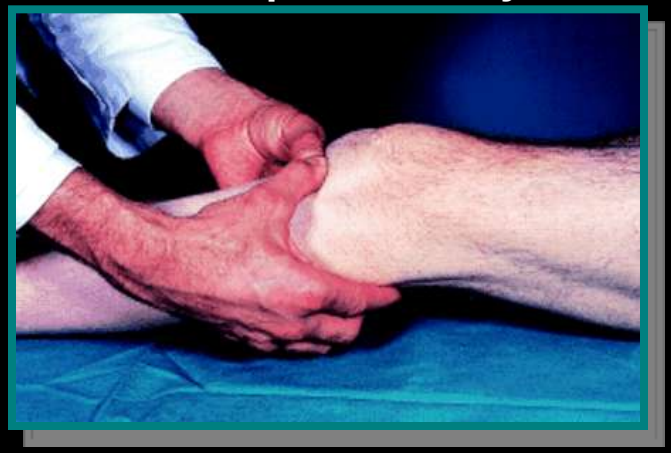
Newman AB, et al. *Circulation.* 1993;88:837-845

Clinical examination

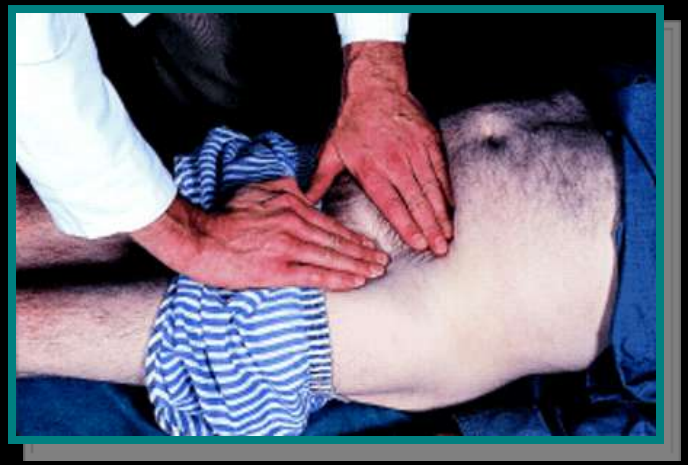
Dorsalis Pedis



Popliteal Artery



Posterior Tibial

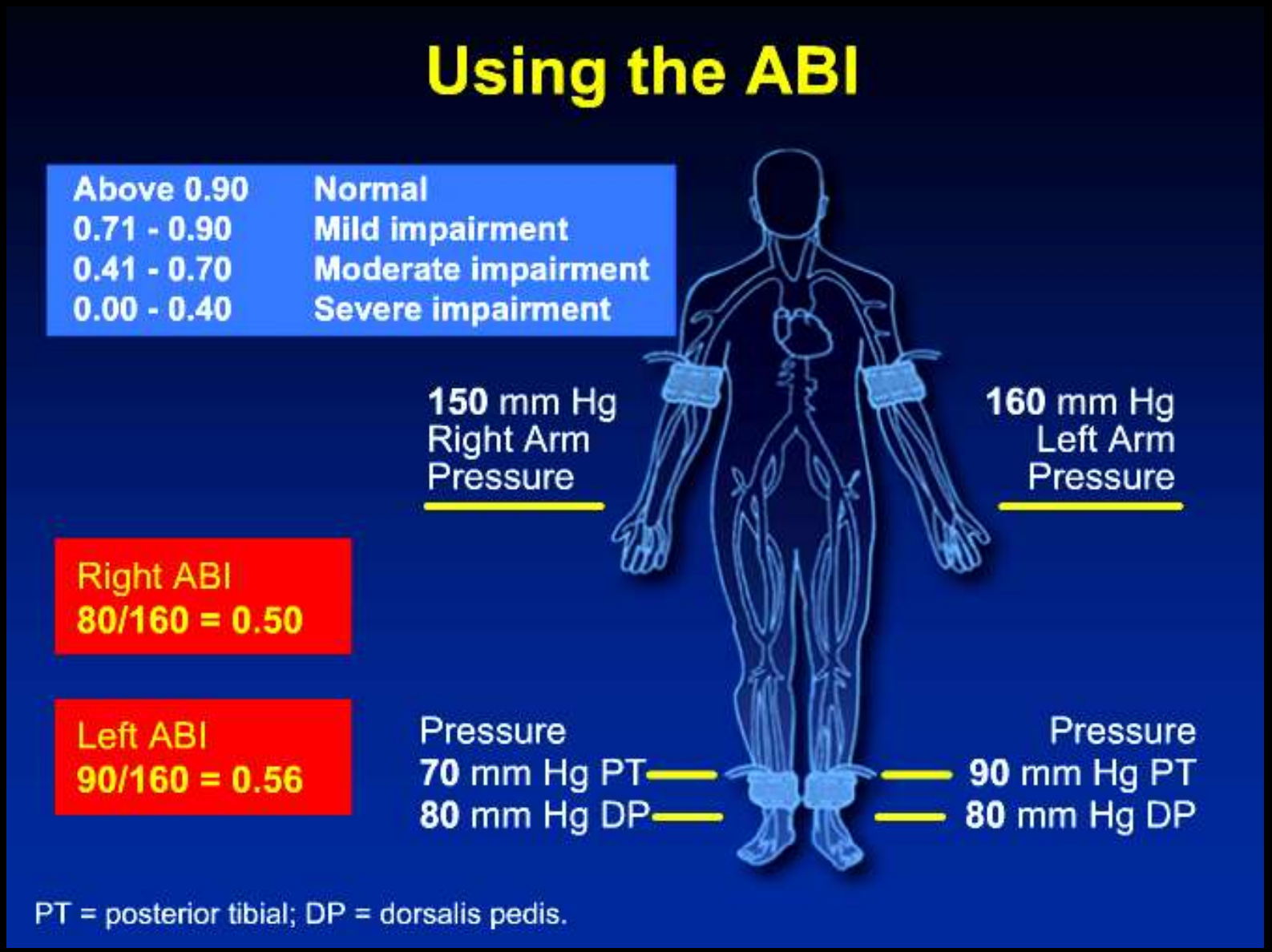


Femoral Pulse

Fontaine Classification

Stage	Clinical
I	Asymptomatic
II	Intermittent claudication
III	Ischemic rest pain
IV	Ulceration or gangrene

Ankle – Brachial Index (ABI)



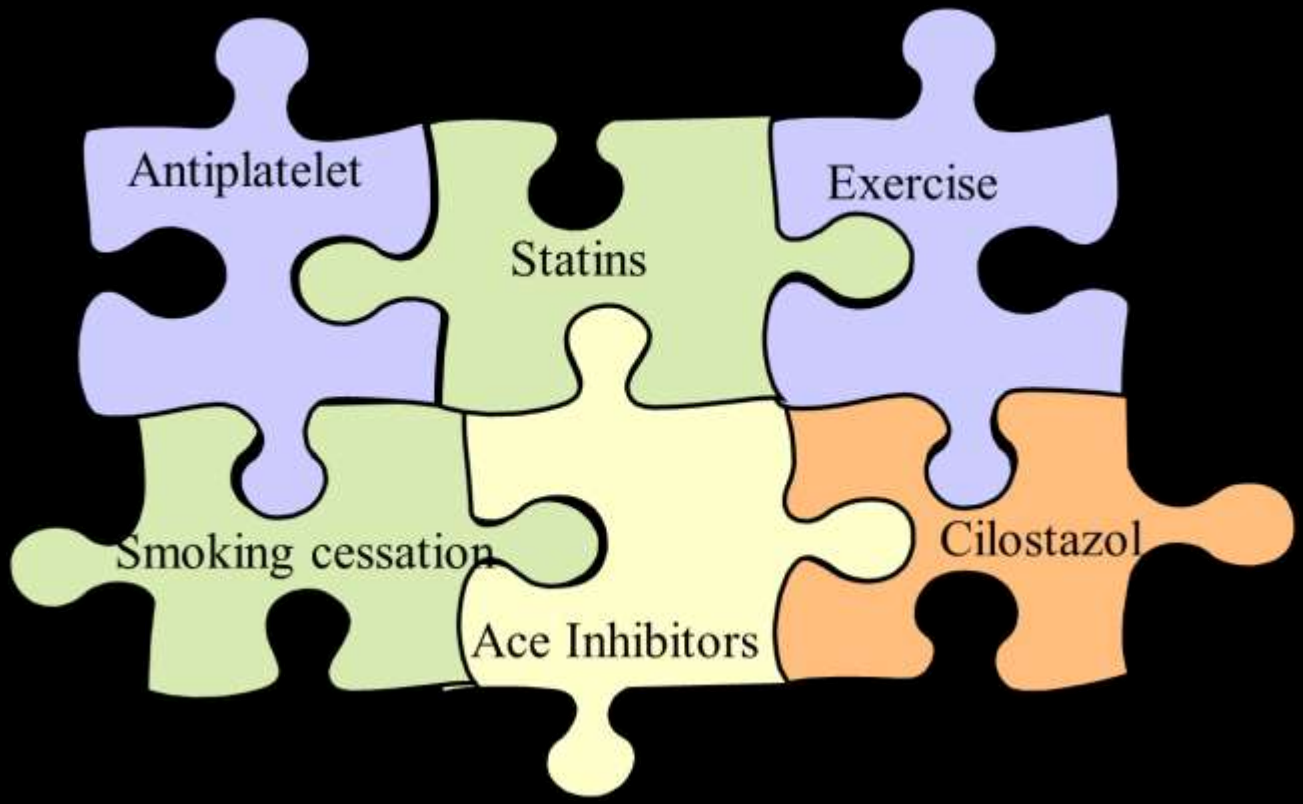
ABI vs Other Common Screening Tests

Diagnostic Test	Sensitivity, %	Specificity, %
Pap smear [1]	30 - 87	86 – 100
Fecal occult blood test [2]	37 - 78	87 – 98
Mammography [3]	75 - 90	90 – 95
ABI [4,5,6]	95	100

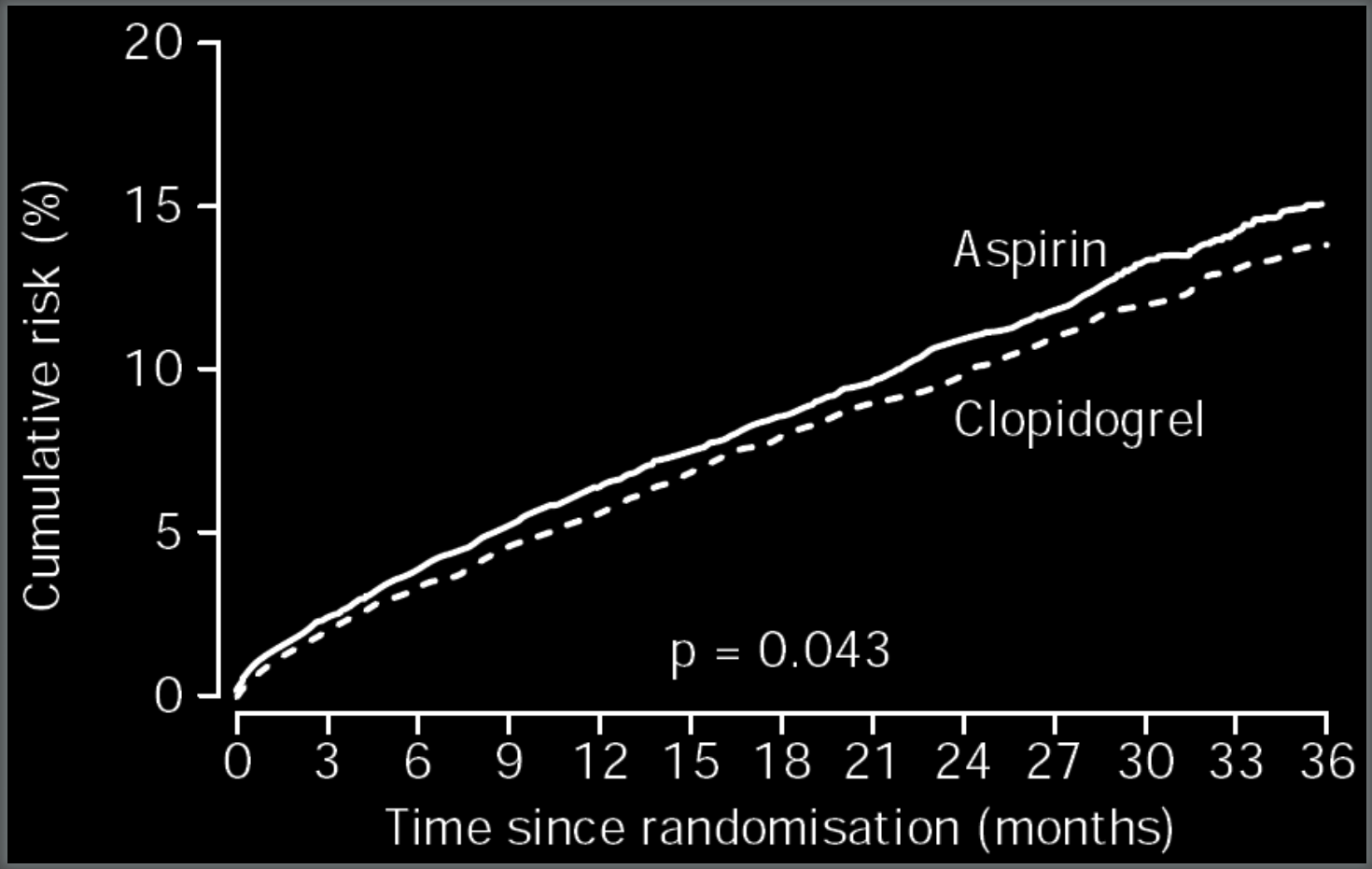
Nanda et al Ann Intern Med 2000;132:810-9
Allison et al New Eng J Med 1996;334:155-9
Ferrini et al Ame J Prev Med 1996;12:340-1
Dormandy et al Semin Vasc Surg 1999;12:96 -108
Fowkes et al Inter J Epid 1991; 20:384-392
Newman et al Arterioscler Thromb Vasc Biol. 1999;19:538–545

Goals of treatment

- ✓ Treat co-existing diseases
- ✓ Reduce cardiovascular risk
- ✓ Improve walking ability

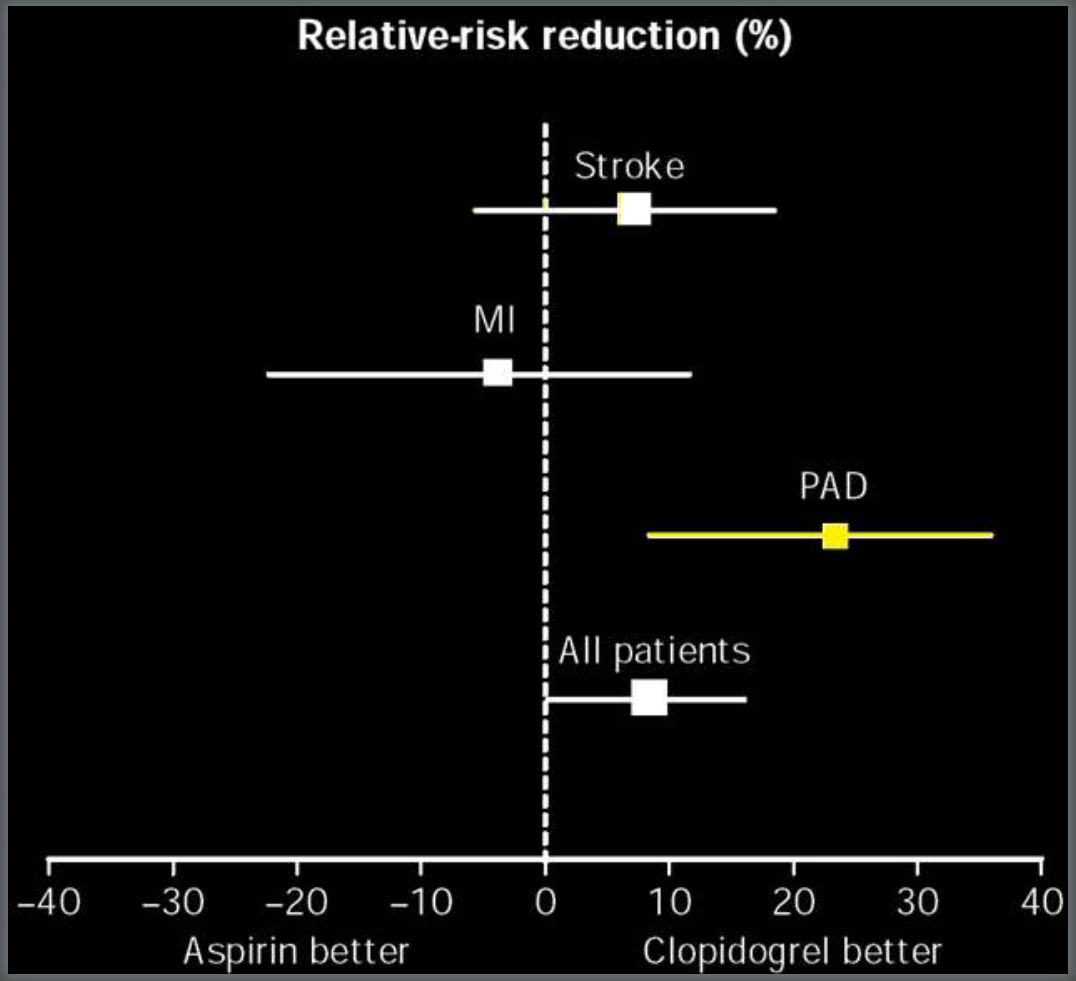


CAPRIE: Clopidogrel vs. aspirin



Lancet 1996; 348: 1329–39

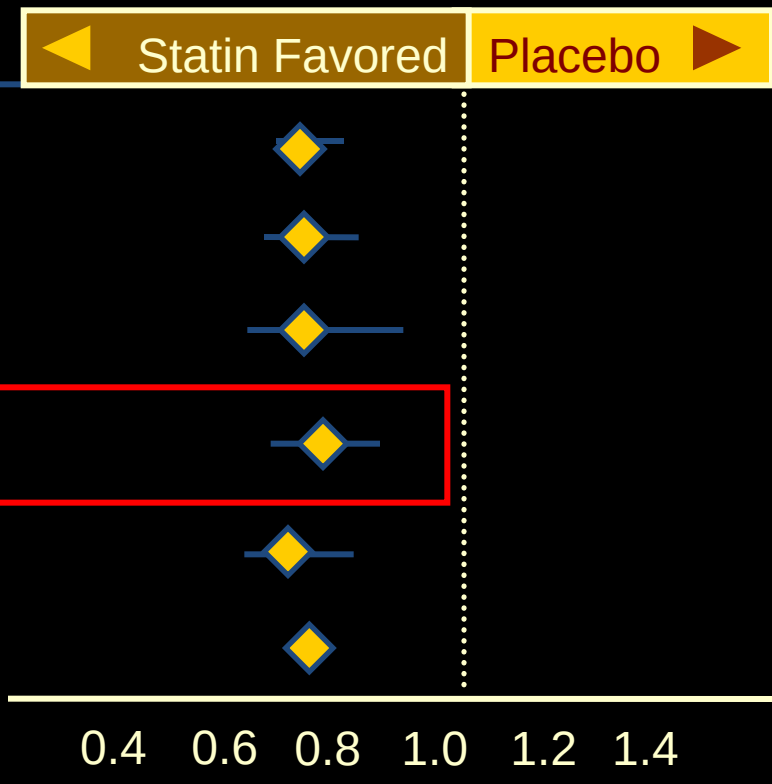
CAPRIE: Clopidogrel vs. aspirin



Lancet 1996; 348: 1329–39

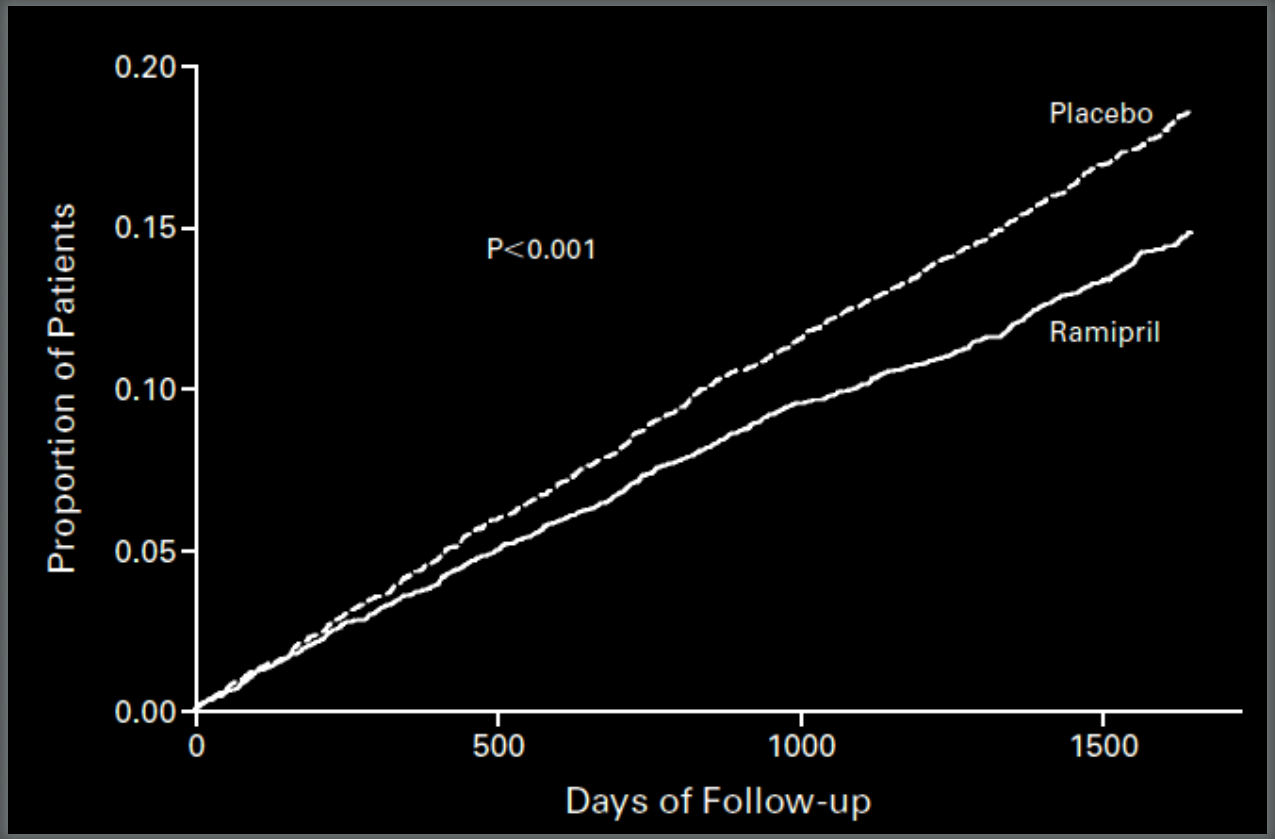
Statins and PAD outome

Existing Disease	Incidence of Events: Statin (n=10,269)	Incidence of Events: Control (n=10,267)
Previous MI	23.5	29.4
Other CHD	18.9	24.2
No prior CHD or CVD	18.7	23.6
Peripheral arterial disease	24.7	30.5
Diabetes	13.8	18.6
All patients	19.8	25.2



Heart Protection Study Collaborative Group. Lancet. 2002;360:7-22.

ACE inhibitors and PAD outome



The Heart Outcome Prevention Evaluation Study. *NEJM* 2000;342:145-53.

Cilostazol

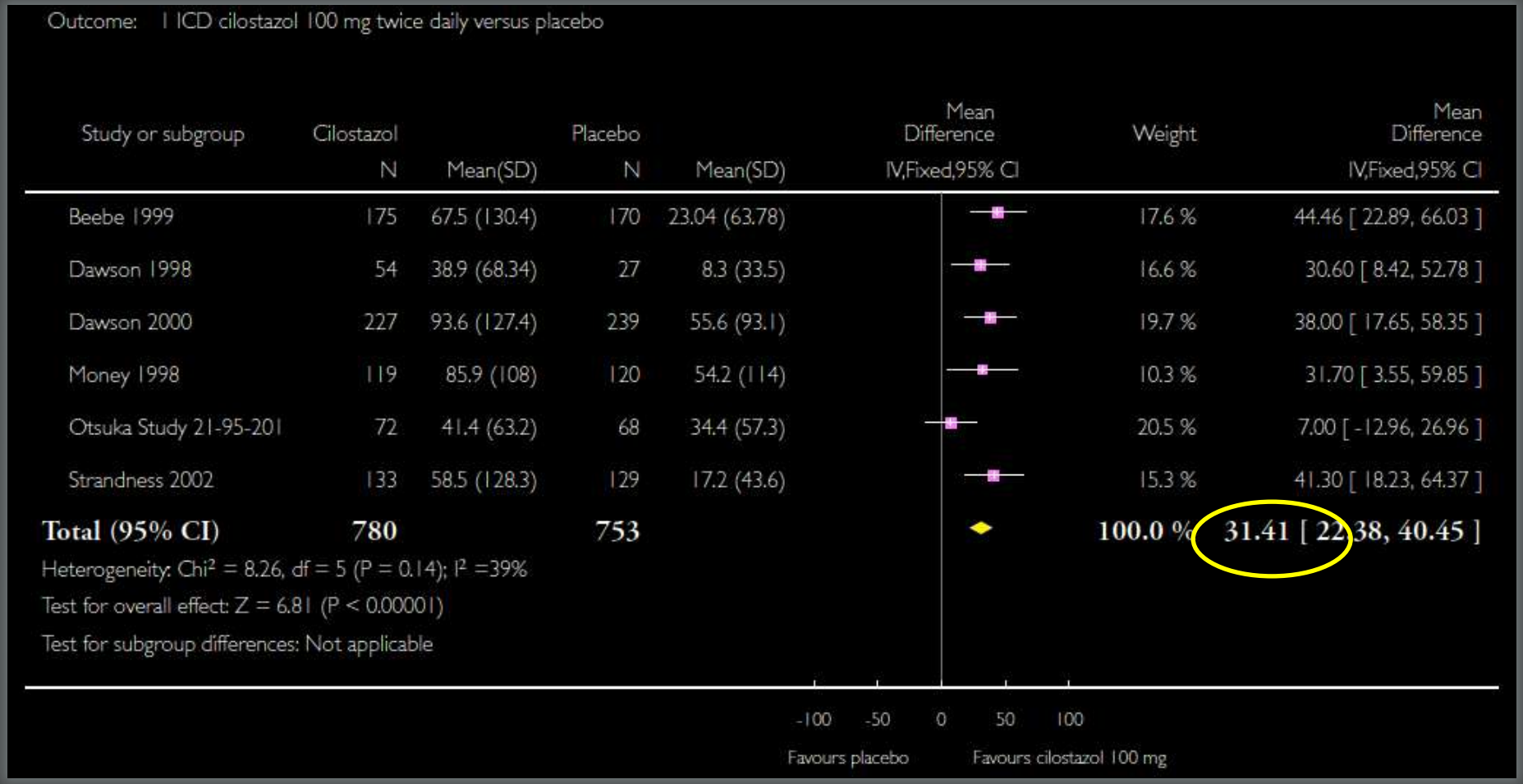

CILOS
50 mg
CILOSTAZOL
60 διακία
WinMedica
CILOS
100 mg
CILOSTAZOL
60 διακία
WinMedica

Cilostazol for intermittent claudication (Review)

Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G

THE COCHRANE COLLABORATION®

Cilos 100mg x2 & Initial Claudication Distance



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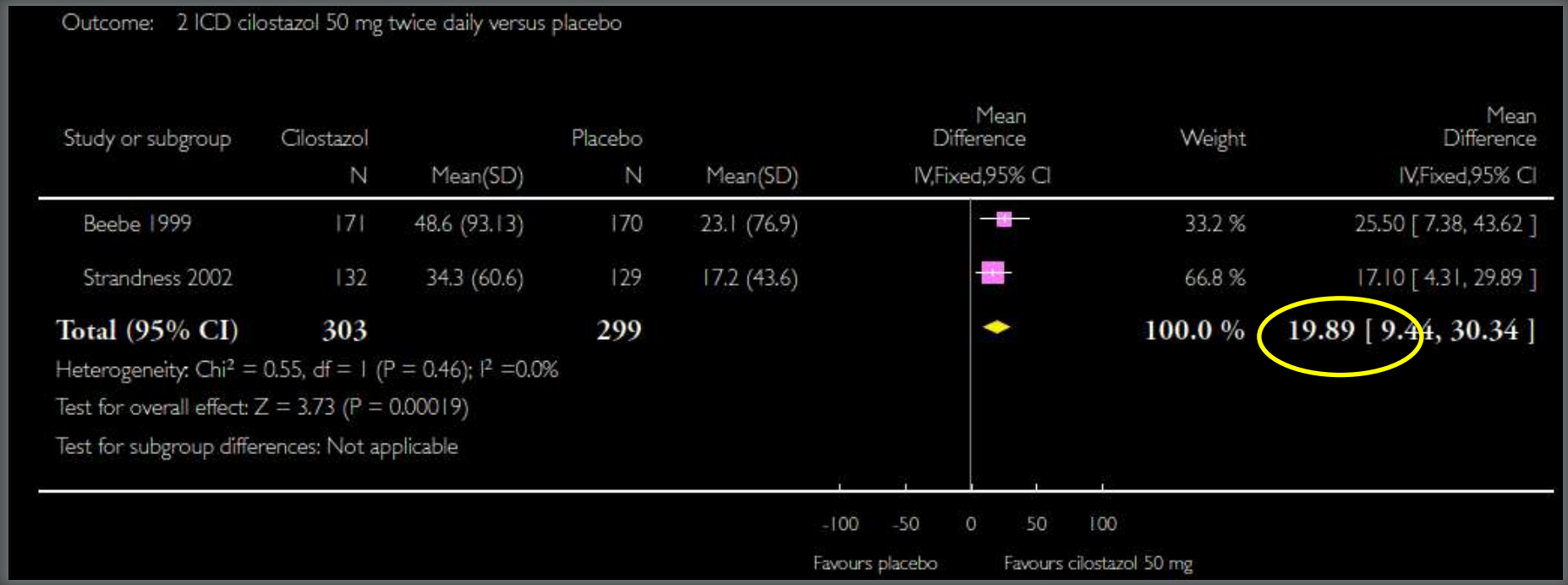

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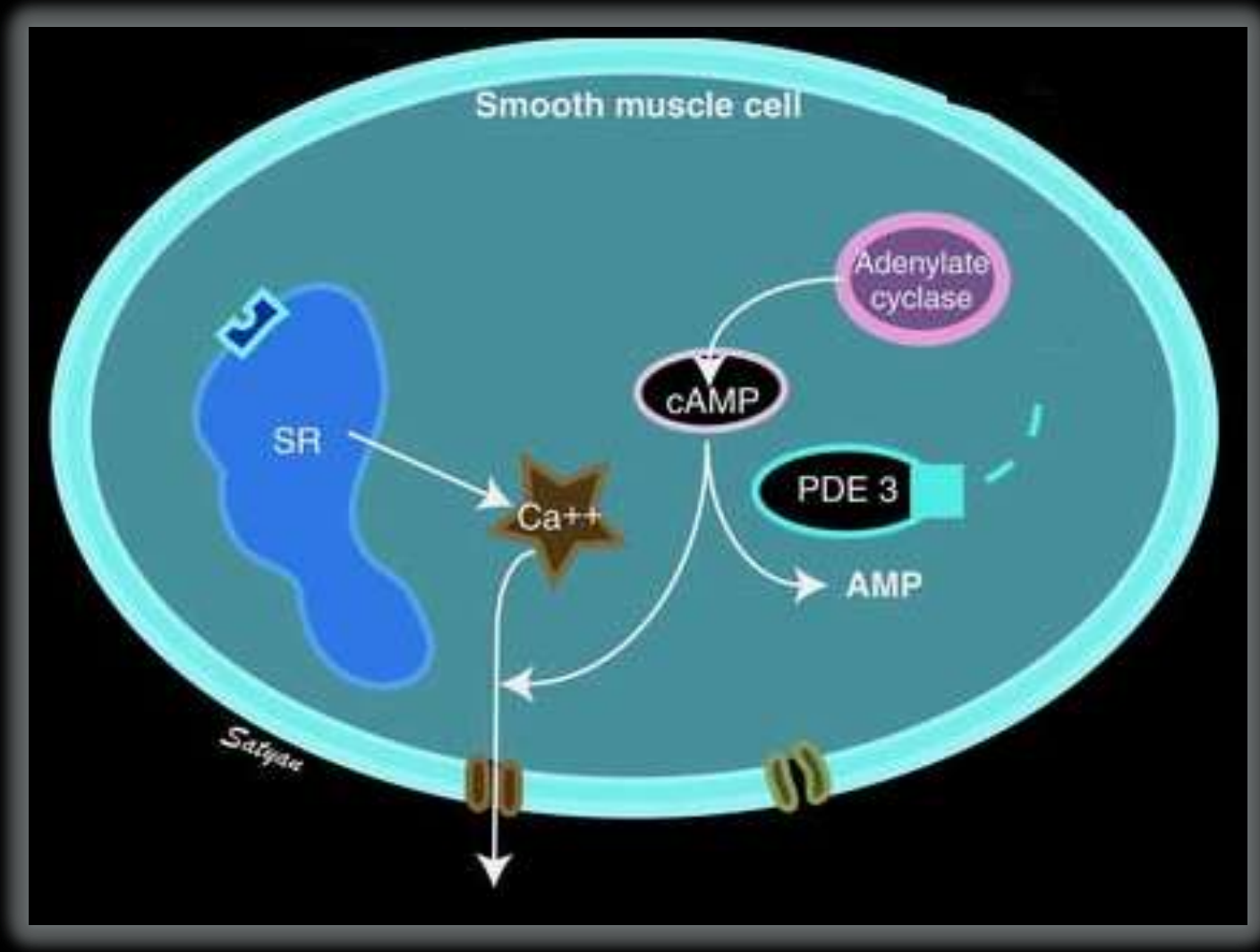
Authors' conclusions

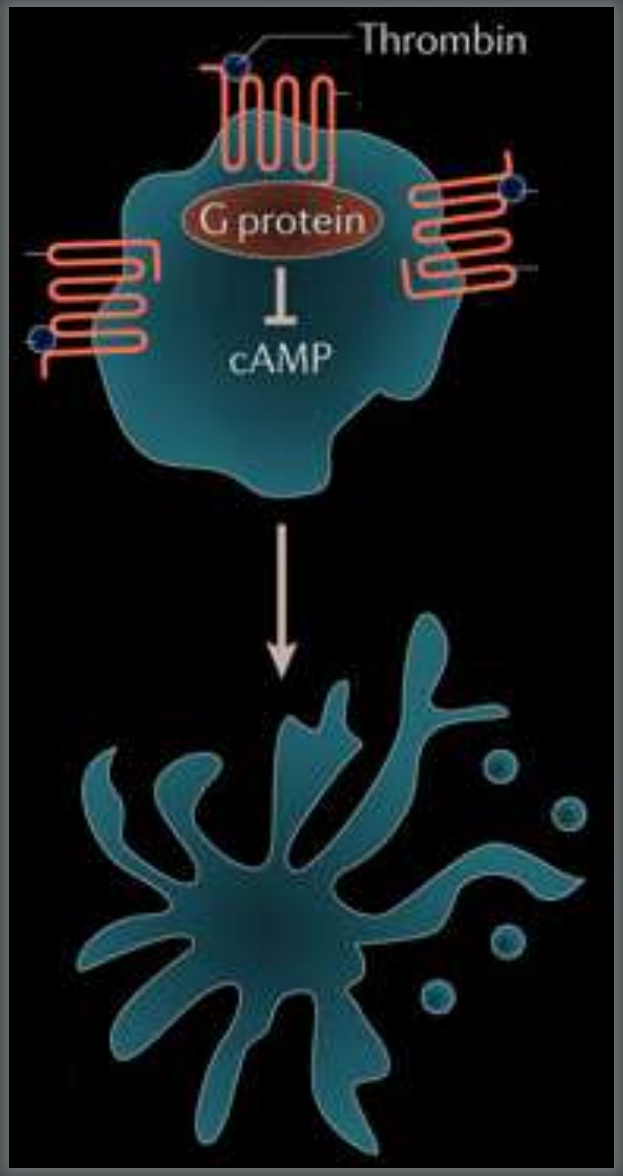
Cilostazol has been shown to be of benefit in improving walking distance in people with intermittent claudication secondary to PAD. Although there is an increase in adverse side effects, they are generally mild and treatable. There is currently insufficient data on whether taking cilostazol results in a reduction of all-cause mortality and cardiovascular events or an improvement in quality of life. Future research into the effect of cilostazol on intermittent claudication should carefully consider comparability, sample size and homogeneity when designing a study.

THE COCHRANE COLLABORATION®

Cilostazol: mechanism of action (smooth muscle)



Cilostazol: mechanism of action (platelet)



Cilostazol: safety profile

Outcome: 1 All-cause mortality cilostazol 100 mg twice daily versus placebo

Table IV. Serious bleeding events

Events	*Cilostazol, No (%)*	*Placebo, No (%)*
Serious bleeding events*	18 (2.5)	22 (3.1)
On aspirin	15 (2.1)	15 (2.1)
On aspirin + clopidogrel	3 (0.4)	7 (1.0)
Anticoagulated	6 (0.8)	9 (1.3)

Odds Ratio M-H,Fixed,95% CI

0.97 [0.14, 6.97]
2.97 [0.12, 73.81]
1.54 [0.06, 39.12]
2.12 [0.19, 23.49]
0.33 [0.01, 8.26]
1.01 [0.06, 16.30]
0.20 [0.01, 4.17]

Strandness 2002 2/133 0/129 5.2 % 4.92 [0.23, 103.56]

Total (95% CI) **1181** **1158** **100.0 %** **1.14 [0.48, 2.71]**

Total events: 9 (Cilostazol 100 mg), 7 (Placebo)

Heterogeneity: $Chi^2 = 3.37$, df = 7 (P = 0.85); $I^2 = 0.0\%$

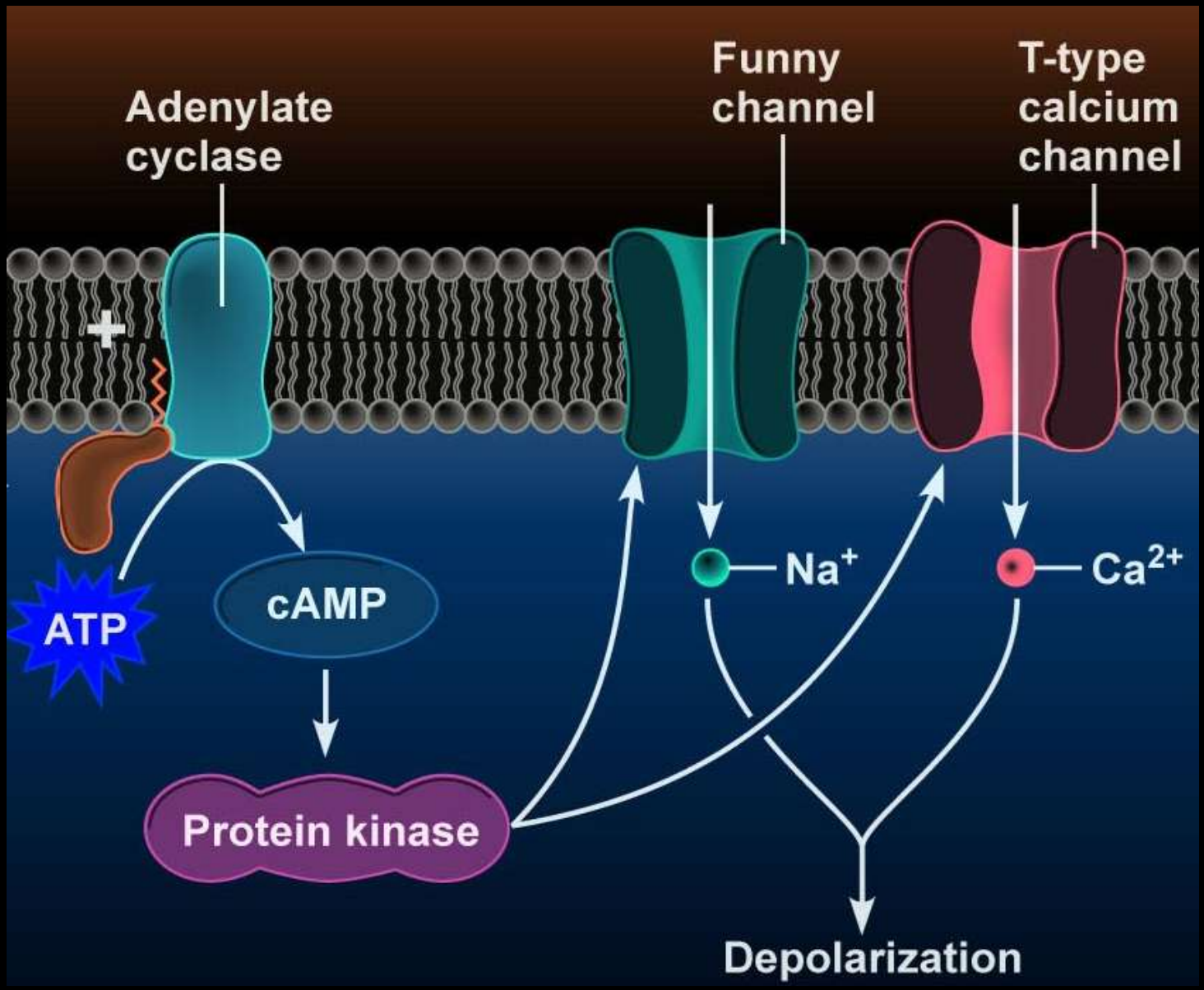
Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Not applicable

0.002 0.1 1 10 500

Favours cilostazol 100 mg Favours placebo

Cilostazol: mechanism of action (heart muscle)



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THE COCHRANE COLLABORATION®

ACCF/AHA Practice Guidelines

Management of Patients With Peripheral Artery Disease (Compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations)

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

*" **Cilostazol** (100 mg orally 2 times per day) **is indicated as an effective therapy** to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure). "*

(Level of Evidence: A)

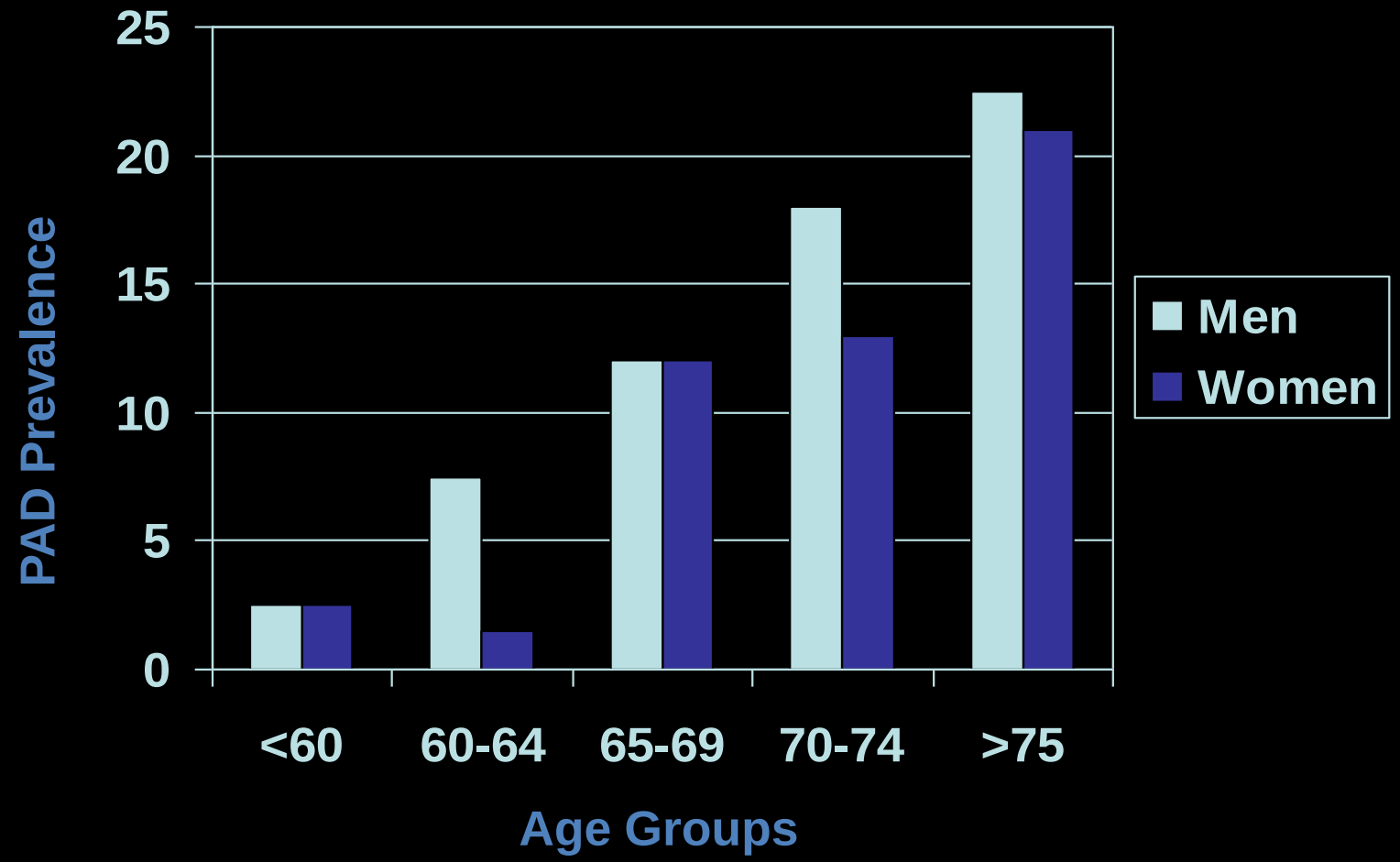
Cilostazol: dose & contraindications

- ✓ Heart failure
- ✓ Recent (<6months) myocardial infarction coronary intervention
- ✓ Double or triple antithrombotic treatment
- ✓ Bleeding tendency
- ✓ Severe renal failure (GFR<25ml/min)
- ✓ Hepatic failure
- ✓ History of dangerous arrhythmias

Take-home messages

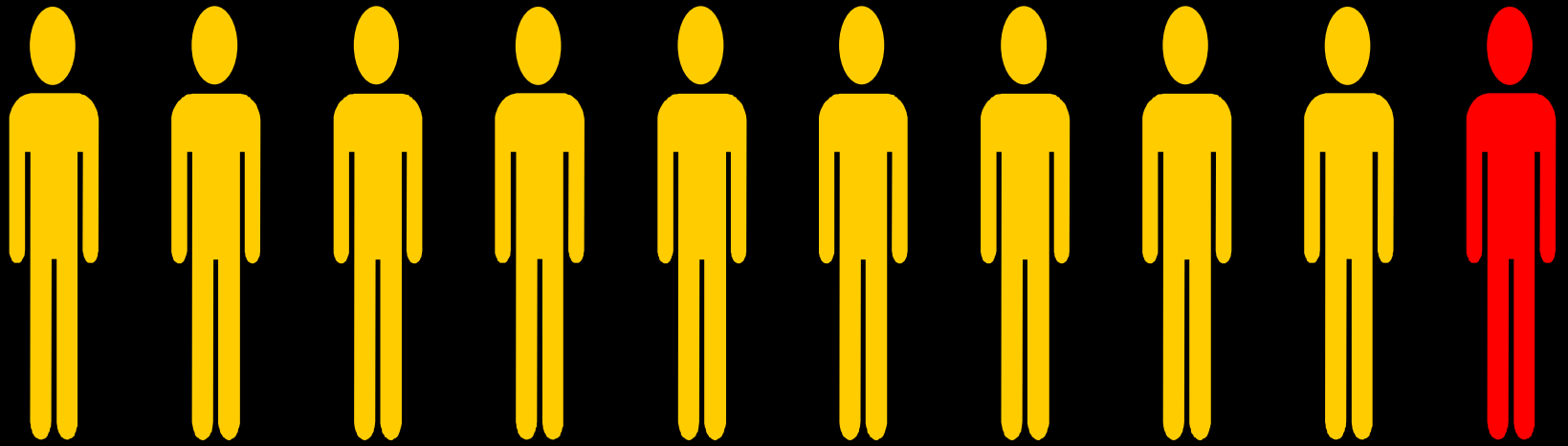
- ✓ PAD is all around – look for it, and treat it !
- ✓ Cilostazol increases walking capacity in PAD patients.
- ✓ Side effects are mild and easily treatable.

Peripheral Arterial Disease Prevalence by age

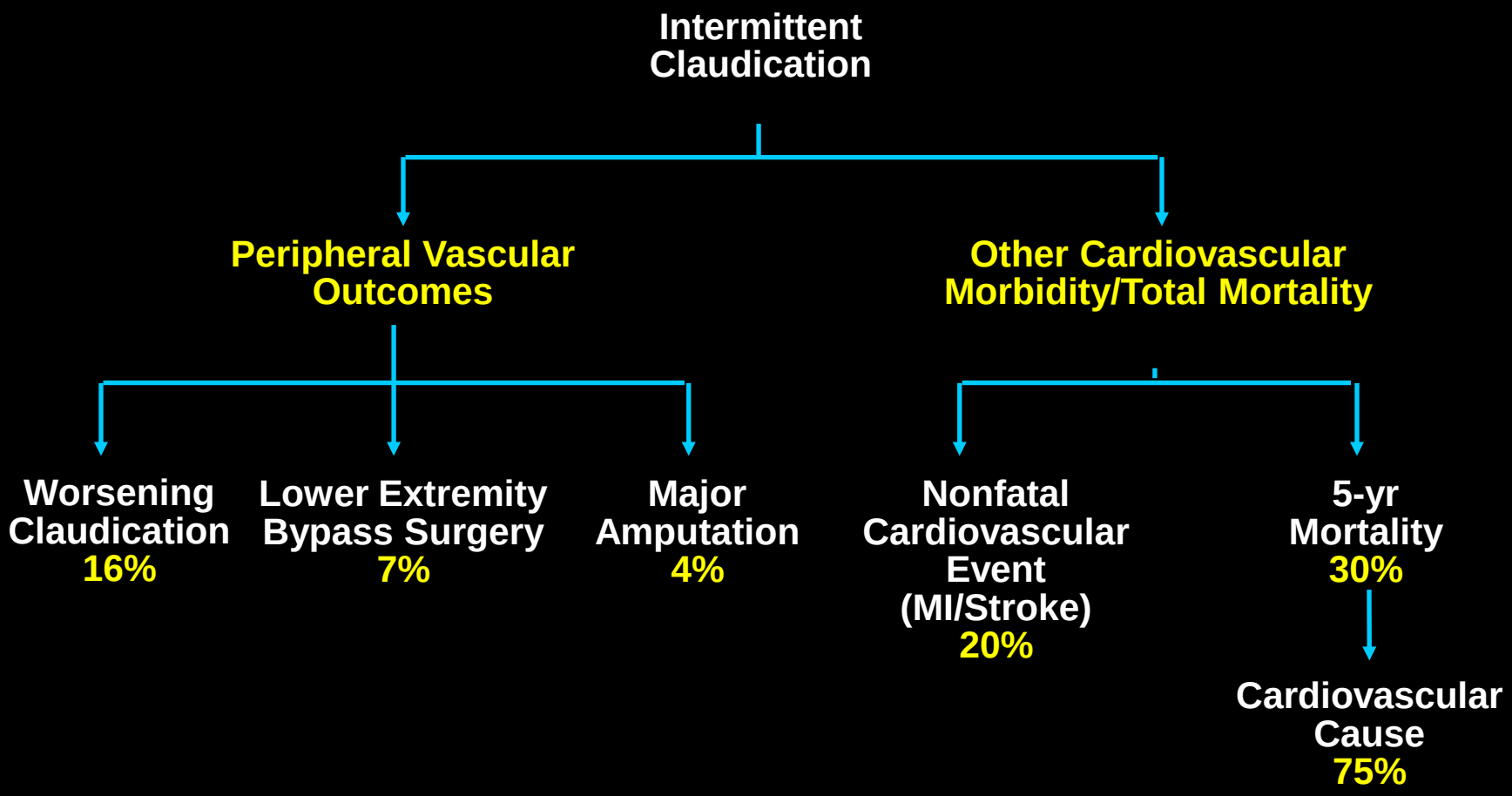


Criqui et al Circulation 1985; 71: 510-5 (77)

PAD: mostly asymptomatic



PAD and clinical outcome



Weitz JI et al. *Circulation*. 1996;94:3026–3049.

Classification of Peripheral Arterial Disease

FONTAINE		RUTHERFORD		
Stage	**Clinical**	**Grade**	**Category**	**Clinical**
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate–severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		IV	6	Ulceration or gangrene

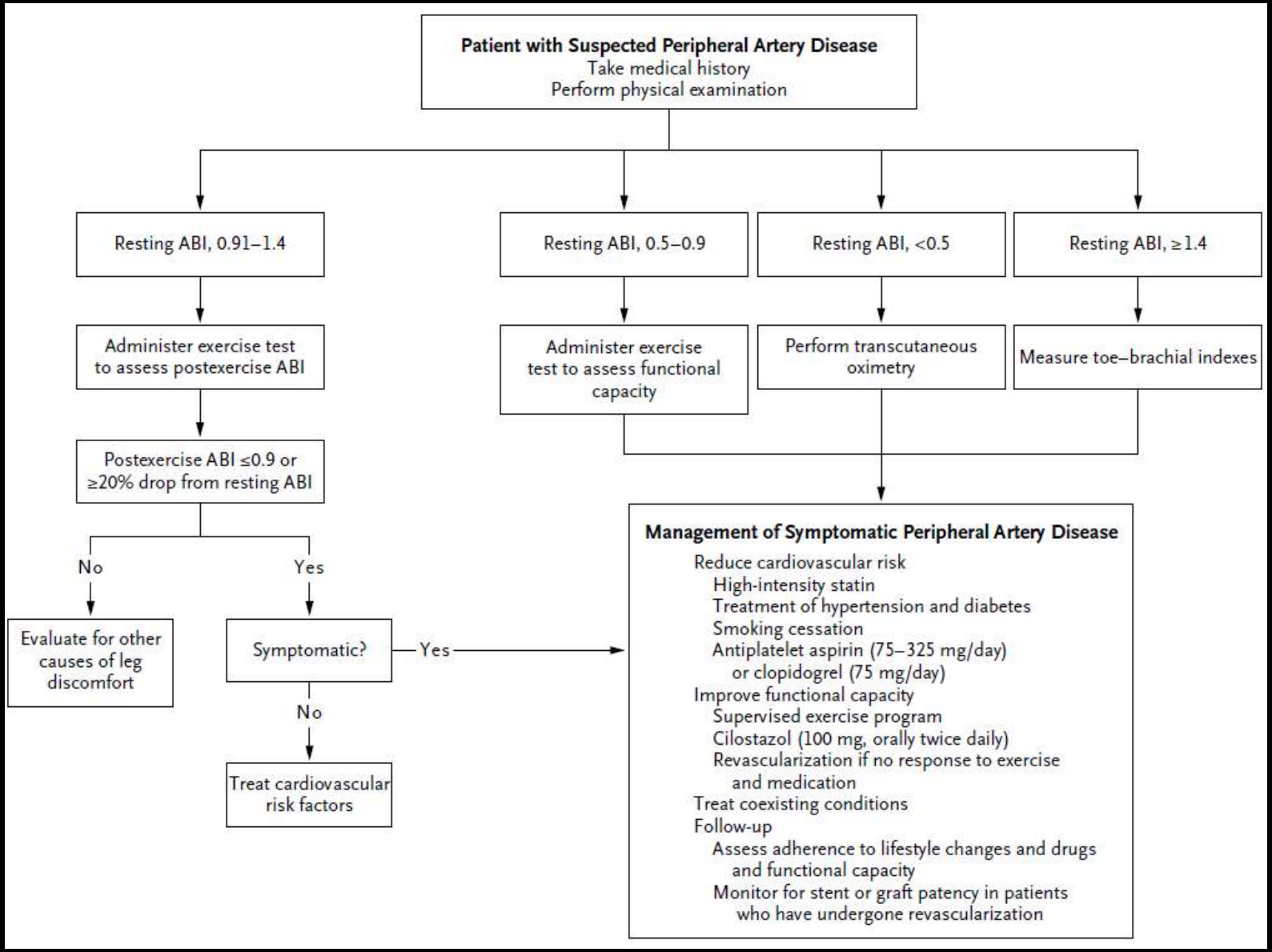
…

$$\text{ABI} = \frac{\text{Ankle systolic pressure}}{\text{Brachial systolic pressure}}$$

- Ankle and brachial systolic pressures taken using a hand-held Doppler instrument
- Supine, after ~10 minutes rest

Normal	**ABI**	**0.90-1.30**
PAD	**ABI**	**<0.90**
Rest pain/ulceration	**ABI**	**<0.40**
Non-compressible	**ABI**	**>1.30**

Diagnostic approach



Ποιος Διαγιγνώσκει την ΠΑΝ;

ΥΠΕΝΘΥΜΙΣΗ

Πολλοί ασθενείς με ασυμπτωματική ή και ήπια συμπτωματική ΠΑΝ μπορούν εύκολα να διαγνωσθούν από το
-Γενικό Ιατρό
-Παθολόγο
-Καρδιολόγο
και ακολούθως να παραπεμφθούν στον
-Ειδικό Αγγειοχειρουργό

ΕΝΕΡΓΕΙΕΣ

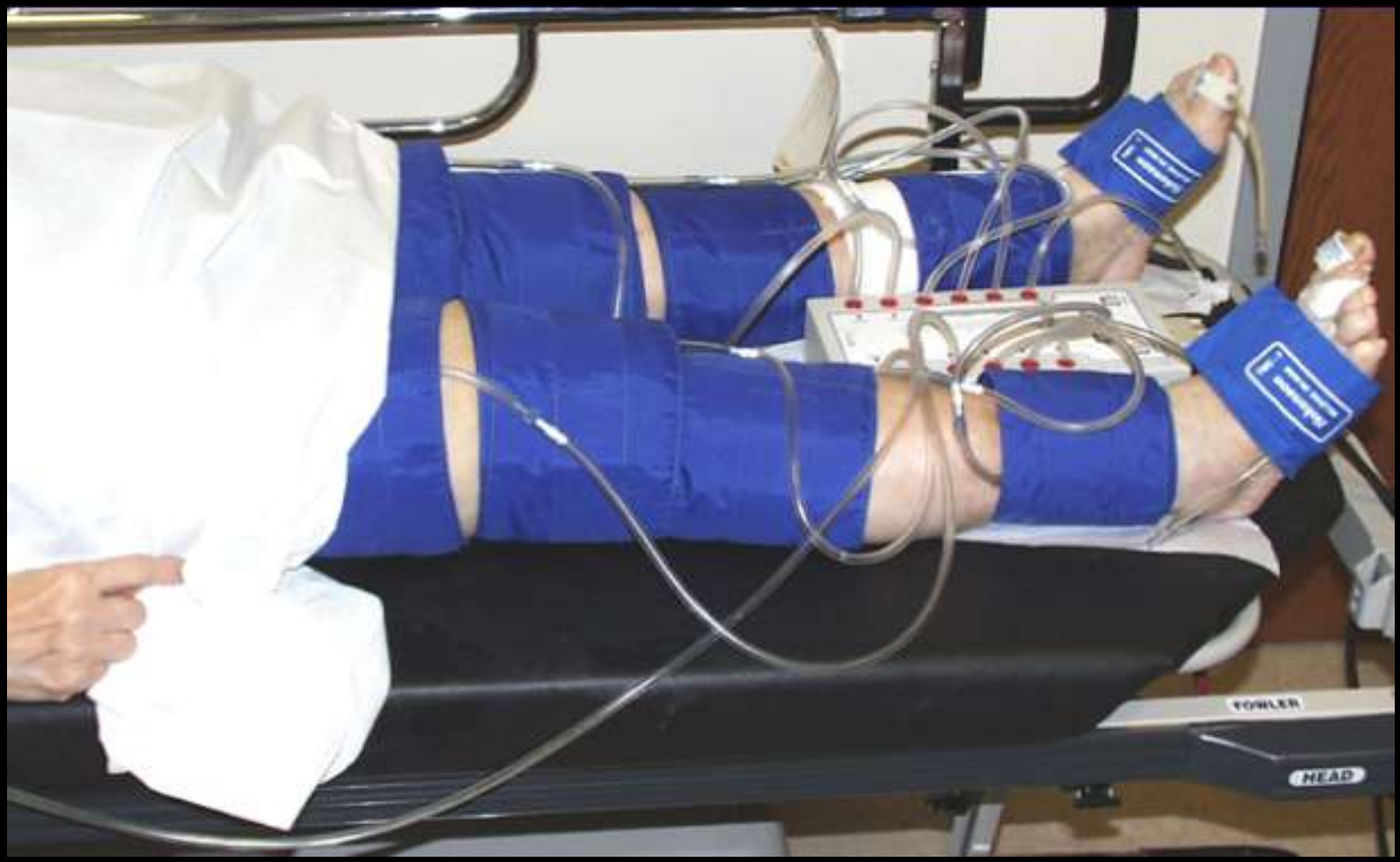
Φυσική εξέταση για ΠΑΝ σε ασθενείς με παράγοντες κινδύνου και/ ή άτυπα συμπτώματα

Εκτίμηση ικανότητας βάδισης / άλγους κατά την άσκηση

Χρήση ειδικού ερωτηματολογίου για υποβοήθηση της διάγνωσης

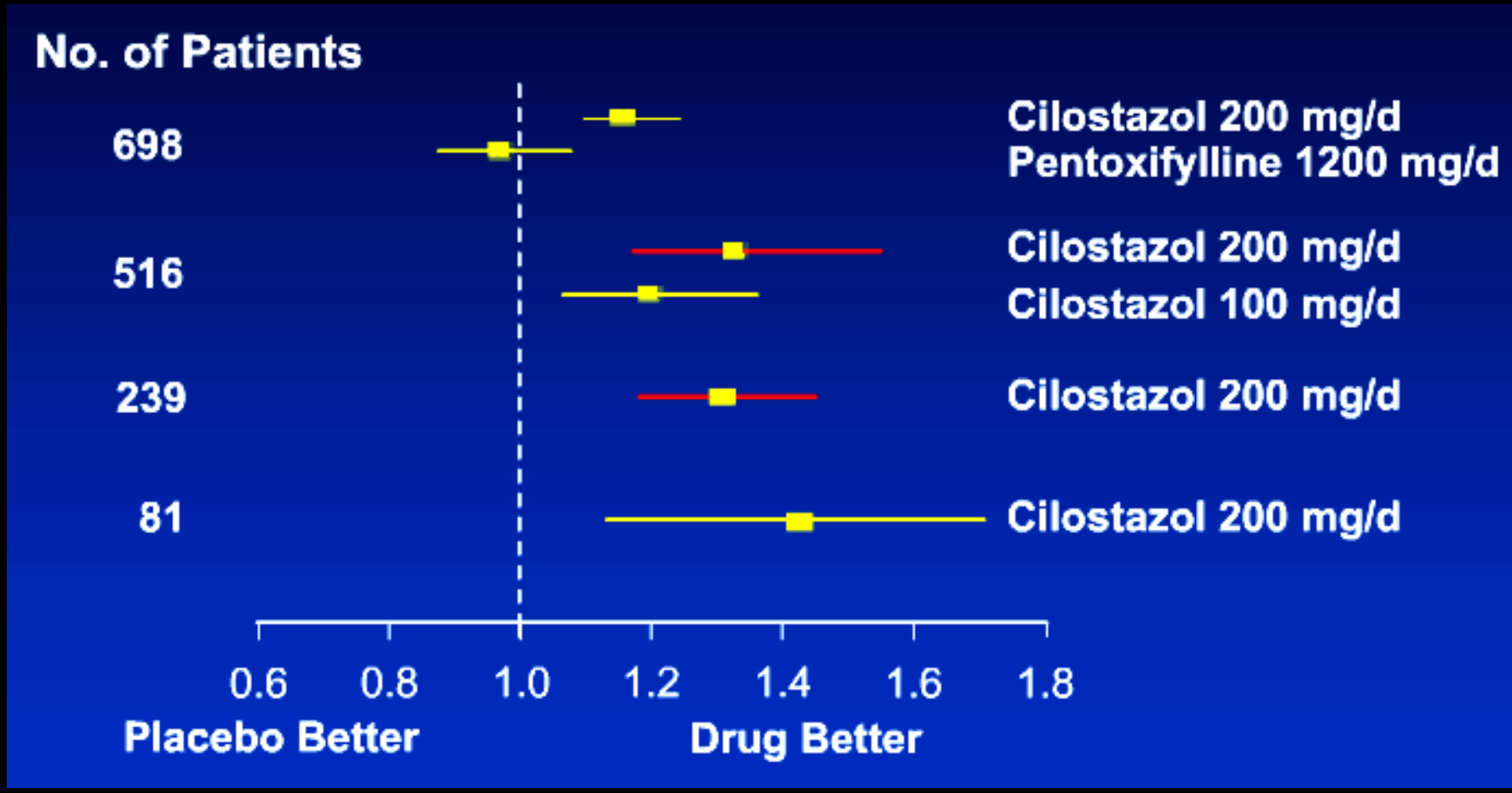
Επιβεβαίωση της διάγνωσης με την μέτρηση του ΣΒΔ

Segmental Pressures/ Pulse Volume Recordings



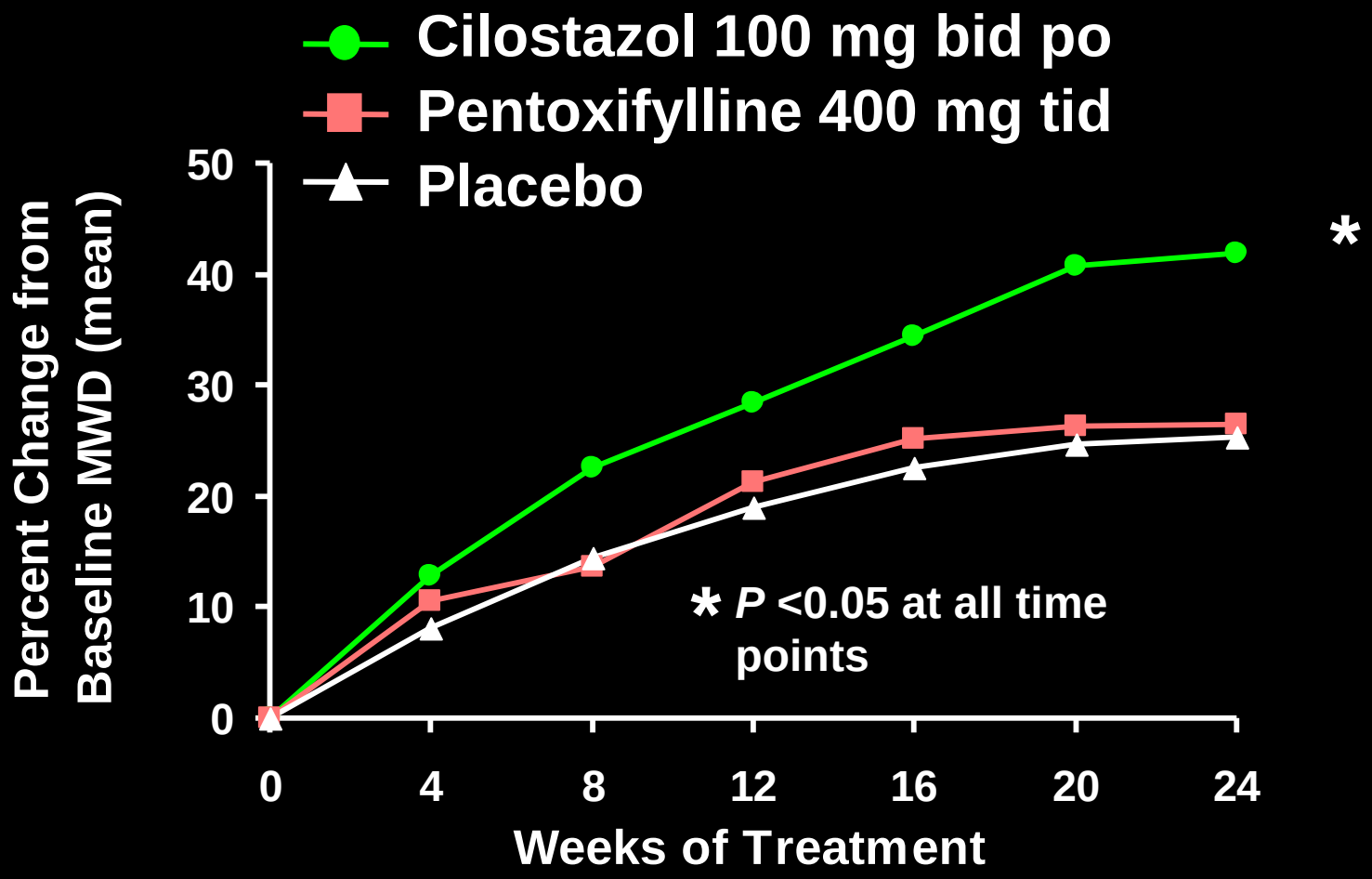
TCT 2005

Effect of Cilos on walking distance in patients with intermittent Claudication



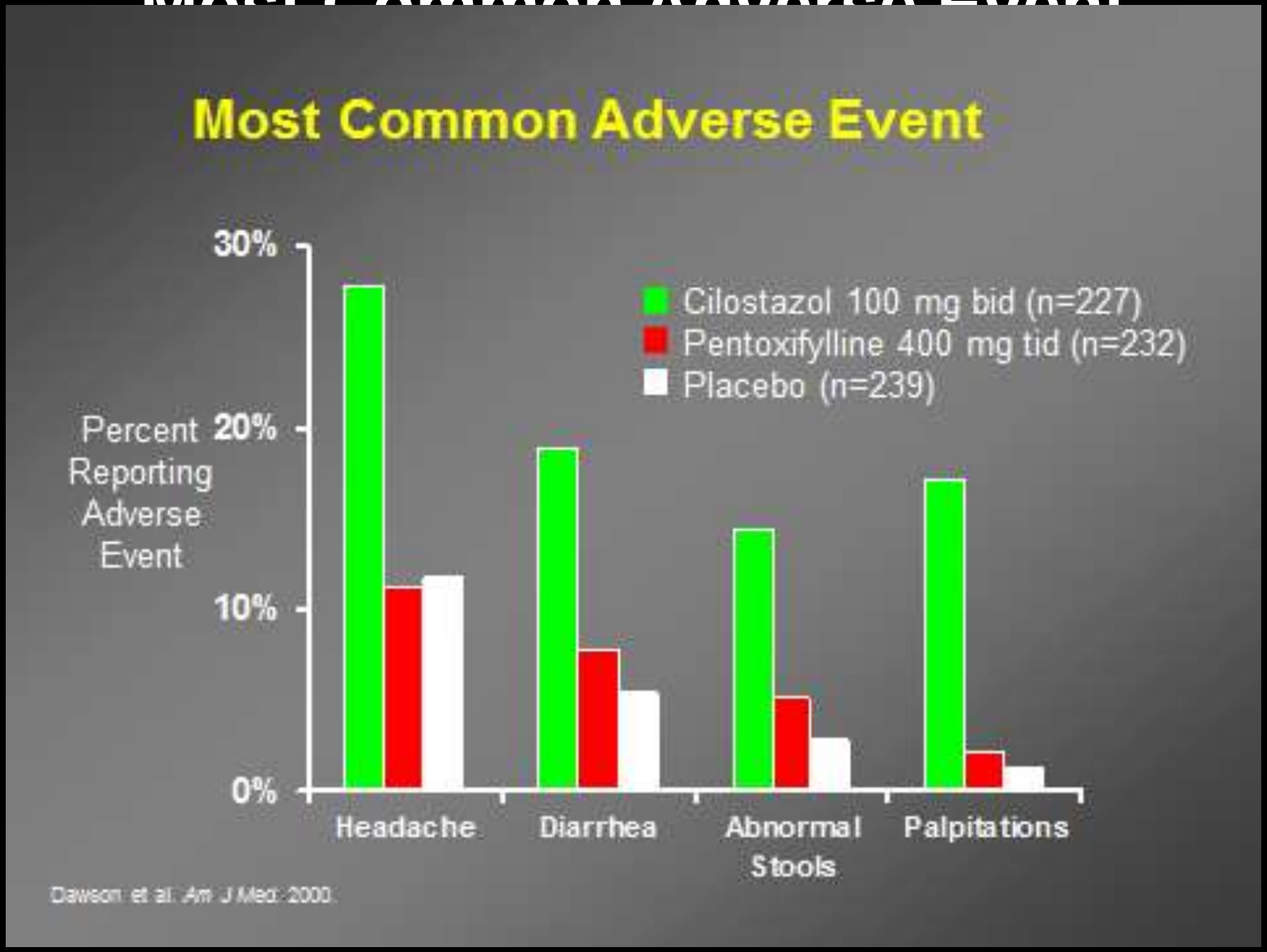
Hiatt WR N Engl J Med 2001; 344: 1608 - 1621

Effect of Cilos vs. Pentoxifylline on Walking Distance in Patients with Claudication

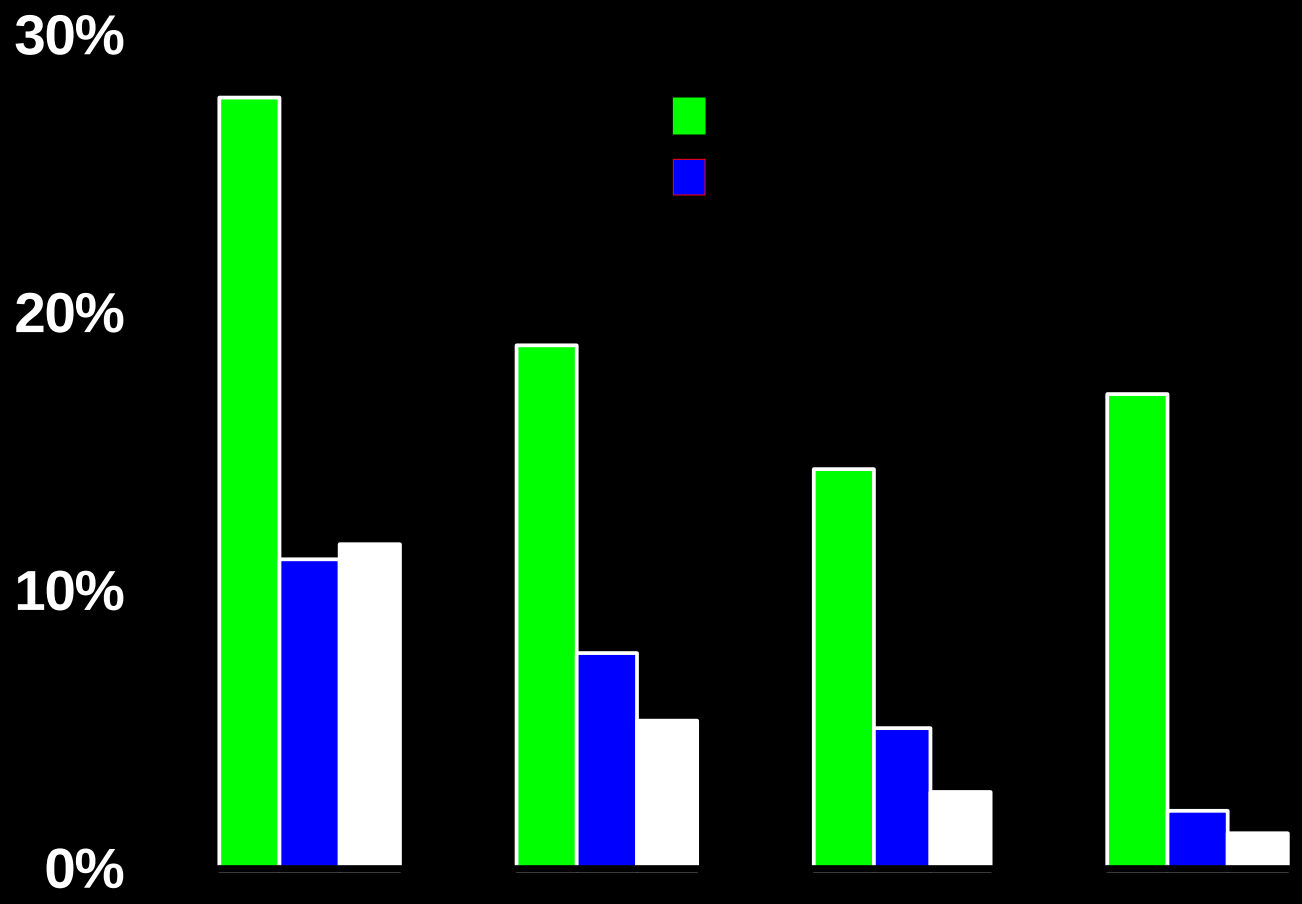


Dawson, et al. Am. J. Med., 2000.

Most Common Adverse Event



Most Common Adverse Event



Drugs to improve walking ability

Pentoxifylline for intermittent claudication (Review)

Salhiyyah K, Forster R, Senanayake E, Abdel-Hadi M, Booth A, Michaels JA

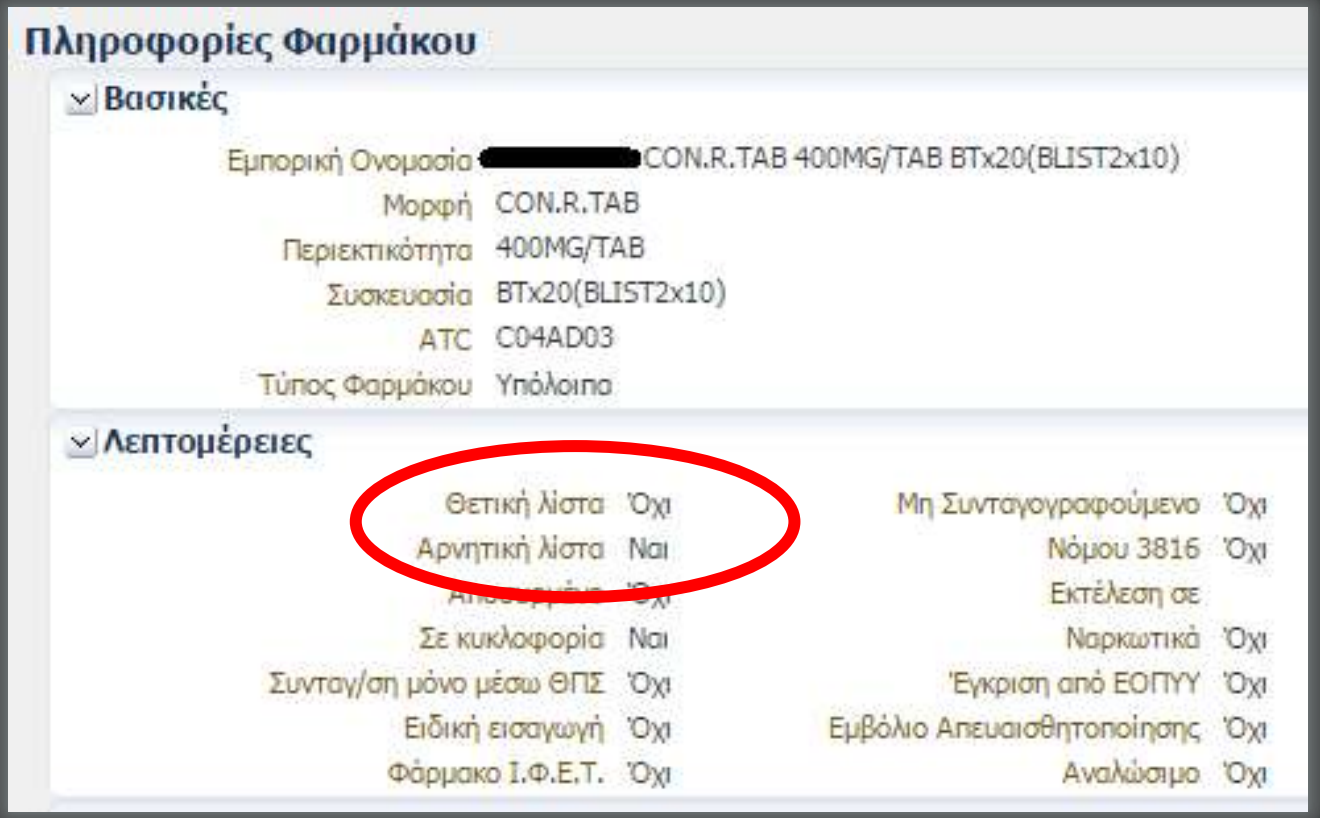
Authors' conclusions

Given the generally poor quality of published studies and the large degree of heterogeneity evident in interventions and in results, the overall benefit of pentoxifylline for patients with Fontaine class II intermittent claudication remains uncertain. Pentoxifylline was shown to be generally well tolerated.

Based on total available evidence, high-quality data are currently insufficient to reveal the benefits of pentoxifylline for intermittent claudication.

THE COCHRANE COLLABORATION®

Pentoxifylline for PAD ?



Πληροφορίες Φαρμάκου

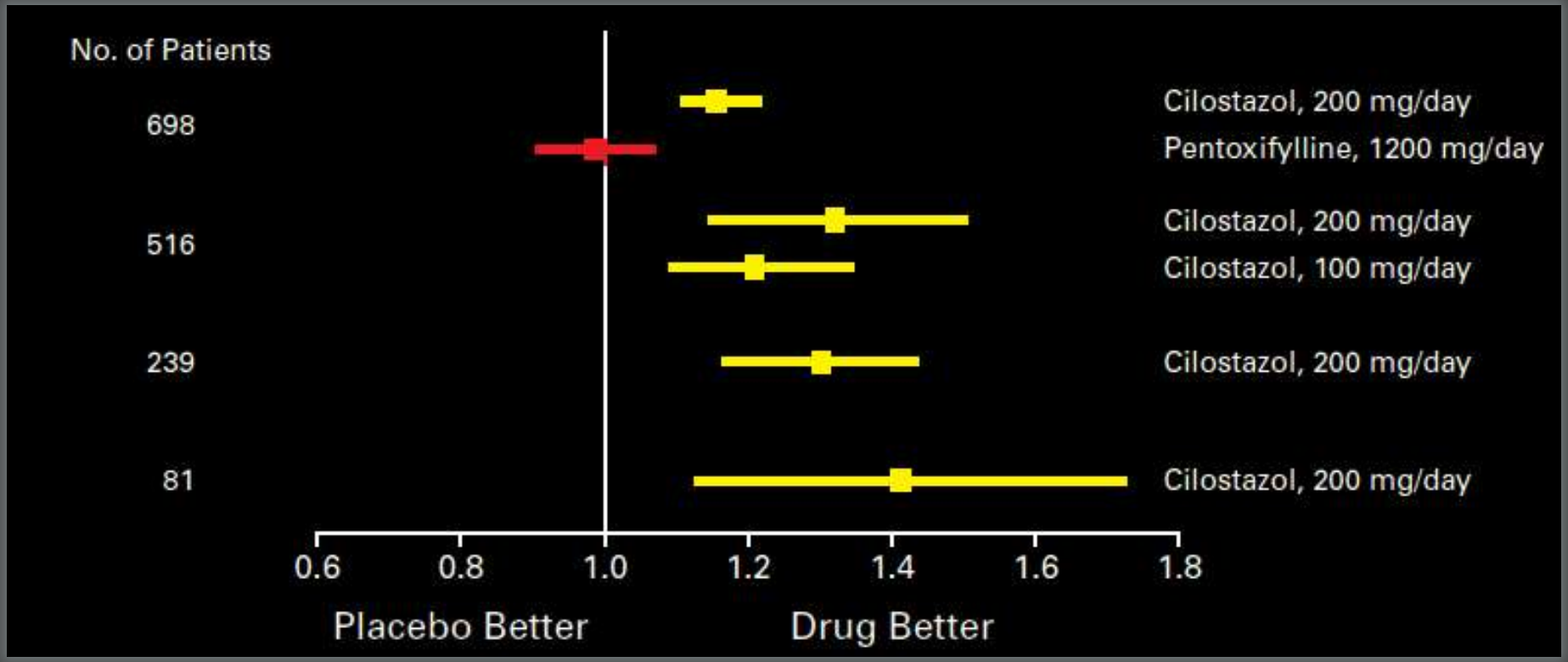
Βασικές

Εμπορική Ονομασία	[redacted]CON.R.TAB 400MG/TAB BTx20(BLIST2x10)
Μορφή	CON.R.TAB
Περιεκτικότητα	400MG/TAB
Συσκευασία	BTx20(BLIST2x10)
ATC	C04AD03
Τύπος Φαρμάκου	Υπόλοιπα

Λεπτομέρειες

Θετική λίστα	Όχι	Μη Συνταγογραφούμενο	Όχι
Αρνητική λίστα	Ναι	Νόμου 3816	Όχι
[illegible]	Όχι	Εκτέλεση σε	
Σε κυκλοφορία	Ναι	Ναρκωτικά	Όχι
Συνταγ/ση μόνο μέσω ΘΠΣ	Όχι	Έγκριση από ΕΟΠΥΥ	Όχι
Ειδική εισαγωγή	Όχι	Εμβόλιο Απευαισθητοποίησης	Όχι
Φάρμακο Ι.Φ.Ε.Τ.	Όχι	Αναλώσιμο	Όχι

Effect of Drug Therapy on Walking Distance



Hiatt WR. *N Engl J Med.* 2001; 344;1608-1621.