

Peripheral Arterial Disease (PAD)



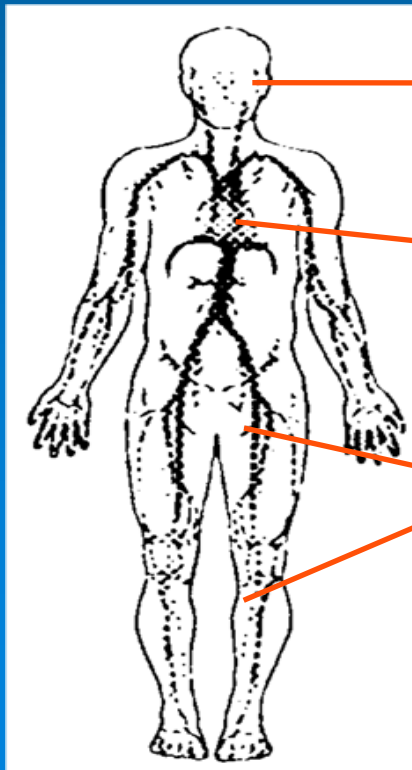
**A marker for myocardial infarction
and ischaemic stroke**

Overview

- PAD (peripheral arterial disease) – a marker for MI and IS
- Epidemiological data on PAD
 - *Risk factors*
 - *Prevalence*
 - *Atherothrombosis – coexistence of PAD, coronary and cerebrovascular disease*
 - *Natural history*
 - *Low ABPI as an independent predictor of ischaemic risk*
- Symptomatology of PAD
- Diagnosis and management of PAD

PAD – a marker for MI and IS

- Atherothrombosis = thrombus formation on top of existing atherosclerosis
- Occurs in multiple arterial beds

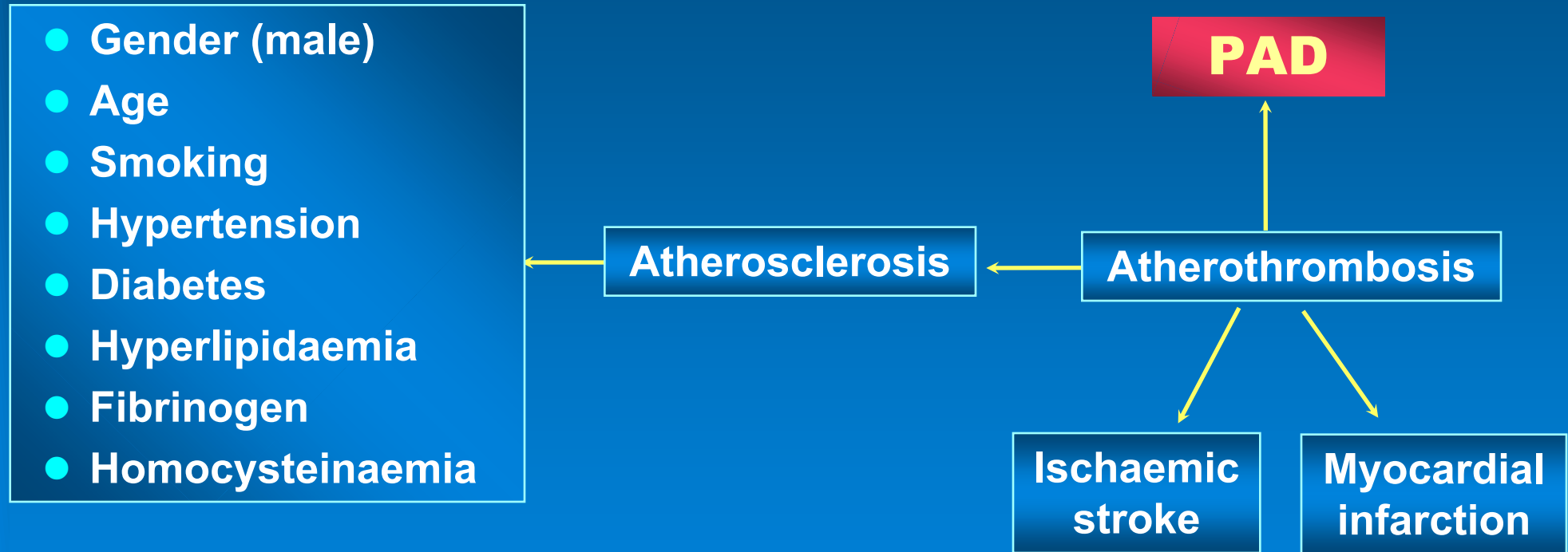


Cerebrovascular disease
(*ischaemic stroke, transient ischaemic attack*)

Coronary artery disease
(*stable/unstable angina, myocardial infarction*)

PAD (*intermittent claudication, critical leg ischaemia, amputation, gangrene, necrosis*)

Risk factors for PAD



Prevalence of PAD – variation according to diagnostic criterion

- 6.3 million individuals with symptomatic, established PAD are diagnosed in the USA and EU¹
- Epidemiological studies imply that real* prevalence may be approx. 20 million (= 9.5% of the population > 50 years old)
- In 613 men and women (mean age 66 years), real prevalence was found to be underestimated by two- to seven-fold²
- ABPI (ankle:brachial pressure index) correlates with angiographically determined disease³
- ABPI < 0.9 is a marker of diffuse atherothrombosis⁴

¹ 17 Western European countries. Statistical Supplement; WHO Yearbooks, Annual Statistics, 1997;

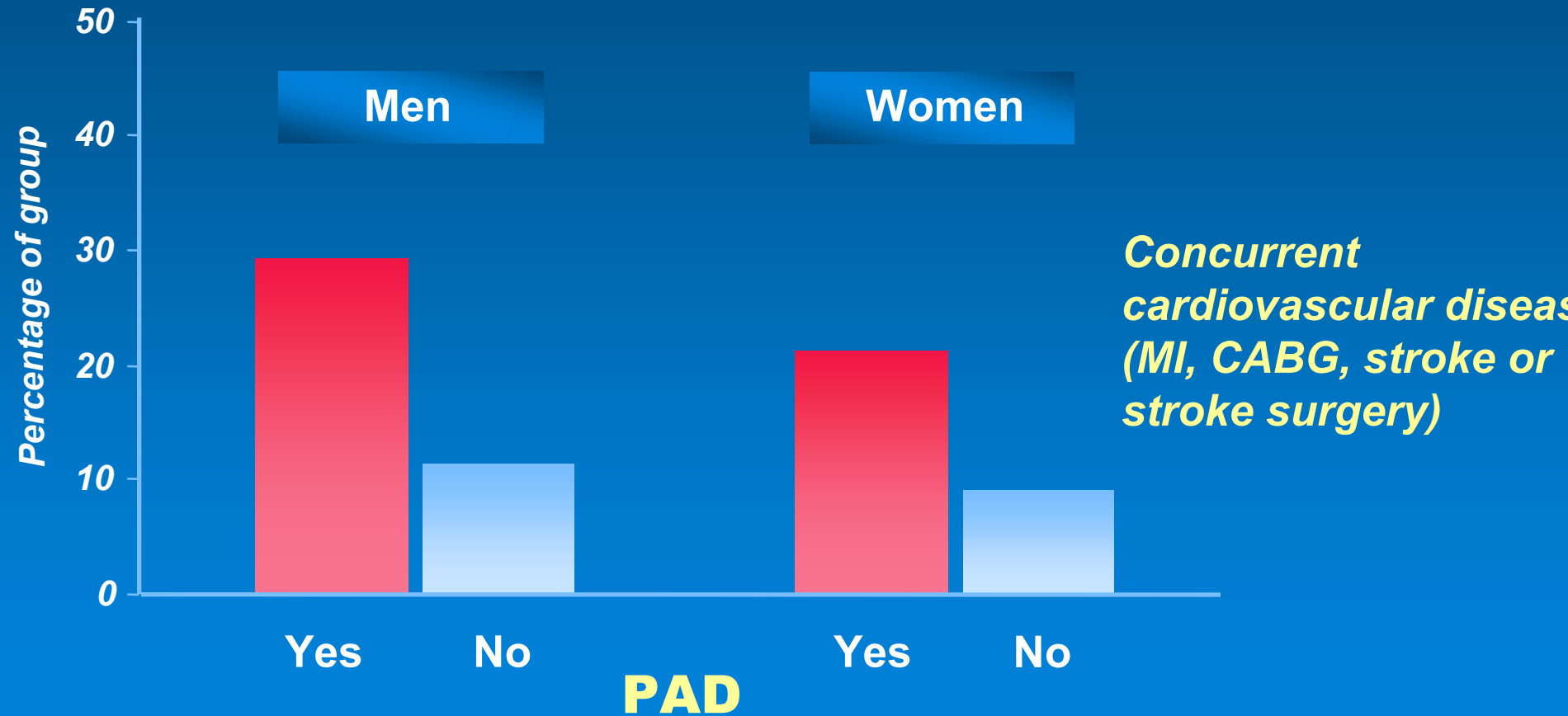
² Criqui MH et al. Vasc Med 1997;2:221–226; ³Shinozaki T et al. J Clin Epidemiol 1998;15:1263–1269; ⁴Kornitzer M et al. Angiology 1995;46:211–219.

*ABPI < 0.9, symptomatic or not, diagnosed or not.

Epidemiology of PAD – effect of age and gender

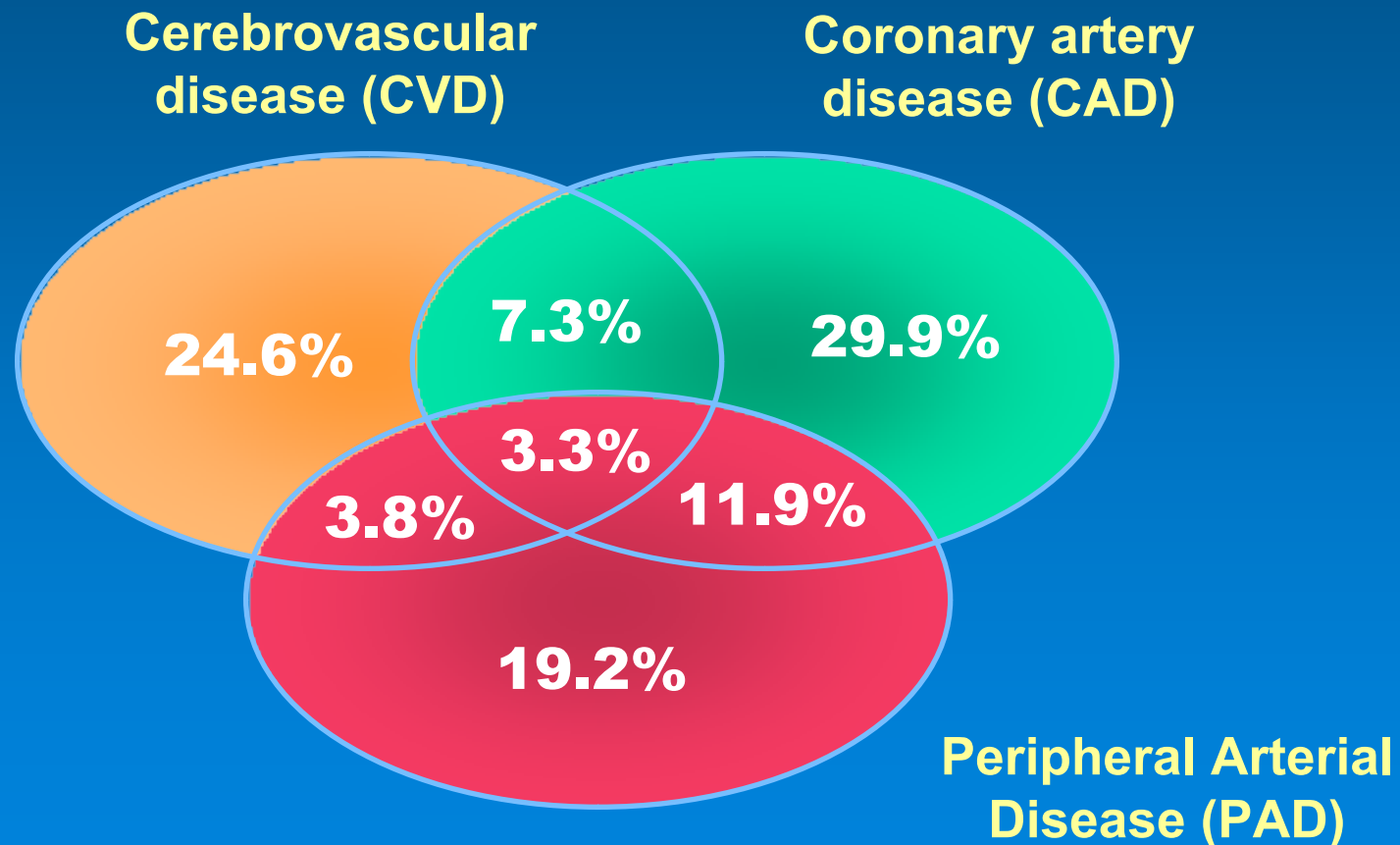
- Epidemiological data on PAD vary according to:
 - *Population studied*
 - *Method of diagnosing PAD*
- Incidence and prevalence of intermittent claudication* increase with age
 - *Prevalence in men aged 45–50 years is 1%*
 - *Prevalence is 3–3.5% in men aged > 50 years*
 - *Similar trend in women, increase with age*
- More common in men than in women
 - *Twice as many men as women aged > 50 years have intermittent claudication (3.5% and 2%, respectively)*
- **Predominance in males disappears after age of 70**

Atherothrombosis – coexistence of symptomatic PAD and coronary or cerebrovascular disease



Atherothrombosis – symptomatic atherosclerosis in CAPRIE (overlap between PAD, CAD and CVD)

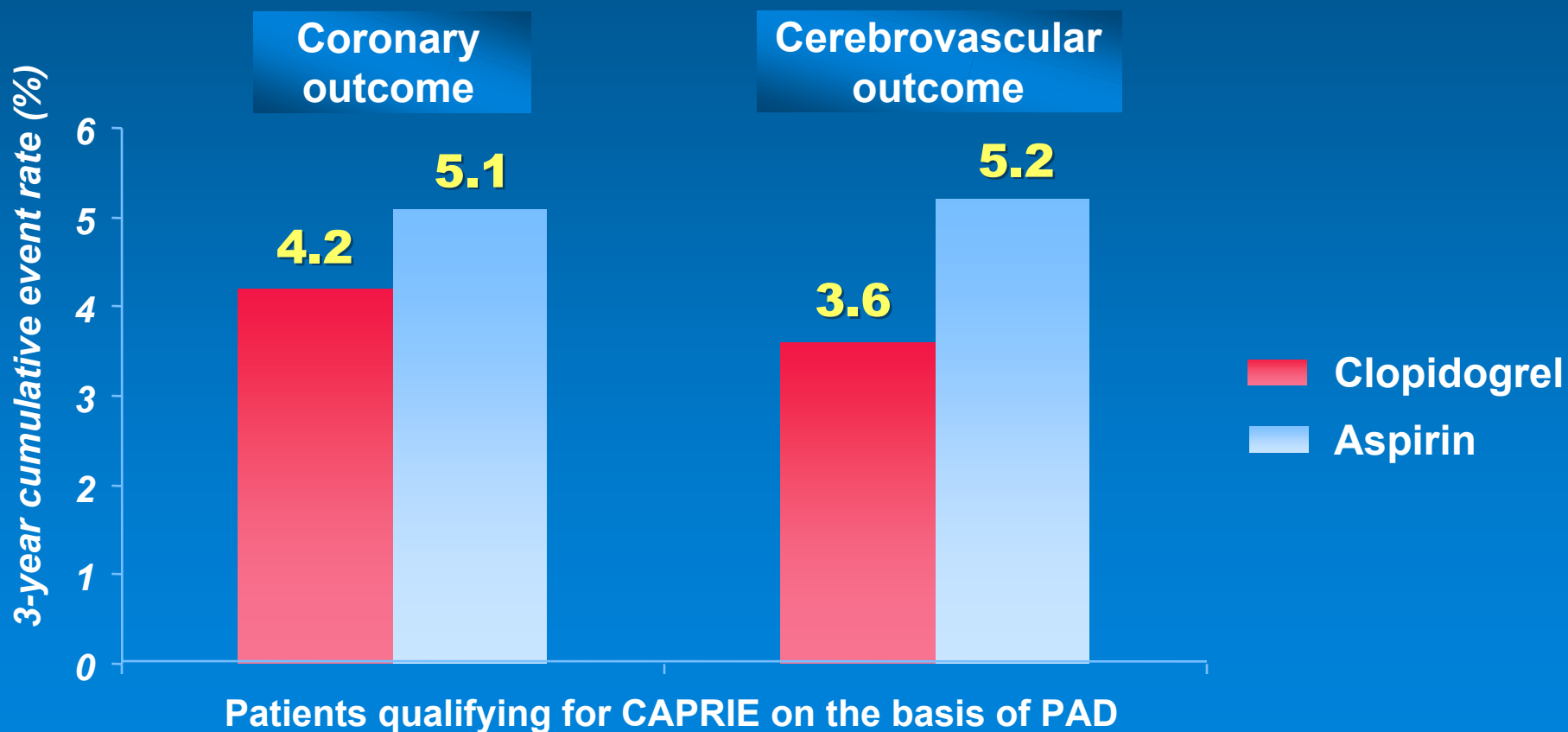
CAPRIE¹ (n = 19185)



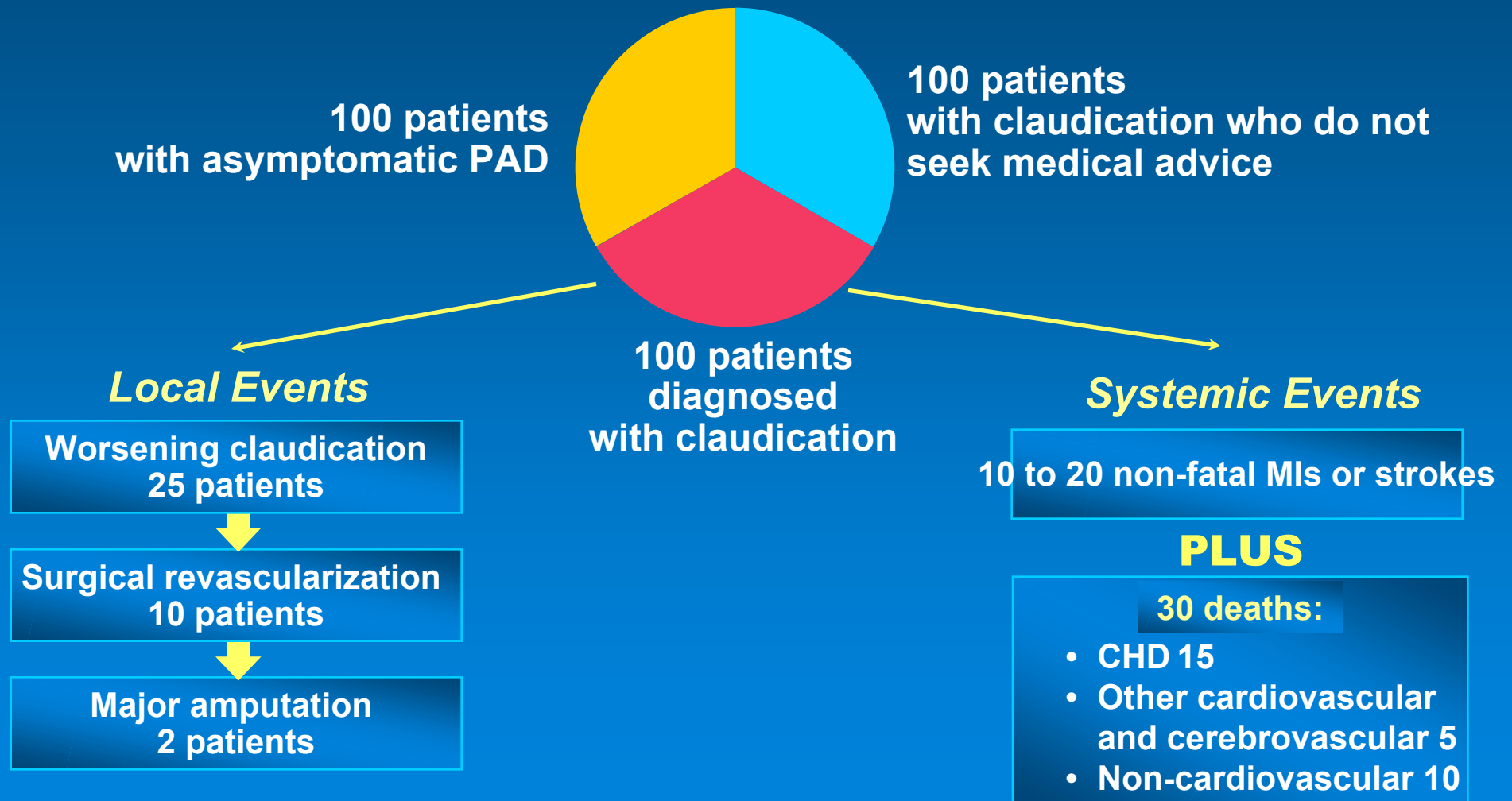
¹CAPRIE Steering Committee. *Lancet* 1996;348:1329–1339.

Patients with PAD are at risk of MI, IS and death

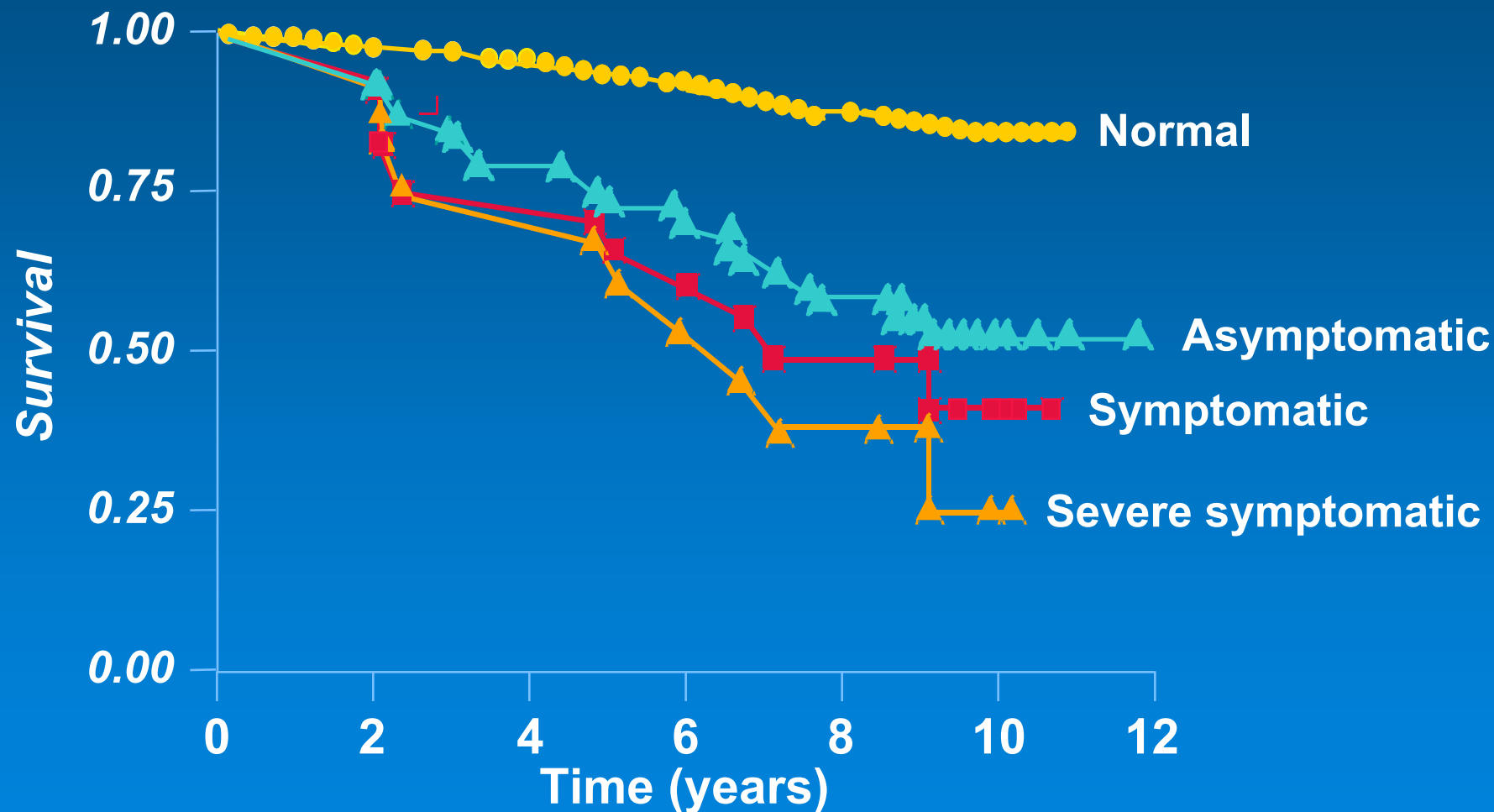
CAPRIE data



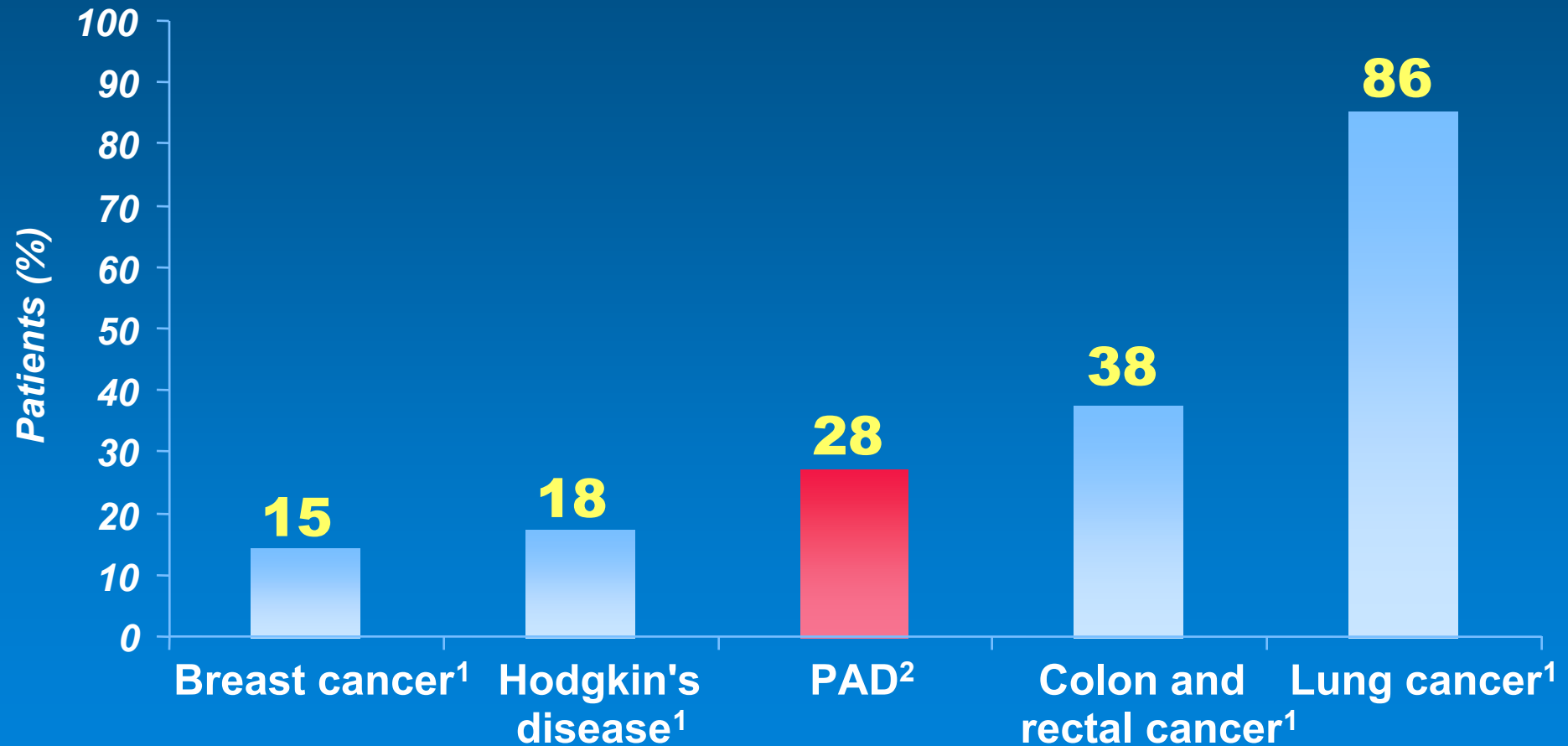
5-year natural history of PAD



PAD mortality – 10-year survival rates of subjects in the San Diego Artery Study



Relative 5-year PAD mortality rates versus other common pathologies



¹American Cancer Society. *Cancer Facts and Figures* – 1997.

²Kampozinski RF, Bernhard VM. In: *Vascular Surgery* (Rutherford RB, ed). Philadelphia, PA: WB Saunders: 1989;chap 53.

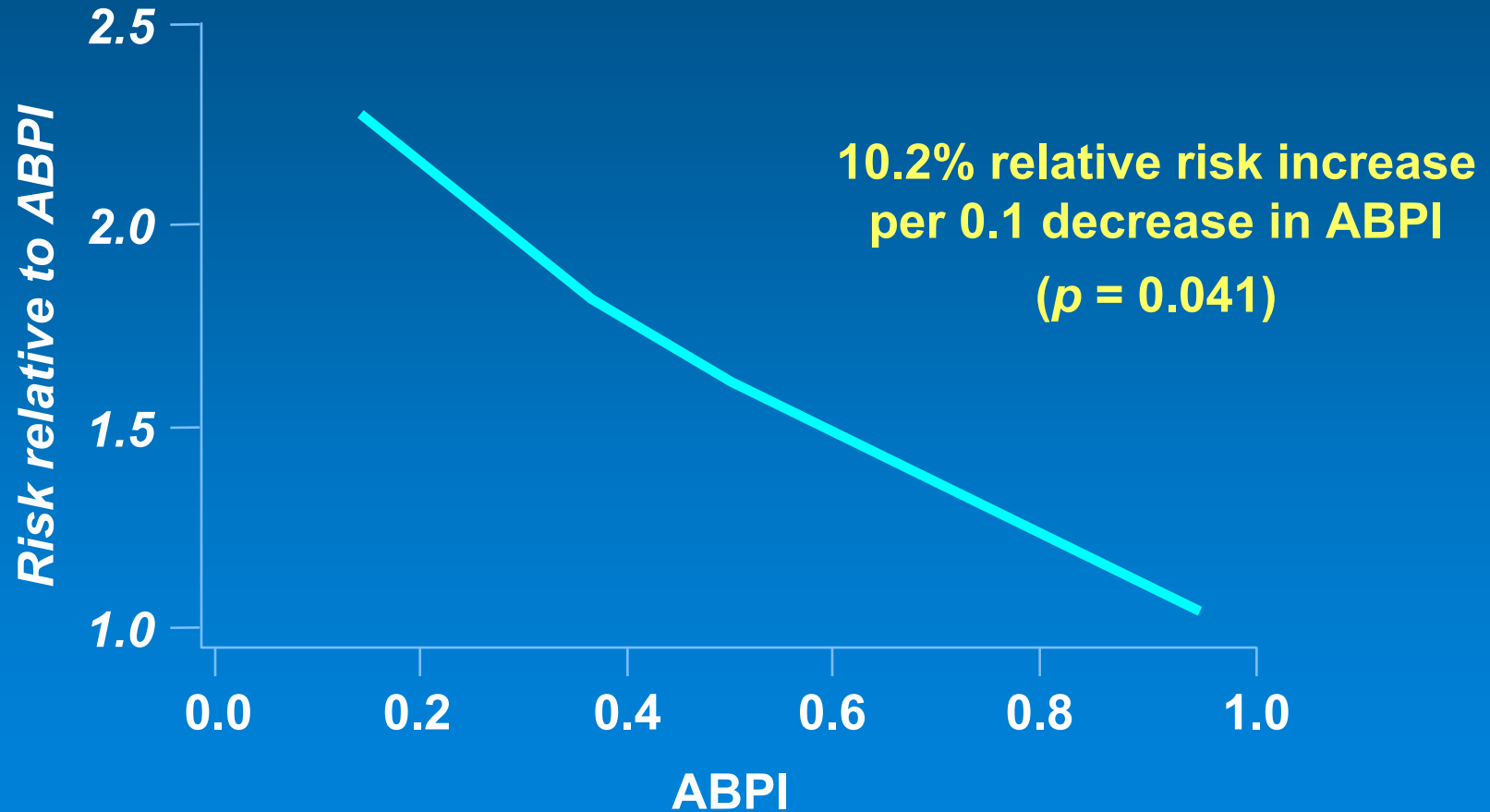
Intermittent claudication – an independent risk factor for increased mortality rates

- In the Whitehall study ($n = 18\ 388$), mortality rates in individuals with intermittent claudication were twice as high as those in healthy controls (*17 years' follow-up study*)
- Increased mortality even after adjustment for coronary risk factors
 - *Cardiac ischaemia at baseline*
 - *Systolic blood pressure*
 - *Plasma cholesterol concentration*
 - *Smoking behaviour*
 - *Employment grade*
 - *Degree of glucose intolerance*

Low ABPI is a strong predictor of cardiovascular mortality

- Reduced ABPI is a significant independent predictor of cardiovascular and coronary mortality
- Age-adjusted relative risks for 10-year cardiovascular and coronary mortality are higher in those with ABPI < 0.9
- The risk of cardiovascular death increases with decreasing ABPI
- ABPI measurement is underutilized and can be usefully incorporated in risk assessment and screening programmes
- ABPI measurements are inexpensive, simple and non-invasive

ABPI – inverse relationship with 5-year risk of cardiovascular events and death



Symptomatology of PAD

● Intermittent claudication

- Exercise-induced ischaemic calf-muscle pain while walking and/or weakness, relieved by rest
- Mortality rate from stroke and MI two to three times greater than in age-matched controls¹
- Prognosis varies with multiple risk factors and/or severity of disease

● Critical limb ischaemia

¹Dormandy JA et al. *J Cardiovasc Surg* 1999;30:50–67.

²European Working Group on Critical Leg Ischemia. *Circulation* 1991;84(Suppl IV):IV1–IV26.

- Pain at rest, eventually resulting in gangrene and

Diagnosis of PAD

- Evaluation of pulses and auscultation of bruits
- Ankle:arm blood pressure index (ABPI)
 - Ratio of ankle:brachial systolic blood pressure
 - Simple, non-invasive, suitable for routine screening
- Exercise testing
 - Pain-free and maximal walking distance
 - Size and duration of drop in ankle systolic BP upon claudication

Management of PAD patients

- **Lifestyle modification**

- Smoking cessation
- Regular exercise training
- Diet

- **Pharmacological treatment**

- Antiplatelet therapy
- Control risk factors (e.g. hypertension, blood glucose)
- Vasodilators for symptomatic relief?

Management of PAD – intervention

- **Endovascular**
 - Revascularization (angioplasty)
 - Stent placement
- **Surgical**
 - Endarterectomy
 - Peripheral bypass graft
 - Amputation

Management of PAD – antiplatelet agents are a key component of treatment

Rationale:

- Platelet aggregation, a key event in atherothrombosis, can be inhibited by antiplatelet agents
- Risk levels of stroke and MI are significantly greater than those of gangrene and amputation

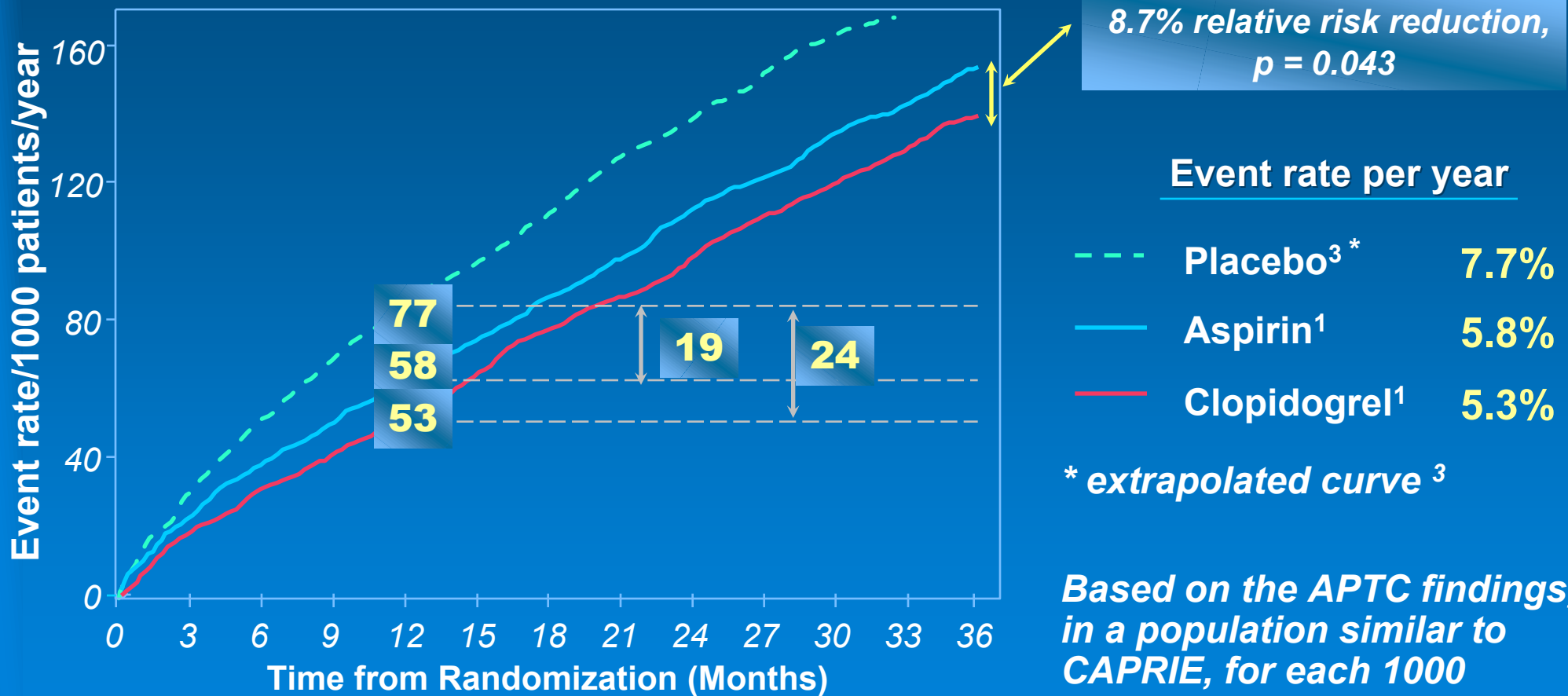
→ **Modify natural history of PAD**

Compound	Mode of action	PAD indication
Ticlopidine	ADP receptor antagonism	Yes (some countries)
Clopidogrel	ADP receptor antagonism	Yes
Aspirin	Inhibition of TxA ₂ synthesis	No

CAPRIE – study design

- **19 185 patients with recent IS, recent MI or established PAD**
- **Clopidogrel 75 mg od *versus* aspirin 325 mg od**
- **Follow-up of 1–3 years (mean 1.91 years)**
- **Combined primary endpoint of IS, MI or vascular death**

CAPRIE – efficacy profile of clopidogrel

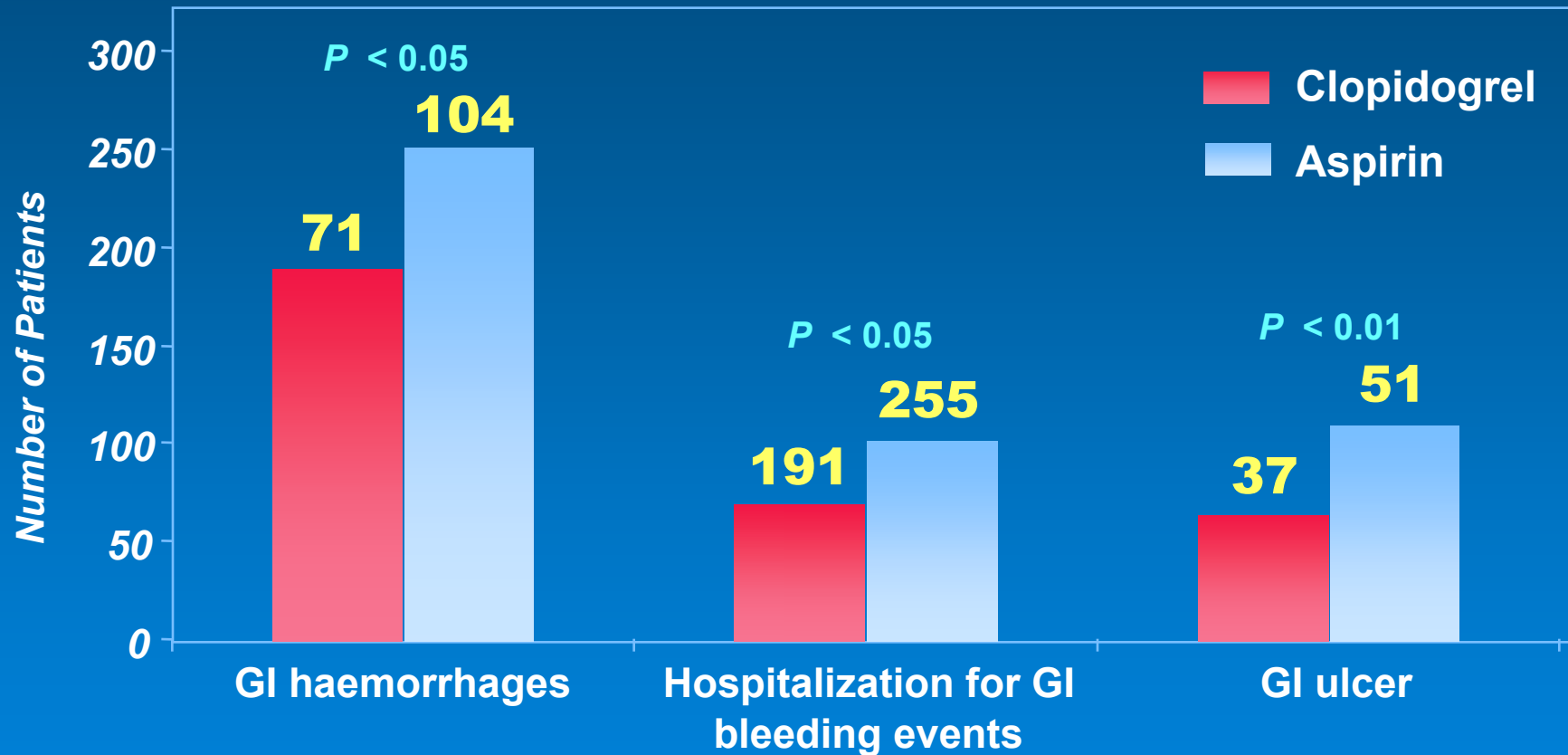


¹CAPRIE Steering Committee. *Lancet* 1996;348:1329–1339.

²Antiplatelet Trialists' Collaboration. *BMJ* 1994;308:81–106.

³Fisher LD. *J Am Coll Cardiol* 1998;31(Suppl A):49A.

CAPRIE – safety profile of clopidogrel



*** The proportions of patients with diarrhoea, rash or pruritus were higher in the clopidogrel group than in the aspirin group**

¹CAPRIE Steering Committee. *Lancet* 1996;348:1329–1339; ²Bogousslavsky J. *Cerebrovasc Dis* 1998;8(Suppl 4):43;

³Lok DJA. *Eur Heart J* 1998;19(Abstract Suppl):52.

Summary – 1

- PAD is a marker of atherosclerosis in the coronary and cerebral arteries
- PAD is often underestimated and underdiagnosed, and requires proper diagnosis:
 - ABPI is a non-invasive, easily performed measurement that reliably predicts ischaemic risk in PAD patients
- Risk factors need to be managed: smoking cessation, regular exercise training
- Antiplatelet therapy is a key component of treatment

Summary – 2

- **Clopidogrel provides increased benefit over aspirin for secondary prevention in atherothrombotic patients, including those with diagnosed PAD**
 - **Reduces the risk of all major events (IS, MI, vascular death)**
 - **Offers better gastrointestinal safety and tolerability in comparison with aspirin**