Hypertension Peripheral artery disease (PAD)

D.L.Clement, Ghent, Belgium

Poor control
of
Hypertension
PAD

Poor control of Hypertension

Guidelines and… Reality

Guidelines and Reality

- **In the past:** Rules of the 50%'s: 12.5% of hypertensives controlled
- **Presently:** see Results of National Health and Nutrition Surveys (JNC 7, 2003)

Blood pressure control:

- in 1976-80: 10%
- in 1988-91: 29%
- in 1991-94: 27%
- in 1999-2000: 34%

Guidelines and Reality

Euroaspire surveys I and II in diabetic and non-diabetic patients with coronary heart disease

- CHD patients (acute MI, ischemia treated with intervention
- Survey II Prevalence data(diabetic/ non-diabetic)
  - Smoking: 17/22%
  - Obesity: 43/23%
  - **Hypertension: 57/49%**
  - Cholesterol: 55/59%

Pyorala et al. Diabetologia: 2004:47:1257-65

Guidelines and Reality

Euroaspire surveys I and II in diabetic and non-diabetic patients with coronary heart disease

Trends in prevalence between Survey I and II:

for both diabetic/ non-diabetic patients:

- Smoking: slight increase
- Obesity: clear increase
- **Hypertension: no decrease!!**
- Cholesterol: decreased (increased use LLdrugs)

Pyorala et al. Diabetologia: 2004:47:1257-65

Kotseva K et al. Atherosclerosis: 2008: 197: 710-7

Guidelines and Reality

Disappointing!!

Means to better control Hypertension

HOME BP

See Guidelines: J.Hypertension: 2008: 26: 1505-26

HOME BP

Arguments Pro

- Cheap,easy
- “normal” conditions
- over several days
- objective documentation of BP

HOME BP

Arguments Contra

- Emotions of/to the patient
- Danger for “autocorrection” of treatment
- No night recordings

HOME BP

Indications

- Evaluation of Isolated office Hypertension (White Coat)
- Evaluation of Masked Hypertension (Reverse White Coat)
- Evaluation of effect antihypertensive therapy in “normal” conditions
- Improving compliance and poor control

Means to better control Hypertension

Control of Total CV risk

2007 Guidelines for the Management of Arterial Hypertension

European Society of Hypertension
European Society of Cardiology

Journal of Hypertension 2007;25:1105-1187

Stratification of risk to quantify prognosis

Other risk factors and disease history	Blood pressure (mmHg) High Normal SBP 130-139 or DBP 85-89
No other risk factors	Average risk
1–2 risk factors	Low added risk
3 or more risk factors or TOD or diabetes	High added risk
ACC	Very High added risk

ACC, associated clinical conditions; TOD, target organ damage; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Stratification of risk to quantify prognosis

	Blood pressure (mmHg)				
Other risk factors & disease history	Normal SBP 120-129 or DBP 80-84	High Normal SBP 130-139 or DBP 85-89	Grade 1 SBP 140-159 or DBP 90-99	Grade 2 SBP 160-179 or DBP 100-109	Grade 3 SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very High added risk
3 or more risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very High added risk
ACC	High added risk	Very High added risk	Very High added risk	Very High added risk	Very High added risk

ACC, associated clinical conditions; TOD, target organ damage; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Means to better control Hypertension

Better antihypertensive drugs?

Better antihypertensive drugs?

Aliskiren

Aliskiren

Oral Direct Renin inhibitor

Angiotensinogen to Angiotensin I: Renin (Renin inhibitors: Aliskiren)

Angiotensin I to Angiotensin II: ACE (ACE inhibitors)

Angiotensin II to Receptor: ARB (sartans)

Aliskiren

Aliskiren combined to Losartan in type 2 diabetes nephropathy

NEJM 2008:358:2433-2446

599 patients with diabetes nephropathy

All received Losartan 100 mg/

Aliskiren or placebo added double blind, randomly

Aliskiren reduced albumin to creatinin ration by 20% ($p<0.001$)

Renal effect independent of BP effect

Aliskiren

Aliskiren combined to Losartan in type 2 diabetes nephropathy

NEJM 2008:358:2433-2446

Message:

We have a new BP lowering drug

Acting on RAA axis

Effect independent of BP lowering

Better antihypertensive drugs?

SARTANS

Angiotensinogen to Angiotensin I: Renin (Renin inhibitors: Aliskiren)

Angiotensin I to Angiotensin II: ACE (ACE inhibitors)

Angiotensin II to Receptor: ARB (sartans)

Means to better control Hypertension

Telmisartan

Means to better control Hypertension

ONTARGET

NEJM: 2008: 358:1547-1559

25620 patients; Hypertensives?

3 weeks Run in; double-blind randomisation to ramipril, telmisartan, combination of these

Goal: non inferiority of Telmisartan, superiority of Telmisartan, combination more effective

Follow-up: end of the study (median 56 months) or occurence of first primary event

Means to better control Hypertension

ONTARGET

NEJM: 2008: 358:1547-1559

Event rates (%)

Ramipril (n=8576): 16.5 %

Telmisartan (n=8542): 16.7 %

Combination (n=8502): 16.3 %

Less cough rate (1.1% vs. 4.2%) and angioedema (0.1 vs. 0.3%) with Telmisartan alone

Means to better control Hypertension

ONTARGET

NEJM: 2008: 358:1547-1559

Messages

Proven antihypertensive effect

Telmisartan not inferior

But not superior to Ramipril

except for Cough (and hypotensive episodes)

Combination not superior and more side effects

Means to better control Hypertension

ONTARGET

The Lancet: 2008: 372:547-53

In the combination arm:

At median follow up of 56 months:

The composite end point of dialysis, doubling of creatinin, and death occured in:

Ramipril alone: 13.5%

Telmisartan alone: 13.4%

Combination: 14.5% (p<0.037)

Is the polypill the solution?

Position statement: Choice of antihypertensive drugs

- Emphasis on identifying the first class of drugs to be used is probably outdated by the need to **use two or more drugs in combination** in order to achieve goal blood pressure (2003).
- Combination therapy should be preferred when BP is grade 2 or 3 or total CV risk high (2007)
- Fixed combinations can simplify tretament and favour compliance (2007)

On average, 2–3 antihypertensive agents needed to achieve target BP

	LIFE	ABCD	HOT	UKPDS
Goal blood pressure	<90 mmHg DBP	<75 mmHg DBP	<80 mmHg DBP	<85 mmHg DBP
Achieved blood pressure	~81	~75	81	82
Average number of drugs per patient	2.3	2.7	3.3	2.8

Definition

The polypill is a fixed-dose combination containing three or more drugs in a single pill

From where comes the idea?

A strategy to reduce cardiovascular disease by more than 80%

by

NJ Wald and MR Law

BMJ: 2003: 326:1419-1428

From where comes the idea?

Design: quantification of efficacy and adverse effects of the polypill from published meta-analysis of randomided studies

Formulation: a statin, 3 BD lowering drugs (a thiazide, an ACE inhibitor, a beta blocker), folic acid, aspirine (75 mg)

Conclusion: The polypill could largely prevent heart attacks and stroke if taken by everyone aged 55 and older and everyone with existing CV disease. ***(Wald and Law, 2003)***

Main lines of questioning

Giving the polypill to everyone above 55? i.e. without checking the risk factor profile?

Before doing so, we need objective evidence

...

Is the polypill a solution?
YES!

- Practical solution for combination therapy
- Solution to control BP better, also when target BP is lower (diabetes, renal disease, maybe PAD…)
- Solution for the compliance problem (more drugs, less compliance)

Is the polypill a solution?
YES!

- Solution for mistakes in drug intake: identity of the drugs, doses…(elderly, others…)
- Solution to act on different risk factors (total CV risk) such as BP, atherosclerosis etc. Solution for getting at target quicker (see VALUE trial)
- Solution to get a target BP quicker (see VALUE trial)
- …..

Is the polypill a solution?
NO!

- **No possibilities anymore for titration of individual drug doses (still: see concept of present drug combinations; consider possibility of different polypills…)**
- **Physicians (patients alike) do no longer fully "see" the content of a pill (cave side effects: aspirine, beta blockers …)**
- **Registerability of the polypill: what studies will be needed?**
- ….

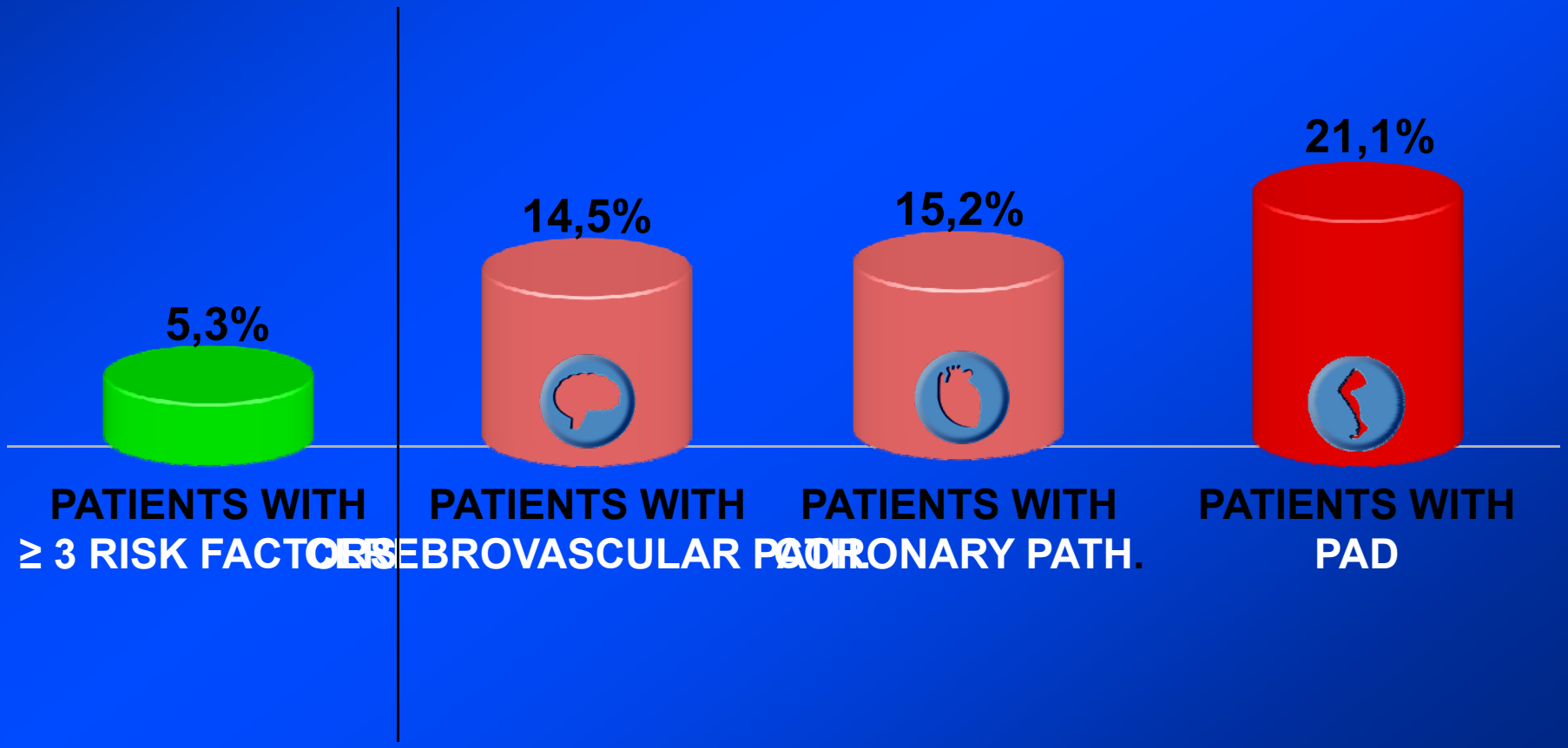
Poor control
of
PAD

Developments in PAD: TASC II guidelines

TASC II Inter-society consensus for the management of PAD, 2007.
J.Vasc.Surgery: 2007:45:S1-S68
Eur. J. Vasc.Endovasc. Surgery: 2007:33: suppl.1: S1-S70
Int. Angiology: 2007: 26: 81-157

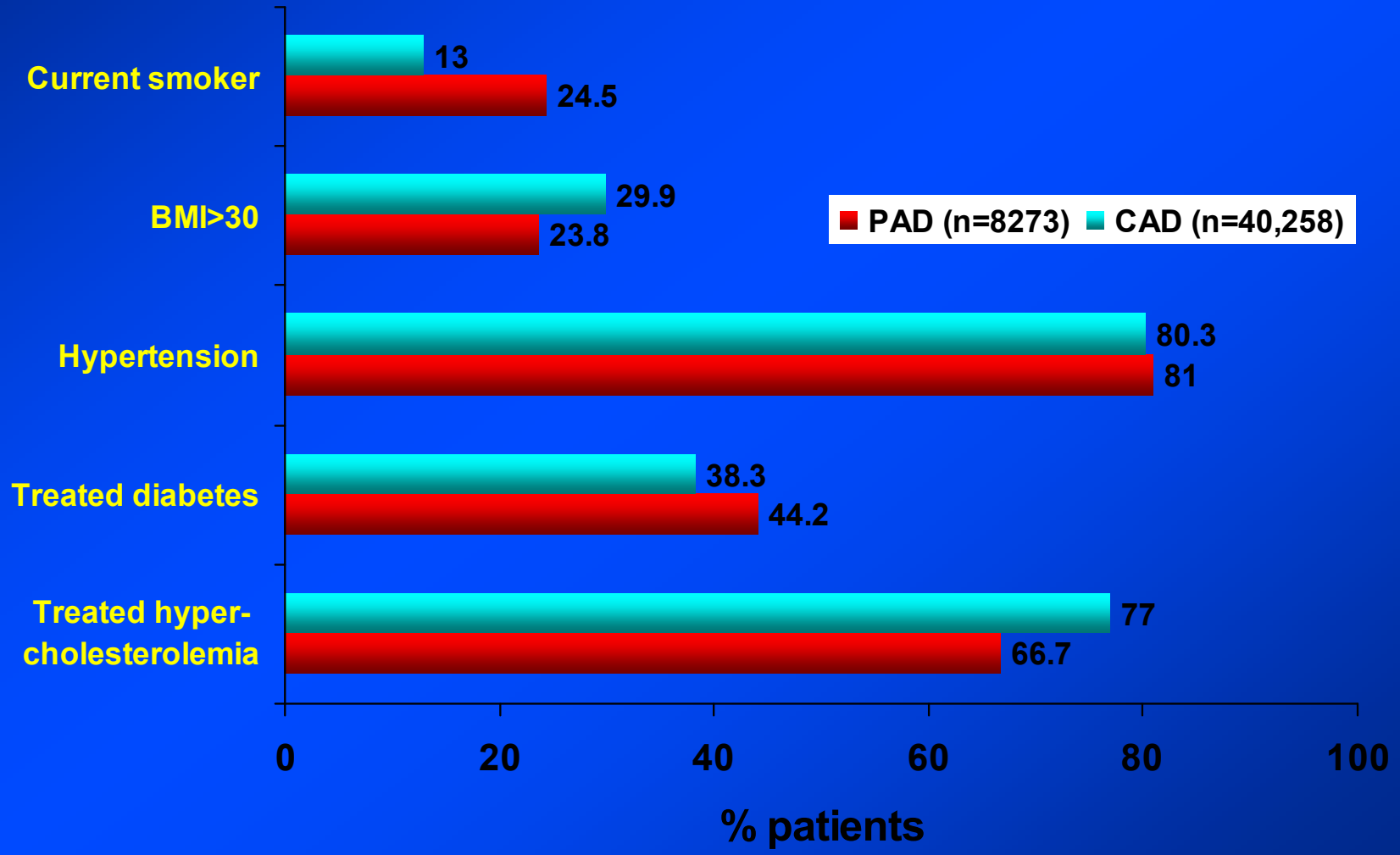
CV Morbidity and Mortality at 1 year

Cumulative risk of cardiovascular mortality, myocardial infarction, CVA and hospitalization after 1 year follow-up



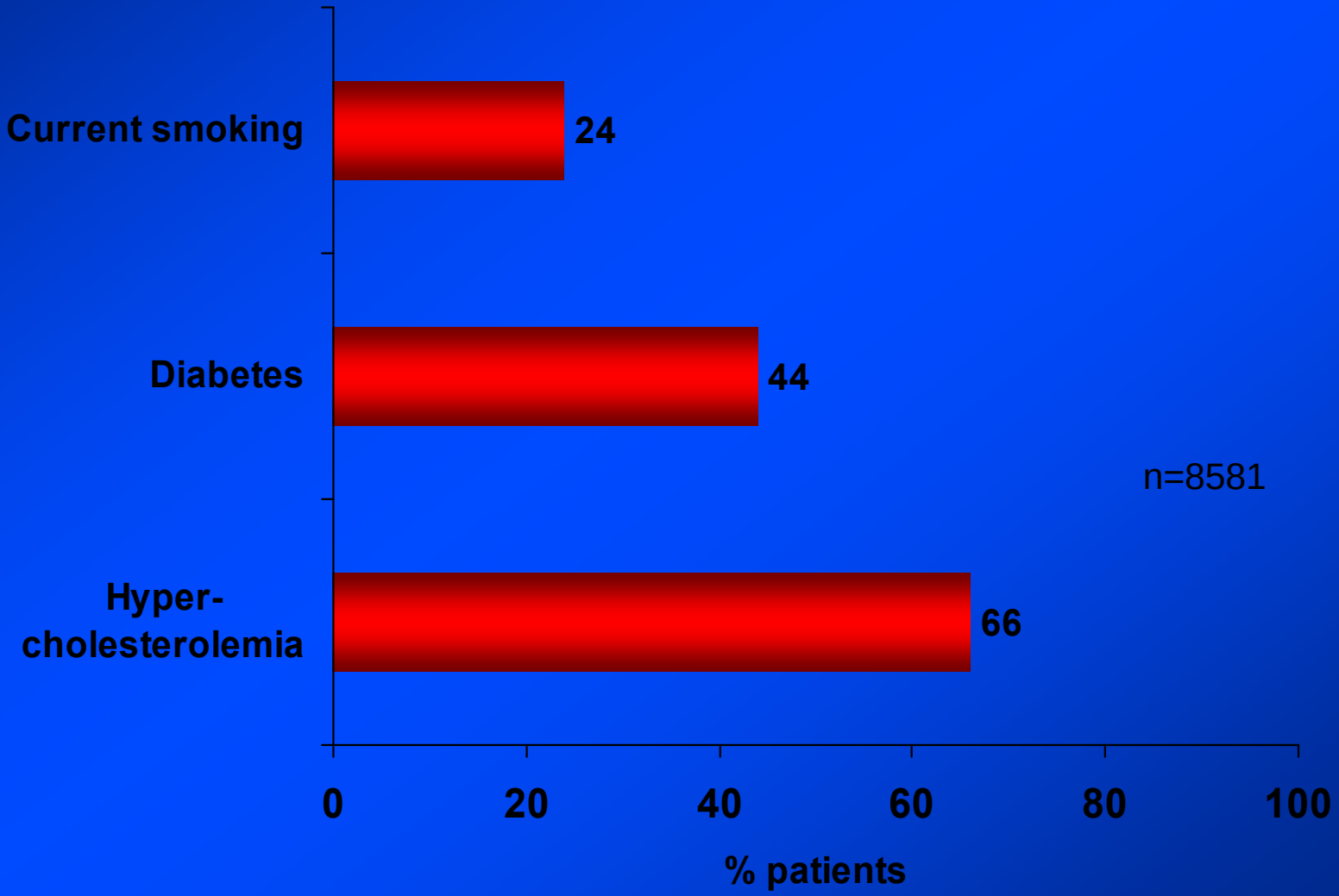
Steg et al. *JAMA*. 2007; 297: 1197-120

REACH at baseline: risk factors are prevalent in PAD and CAD patients



Bhatt et al. JAMA 2006;295:180

REACH at 2 years: risk factors remain prevalent in PAD patients



Hirsch et al. Eur Heart J 2007;28: Suppl 757

Quality of Life in PAD

Regensteiner et al. (Partners Study)

Vascular Medicine: 2008: 13:15-24

Compared 4 QoL scales in patients with PAD to patients with other CVD

Performed in 350 primary care practices; 6.499 participants

Conclusions: the burden on QoL linked to PAD is comparable to the burden linked to other CVD (like angina pectoris)

Identifying PAD

- The classical symptom is intermittent claudication
- But the majority of patients are asymptomatic
- Or present with atypical symptoms

1. McDermott MM et al. JAMA 2001;286:1599–1606.
2. Hirsch AT et al. J Am Coll Cardiol 2006;47:1239–1312.

Interpretation of the ABI

ABI	Interpretation
1.00–1.29	Normal
0.91–0.99	Equivocal
0.41–0.90	Mild-to-moderate PAD
0.0–0.40	Severe PAD

Interpretation of the ABI

ABI	Interpretation
1.00–1.29	Normal
0.90–lower	Abnormal
1.30 or higher	High

Prevalence of low ABI

Price et al (Scotland Study)

Eur. J. CV Prev Rehabilitation: 2008: 15:370-5

Prevalence of low ABI at 0.9 or lower

Performed in 28 890 subjects, above 50, general population

Results: A total of 10.9% had low ABI

More in women than in man!

Increased with age

Increased in lower social class

Technical issues on low ABI

- Pulse palpation nor automatic oscillometric devices can replace the Doppler device (Aboyans et al. 2008)
- Perform each measurement at least twice (and average them?) (Espeland et al . 2008)
- If pressures in both foot arteries are different, wich one to take: the highest or the lowest?

Technical issues on low ABI

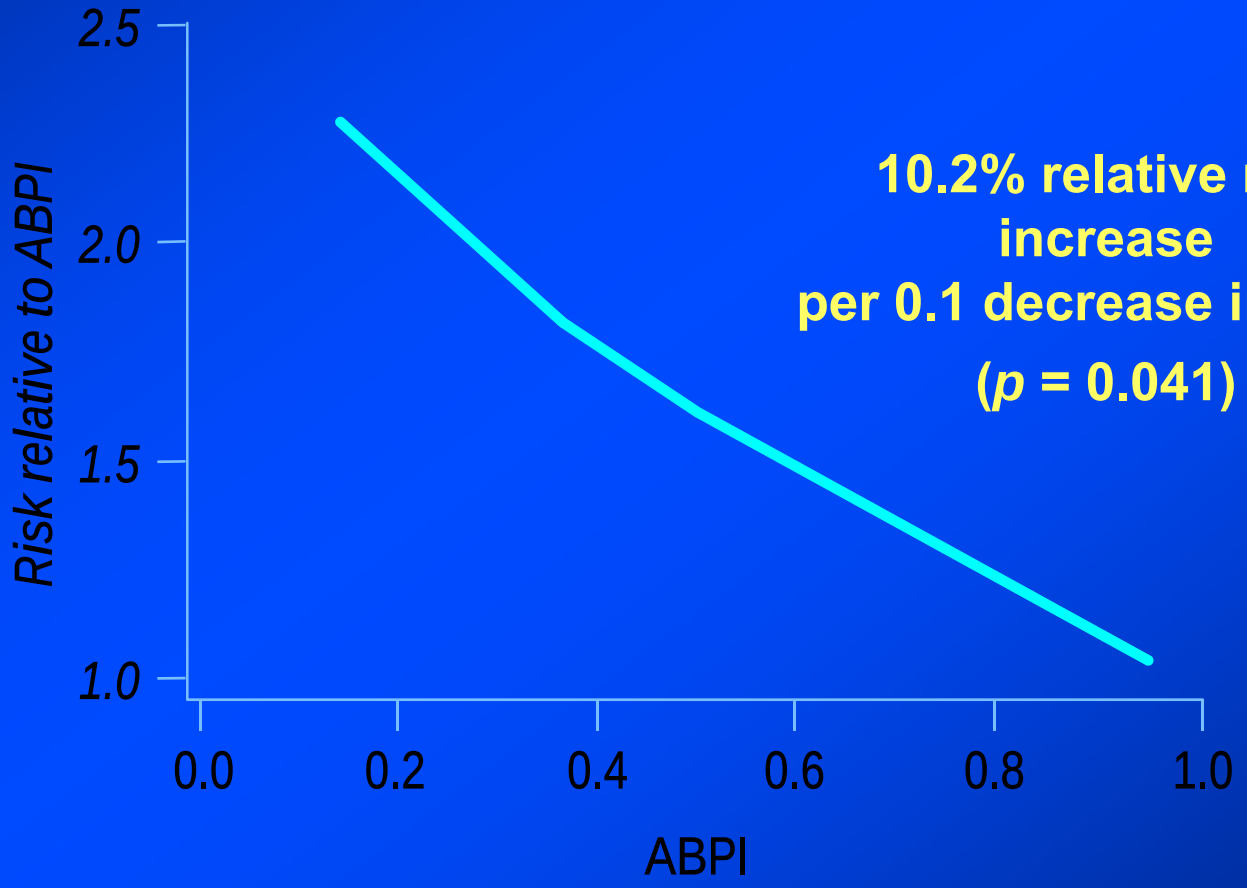
getABI study group (C.Diehm)

- Prevalence almost doubled if lowest value is taken
- Highest value gives total inflow in the foot, but will understimate PAD frequency
- Lowest value informs better on a local vascular problem but is technically more difficult (less accurate)

(Espinola-Klein et al. Circulation: 2008)

- No proof that these differences matter on long term prognosis: all are high risk compared to normal ABI

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



Dormandy JA, Creager MA. Cerebrovasc Dis 1999;9(Suppl 1):1–128 (Abstr 4).

Low ABI combined with Framingham risk scores

Fowkes et al. (JAMA: 2008: 197-208)

- Metaanalysis on 16 published papers
  - 24955 men and 23339 women
  - 480325 person-years follow up

Low ABI combined with Framingham risk scores

Fowkes et al. (JAMA: 2008: 197-208)

Results: Low ABI significantly increases risk

- 10 y CV mortality in men (low versus normal): 18.7% versus 4.4%; in women: 12.6% versus 4.1%
- Low ABI doubles the risk for CV mortality and major coronary event in each class of Framingham score

Conclusion: ABI improves accuracy of risk prediction beyond Framingham scores

High ABI and prognosis

Sutton-Tyrell K et al Stroke: 2008: march: 39:863-9

Allison MA et al. JACC: 2008: Apr.:51:1292-8

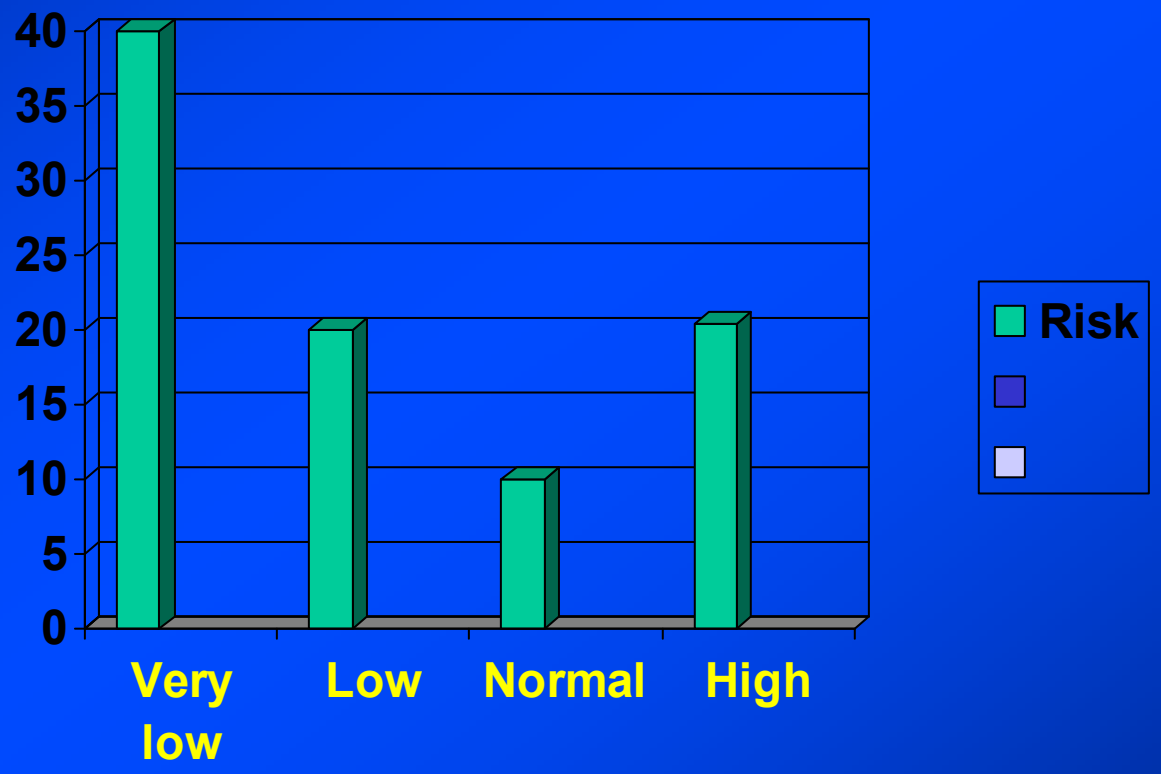
Suomen V et al. Eur. J.Vasc. Endovasc. Surgery: 2008:jun.: 35: 709-14

High ABI and prognosis

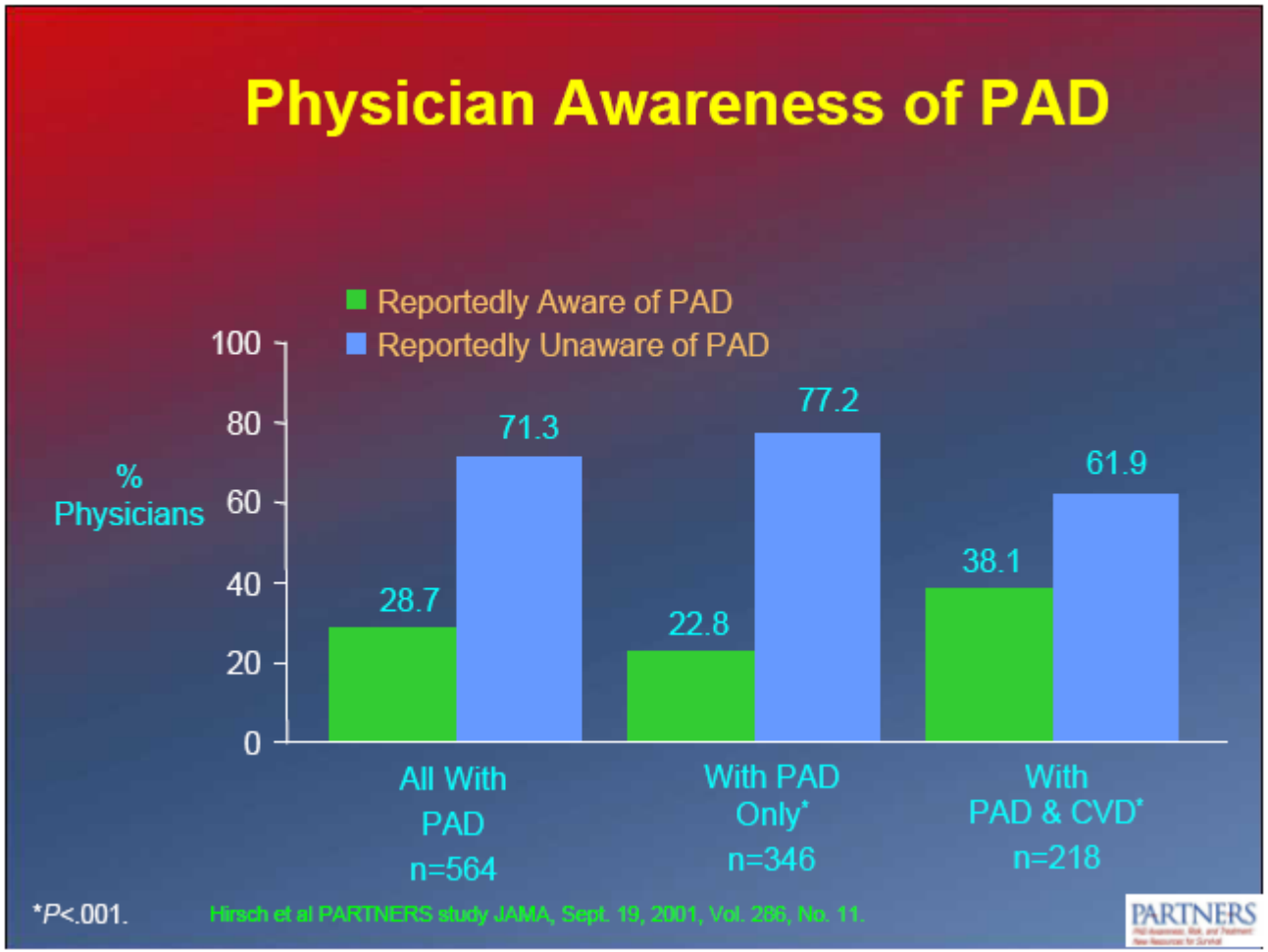
In older adults, low and high ABI carry elevated risk for CV events…stroke and heart failure (Sutton-Tyrell K et al)

Higher ABI increases risk for foot ulcers and neuropathy and decreases QoL (Allison MA et al.)

ABI and cardiovascular risk



Physician Awareness of PAD



*P<.001.

Hirsch et al PARTNERS study JAMA, Sept. 19, 2001, Vol. 286, No. 11.

PARTNERS

Summary: TASC II recommendations for risk factor modification

- Lifestyle modification
  - Smoking cessation
  - Weight reduction
- Lipid control
  - PAD (no ACS): LDL <2.59 mmol/L (<100 mg/dL)
  - PAD (and history of ACS): LDL <1.8 mmol/L (<70 mg/dL)
- Blood pressure control
  - PAD (no diabetes or renal insufficiency): <140/90 mm Hg
  - PAD (with diabetes or renal insufficiency): <130/80 mm Hg
- Glycemic control
  - HbA_{1c} <7.0%
- All PAD patients should receive an antiplatelet agent (aspirin or clopidogrel)

Norgren L, Hiatt WR (eds) et al. Eur J Vasc Endovasc Surg 2007;33(Suppl 1):S1

TASC II recommendations on antiplatelet therapy in PAD

- **All symptomatic patients with or without a history of other CV disease should be prescribed an antiplatelet drug to reduce the risk of CV morbidity and mortality [A]**
- **The use of aspirin in patients with PAD who do not have clinical evidence of other forms of CV disease can be considered [C]**
- **Clopidogrel is effective in reducing CV events in patients with symptomatic PAD, with or without other clinical evidence of CV disease [B]**

Norgren et al. Eur J Vasc Endovasc Surg 2007;33(Suppl. 1):S1

PAD - Hypertension: undertreated

- Recent data show (Reach Register):
- Less than 25% of PAD patients get any treatment
- Undertreatment with antiplatelets and statins is common
- Less than 46% had any risk factor control
- Less than 28% had full risk factor control

PAD - Hypertension: a similar problem

- **Both are pressure related**
- **Both carry a high risk**
- **Both are under diagnosed**
- **Both are under treated**

Poor control
of
Hypertension
PAD

Hypertension Peripheral artery disease (PAD)

D.L.Clement, Ghent, Belgium

Quality of Life in PAD

Regensteiner et al. (Partners Study)

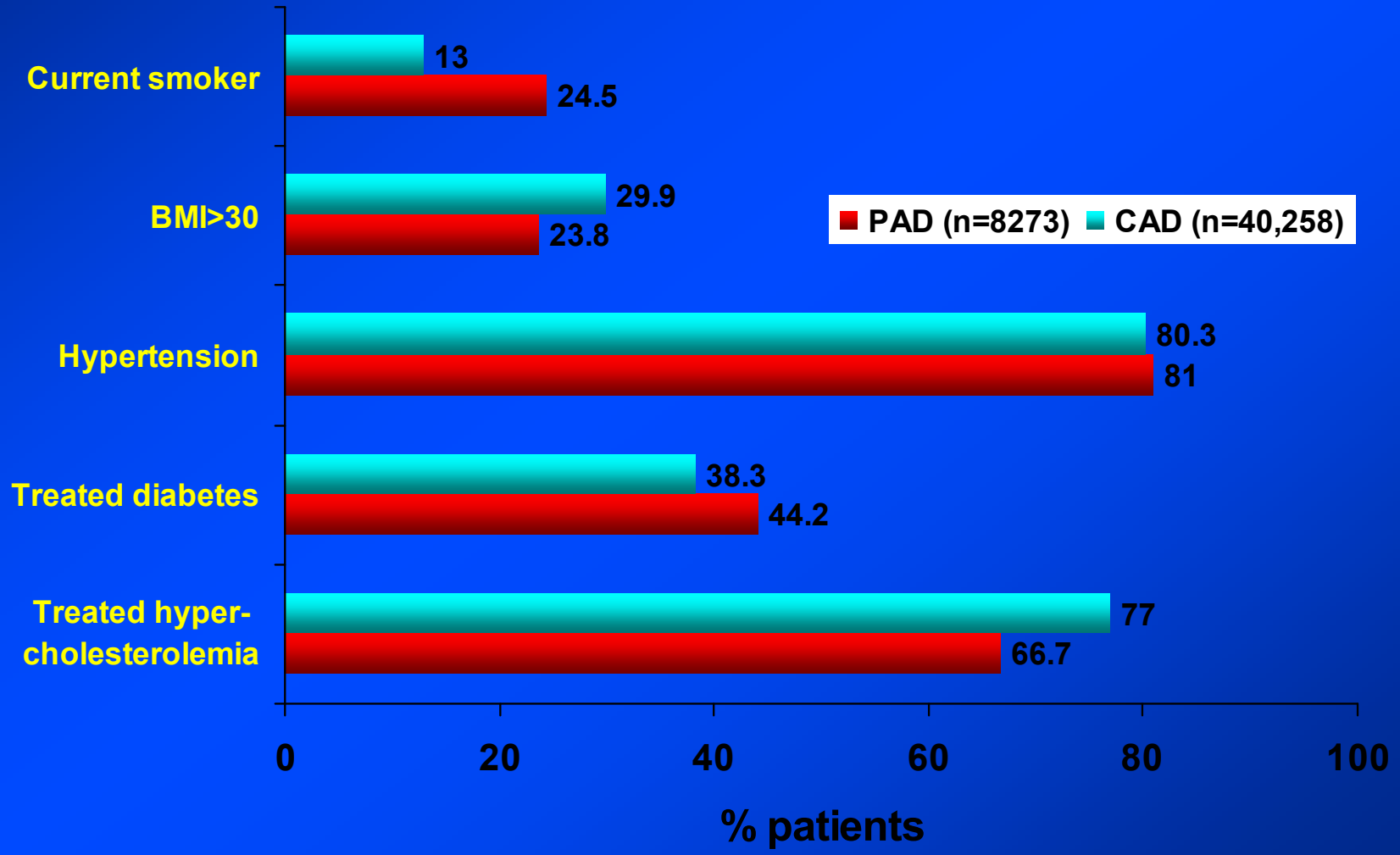
Vascular Medicine: 2008: 13:15-24

Compared 4 QoL scales in patients with PAD to patients with other CVD

Performed in 350 primary care practices; 6.499 participants

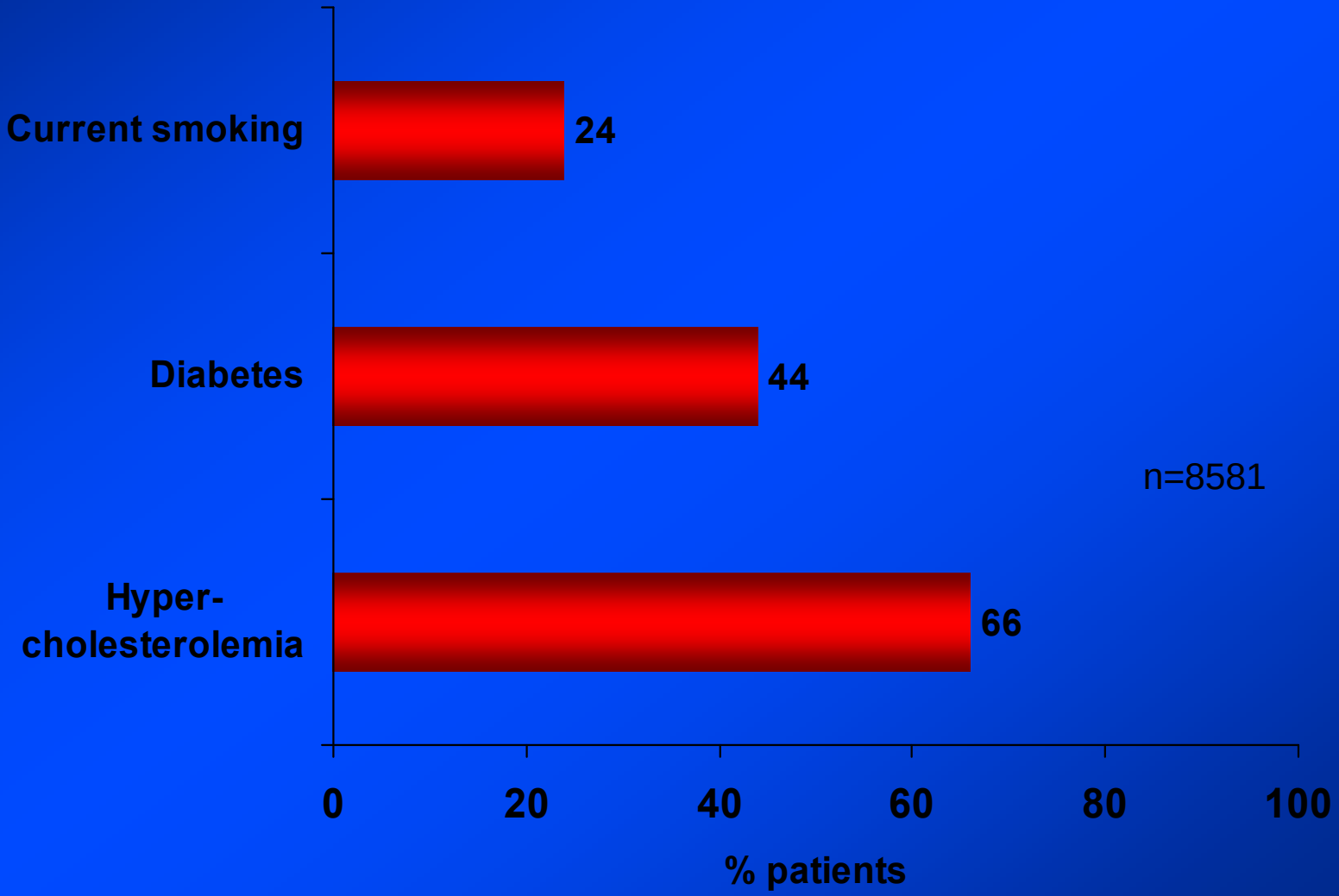
Conclusions: the burden on QoL linked to PAD is comparable to the burden linked to other CVD (like angina pectoris)

REACH at baseline: risk factors are prevalent in PAD and CAD patients



Bhatt et al. JAMA 2006;295:180

REACH at 2 years: risk factors remain prevalent in PAD patients



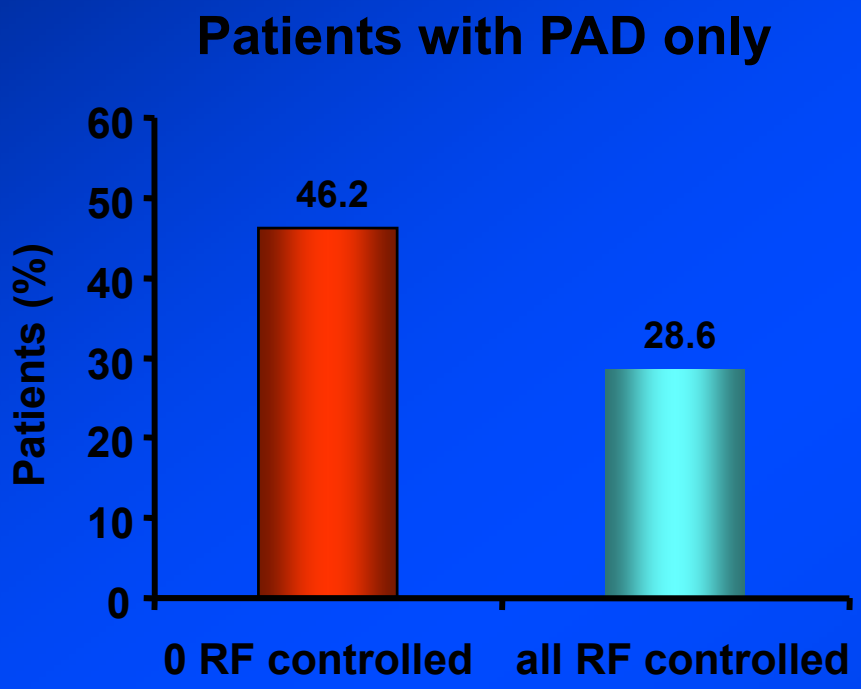
Hirsch et al. Eur Heart J 2007;28: Suppl 757

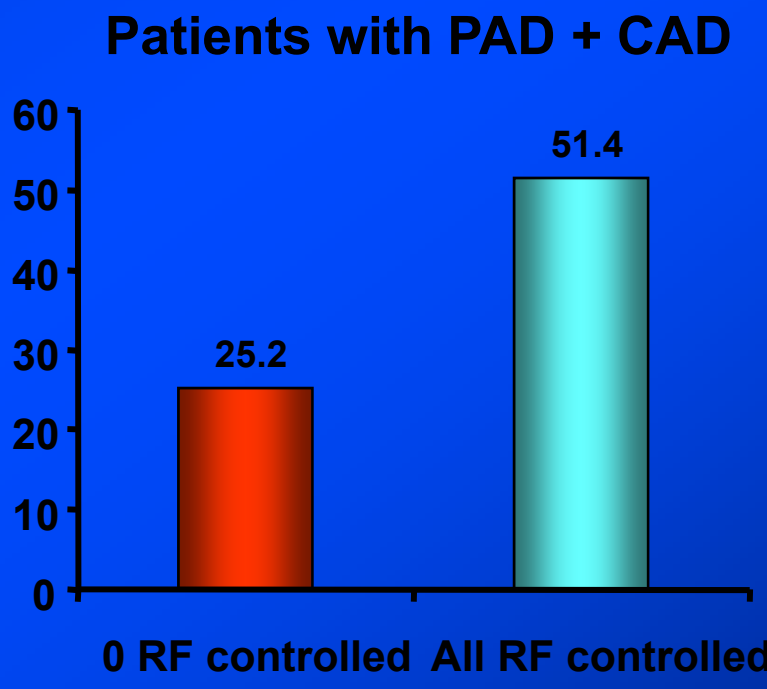
HOME BP

Indications

- Evaluation of Isolated office Hypertension (White Coat)
- Evaluation of Masked Hypertension (Reverse White Coat)
- Evaluation of effect antihypertensive therapy in “normal” conditions
- Improving compliance and poor control

Control* of CV risk factors: PAD only vs. PAD + CAD

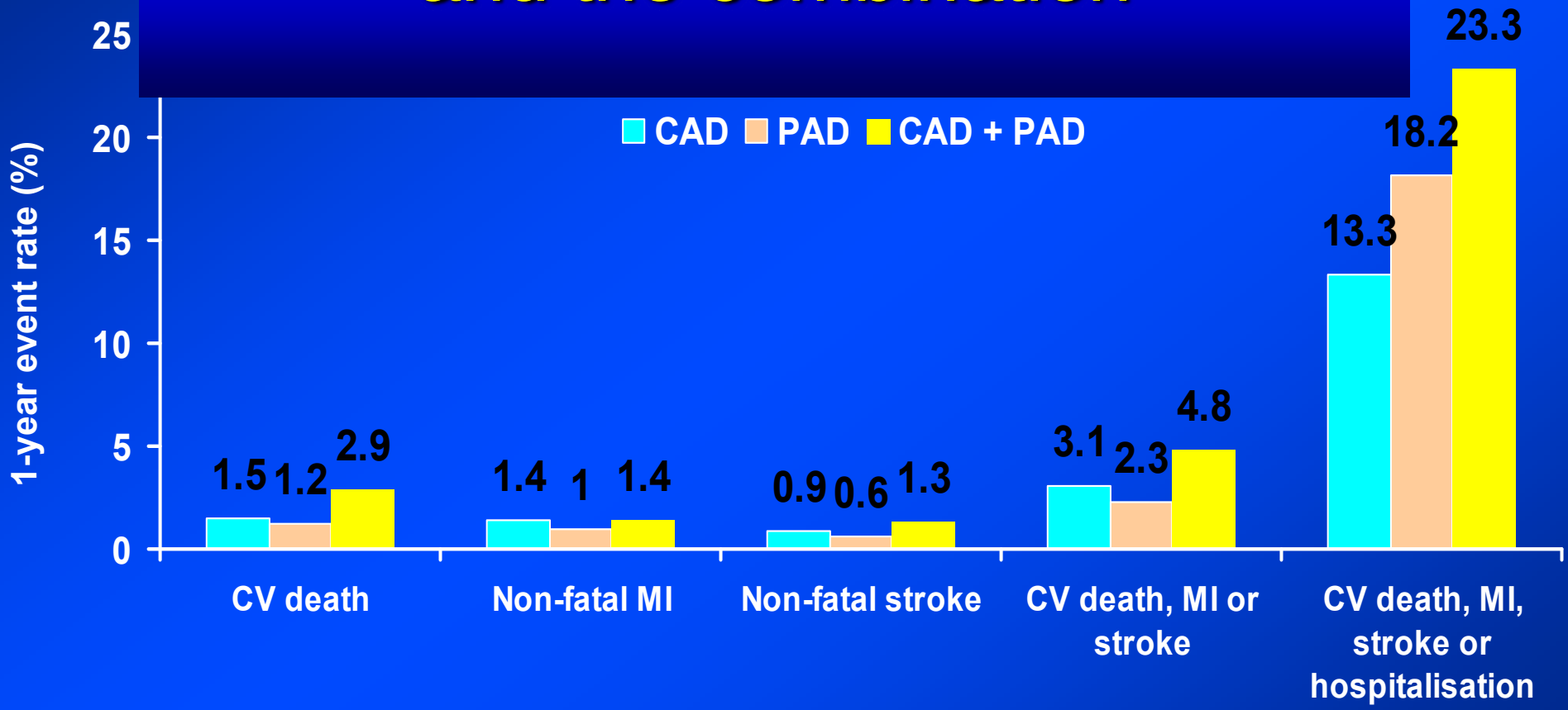




* systolic BP <140 mmHg, diastolic BD <90 mmHg, glycemia <7 mmol/l (<126mg/dL), total cholesterol <5.18 mmol/L (<200mg/dL), non-smoking >12 months

Cacoub P et al. AHA 2006, Abstract 4022

REACH: Patients with CAD, PAD and the combination



*TIA, UA, other ischaemic arterial event including worsening of PAD

CAD, coronary artery disease; REACH, Reduction of Atherothrombosis for Continued Health; TIA, transient ischaemic attack; UA unstable angina

Steg PG et al. 55th Annual Scientific Session of the ACC, 2006. Available at: http://acc06online.acc.org/Lectures.aspx?sessionId=30&date=12. Accessed 28/06/06.

TASC II recommendations: treatment of claudication

Drugs with proven favourable effect on claudication

A three- to six-month course of:

- **Cilostazol**
- **Naftidrofuryl**