

# Peripheral vascular disease and stroke

# PVD in diabetic patients - epidemiology and symptoms

- Subjects with diabetes have a two to four-fold increase in the incidence of peripheral vascular disease
- An abnormal ankle-brachial blood pressure index is present in approximately 15% of such patients
- Peripheral neuropathy may mask the symptoms of limb ischemia

# Investigations of the peripheral circulation in diabetic patients

## A. At the physicians office in every patient

### ■ Inspection

Pallor with elevation

Dependent rubor

Absence of hair growth

Dystrophic toenails

Ulcers or gangrenes

### ■ Palpation

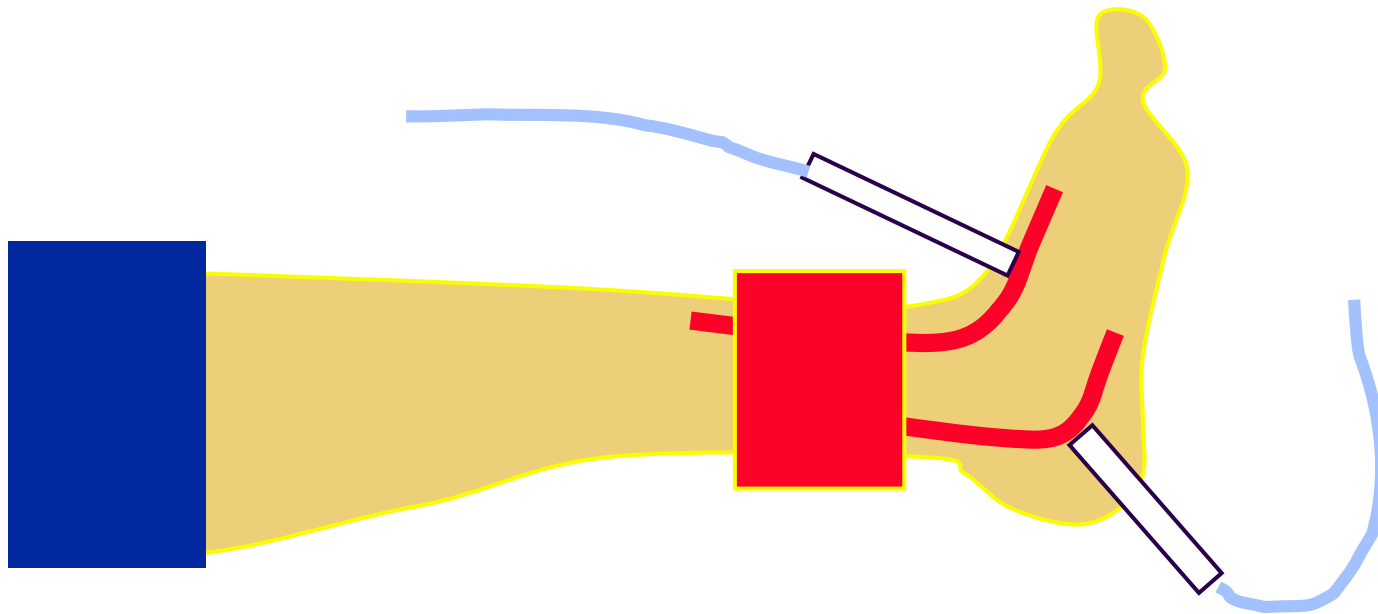
Pulses

Dry and cool skin

Sensibility

### ■ Pressure measurement ankle and arm blood pressure



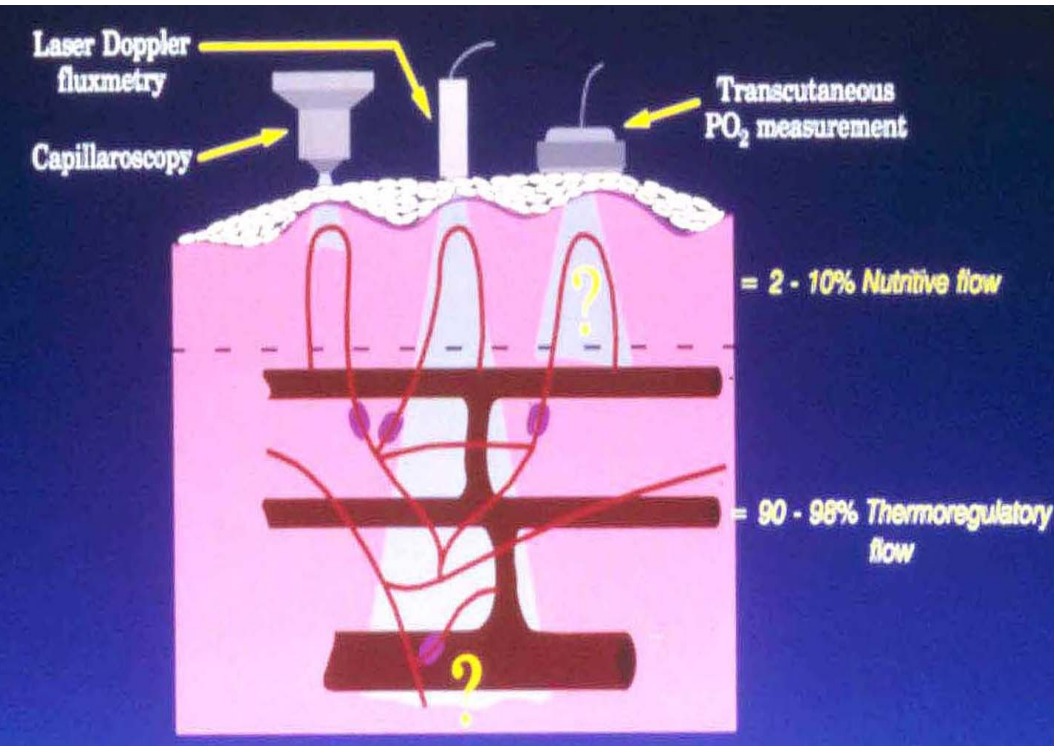


Measurement of blood pressure at the ankle level. A Doppler device is used to detect pulses in the posterior tibial artery and the dorsal pedal artery while slowly deflating the cuff around the ankle. The highest pressure recorded in the artery is the ankle pressure.

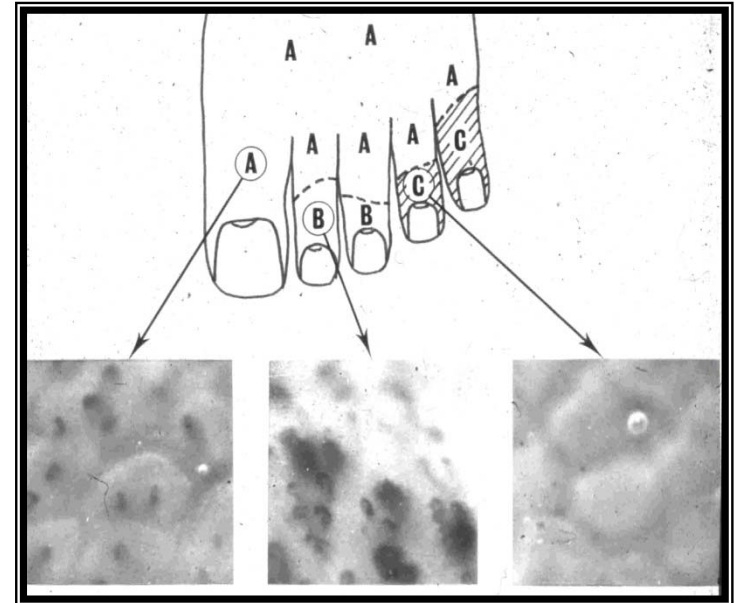
# Investigations of the peripheral circulation in diabetic patients

- B. At the vascular laboratory when appropriate
- Distal and/or segmental pressure measurements
  - Oscillography
  - Treadmill testing (with or without distal pressure after exercise)
  - Duplex sonography
  - *For evaluation of the microcirculation*
    - Transcutaneous oxygen pressure
    - Vital capillaroscopy

# Microcirculatory investigations



## Capillaroscopy



St A

St B

St C

# Investigations of the peripheral circulation in diabetic patients

## C. At the radiology department

- Magnetic resonance imaging
- Angiography



# Revascularisation

In all patients with CLI if possible

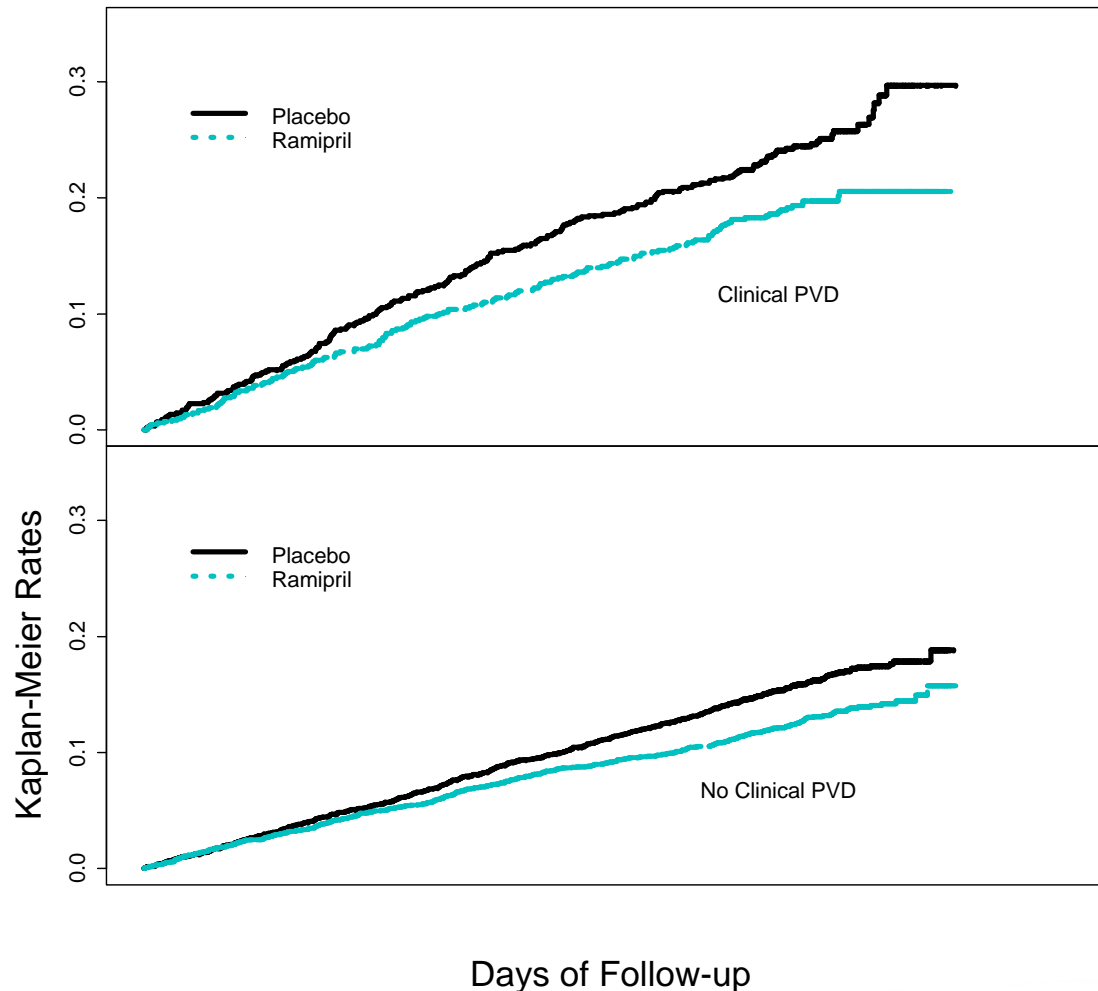
PTA, thrombolysis (with extraction) or surgery

Medical treatment

Anticoagulants and prostacyclin



# Primary outcome (CV-death, stroke and MI) in different PAD categories with and without ramipril in the HOPE-study



(Östergren et al, Eur Heart J, 2003)

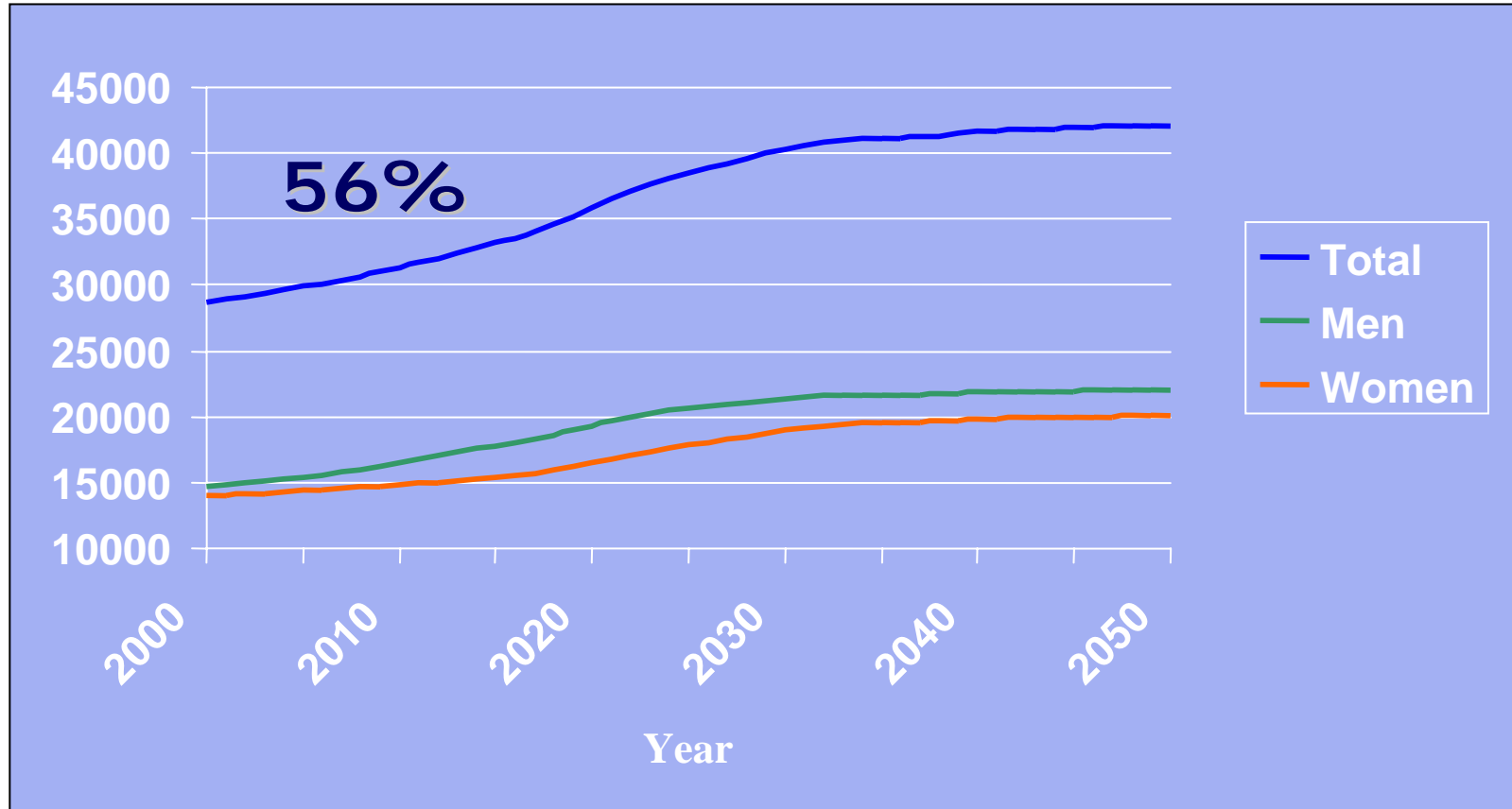
# Peripheral vascular disease

Recommendation	Class	Level
All patients with type 2 diabetes and CVD are recommended treatment with low-dose aspirin.	IIa	B
In diabetic patients with peripheral vascular disease, treatment with clopidogrel or low molecular weight heparin may be considered in certain cases.	IIb	B
Patients with critical limb ischaemia should, if possible, undergo revascularization procedures .	I	B
An alternative treatment for patients with critical limb ischaemia, not suited for revascularization, is prostacyclin infusion.	I	A

# Stroke in diabetic patients

- The relative risk for stroke is increased in subjects with diabetes by a factor 2.5-4.1 for men and 3.6-5.8 for women)
- Diabetes is a strong independent risk factor for stroke
- Diabetic complications such as proteinuria, retinopathy and autonomic neuropathy further increase the risk for stroke
- The type of stroke is usually ischemic and the ratio between ischemic and hemorrhagic stroke is higher in diabetic subjects than in the general population
- The presence of transient ischemic attacks (TIA) predicted occurrence of a stroke within 90 days, thus underlining the severity of TIA especially in diabetic patients

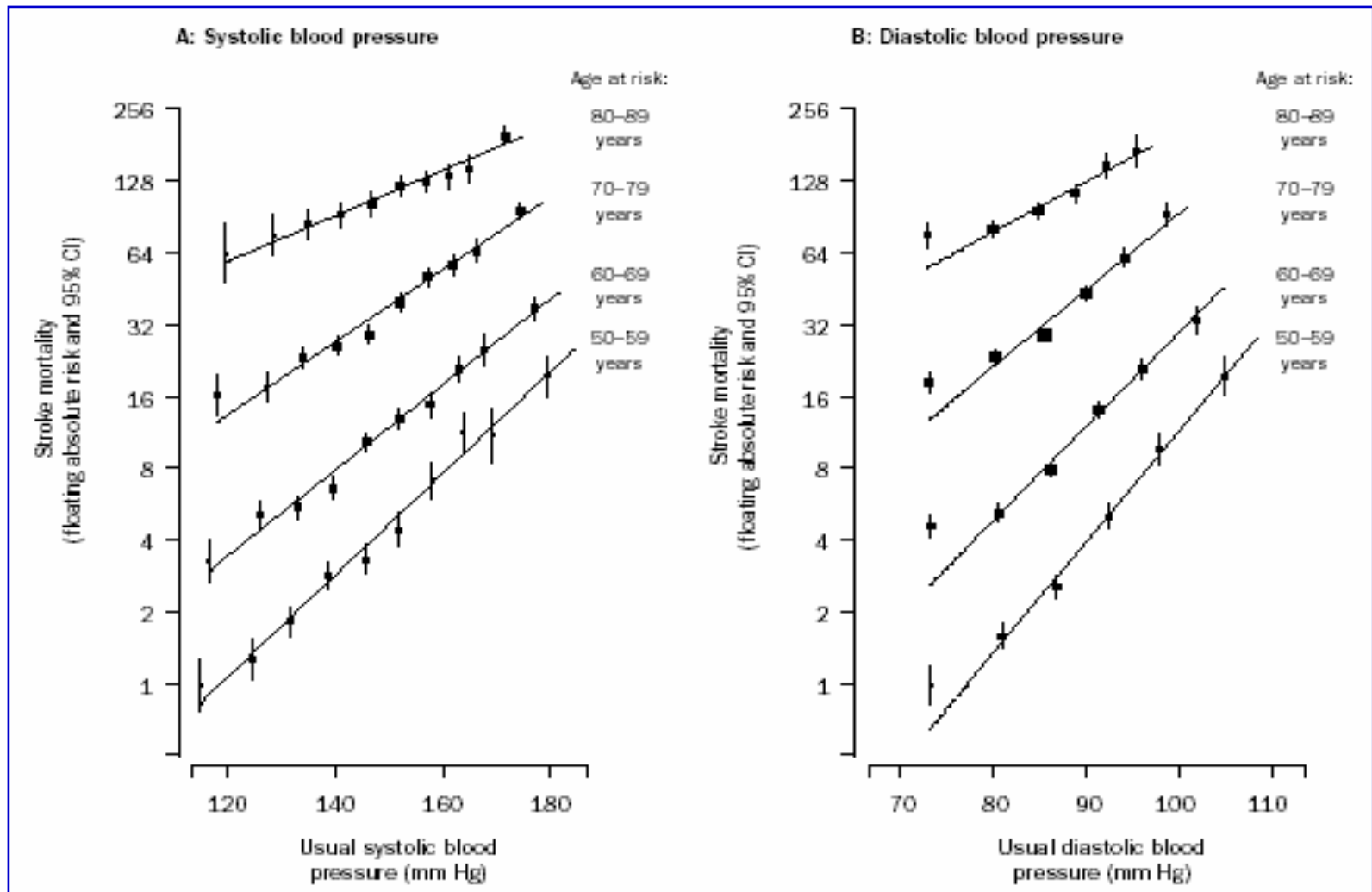
# Primary prevention is needed: Estimated incidence of first stroke in Sweden 2000-2050



# Modifiable risk factors for stroke

Risk factor	Importance	Effects of intervention
Hypertension	Risk increases exponentially with both syst and diast blood pressure	>50% risk reduction if DBT is lowered by 10 mm Hg
Hyperlipidemia	High LDL-C and low HDL-C increase risk moderately	Statins decrease risk by 20-40%
Atrial fibrillation	3-5 times increase in risk	Platelets and anticoagulants reduce risk by 20 and 60%
Diabetes	2-6 times increase in risk	Reduced risk with BP control and with statin treatment
Smoking	1,5-3 times increase in risk	Positive effects of smoking cessation within 1-2 years

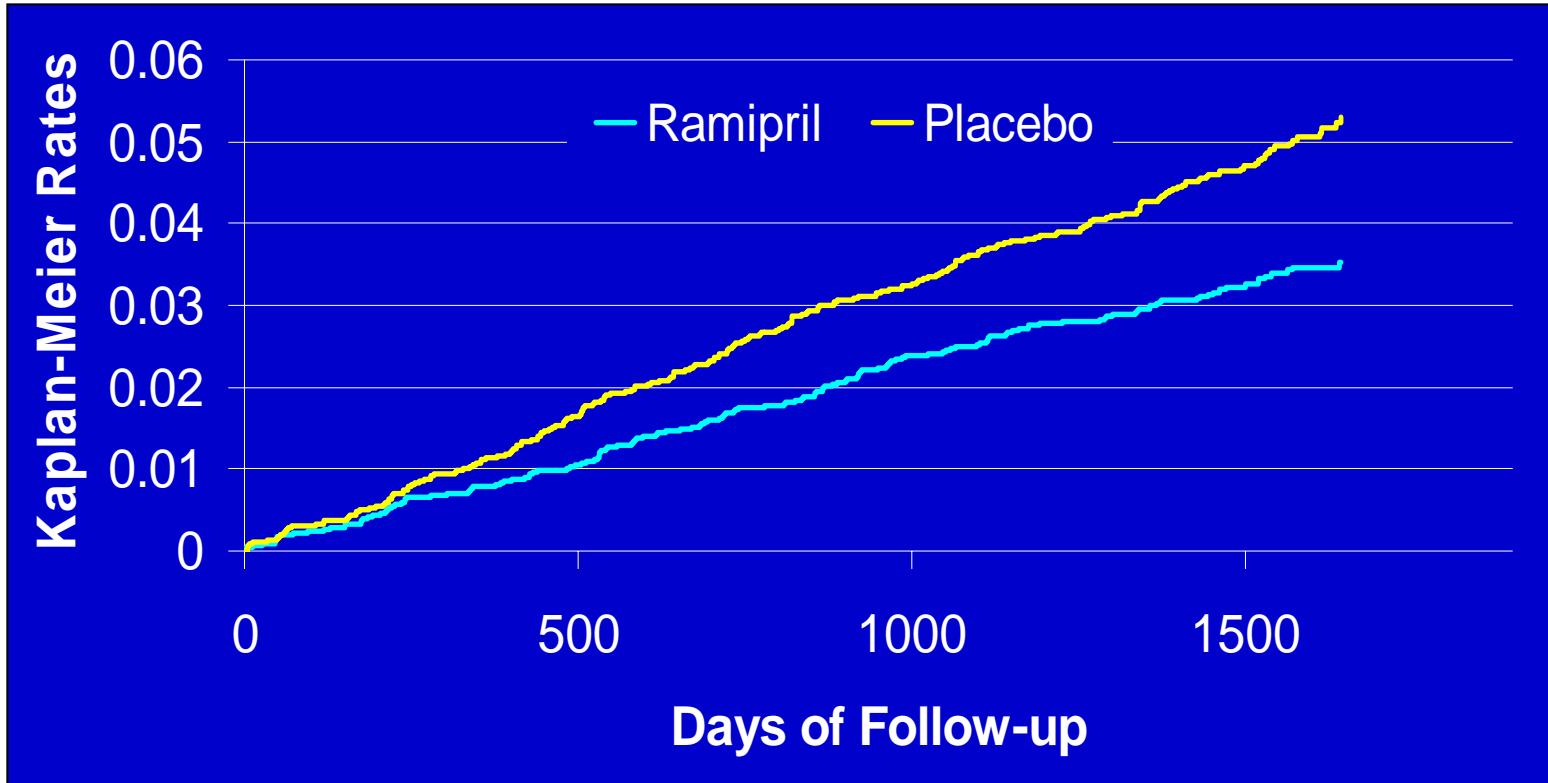
# Stroke mortality and blood pressure



# Effects beyond blood pressure?

The case for inhibition of the RAAS  
(renin-angiotensin-aldosterone-system)

# Stroke incidence in HOPE; ramipril target dose 10 mg od vs placebo

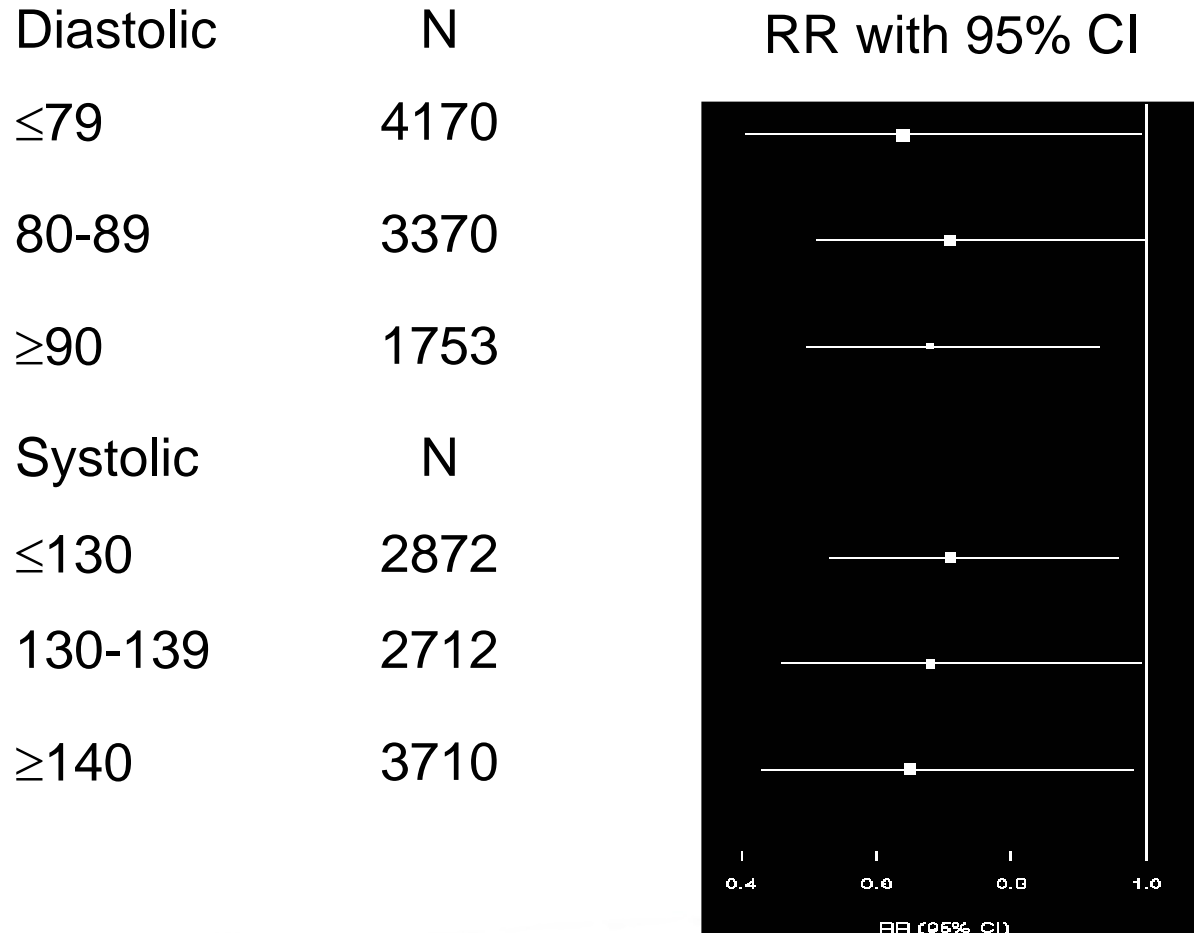


RR=0.68 (0.56-0.84)

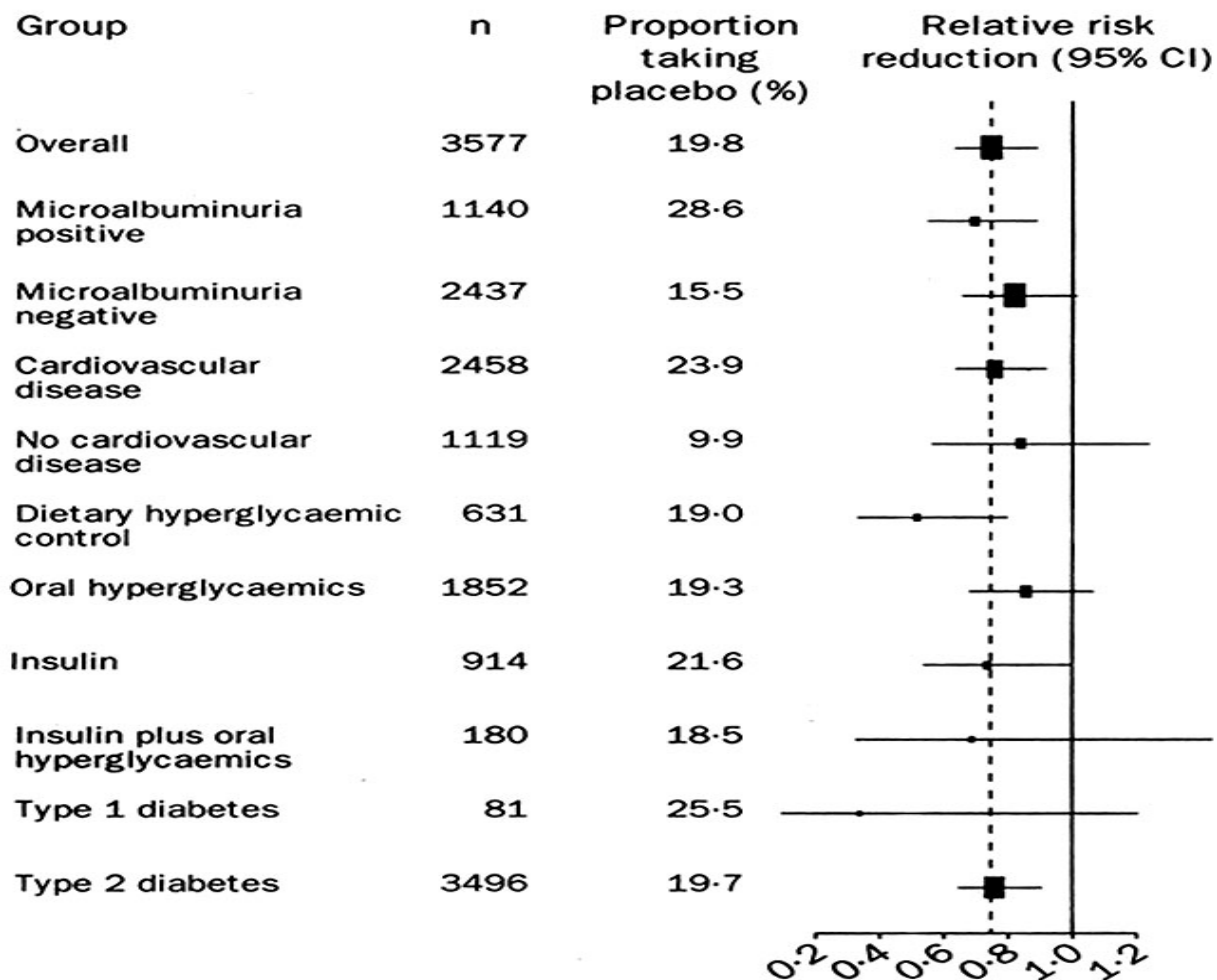
P=0.0002

(HOPE study investigators, NEJM, 2000)

# HOPE: Result in different categories of blood pressure: Stroke



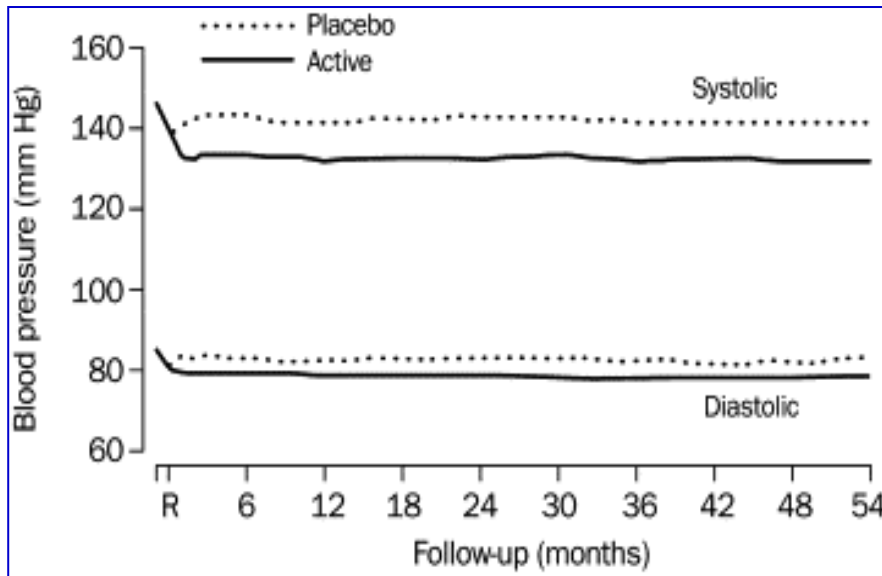
# HOPE-study; results in diabetic subgroups



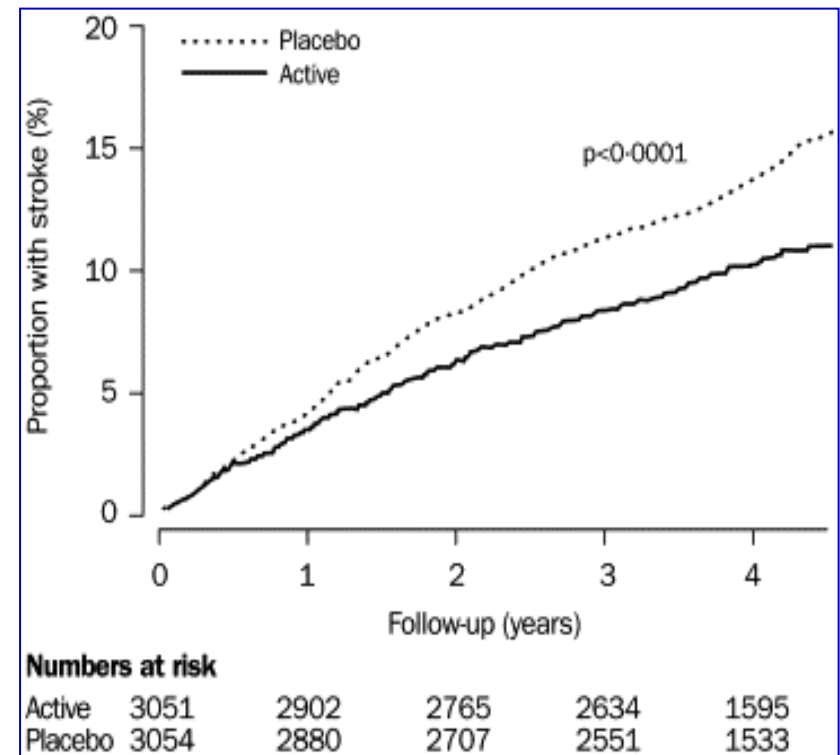
# PROGRESS

– further bp-lowering by indapamide and perindopril after stroke

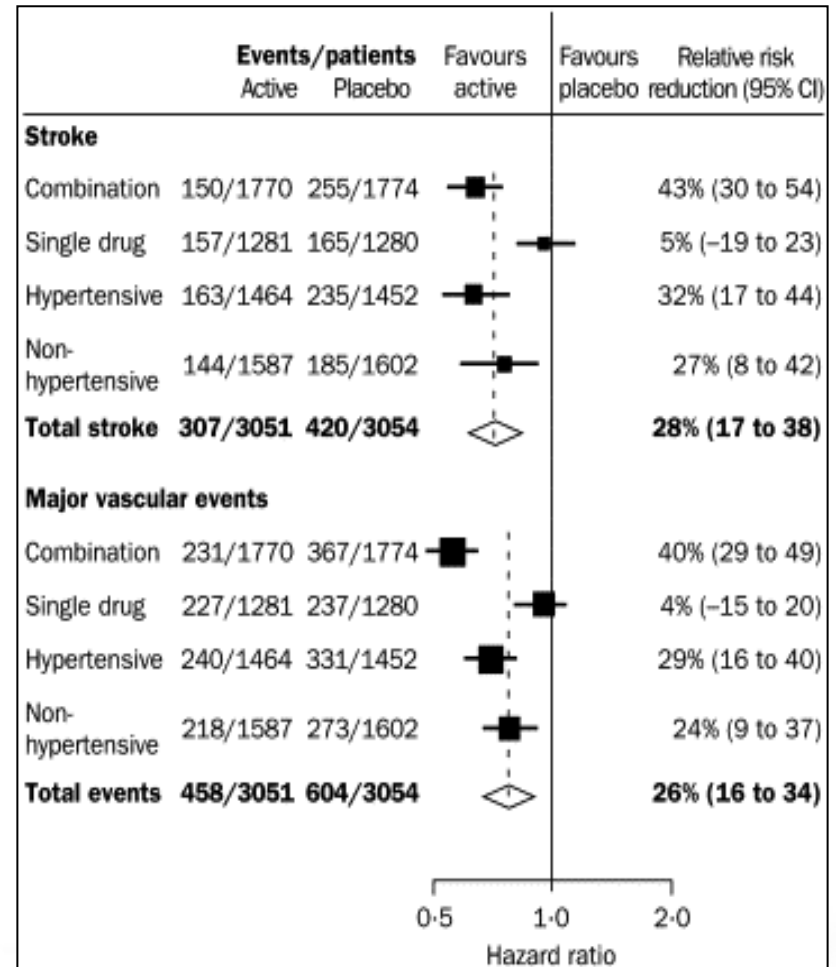
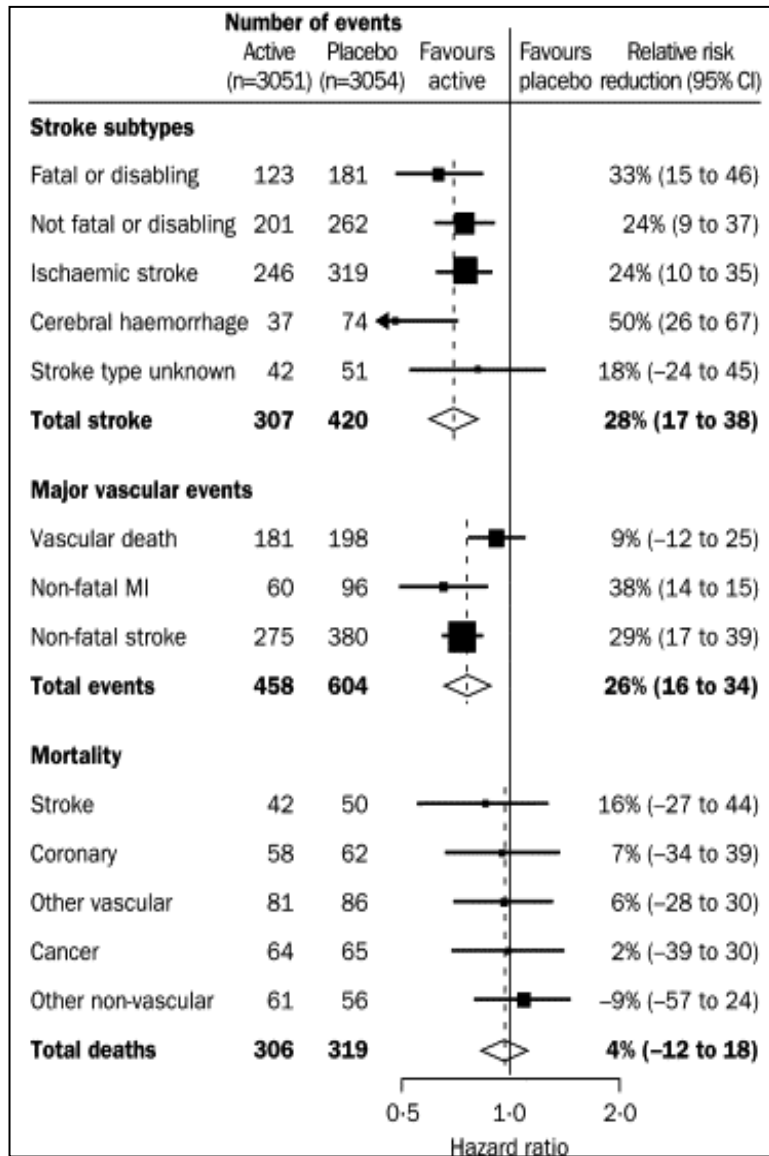
Blood pressure



Stroke incidence



# PROGRESS

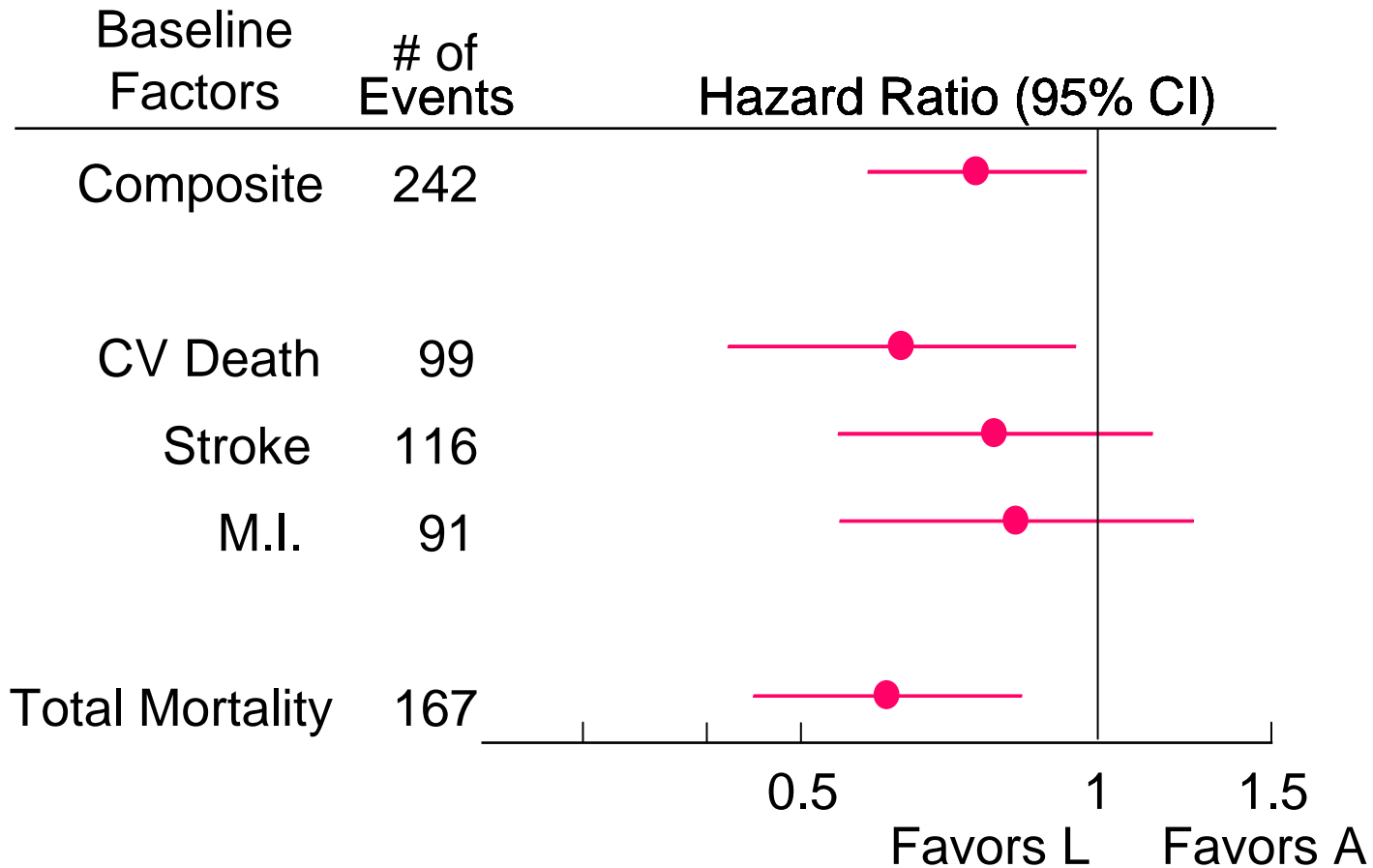


Lancet 2001



EUROPEAN  
SOCIETY OF  
CARDIOLOGY®

# LIFE: Primary Composite Endpoint and Components in Patients with Diabetes



(L H Lindholm et al. Lancet 2002;359:1004-1010)

# ASCOT - Summary of all end points

## Primary

Non-fatal MI (incl silent) + fatal CHD

## Secondary

Non-fatal MI (exc. Silent) +fatal CHD

Total coronary end point

Total CV event and procedures

All-cause mortality

Cardiovascular mortality

Fatal and non-fatal stroke

Fatal and non-fatal heart failure

## Tertiary

Silent MI

Unstable angina

Chronic stable angina

Peripheral arterial disease

Life-threatening arrhythmias

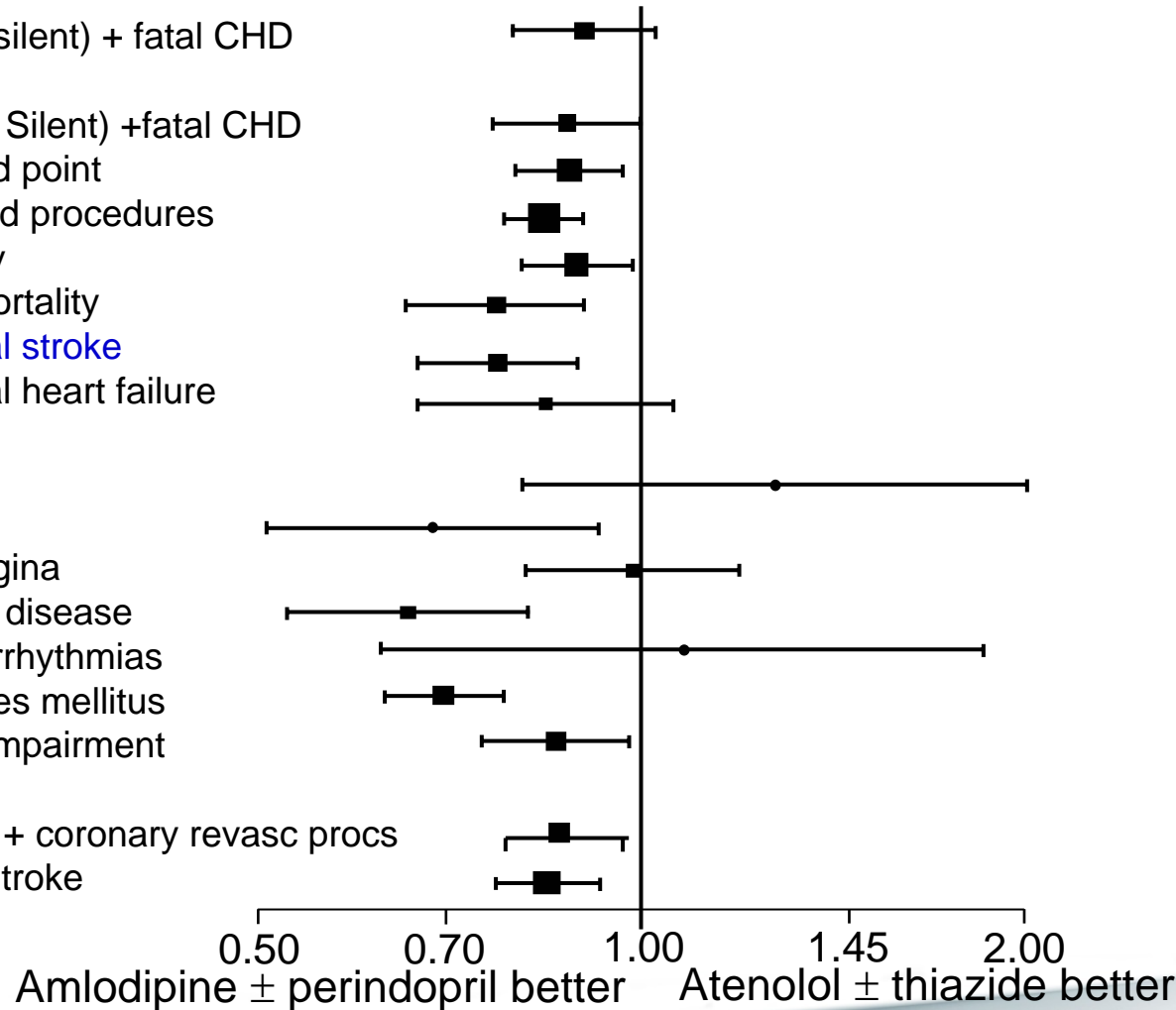
New-onset diabetes mellitus

New-onset renal impairment

## Post hoc

Primary end point + coronary revasc procs

CV death + MI + stroke

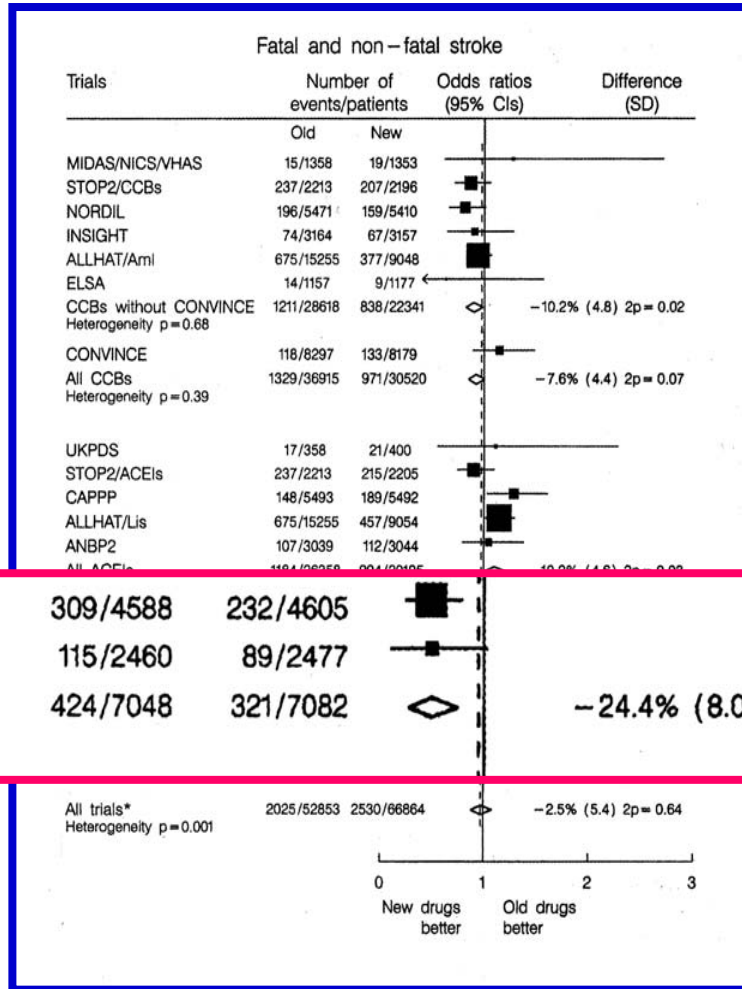


Unadjusted Hazard ratio (95% CI)

(Dahlöf et al. Lancet, sept 10, 2005)

# Stroke incidence on different anti-hypertensive treatments

## Metaanalysis of RCT-trials



LIFE  
SCOPE  
All ARBs  
Heterogeneity p = 0.99

309/4588 232/4605  
115/2460 89/2477  
424/7048 321/7082

-24.4% (8.0) 2p = 0.0002

All trials\*  
Heterogeneity p = 0.001

2025/52853 2530/66864 -2.5% (5.4) 2p = 0.64

0 1 2 3  
New drugs better Old drugs better

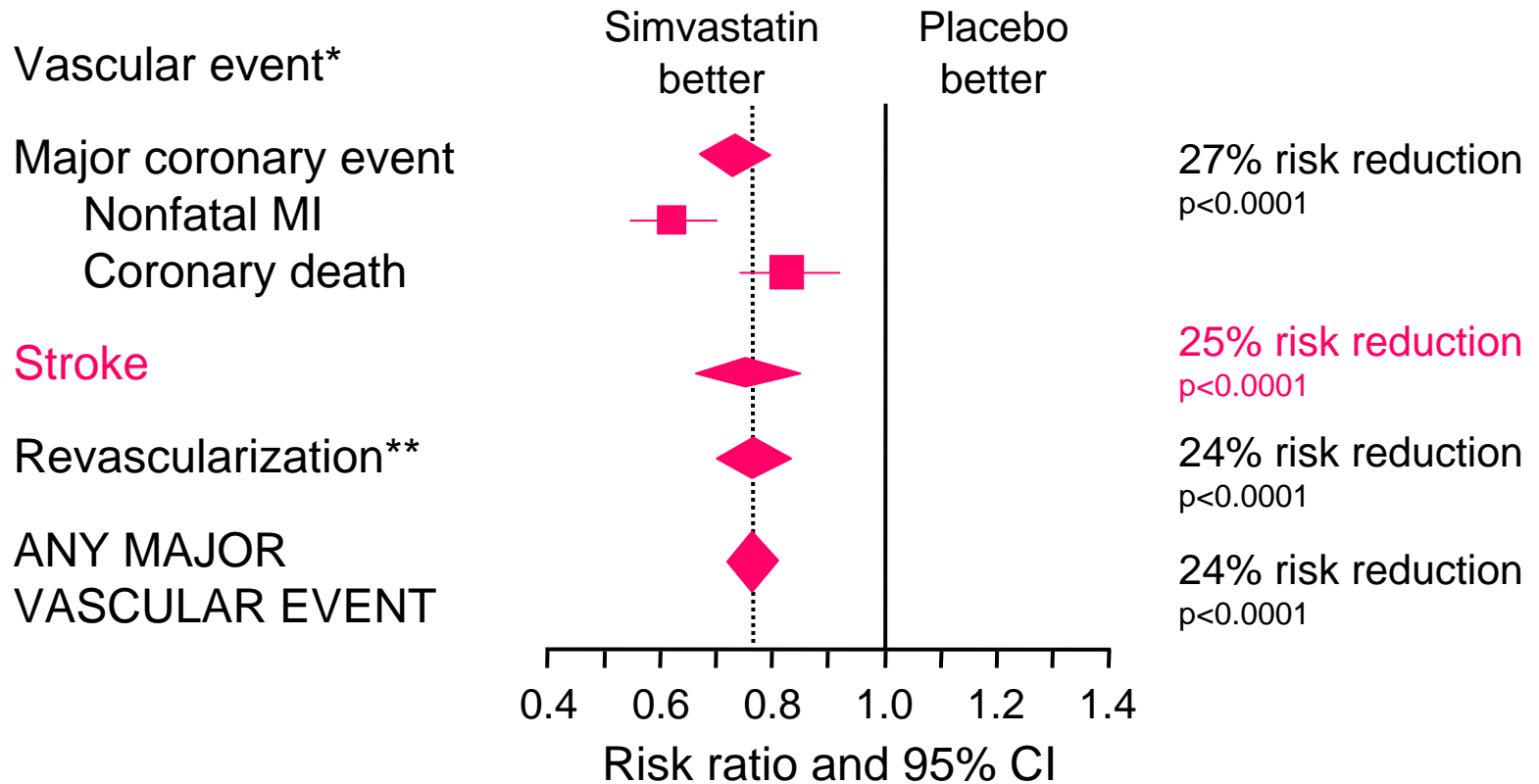
# Stroke reduction published in the large statin vs placebo randomised controlled trials

	% reduction
4S	37
CARE	31
ASCOT-LLA	27
HPS	25
LIPID	19
ALLHAT-LLA	9

# Impact of Simvastatin 40mg in Heart Protection Study

## Major Vascular Events

*hps*



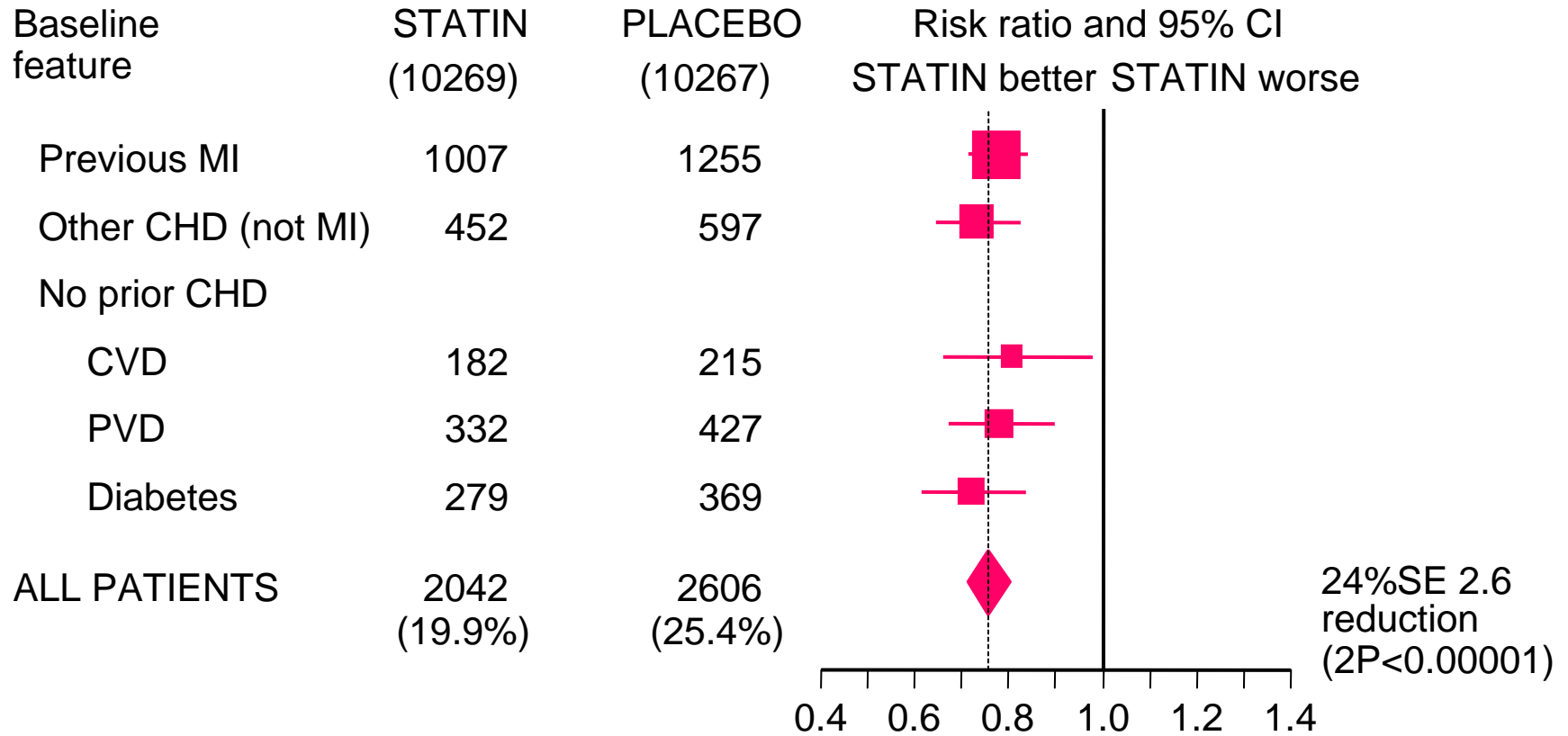
\*Patients could be in more than one vascular event category.

\*\*Includes coronary and noncoronary revascularizations.

(Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22)

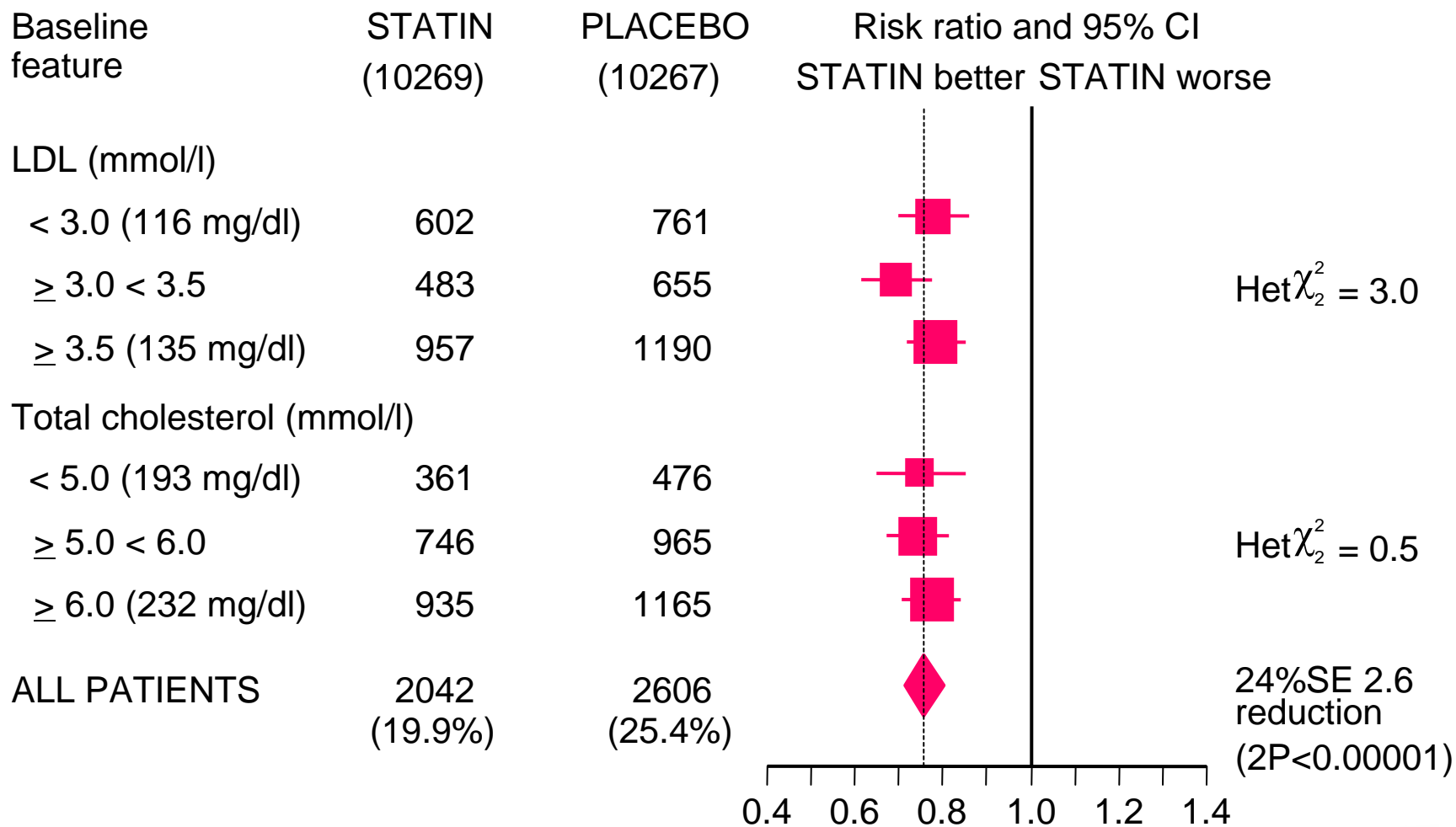
# SIMVASTATIN: VASCULAR EVENT by PRIOR DISEASE

*hps*



(Lancet 2002;360:7-22)

# SIMVASTATIN: VASCULAR EVENT by PRIOR LIPID LEVELS



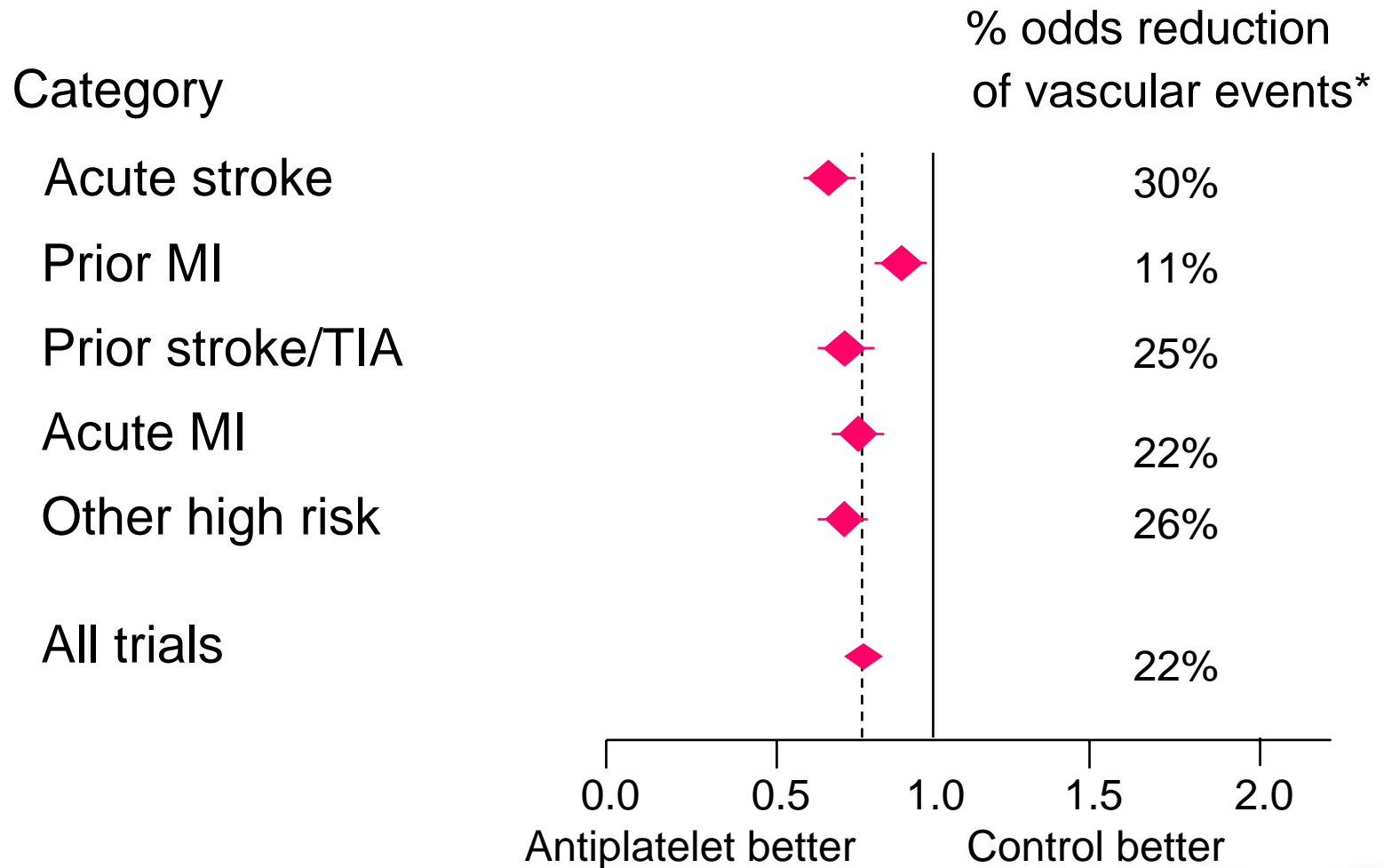
# SPARCL

## Stroke prevention by Aggressive Reduction in Cholesterol Levels

- 4 731 patients who had a stroke or TIA 1-6 months before study entry. LDL 2.6-4.9 mmol/l and no CHD.
- Randomised to atorvastatin 80 mg o.d. or placebo
- Fatal and non-fatal stroke was reduced by 16% ( $p=0.03$ ) and major c-v events (MCVE) by 20% ( $p=0.002$ )
- ARR of stroke was 2.2% and of MCVE 3.5% over 5-years

(Amarenco et al, N Engl J Med. 2006)

# Antiplatelet Therapy is Beneficial



( Antithrombotic Trialists' Collaboration. BMJ 2002; 324: 71–86)

# Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial



Hans-Christoph Diener, Julien Bogousslavsky, Lawrence M Brass, Claudio Cimminiello, Laszlo Csiba, Markku Kaste, Didier Leys, Jordi Matias-Guiu, Hans-Jürgen Rupprecht, on behalf of the MATCH investigators\*

Lancet 2004; 364: 331-37  
See Comment page 305

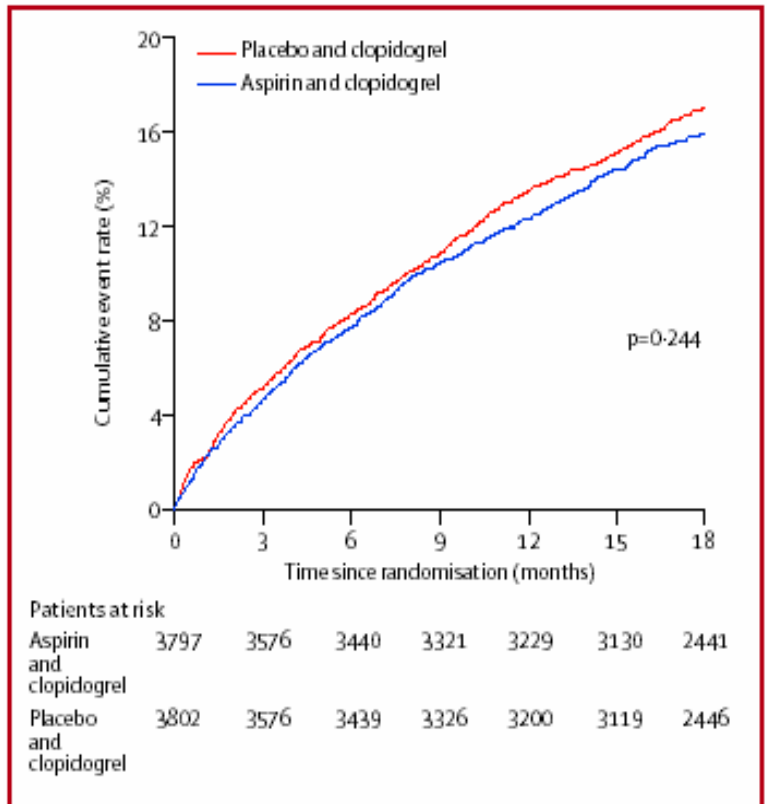


Figure 2: Kaplan-Meier curves for cumulative rates of primary endpoint events

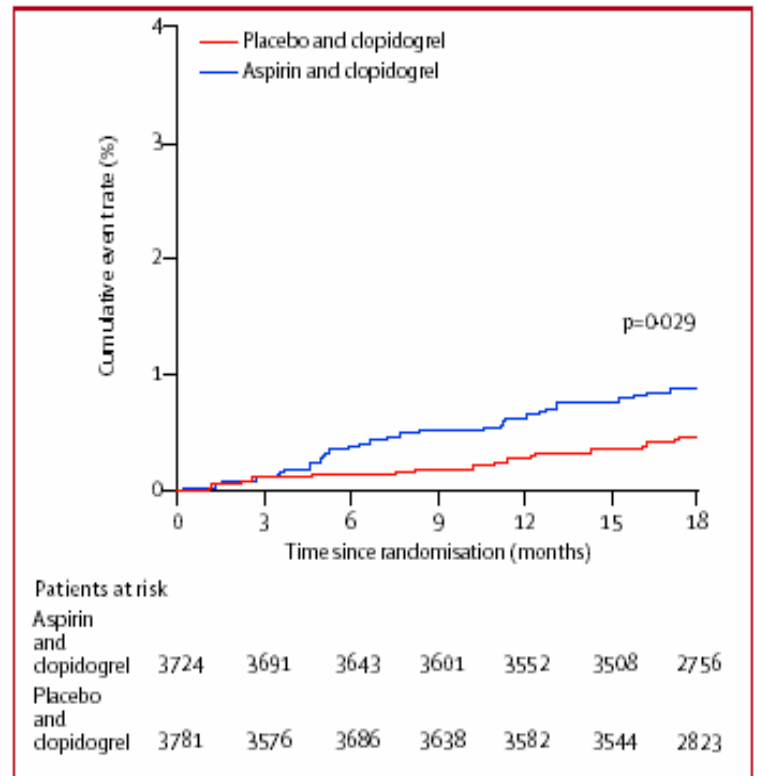
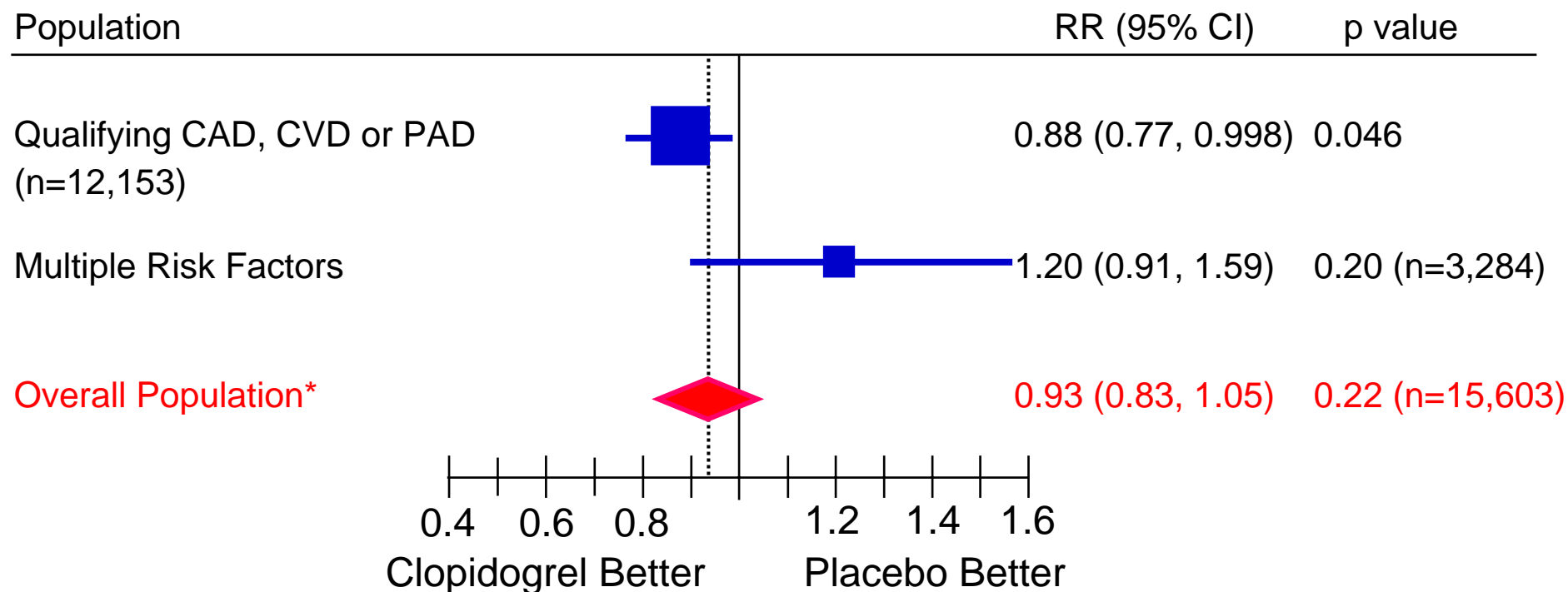


Figure 4: Kaplan-Meier curves for cumulative rates of primary intracranial haemorrhage

(Diener et al, Lancet. 2004)

# CHARISMA- clopidogrel on top of low dose ASA: Primary Efficacy Results (MI/Stroke/CV Death) by Pre-Specified Entry Category



\* A statistical test for interaction showed marginally significant heterogeneity (p=0.045) in treatment response for these pre-specified subgroups of patients

(Adapted from Bhatt DL, Fox KA, Hacke W, et al. NEJM, 2006)

# Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial

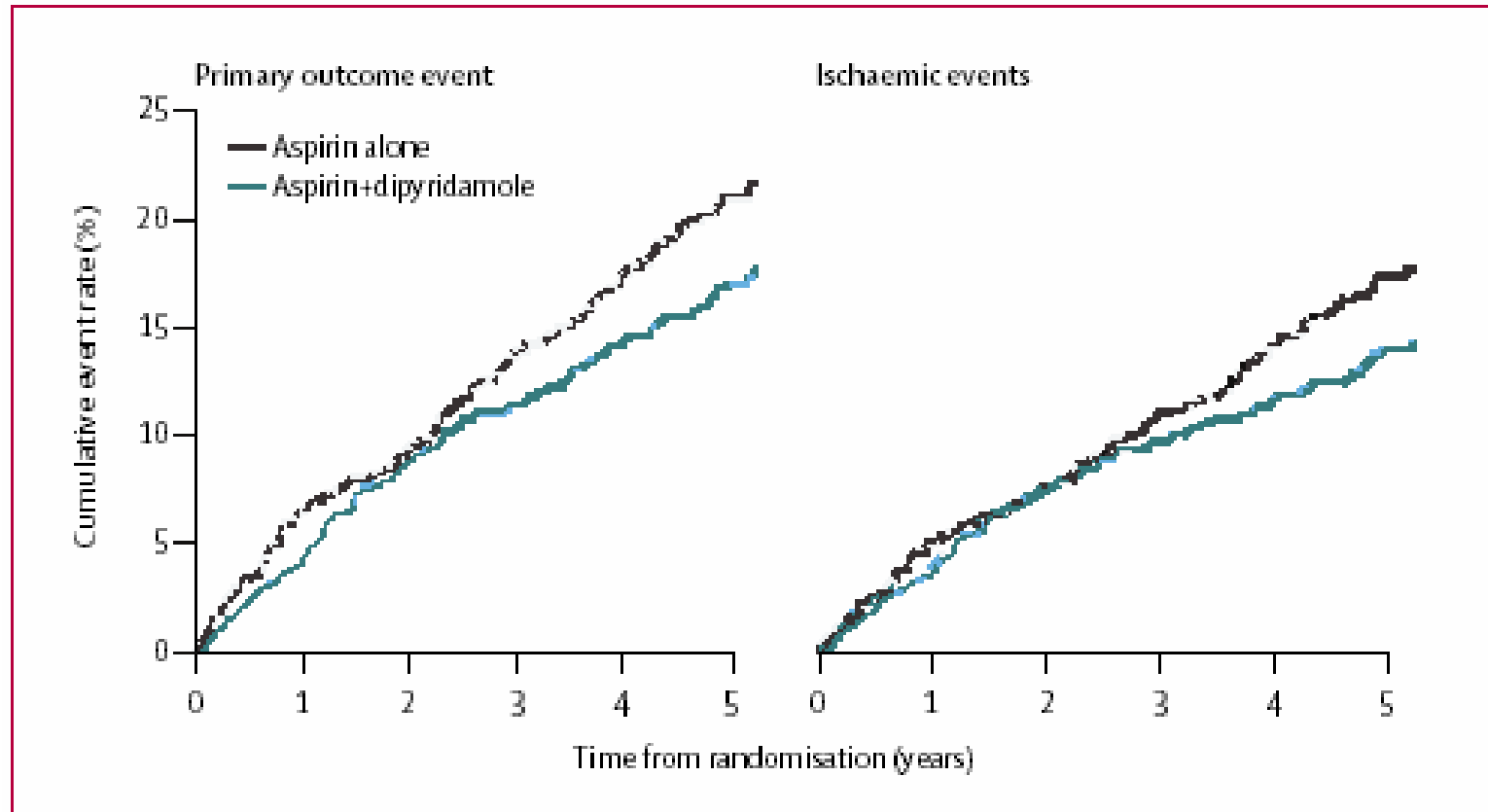


Figure 2: Time-to-event curves for primary outcome event and all Ischaemic events

(The ESPRIT Study Group, Lancet 2006)

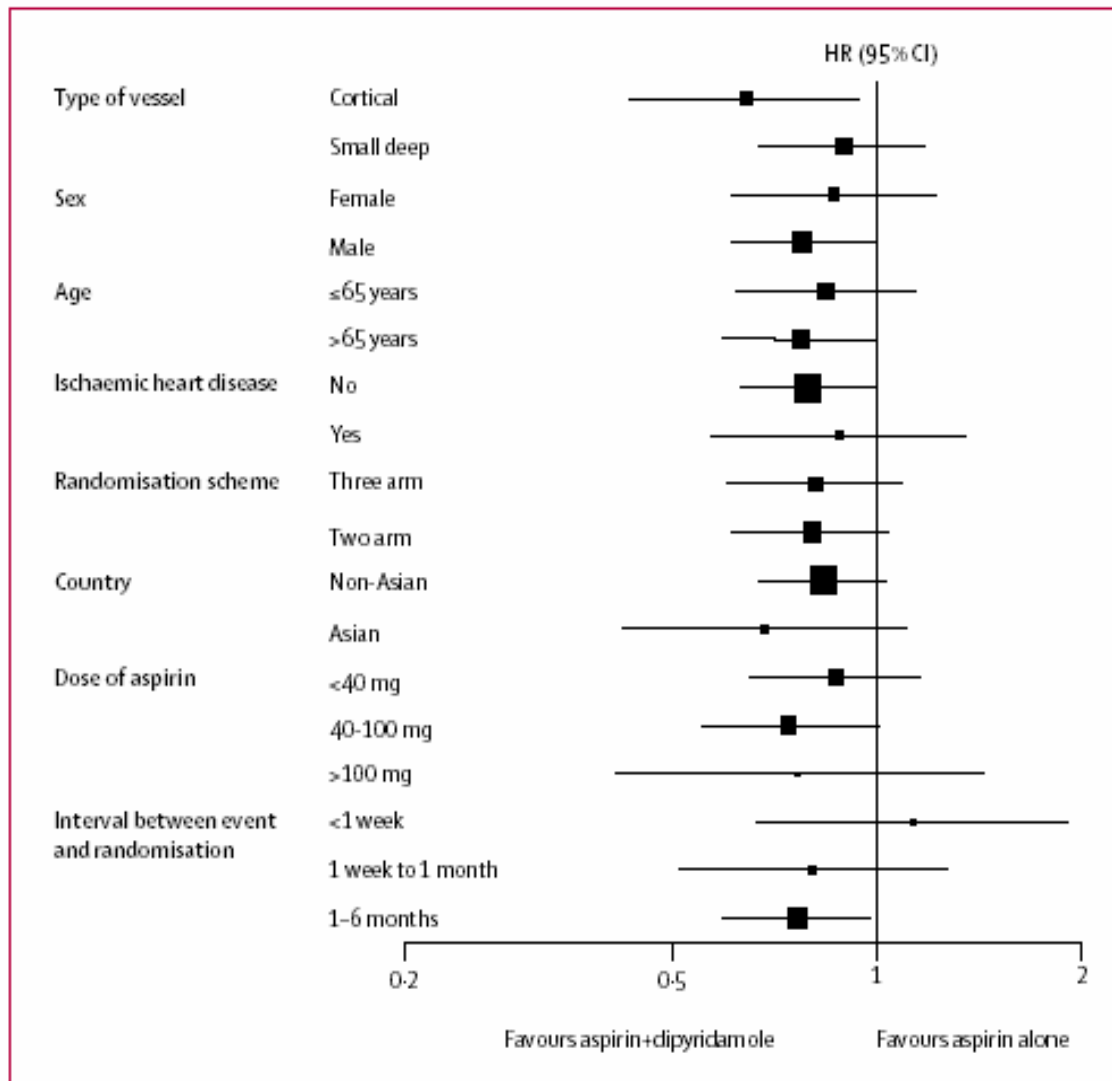
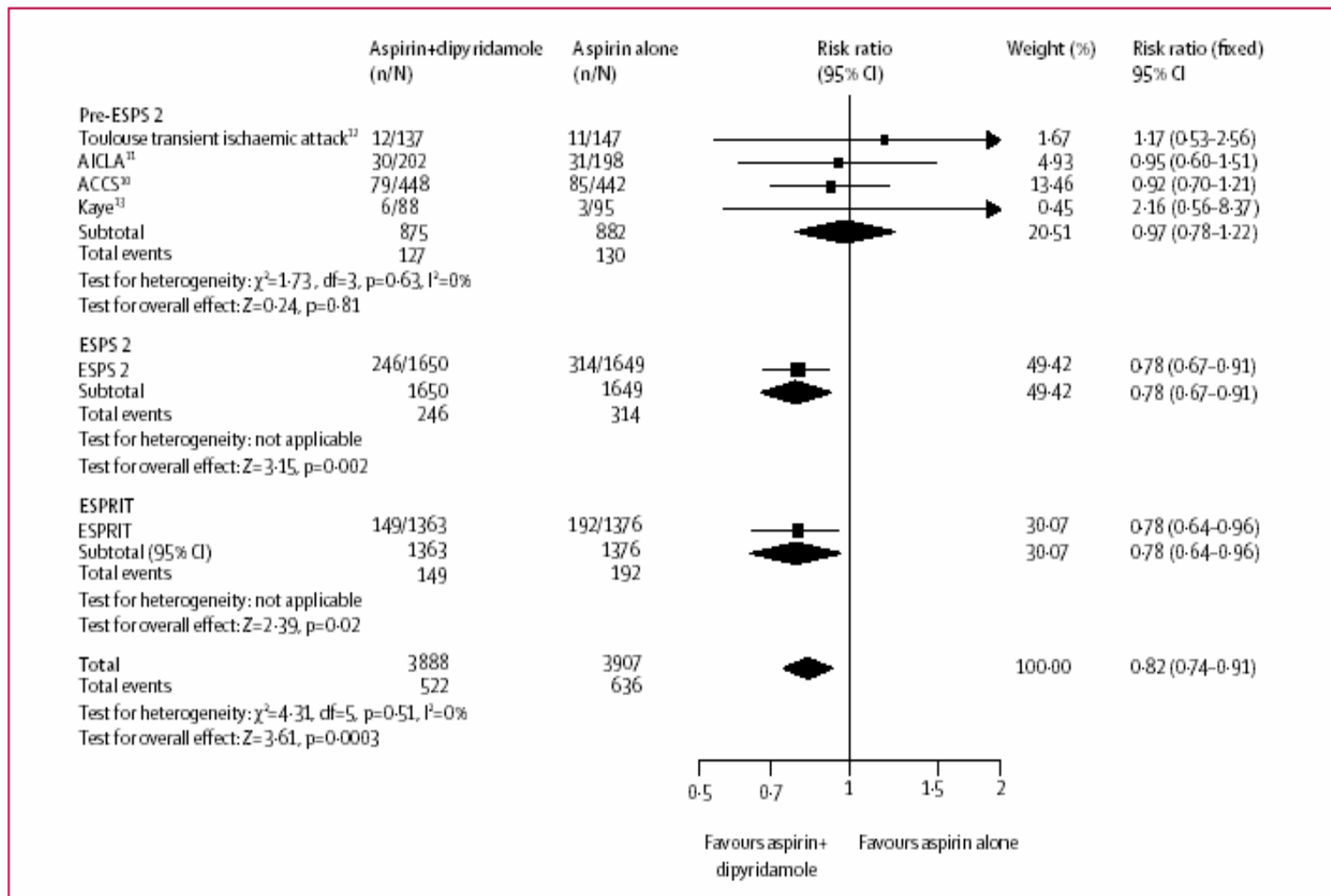


Figure 3: Subgroup analyses for primary outcome event

(The ESPRIT Study Group, Lancet 2006)

# Metaanalysis of effects of combined aspirin and dipyridamol treatment



# Warfarin or aspirin in atrial fibrillation

## CHADS<sub>2</sub> Scheme

CHF, Hypertension, Age>75 y, or Diabetes = 1 point. Stroke or TIA = 2 points

CHADS score	Risk level	Stroke rate/year	Treatment recommendations
0	Low	1%	Aspirin (75-325 mg/d)
1	Low-moderate	1.5%	Warfarin INR 2-3 or aspirin (75-325 mg/d)
2	Moderate	2.5%	Warfarin INR 2-3
3	High	5%	Warfarin INR 2-3

# Summary

## Primary and secondary prevention of stroke

- Stop smoking!
- Treat hypertension!
- Add ACE-i/ARB to high risk patients also below 140 mm Hg systolic
- Liberal use of statin (always in high risk patients if LDL-C > 2.5-3 mmol/l)
- At least aspirin but for most patients with AF warfarin is indicated (CHADS<sub>2</sub> scheme)
- Aspirin or clopidogrel or aspirin/dipyridamol for all high risk patients for platelet inhibition

# Stroke

## Table of recommendations 1

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Normalization of blood pressure is recommended in all patients with diabetes for the prevention of stroke	I	A
For stroke prevention, blood pressure lowering is more important than the choice of drug. Inhibition of the renin-angiotensin-aldosterone system may have additional benefits beyond blood pressure lowering <i>per se</i>	IIa	B
Inhibition of the renin-angiotensin-aldosterone system may be considered also in diabetic patients with normal blood pressure levels	IIa	B

# Stroke

## Table of recommendations 2

Patients with stroke should be treated with statins according to the same principles as non-diabetic subjects with stroke	I	B
Antiplatelet therapy with aspirin is recommended for primary and secondary prevention of stroke	I	B
Patients with acute stroke and diabetes should be treated according to the same principles as stroke patients without diabetes	Ila	C
Optimization of metabolic conditions including glycaemic control should be aimed for	Ila	C