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Further results from the ACTION trial and their clinical implications

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Foam cells

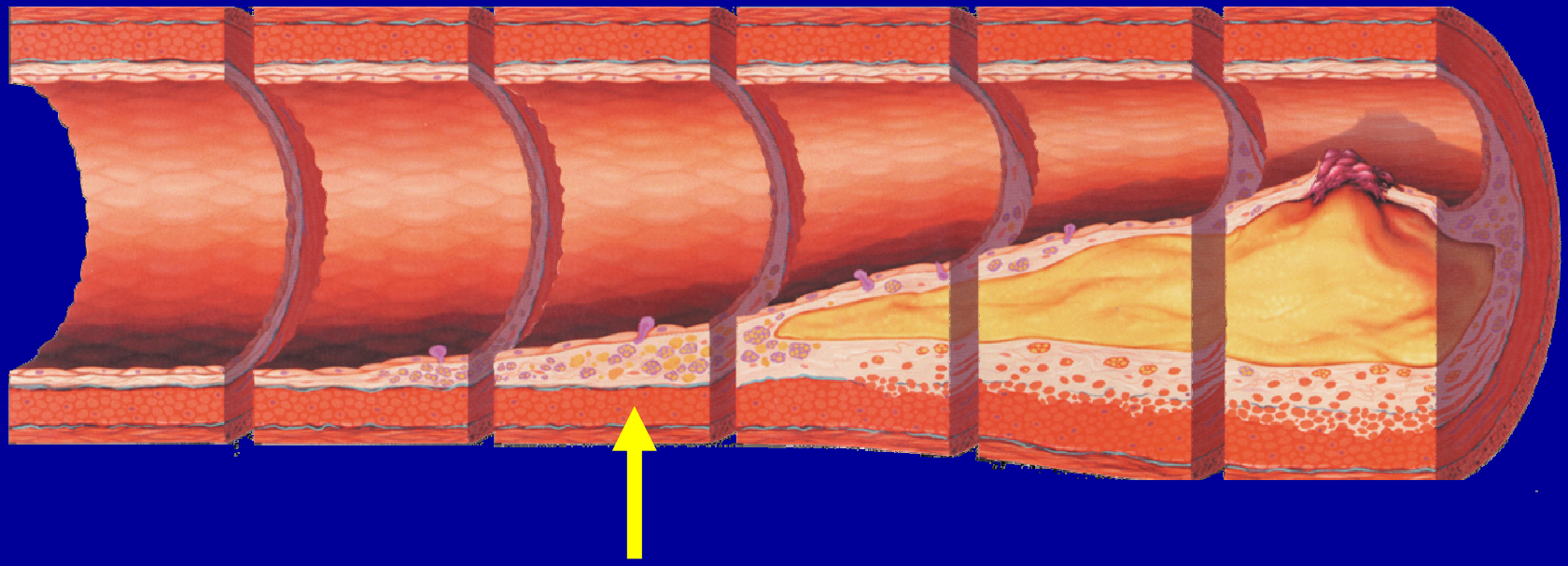
Fatty streak

Intermediate lesion

Atheroma

Fibrous plaque

Complicated lesion/rupture

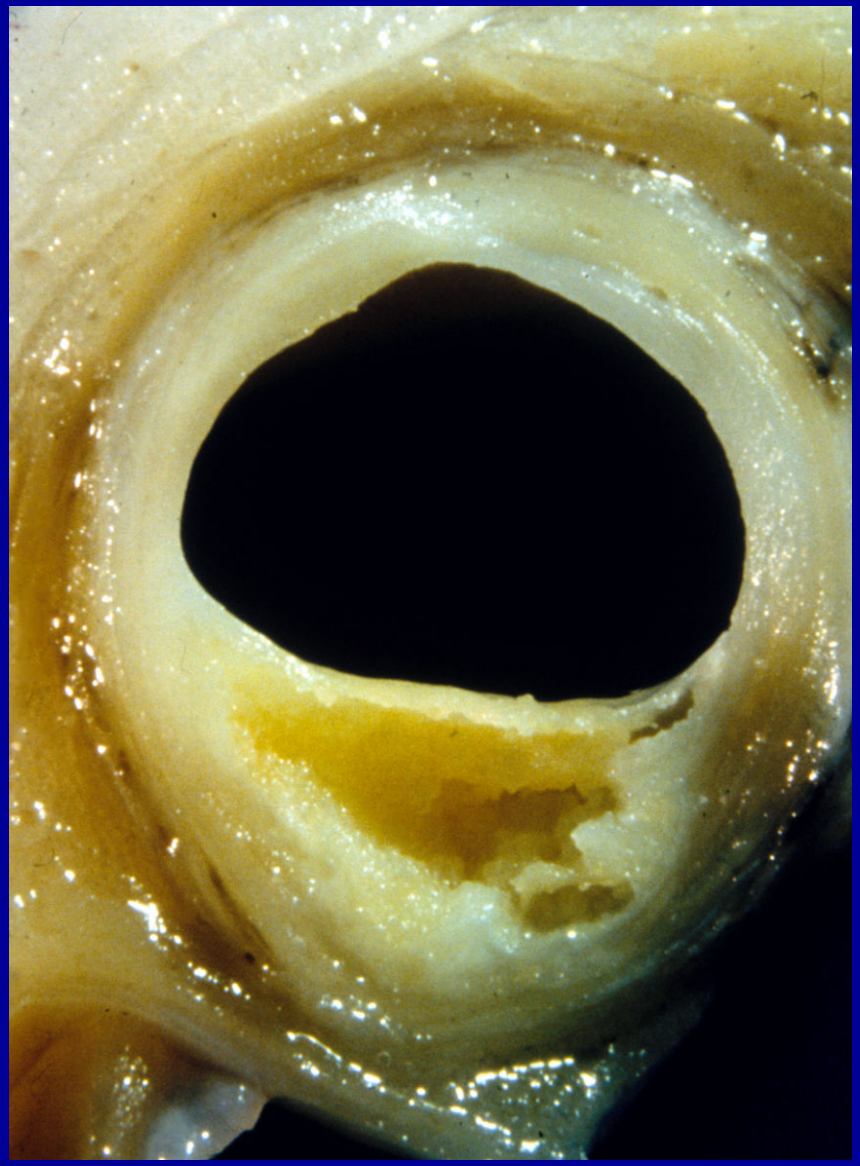


Early atherosclerotic burden

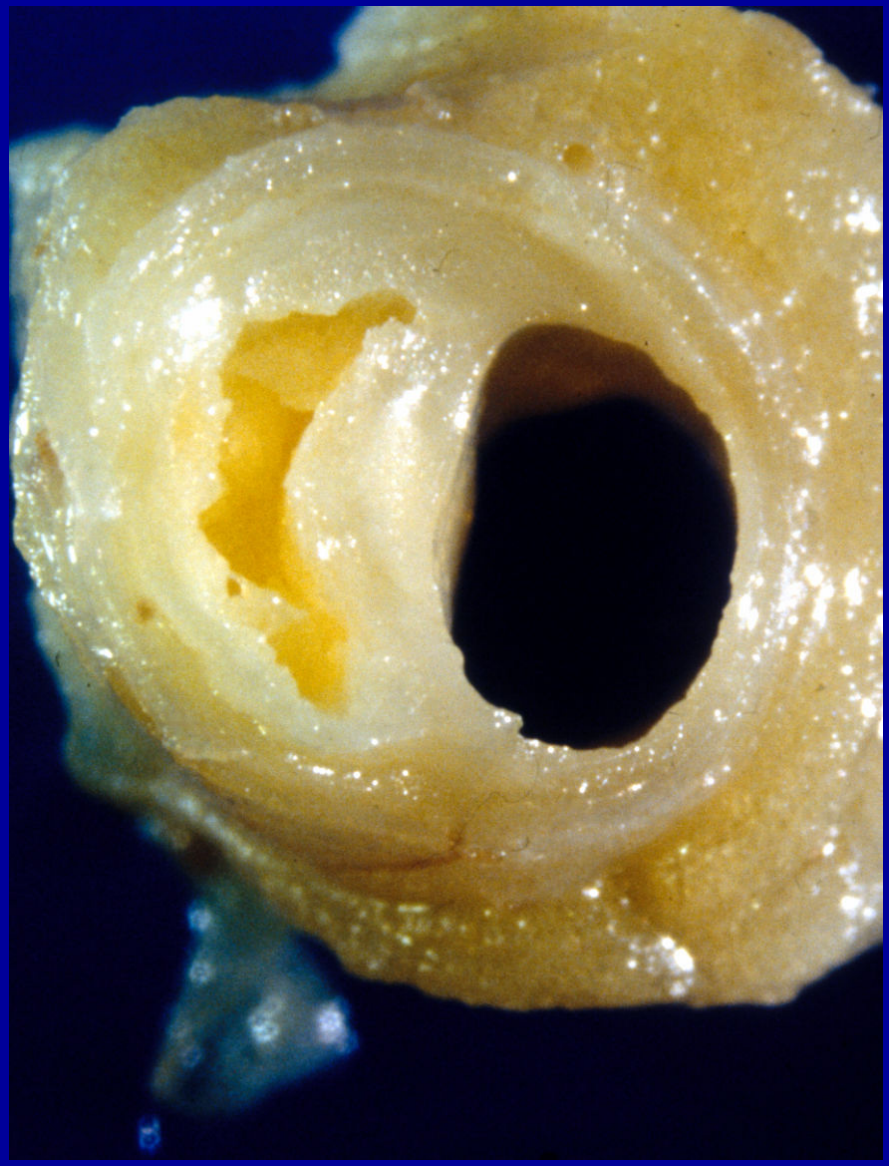
20-30 years 30-50 years 50 years onwards

Decades and years

Atheromatous human coronary arteries

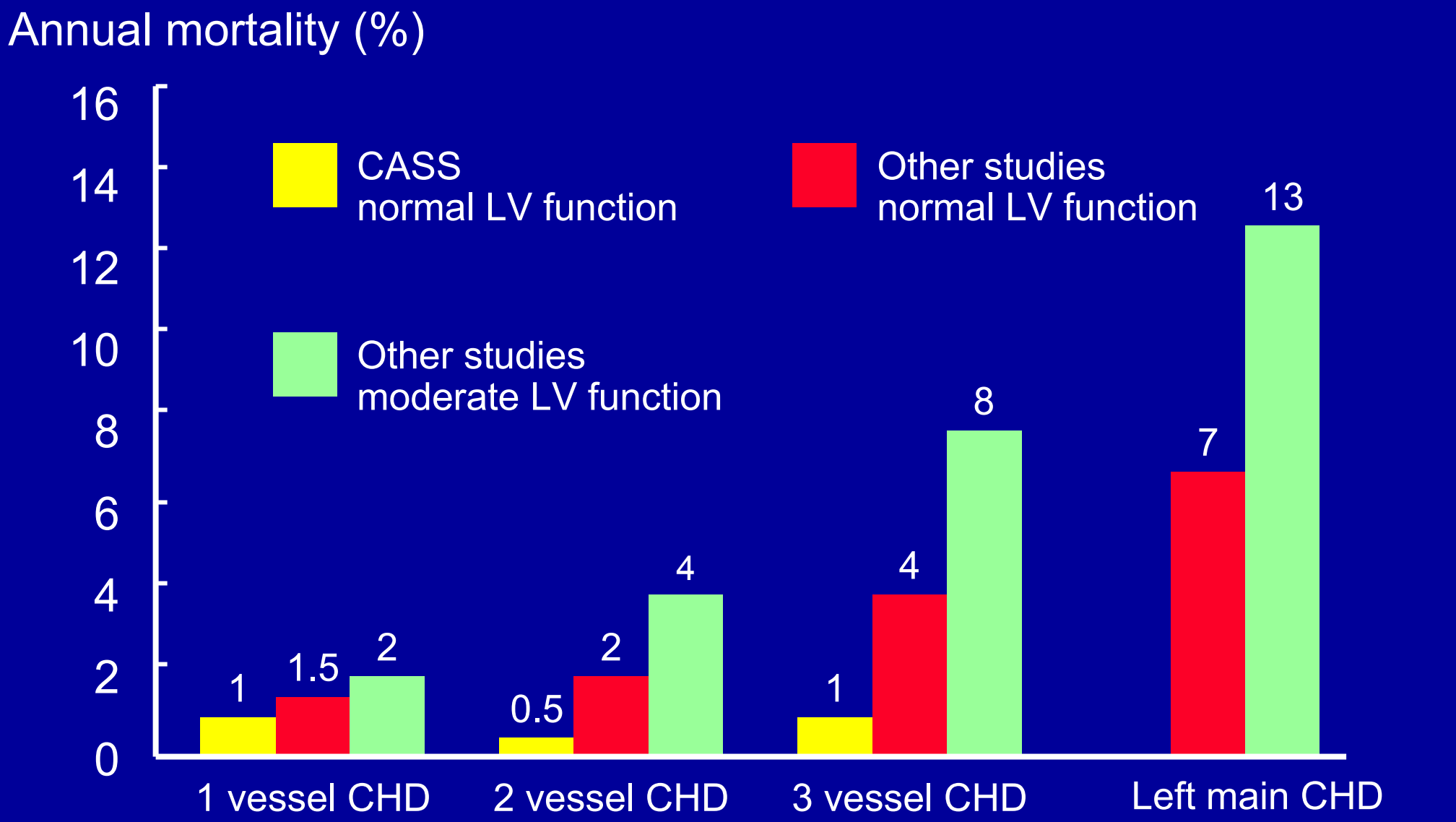


Thin walled plaque



Tick walled plaque

Annual mortality: medically treated patients with angina



adapted from Silverman & Grossman N Eng J Med 1984;310:1712-1717

The four pillars of the treatment of angina pectoris

1 Life style modification

2 Drugs that act on risk factors
such as hypertension or hyperlipidaemia
or have a preventive effect by other mechanisms

3 Drugs that prevent anginal attacks

4 Coronary revascularisation

'natural history' is a complex concept because it reflects disease progression modulated by the effects of treatment.

Drugs in angina and secondary prevention of coronary heart disease

For chest pain

- Nitrates
- Beta-blockers
- Calcium antagonists

For prognosis

1. Aspirin
2. Statin
3. Beta-blocker (after MI)
4. Calcium antagonists
5. ACE inhibitor
   if specific indication

New drugs for the treatment of angina pectoris
Mechanisms of action

1.	Ivabradine	Slows heart rate
2.	Ranolazine	New - Slow Na^+ channel inhibitor Old – Metabolic switch
3.	Nicorandil	Calcium antagonist and nitrate properties
4.	Trimetazadine	Metabolic switch
5.	Fasudil	rho kinase inhibitor. Reduces vasoconstriction

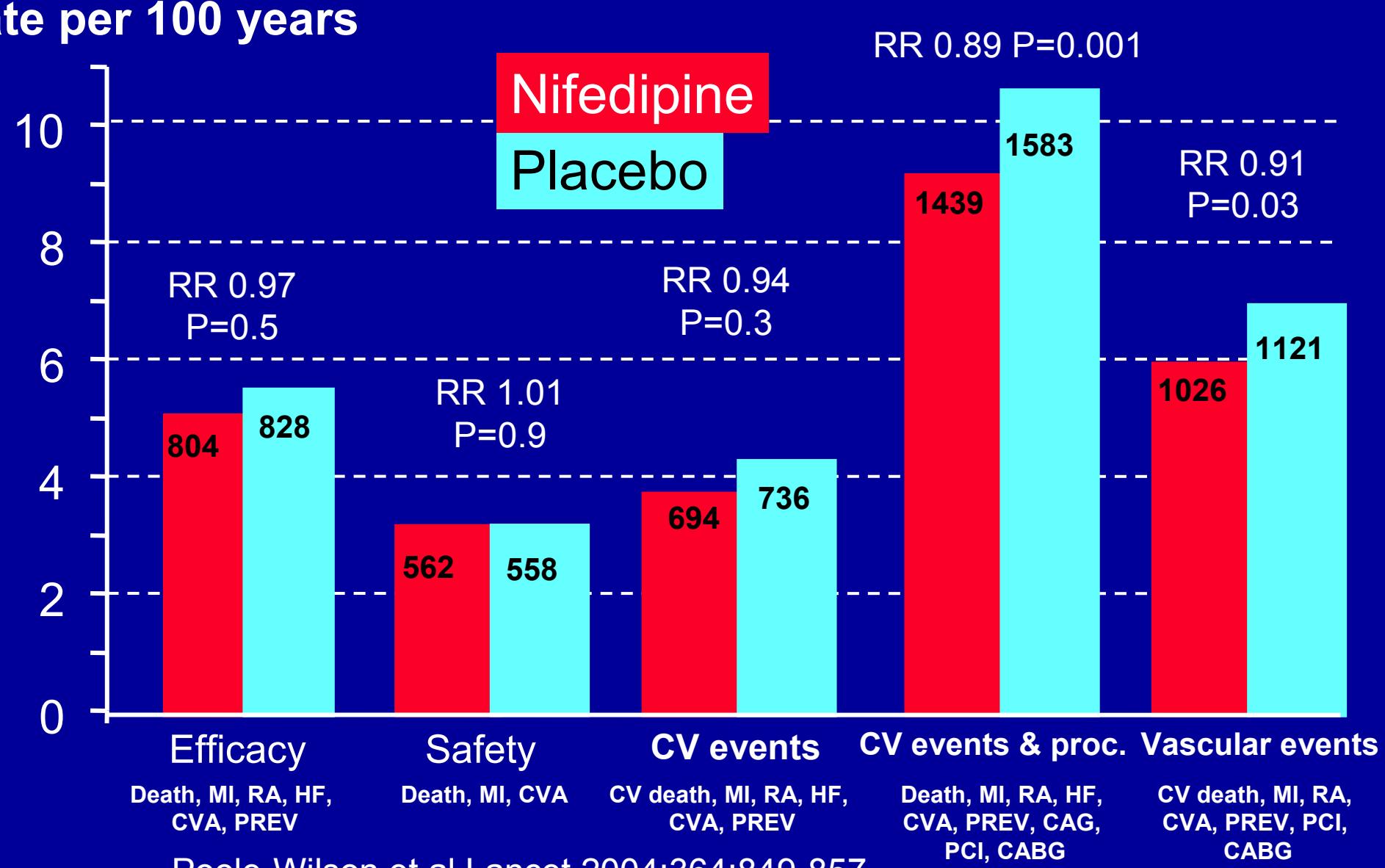
Mechanisms of action for drugs in angina

1. Increase blood flow
   - Reduce vascular resistance
   - Increase diastolic time
2. Improve cardiac efficiency
   - Reduce workload
   - Optimise haemodynamics
3. Slow heart rate
4. Metabolic switch
5. Inhibit/delay ionic movements

ACTION: rationale

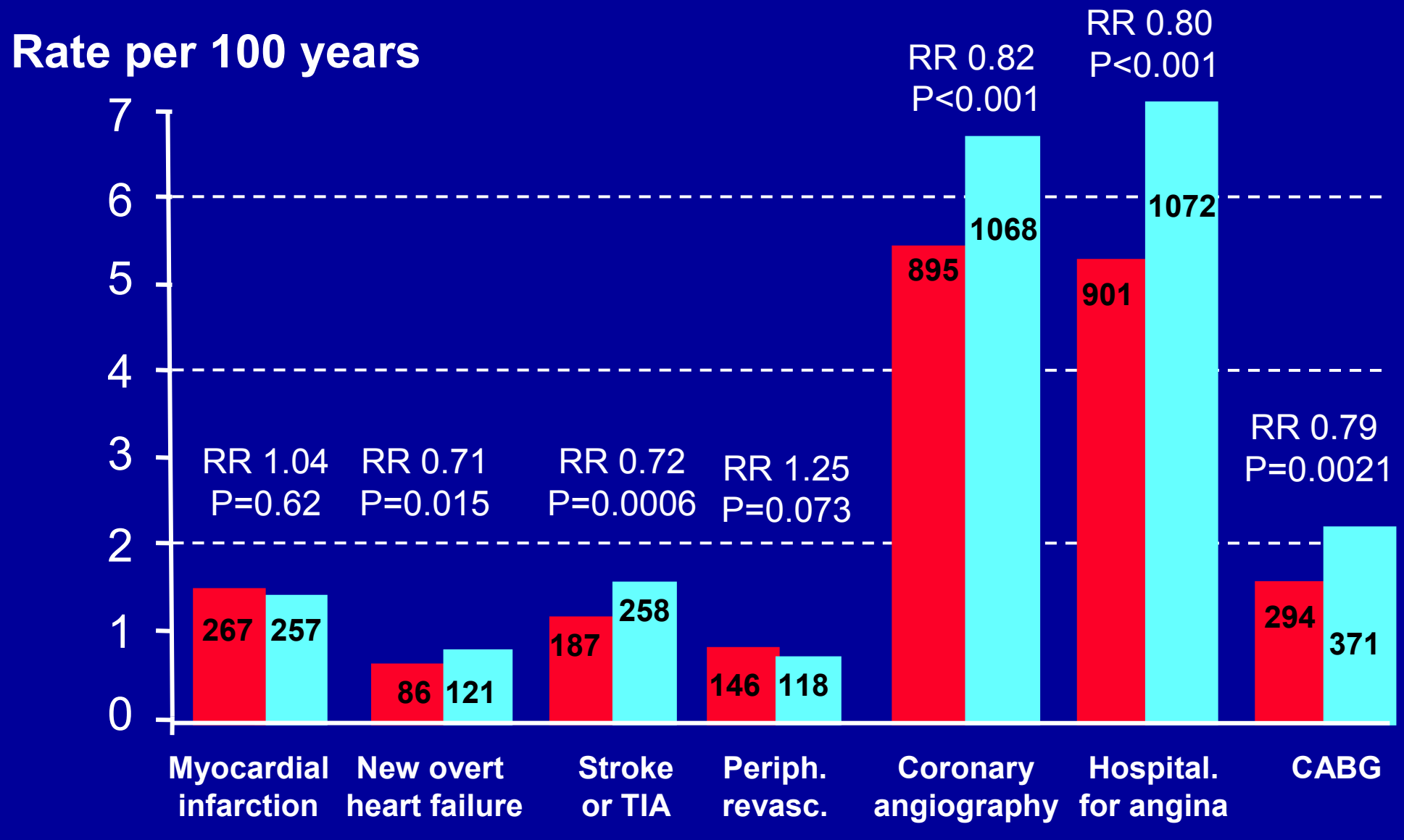
- Nifedipine GITS is widely used to treat angina and hypertension
- Debate circa 1995 on safety based on:
  - Data from unapproved indications
  - Observational studies
  - Meta-analyses (Furberg, 1995)
- Short-acting formulations of nifedipine possibly harmful
- No evidence from outcome trials in patients with stable angina

ACTION: combined endpoints



Poole-Wilson et al Lancet 2004:364;849-857

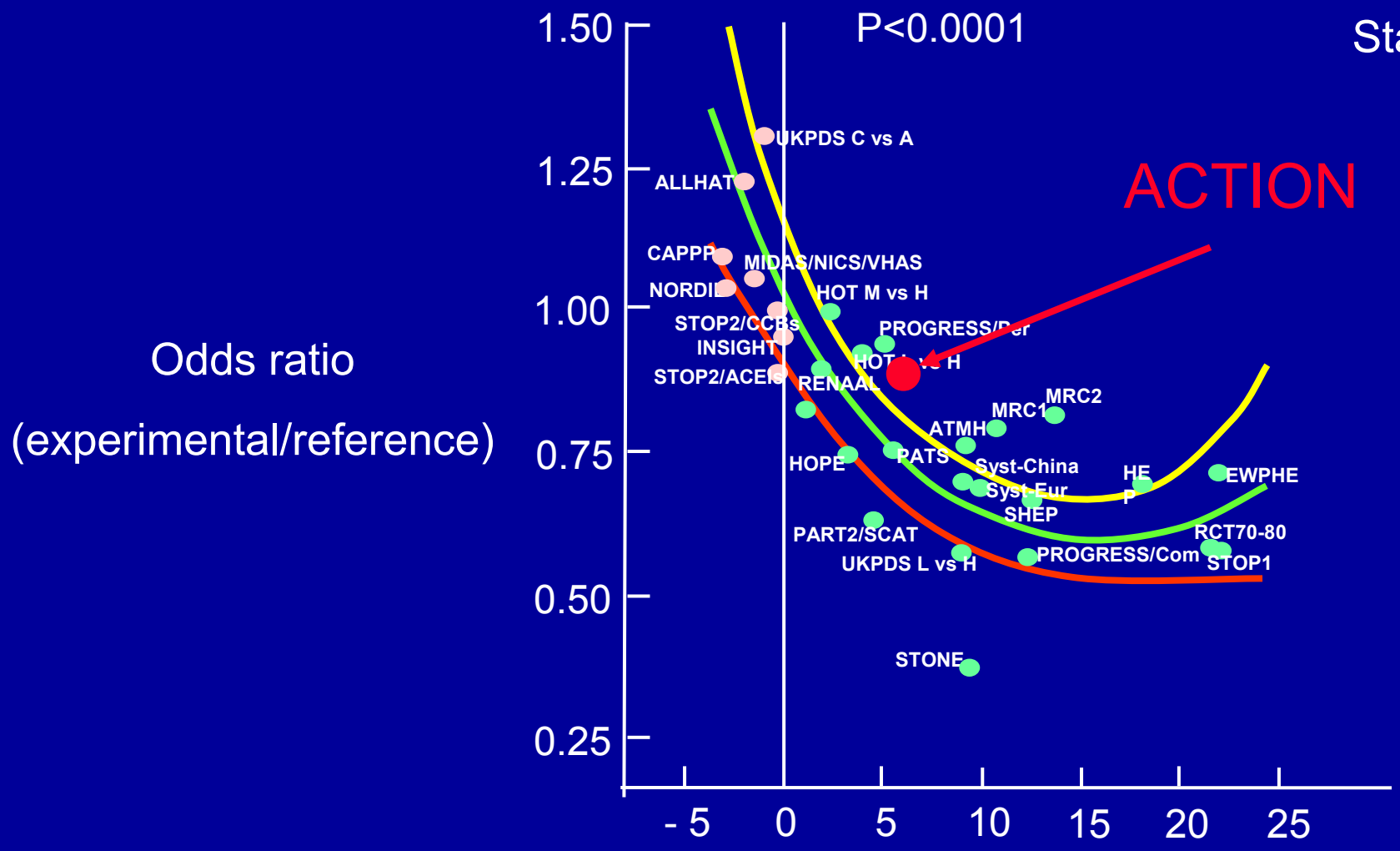
ACTION: clinical endpoints



Poole-Wilson et al Lancet 2004:364;849-857

All cardiovascular events

From Staessen 2003



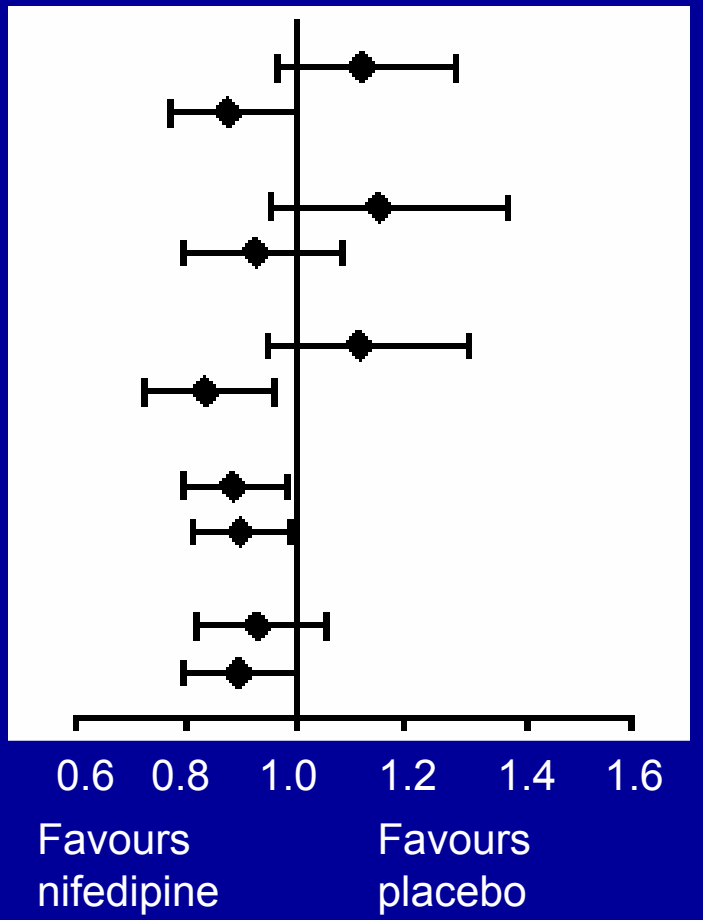
Odds ratio

(experimental/reference)

Difference (reference minus experimental) in systolic pressure (mm Hg)

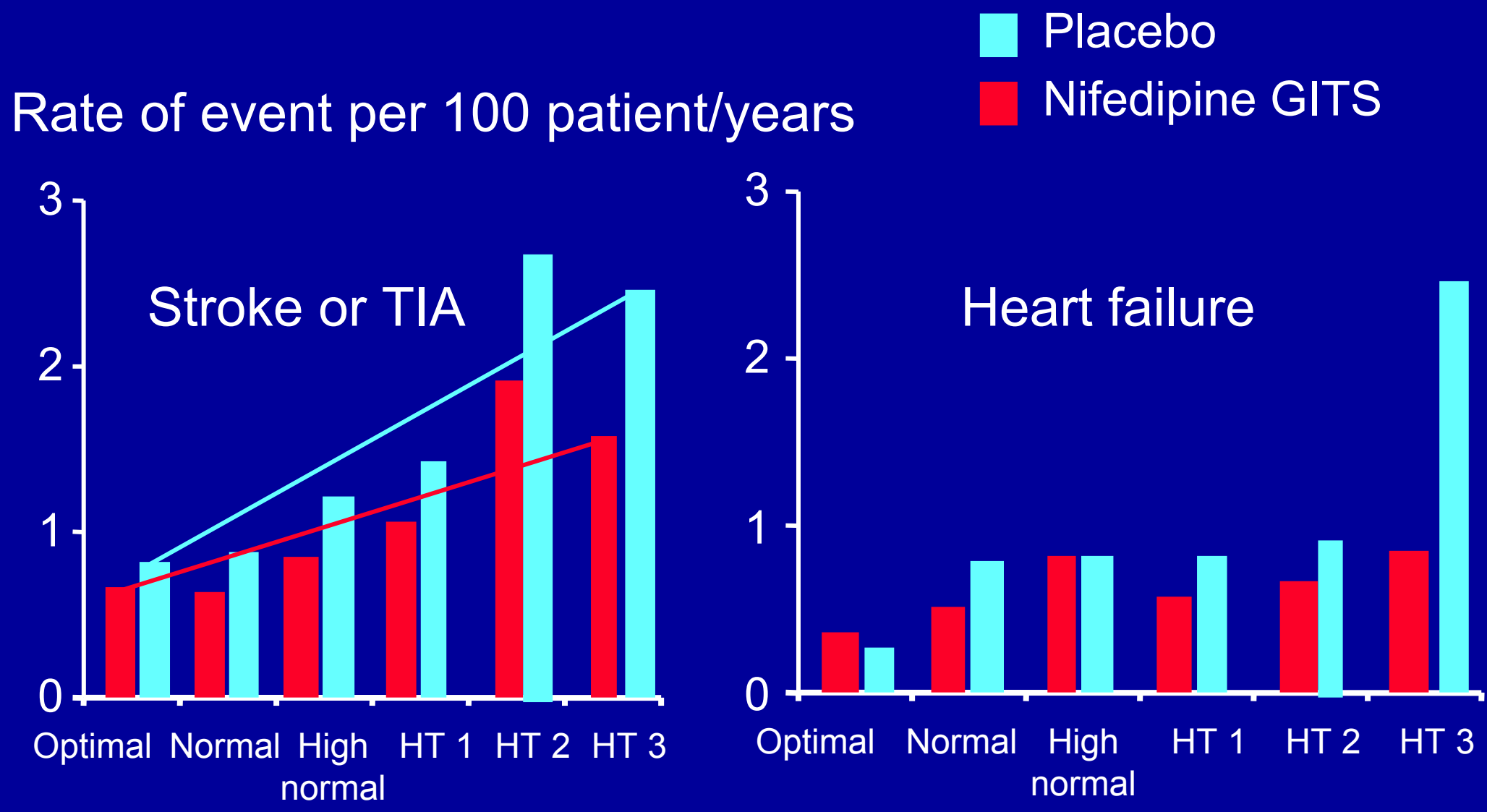
ACTION: hypertension and specified endpoints

Combined endpoint	No. of patients with event (rate /100 pat.years*) Nifedipine	Placebo	Hazard ratio (95% CI)	P
Normotensive	(*n* =1847)	(*n*=1837)		
Hypertensive	(*n*=1975)	(*n*=2002)		
Primary endpoint for efficacy				
Normotensive	364 (4.28)	368 (3.84)		0.02
Hypertensive	439 (4.90)	500 (5.61)		
Primary endpoint for safety				
Normotensive	244 (2.74)	213 (2.40)		0.08
Hypertensive	317 (3.40)	345 (3.67)		
Cardiovascular events				
Normotensive	317 (3.73)	286 (3.35)		0.007
Hypertensive	376 (4.20)	450 (5.05)		
Death, cardiovascular events, or procedures				
Normotensive	670 (8.91)	737 (10.14)		0.8
Hypertensive	768 (9.70)	846 (10.84)		
Vascular event or revascularisation				
Normotensive	479 (5.98)	511 (6.45)		0.7
Hypertensive	546 (6.46)	610 (7.24)		



J Lubsen et al J Hypert. 2005

Effect of nifedipine GITS on events in relation to blood pressure



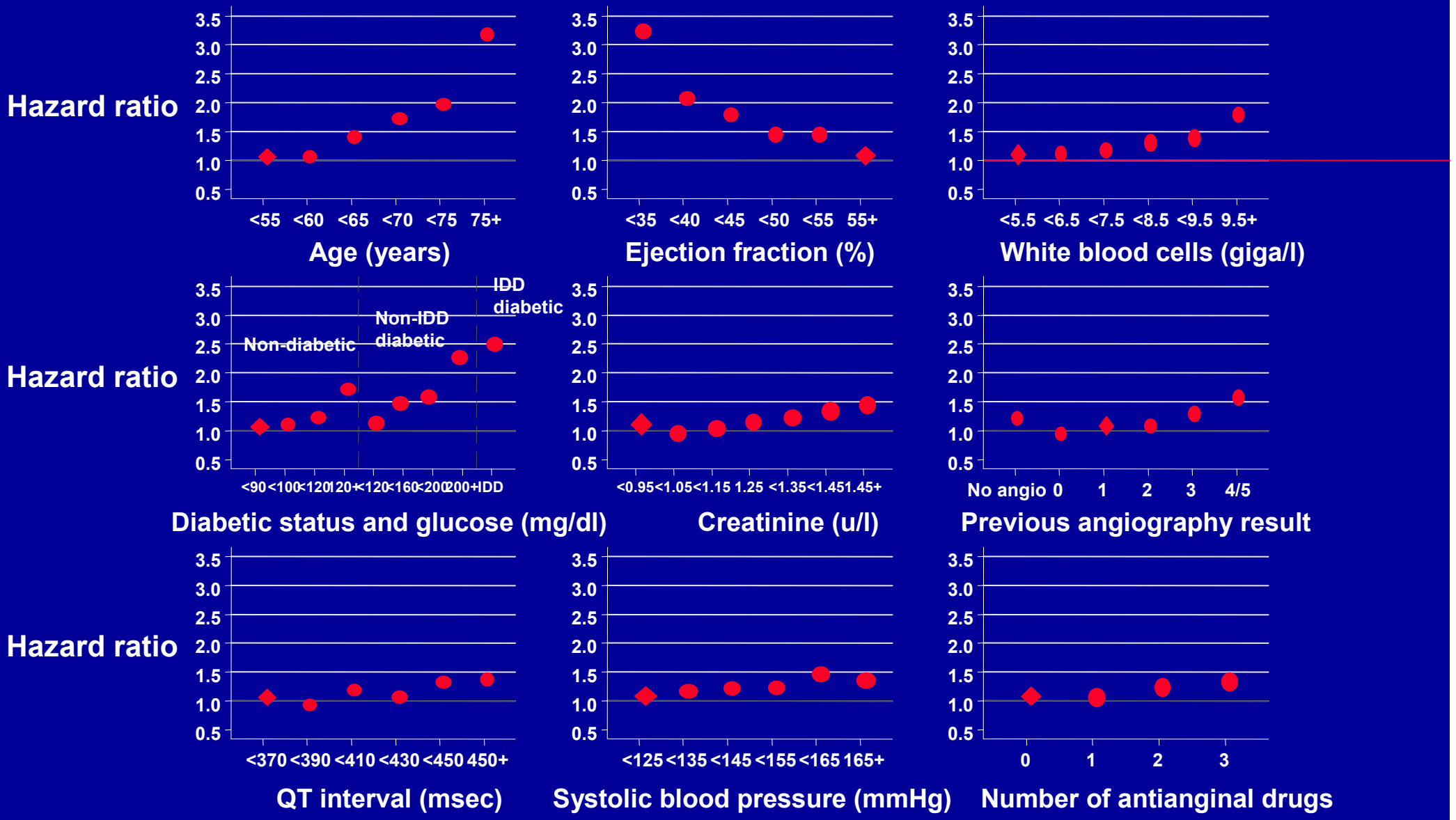
Adapted from Lubsen in press J Clin Epid 2006

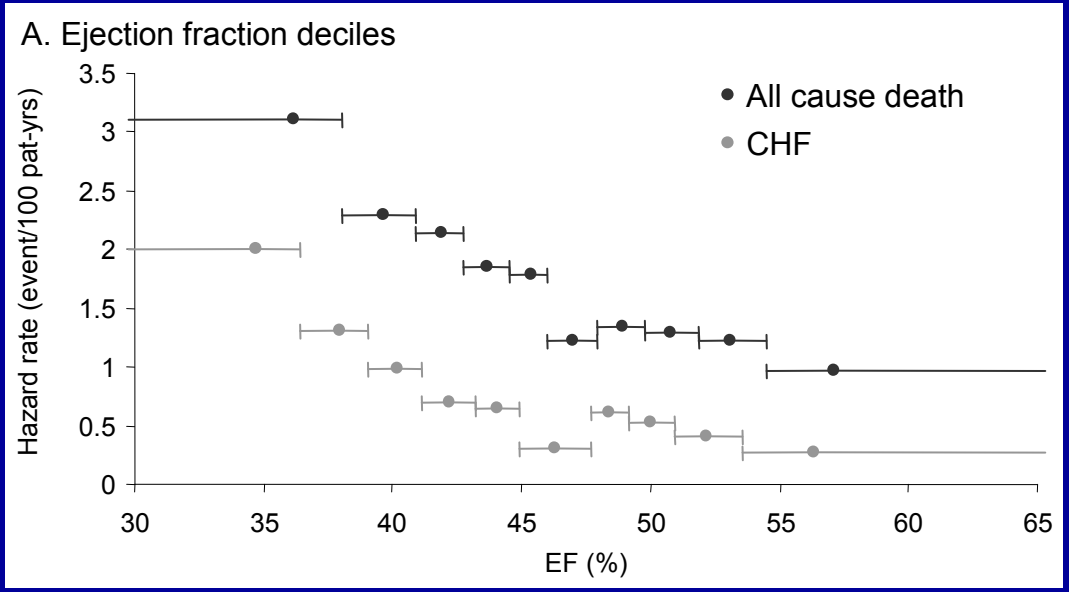
ACTION: stroke or TIA

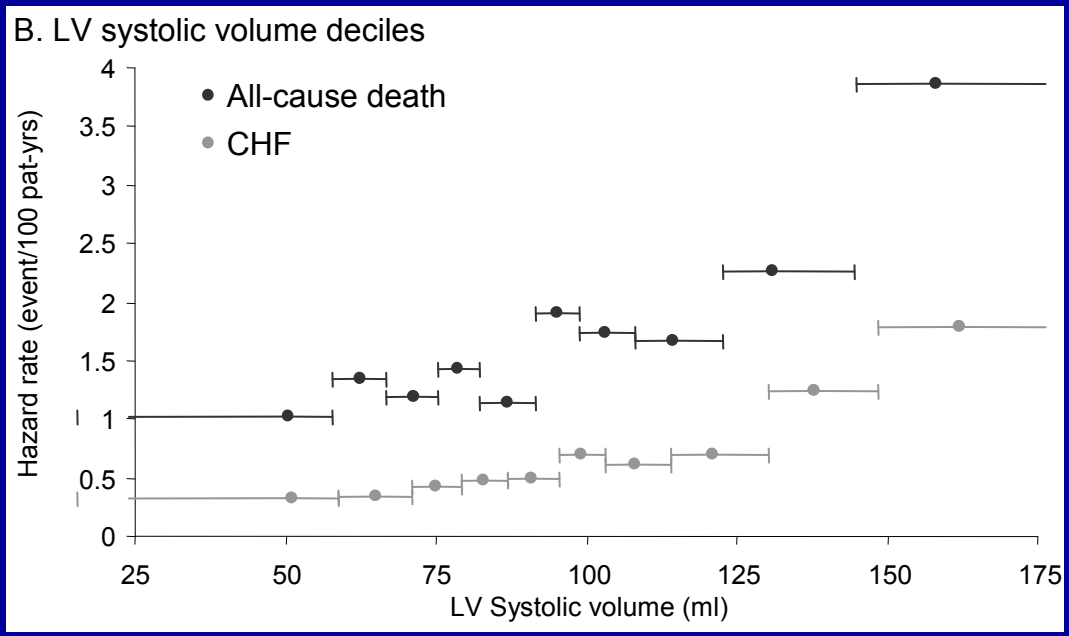
	Nifedipine	Placebo	HR (95% CI)
Disabling stroke (number of patients, rate per 100 patient.years)	77 (0.41)	99 (0.53)	0.78 (0.58-1.05) p=0.10
All strokes and TIAs (number of patients, rate per 100 patient.years)	187 (1.01)	258 (1.40)	0.72 (0.60-0.87) p=0.00063
Strokes	138	174	
TIAs	91	148	

Poole-Wilson et al Lancet 2004:364;849-857

ACTION: hazard ratio for various end-points

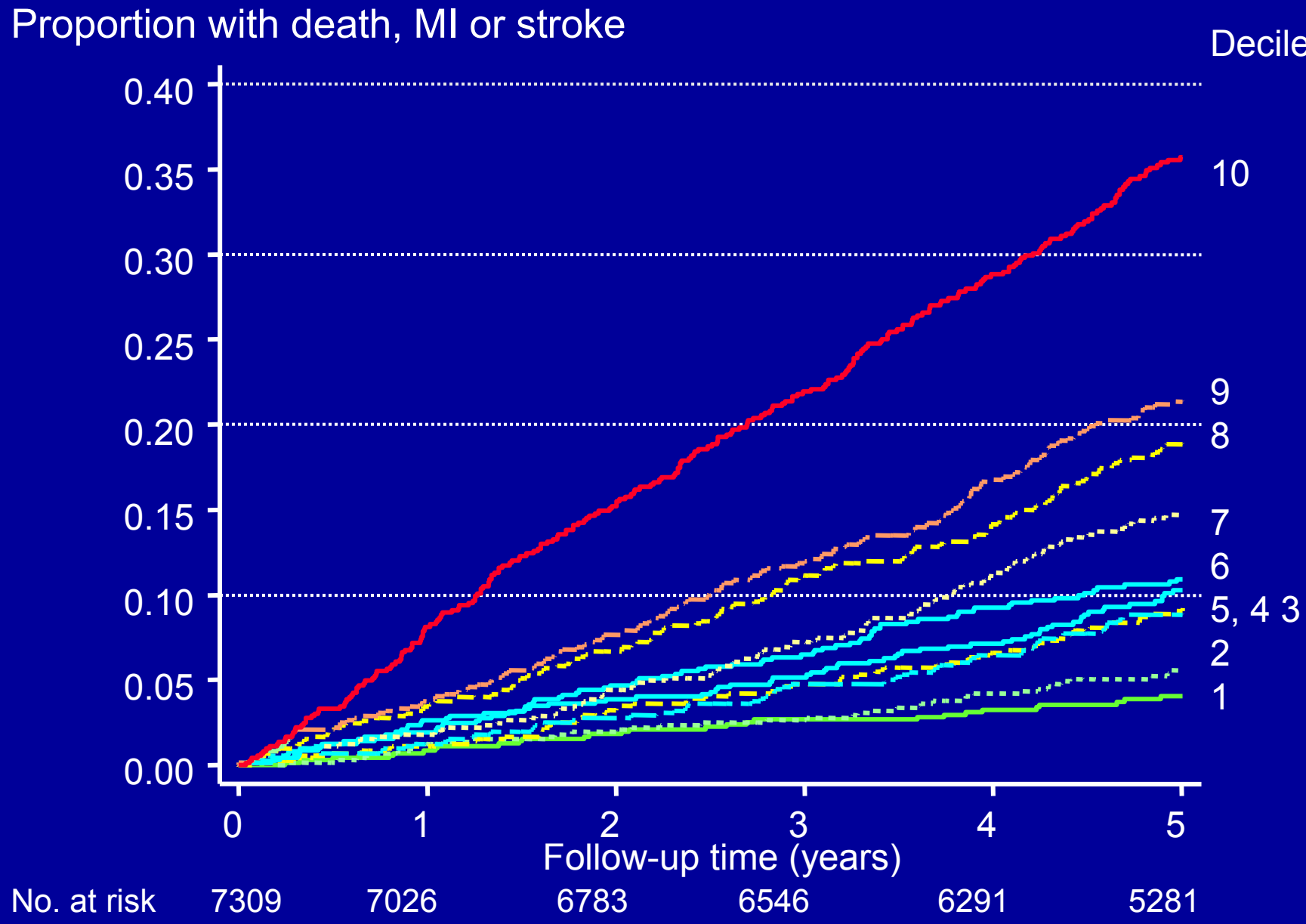






Left ventricular ejection fraction and systolic volume in relation to risk of death or onset of heart failure

ACTION: Life table plots of risk of death, MI or stroke by decile of risk



Clayton TC et al BMJ 2005;331:869

Risk in angina pectoris in order of decreasing contribution

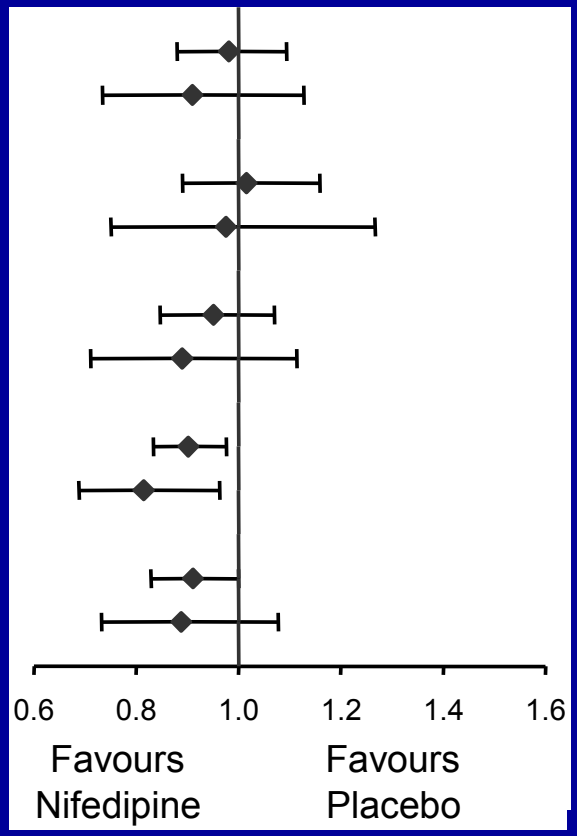
1. age,
2. left ventricular ejection fraction
3. smoking
4. white blood cell count
5. diabetes
6. casual blood glucose concentration
7. creatinine concentration, previous stroke
8. at least one angina attack a week
9. coronary angiographic findings (if available)
10. lipid lowering treatment
11. QT interval
12. systolic BP ≥ 155 mm Hg
13. number of drugs used for angina
14. previous myocardial infarction
15. sex.

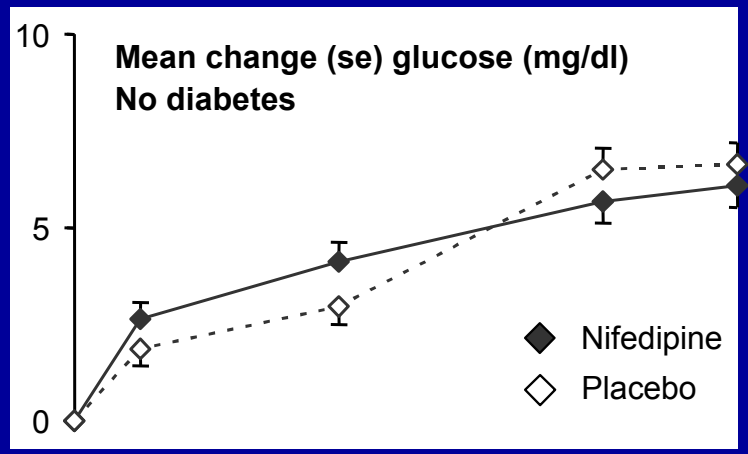
16 variables
in model
predicting outcome

Clayton TC et al BMJ 2005;331:869

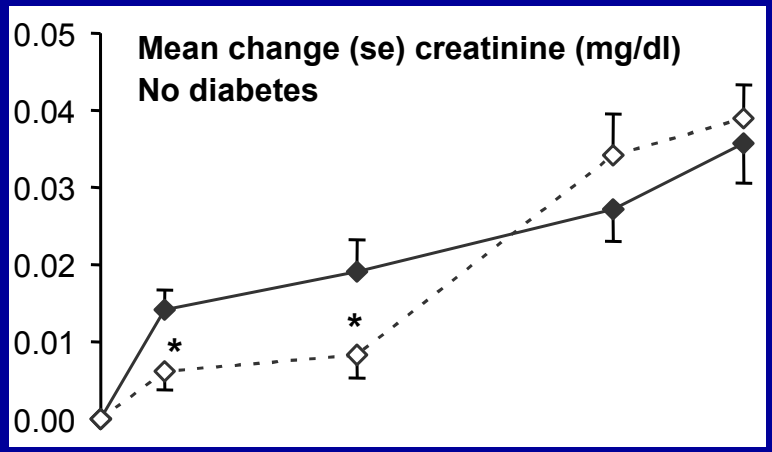
ACTION: impact of diabetes

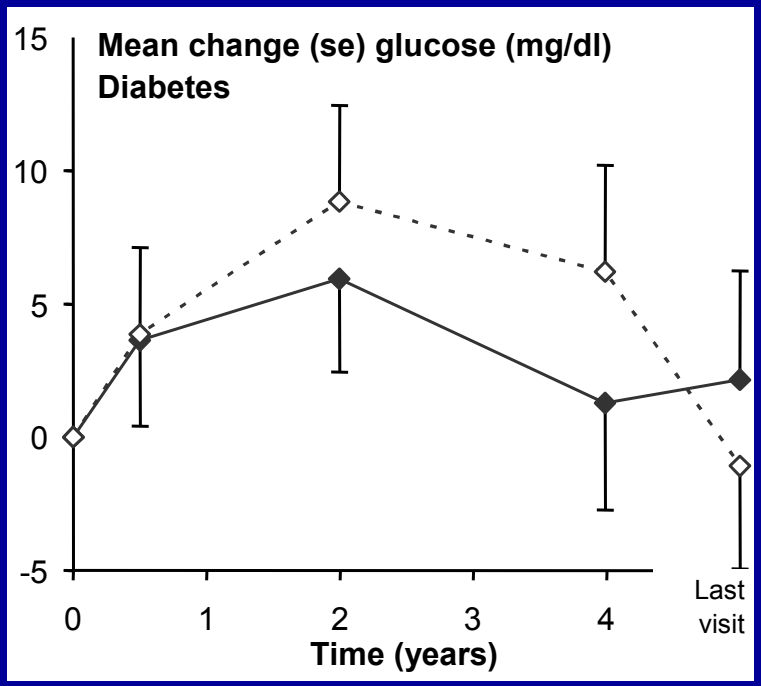
	No. of patients with event (rate/ 100 pat.y			
	Nifedipine	**Placebo**	**Hazard ratio (95% CI)**	***P***
No diabetes	(n=3258)	(n=3294)		
Diabetes	(n=567)	(n=546)		
Primary endpoint for efficacy				
No diabetes	640 (4.25)	657 (4.34)		0.9
Diabetes	164 (6.78)	171 (7.46)		
Primary endpoint for safety				
No diabetes	449 (2.87)	446 (2.83)		0.8
Diabetes	113 (4.37)	112 (4.48)		
Cardiovascular events				
No diabetes	546 (3.63)	578 (3.81)		0.6
Diabetes	148 (6.12)	158 (6.89)		
Death, cardiovascular events, or procedures				
No diabetes	1181 (8.86)	1295 (9.83)		0.3
Diabetes	258 (12.22)	288 (15.12)		
Vascular event or revascularisation				
No diabetes	827 (5.81)	908 (6.39)		0.8
Diabetes	199 (8.80)	213 (9.94)		



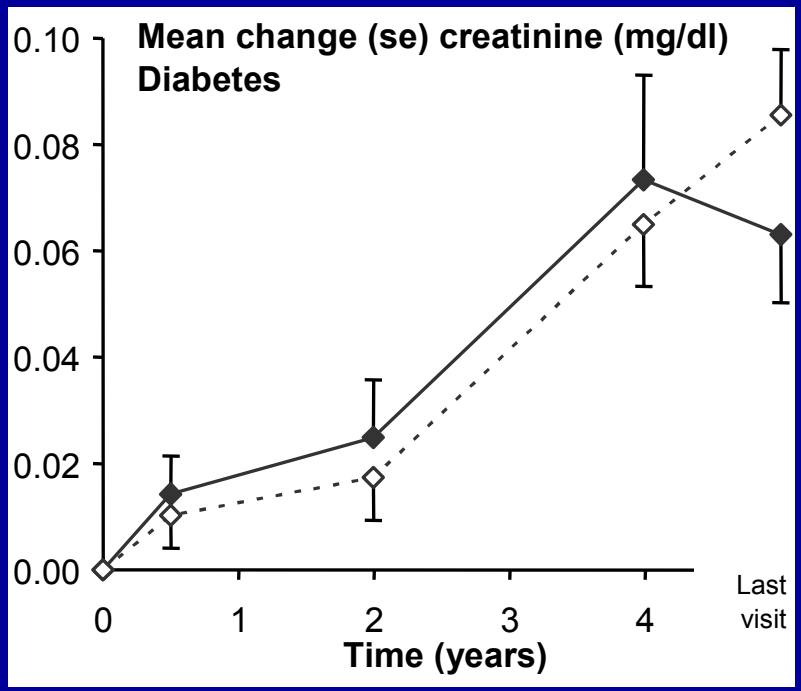


No diabetes





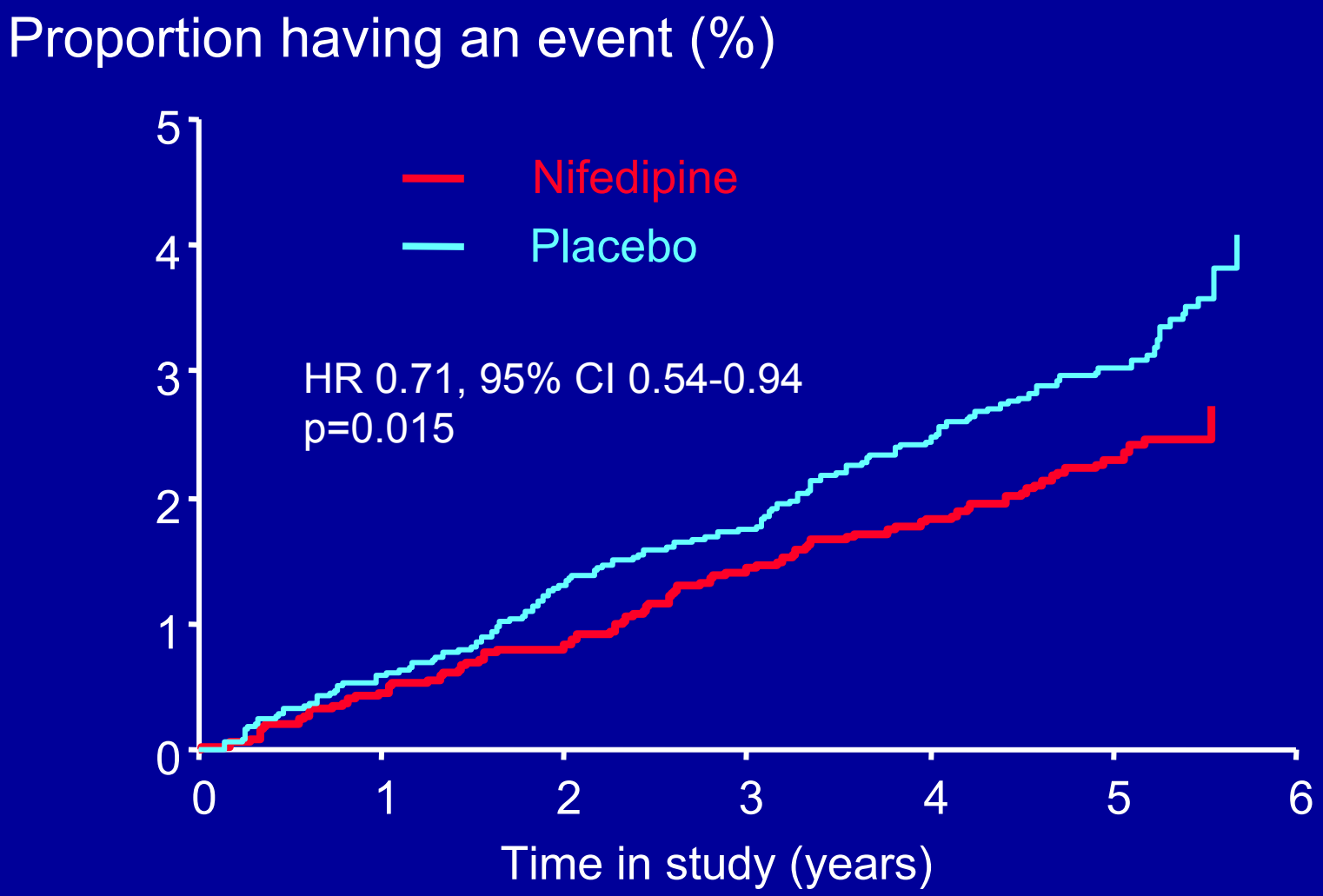
Diabetes



Glucose

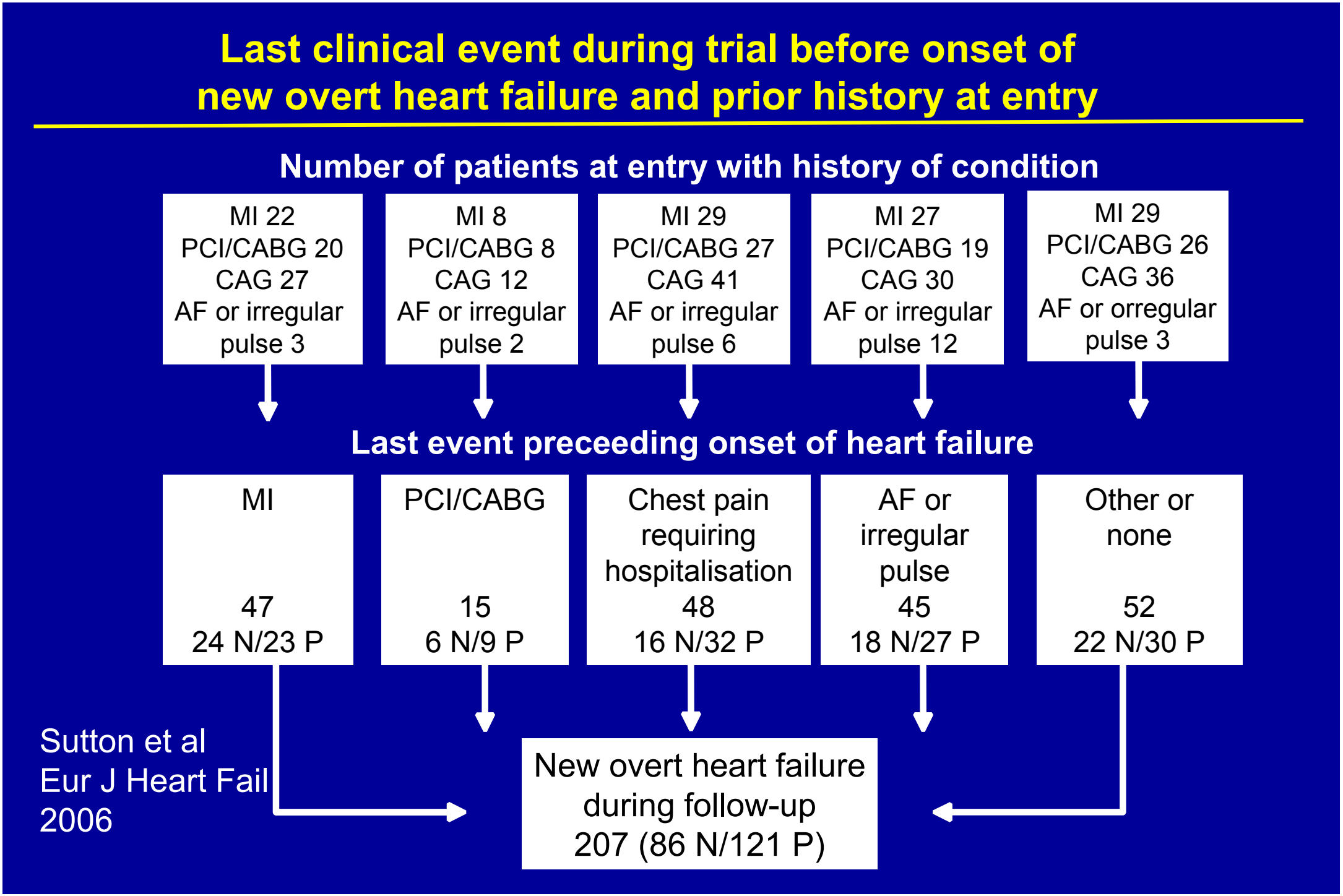
Creatinine

New onset heart failure in ACTION

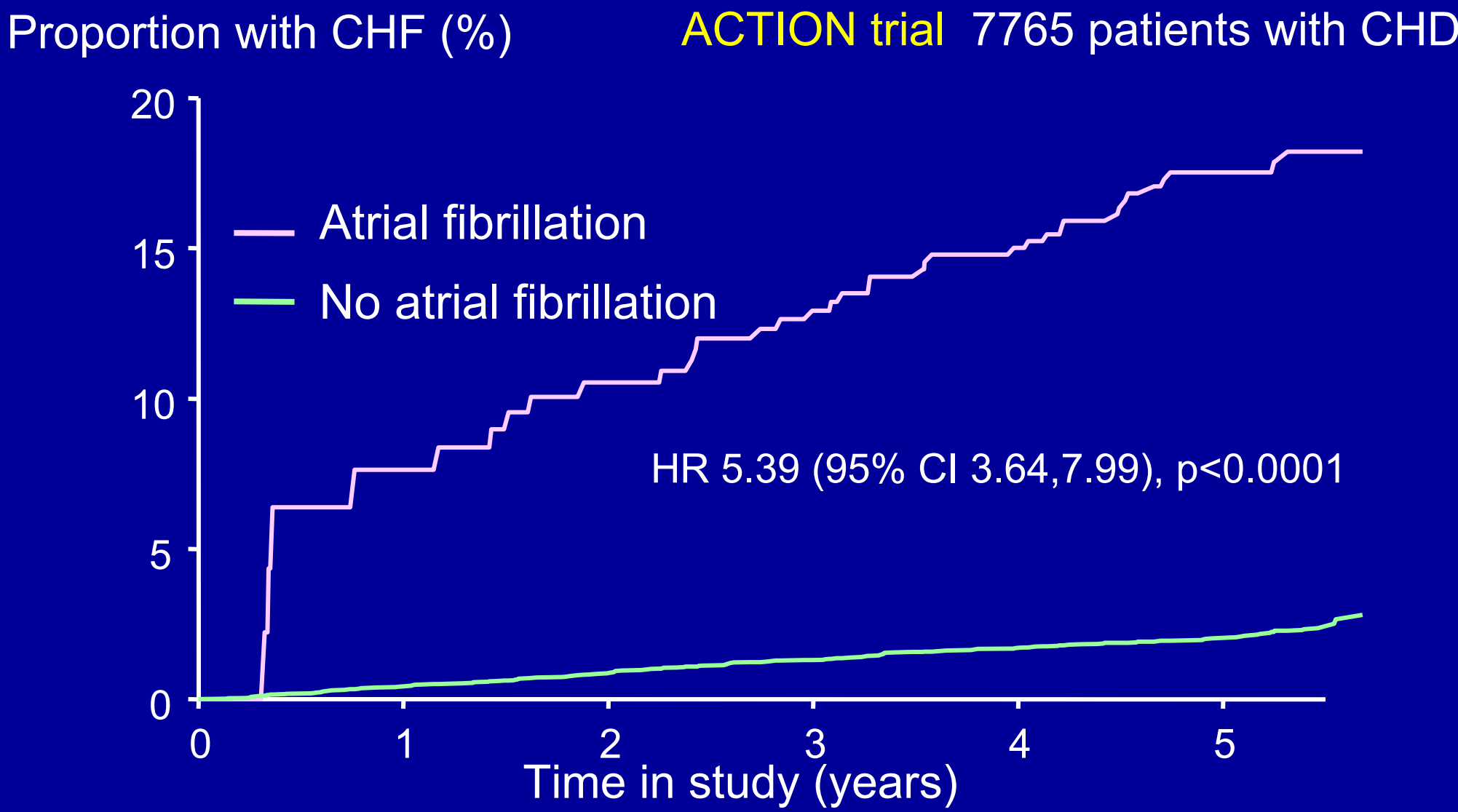


Poole-Wilson et al Lancet 2004:364;849-857

Last clinical event during trial before onset of new overt heart failure and prior history at entry



Development of heart failure in patients with CHD and AF



Poole-Wilson et al Lancet 2004:364;849-857

Clinical course of isolated angina due to coronary heart disease

7765 patients in ACTION trial. Follow-up 4.9 years
2170 had isolated angina pectoris

1.4 deaths/100 patient years. 147/2170
8.7 deaths or cardiovascular event/ 100 patient years 761/2170
0.7 strokes/100 patient years

First event : death 82, MI or HF 112, revascularisation 171, hospitalisation with chest pain 396

612 (6.8/100 patient-years) underwent coronary angiography.
371 revascularised.
Mortality greatly increased after revascularisation

Poole-Wilson et al Eur Heart J 29007;28:1928-1935

ACTION: conclusions

1. Nifedipine GITS is safe
2. No impact on mortality
3. Reduced hospital admission for angina
4. Reduced coronary angiography
5. Reduced CABG
6. Reduced stroke
7. Reduced vascular events
8. Reduced heart failure
9. Marginally improves diabetes
10. Unaffected by renal function
11. Reverse remodelling of the heart
12. Especially effective in hypertension
13. Very cost-effective

Drugs in angina and secondary prevention of coronary heart disease

For chest pain

- Nitrates
- Beta-blockers
- Calcium antagonists

For prognosis

1. Aspirin
2. Statin
3. Beta-blocker (after MI)
4. Calcium antagonists
5. ACE inhibitor
   if specific indication

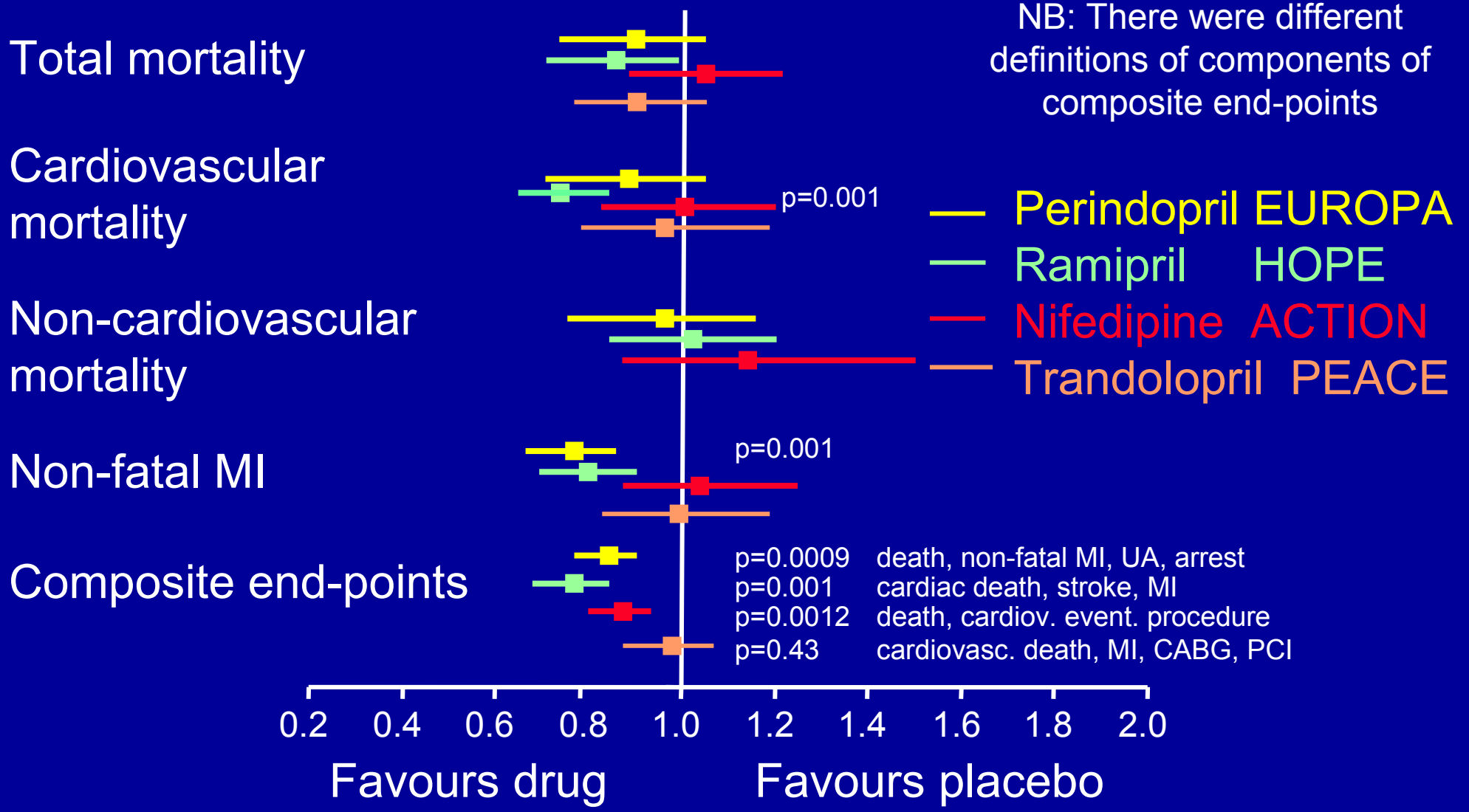
Mortality studies in chronic stable angina, coronary heart disease or high risk patients

				Mean mortality rate/100 patient.years
HOPE	Ramipril	9297	5 y	2.5
EUROPA	Perindopril	10500	3.75 y	1.6
PEACE	Trandolapril	8290	4.9 y	1.1
IONA	Nicorandil	5000	21 months	3.1
ACTION	Nifedipine (Gits)	7765	5 y	1.5
CAMELOT	Amlodipine	1318	2 y	0.9
CAMELOT	Enalapril	1328	2 y	0.9
JMIC-B	Nifedipine/ACEi	1650	3y	0.5

Comparison of patients in recent CHD trials

	HOPE 2000	EUROPA 2003	ACTION 2004	PEACE 2004
Patient number	9297	10500	7765	8290
Age	66	60	63	64
% male	73.5	75.5	80	82
Hist MI	52	64.9	52	55
Periph. vasc. dis.	44	7.3	13	NA
Hypertension	47	27	52	46
Diabetes	38	12	14	17
Hypercholesterol.	65	63	63	NA
Smoking	14	NA	18	14
Aspirin	75	92	71	90
Lipid lowering	28	57	68	70
Beta blockers	39	62	80	60
Ca antagonists	47	32	NR/22 (in past)	36
Nitrates	NA	43	77	NA
HR	69	68	64	NA
SBP	139	137	137	134
DBP	79	82	80	78

Outcomes in recent large trials

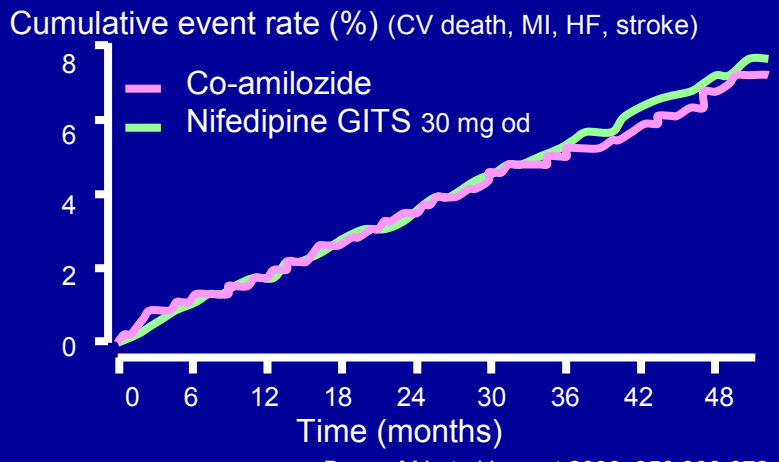


NB: There were different definitions of components of composite end-points

Perindopril EUROPA
Ramipril HOPE
Nifedipine ACTION
Trandolopril PEACE

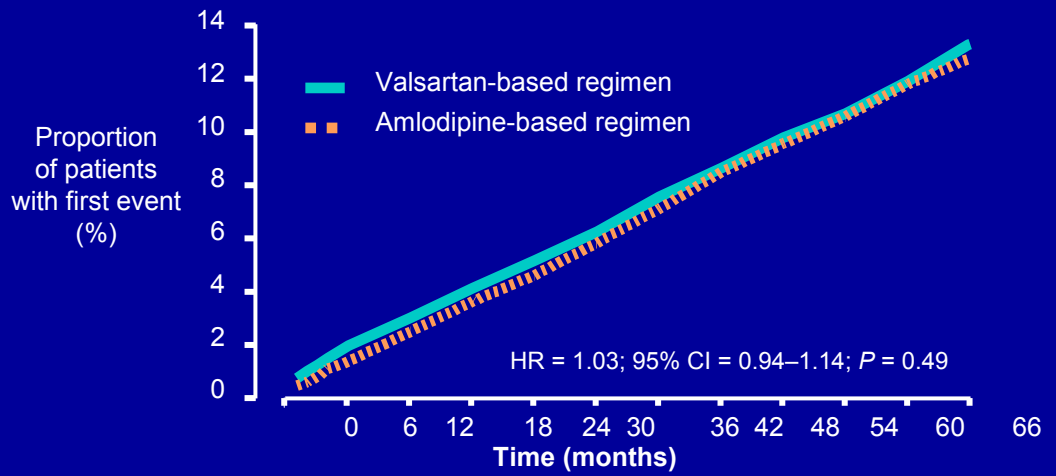
EUROPA Lancet 2003;362;782-788 ACTION Lancet 2004;849-857 HOPE N Engl J Med 2000:342;145-153
CAMELOT Nissen et al JAMA 2004;292:2217-2226 PEACE NEJM 2004;351:2058-2068

INSIGHT: primary end-point



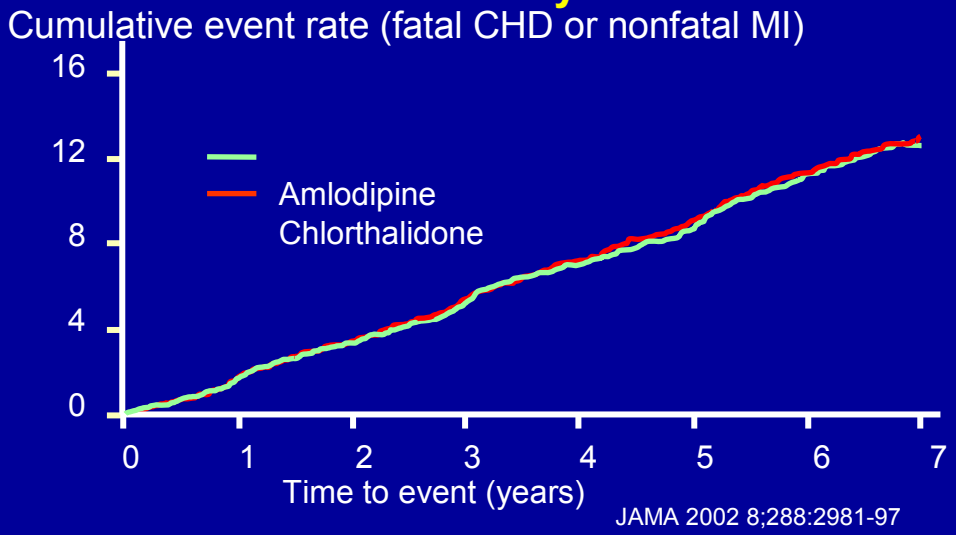
Brown MJ et al Lancet 2000; 356:366-372

VALUE: primary endpoint



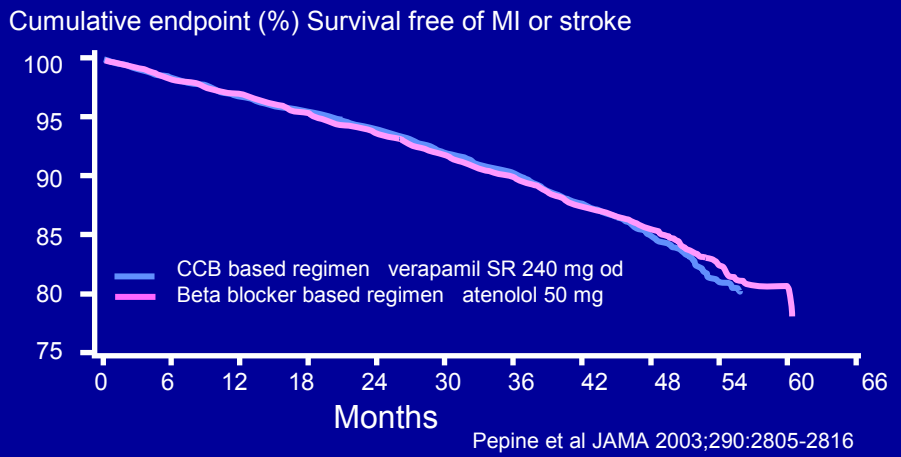
Julius S et al Lancet 2004;363:2022-2031

ALLHAT: Primary outcome



JAMA 2002 8;288:2981-97

INVEST: primary endpoint



Pepine et al JAMA 2003;290:2805-2816

ASCOT: primary and secondary end points for amlodipine and perindopril vs atenolol and bendroflumethiazide

End point	Hazard ratio	95% CI	p
All-cause mortality	0.86	0.78-0.96	0.005
Primary end point: nonfatal MI and fatal CHD	0.90	0.78-1.03	0.12
Total coronary end point: primary end point + new onset angina + fatal and non-fatal heart failure	0.86	0.78-0.96	0.0048
Fatal and nonfatal stroke	0.77	0.66-0.90	0.0007
All CV events and revascularization procedures	0.84	0.77-0.90	<0.0001
CV mortality	0.76	0.65-0.91	0.0017
New onset diabetes	0.68	0.60-0.77	0.0001

Presented at ACC MARCH 2005

Personal view of clinical implications of recent trials for treatment of coronary heart disease

1. Aspirin and a statin should be given to most patients with coronary heart disease.

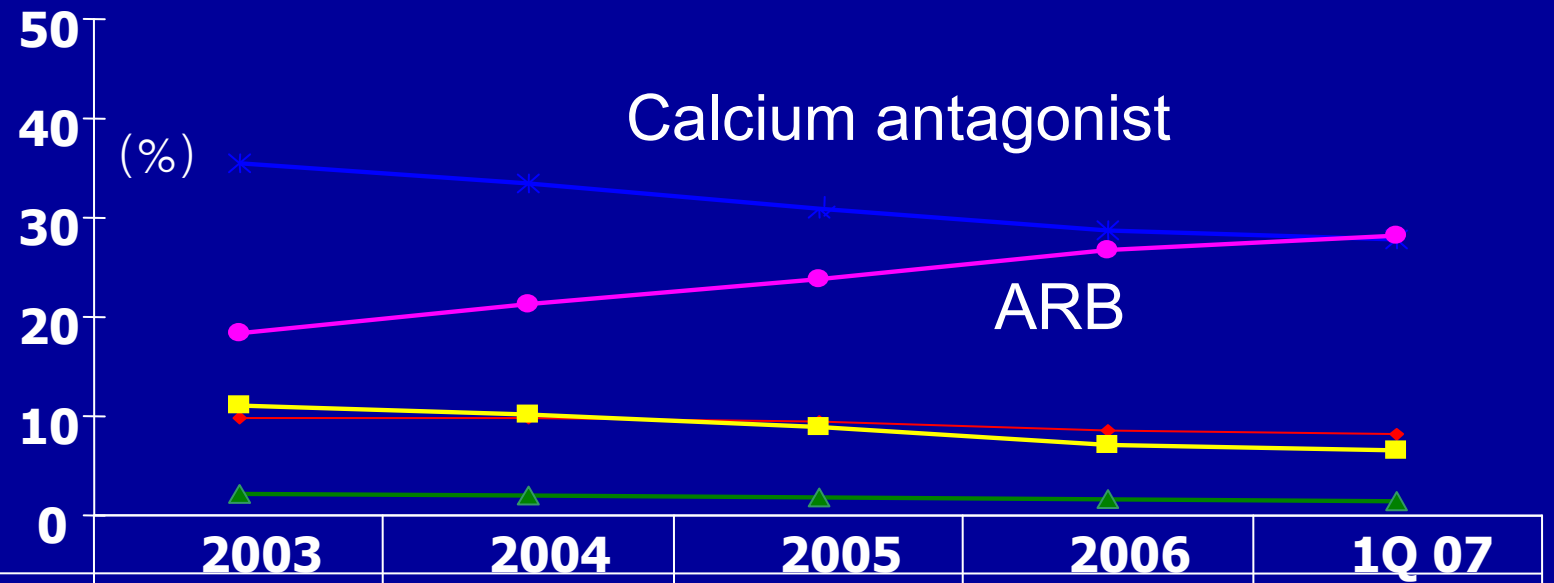
2. Beta-blockers should be given to treat angina and post infarction.

3. Patients with coronary heart disease and angina pectoris should be treated with a long acting calcium antagonist.

4. Patients with hypertension and coronary heart disease should be treated with a calcium antagonist and an ACE inhibitor or ARB.

5. Patients at high risk of a cardiovascular event can be treated with aspirin, a statin and either a calcium antagonist or an ACE inhibitor.

Use of anti-hypertensive drugs in Korea



	2003	2004	2005	2006	1Q 07
Ca-ant	35.5	33.4	31.0	28.8	27.8
ARB	18.4	21.3	23.9	26.7	28.2
Beta-blo	9.9	9.9	9.4	8.5	8.2
ACE-inh	11.1	10.1	8.9	7.1	6.6
Diuretics	2.2	2.0	1.8	1.6	1.5