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Preventing heart failure by preventing coronary artery disease progression

Hypertension

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Disclosure Information

- ***Grants/Research Support:*** **BG Medicine, Roche Diagnostics**

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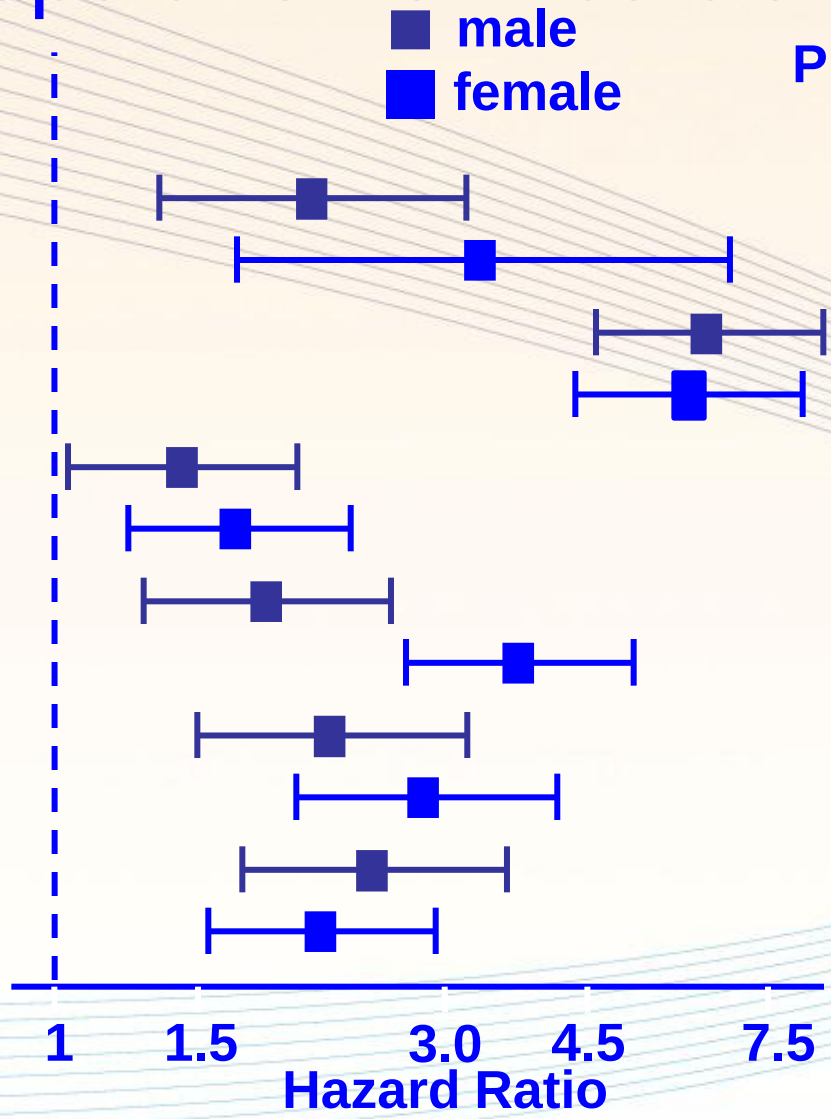
Major risk factors for the development of heart failure?

- Hypertension
- Myocardial infarction
- Diabetes
- Left ventricular hypertrophy
- Valvular disease

Heart failure development: Population-attributable risk

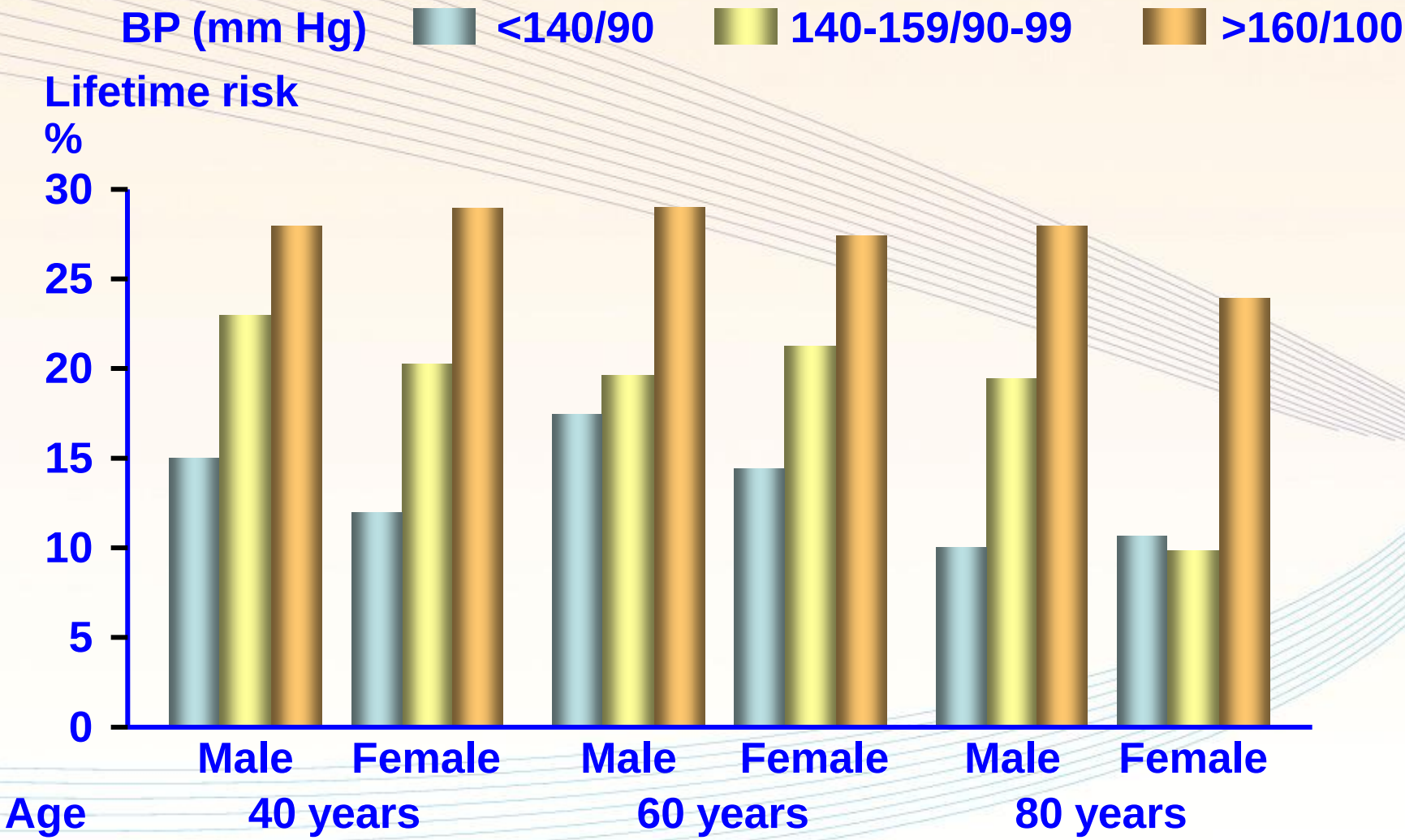


	Prevalence (%)	Attributable risk (%)
Hypertension	60	39
	62	59
MI	10	34
	3	13
Angina pectoris	11	5
	9	6
Diabetes	8	6
	5	12
LVH	4	4
	3	5
Valvular disease	5	7
	8	8

Levy JAMA 1996, 275: 1557

Lifetime risk of heart failure by BP strata

3343 men and 4199 women followed for 25 years – no heart failure at baseline



Lloyd-Jones Circulation 2002, 106: 3038

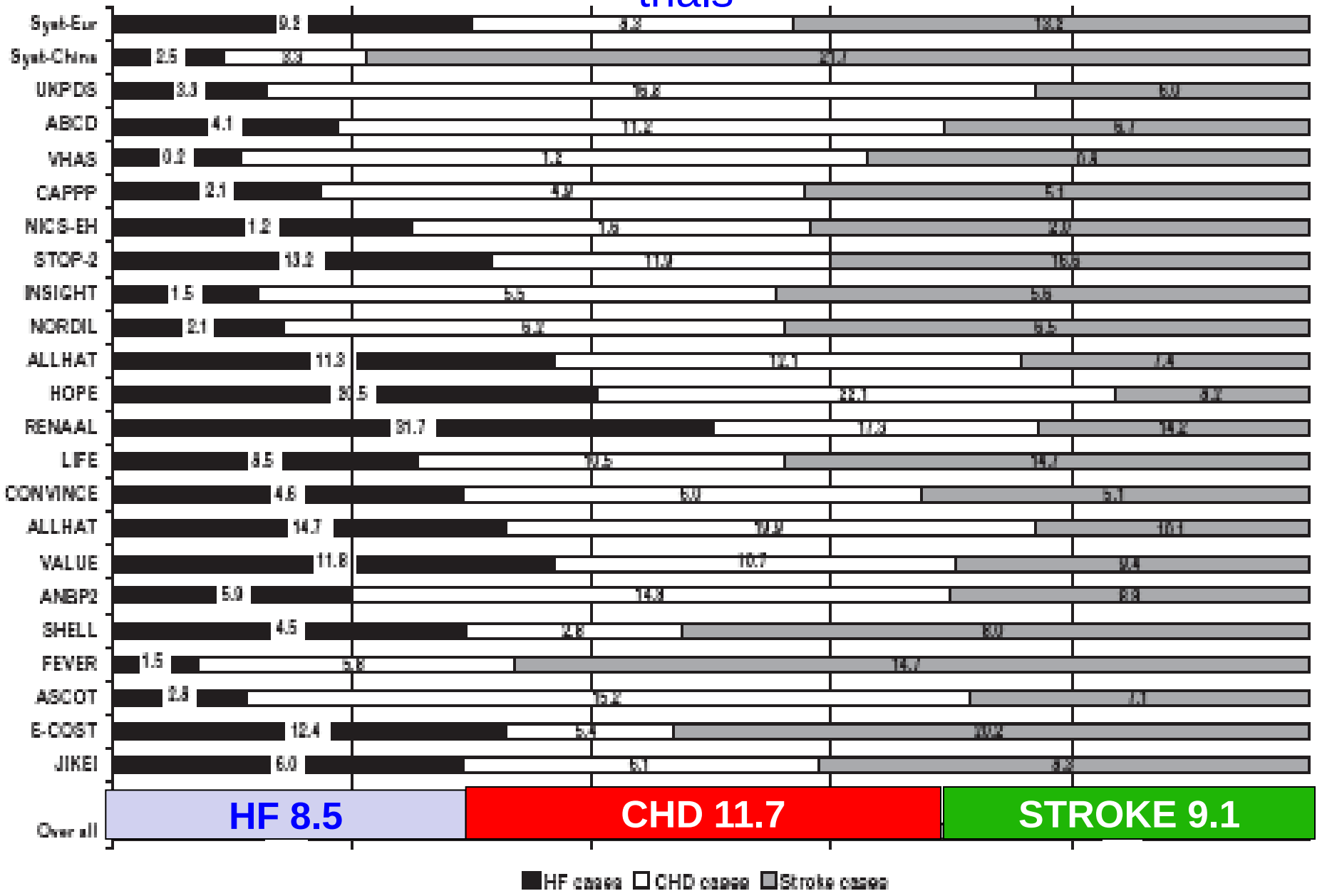
HF event rate in Hypertension trials

Study	HF	Stroke	MI
	rate per 1000 patient years fu		
ALLHAT 6 year rate	0.3	0.2	0.4
LIFE	7.1	10.8	9.2
VALUE	11	10	11.4
ANBP2	5.6	9.2	4.7
EWPHE	13	15	13
Framingham Age adjusted	13.9 men 6.3 women	12.4 men 6.2 women	
Syst-Eur	1.8	3.7	2.6
ONTARGET	6	4.7	4.8

HF incidence is higher than MI incidence in Elderly Hypertensive trials

	EWPHE	STOP	SHEP	SYSTEUR	UKPDS	ALL
n =	840	1627	4736	4695	1148	13046
FU (Months)	56	25	53	24	101	-
Annual rate (%)						
HF	1.8	2.3	1.0	0.9	0.8	1.36
MI	0.9	1.3	0.7	0.6	1.0	0.90

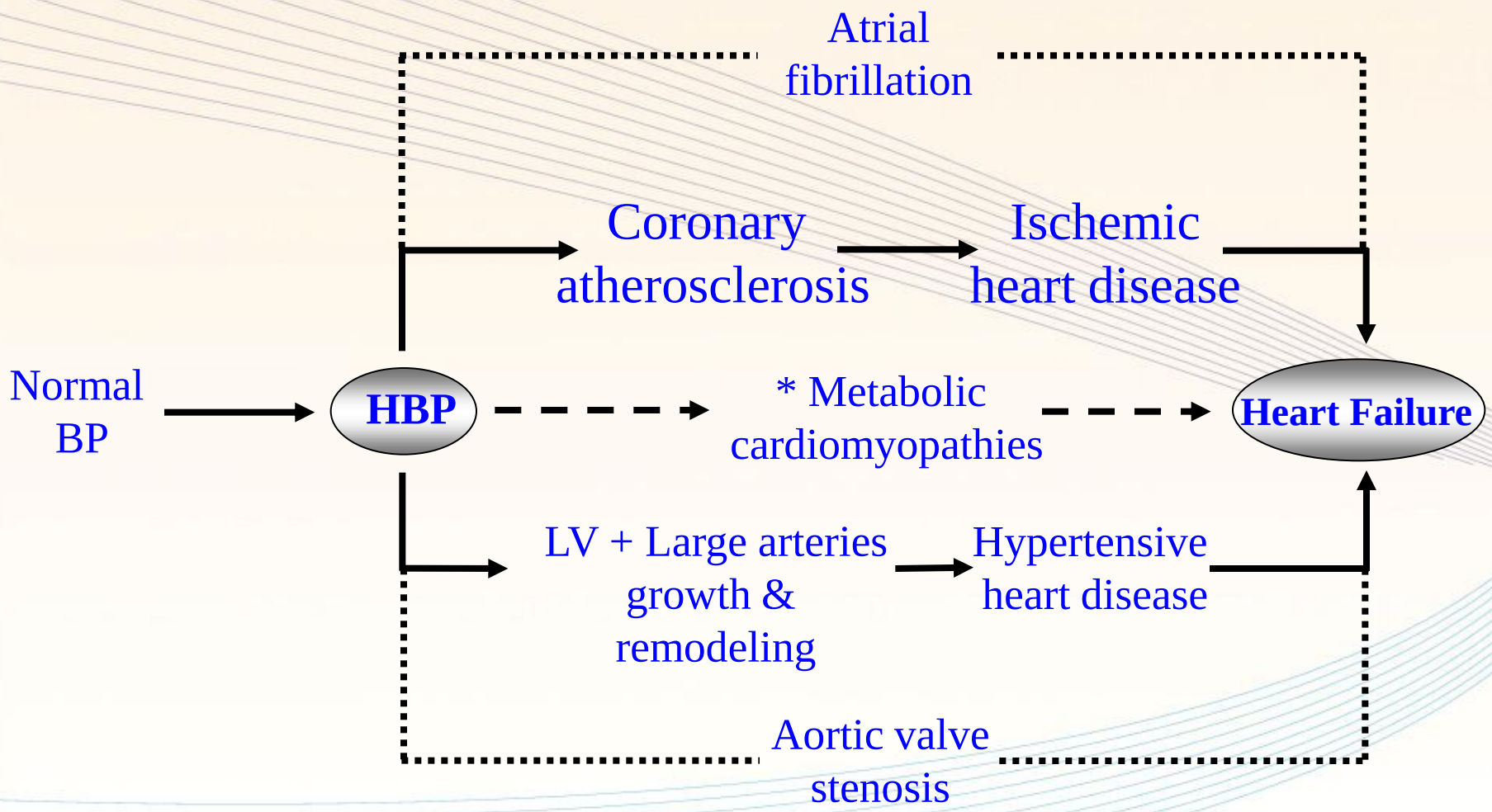
Rate per 1000 patients of major cardiovascular events in HT trials



Mechanisms

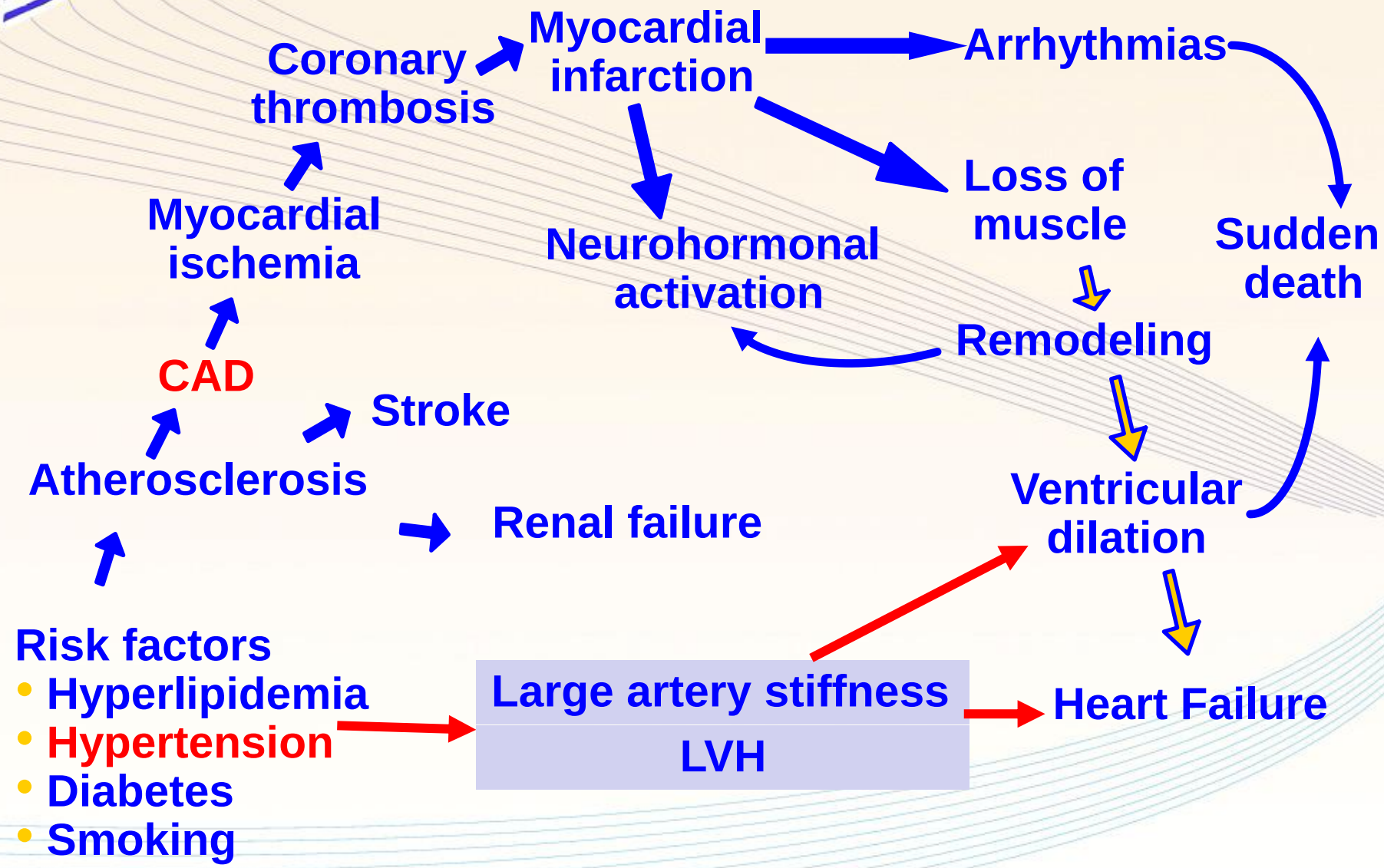
- Hypertensive vasculopathy
  - Endothelial dysfunction
  - Atherosclerosis and CAD
  - Large artery stiffness
- Hypertensive cardiopathy
  - LVH
  - Cardiac fibrosis

Pathways to heart failure in arterial hypertension



* Those associated with diabetes, MetS

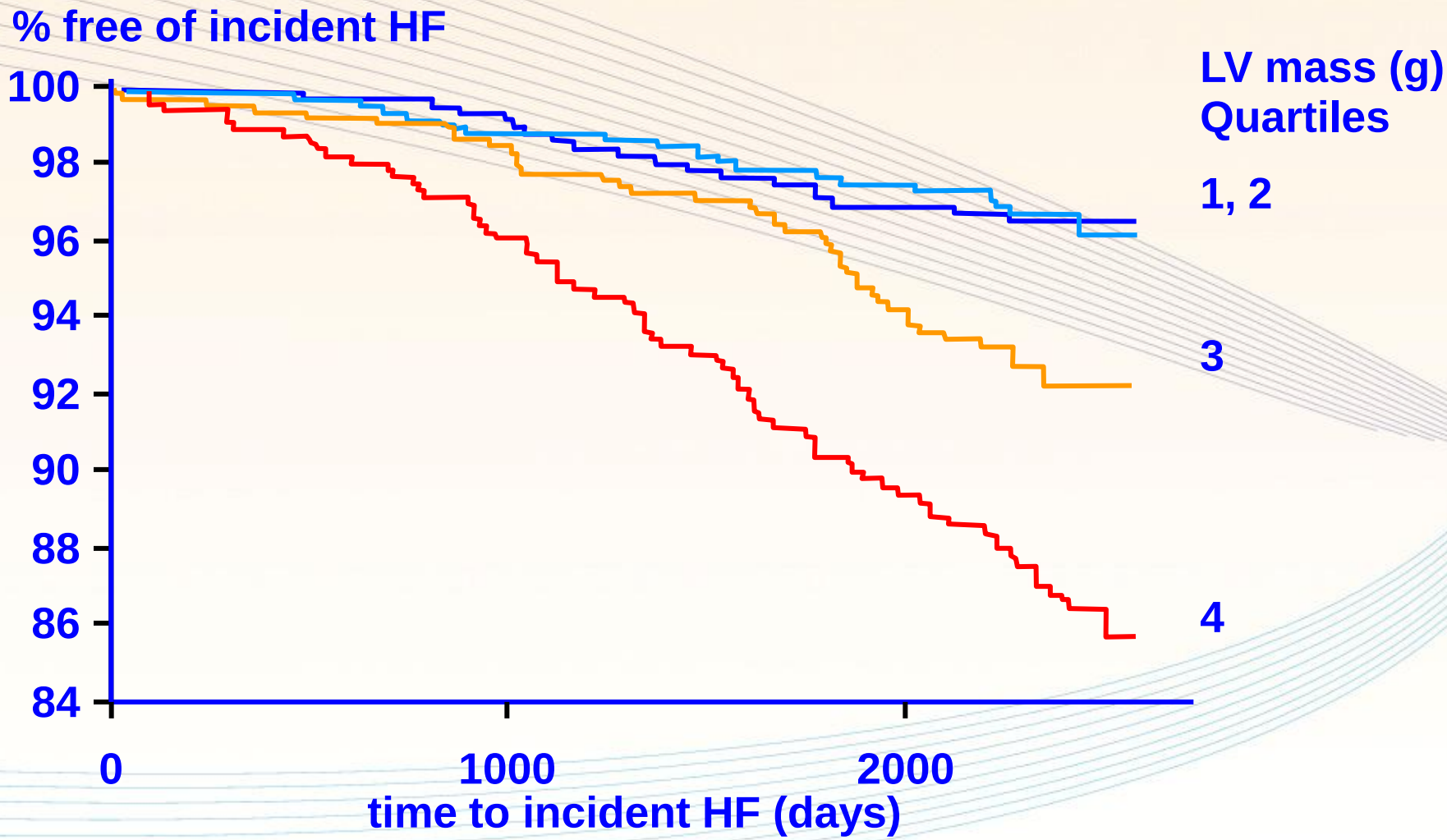
Chain of events leading to heart failure



Modified after Dzau & Braunwald Am Heart J 1991

Influence of LVH on incident heart failure

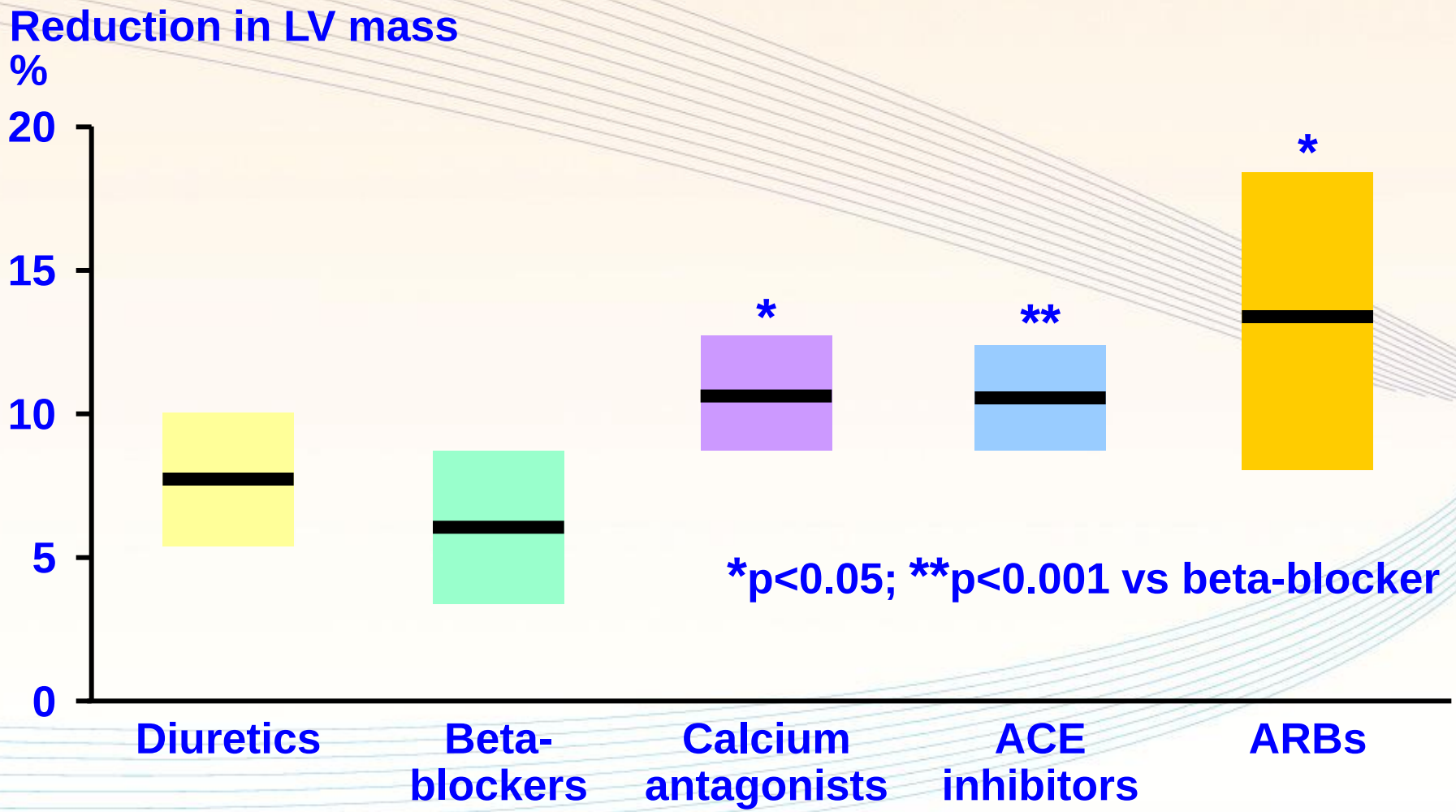
Cardiovascular Health Study: a prospective, longitudinal, population-based study in 2506 subjects with 6-7 years follow-up



Gardin Am J Cardiol 2001; 87:1051

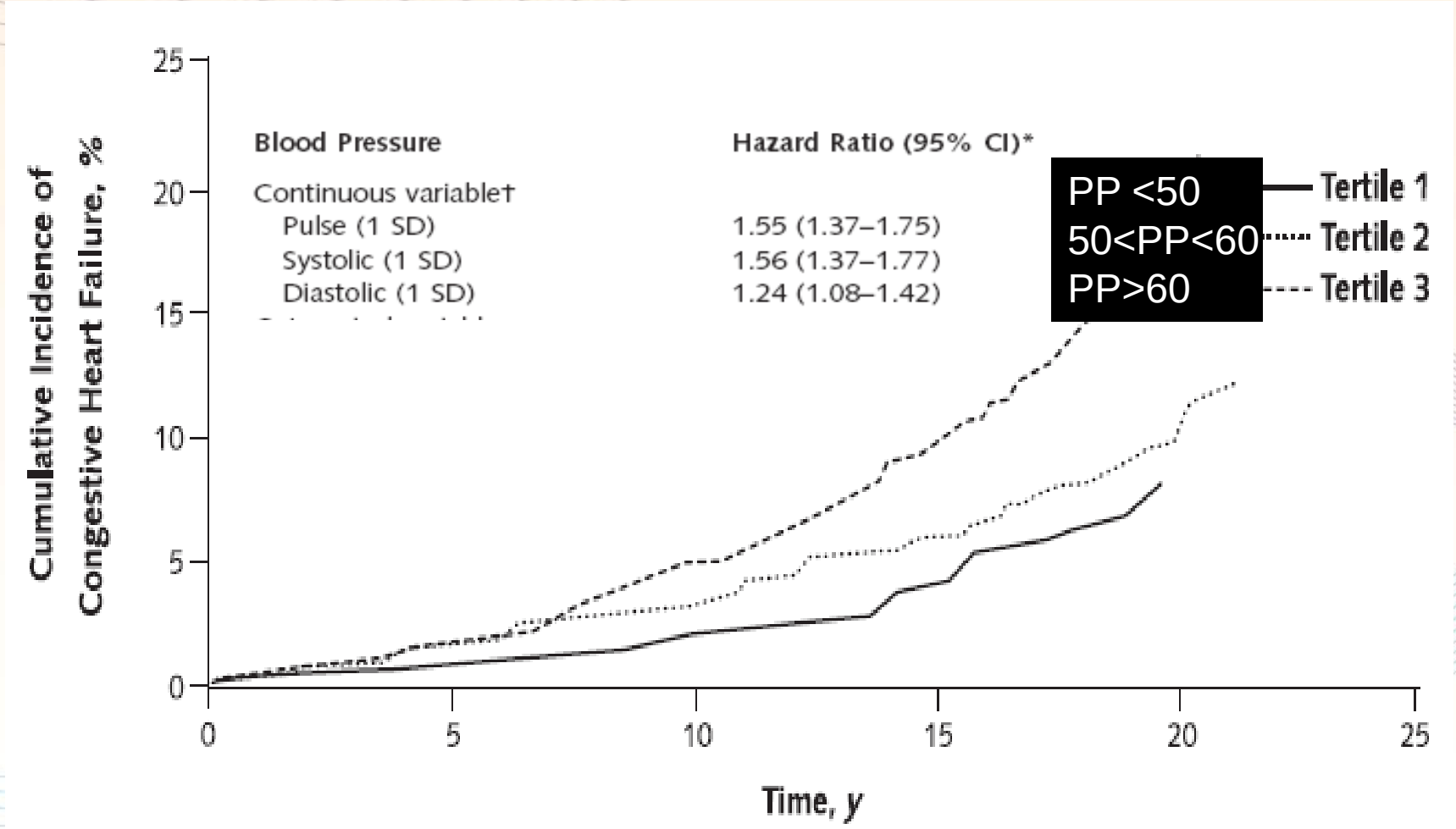
Regression of left ventricular hypertrophy with antihypertensive therapy by drug class

adjusted for change in diastolic BP and duration of treatment



Klingbeil et al Am J Med 2003

Although each component of BP was associated with risk for CHF, PP and SBP conferred greater risk than DBP.

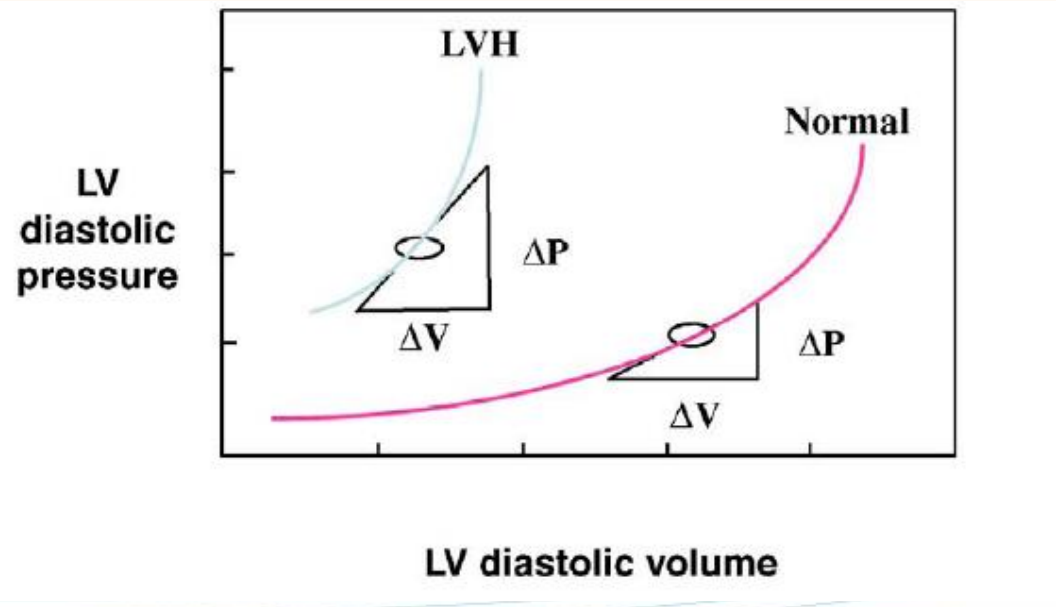


Haider Ann Intern Med, 2003 138: 10

From Hypertension to Heart Failure
Stiff Heart and Stiff Arteries

DBP-Vd

SBP-Vs



Hemodynamic Stress

•LV of hypertensive patients unable to increase the EDV
•LV unable to fill up
• Large arteries unable to help LV empties

•LV end-diastolic pressure
•Left atrial pressure

•Pulmonary stasis develops.

Acute pulmonary oedema + HT

Hemodynamic Stress

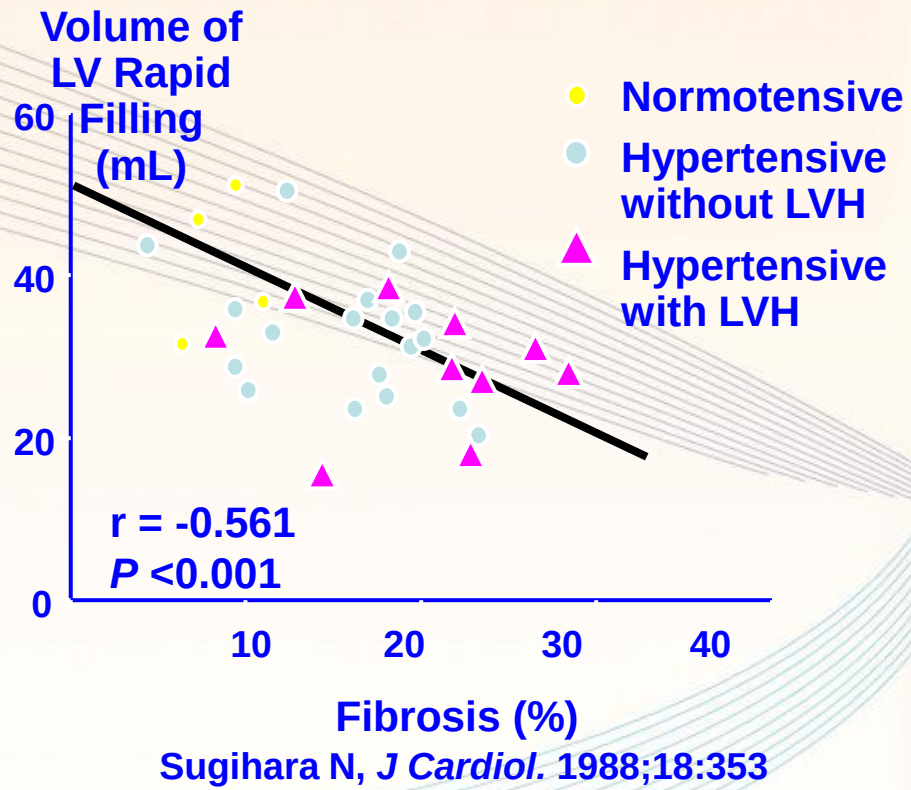
- **LV of hypertensive patients unable to increase the EDV**
- **limited preload reserve**
- **Limited buffering capacity of large arteries**
- **decreased LV relaxation and compliance**

- **LV end-diastolic pressure rises,**
- **Left atrial pressure increases**
- **pulmonary stasis develops.**

Cardiac Fibrosis

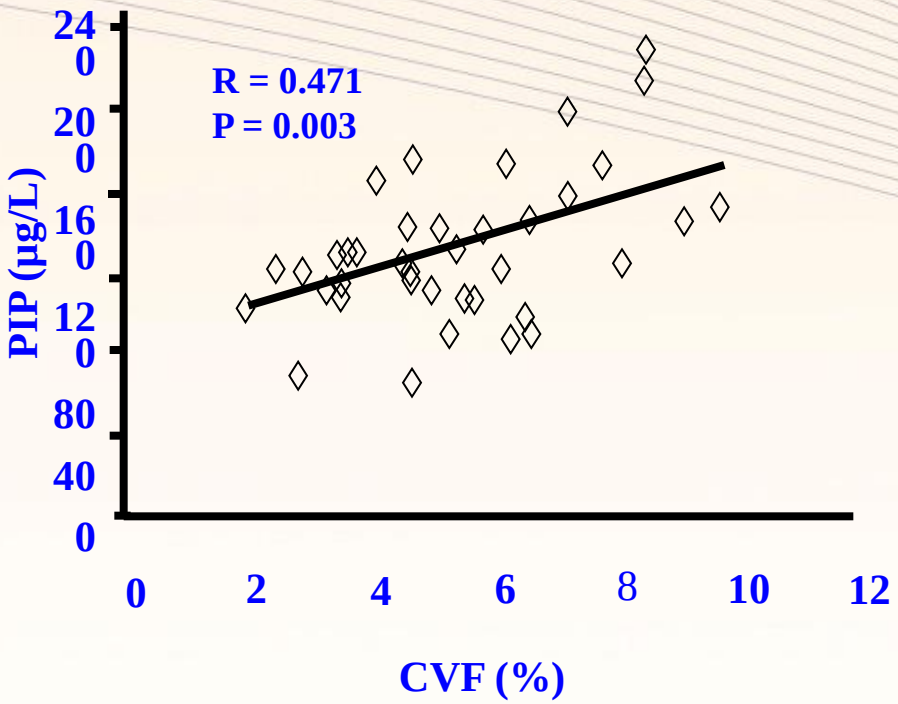
CARDIAC FIBROSIS

- **STIFFNESS**
  - **Diastolic Dysfunction**
    - **HEART FAILURE**
- **HETEROGENEITY**
  - **Systolic Dysfunction**
    - **HEART FAILURE**
  - **Arrhythmias**
    - **SUDDEN DEATH**



Sugihara N, *J Cardiol.* 1988;18:353

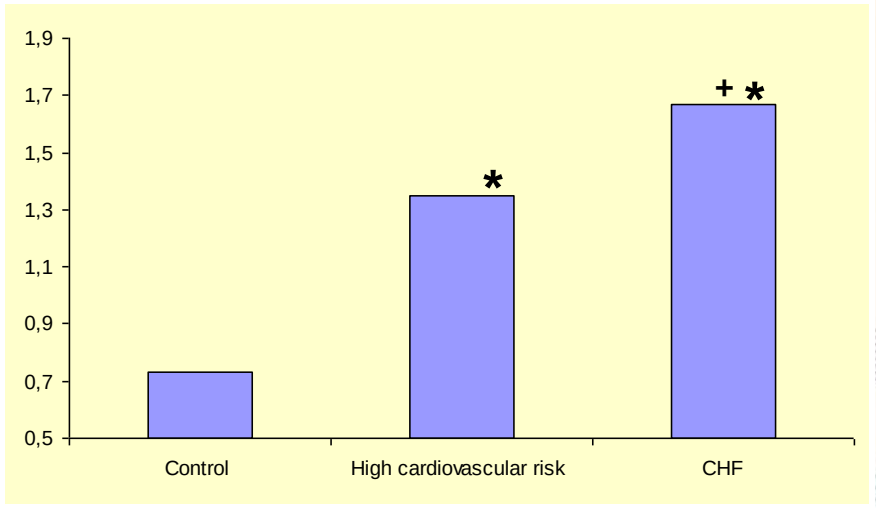
Cardiac ECM Assessment



Querejeta Circulation 2000;101:1729-35

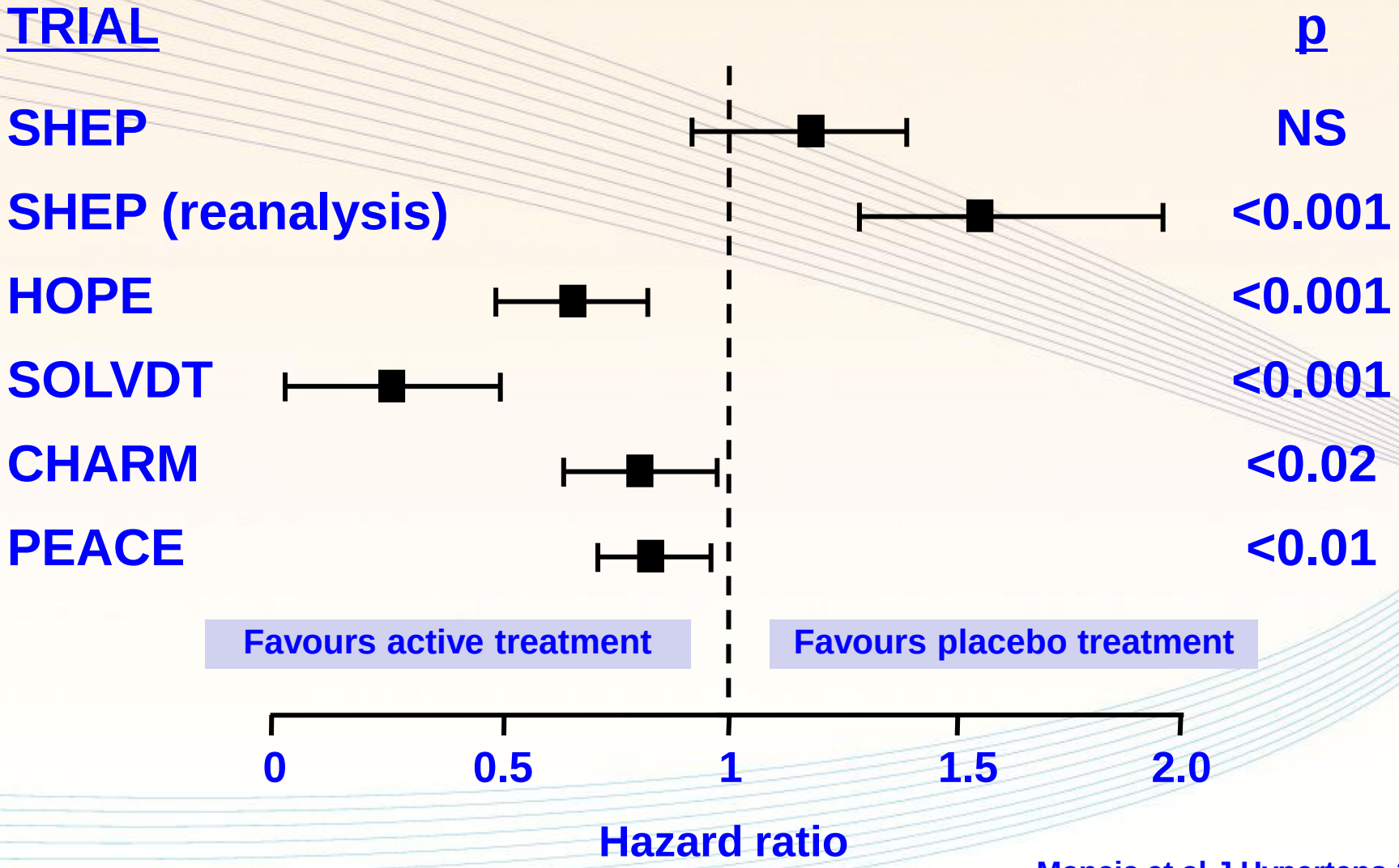
Hypertensive diabetics type 2

PIIINP/(MMP1+1) ratio levels



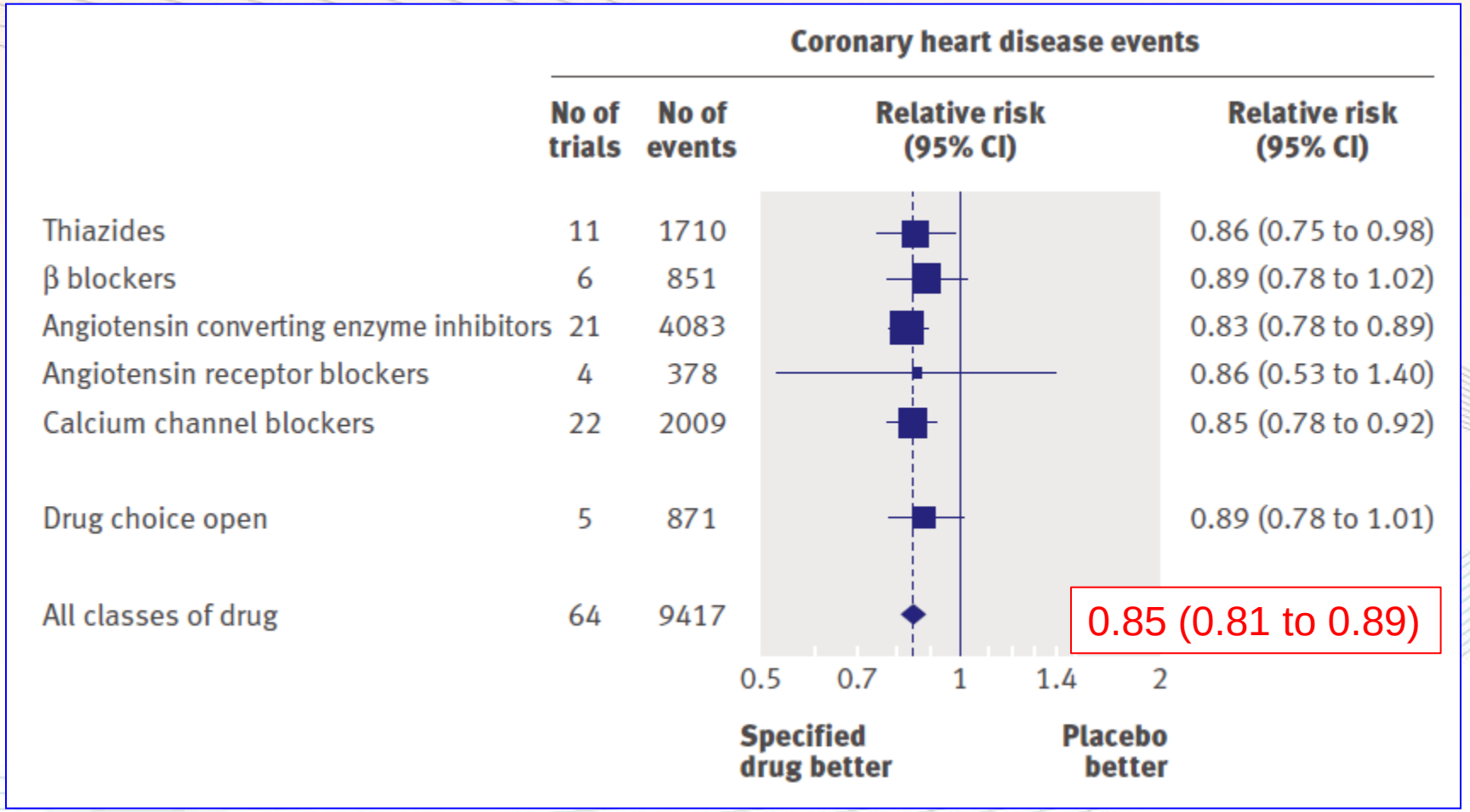
Zannad Eur J Heart Failure

New onset diabetes in placebo-controlled trials



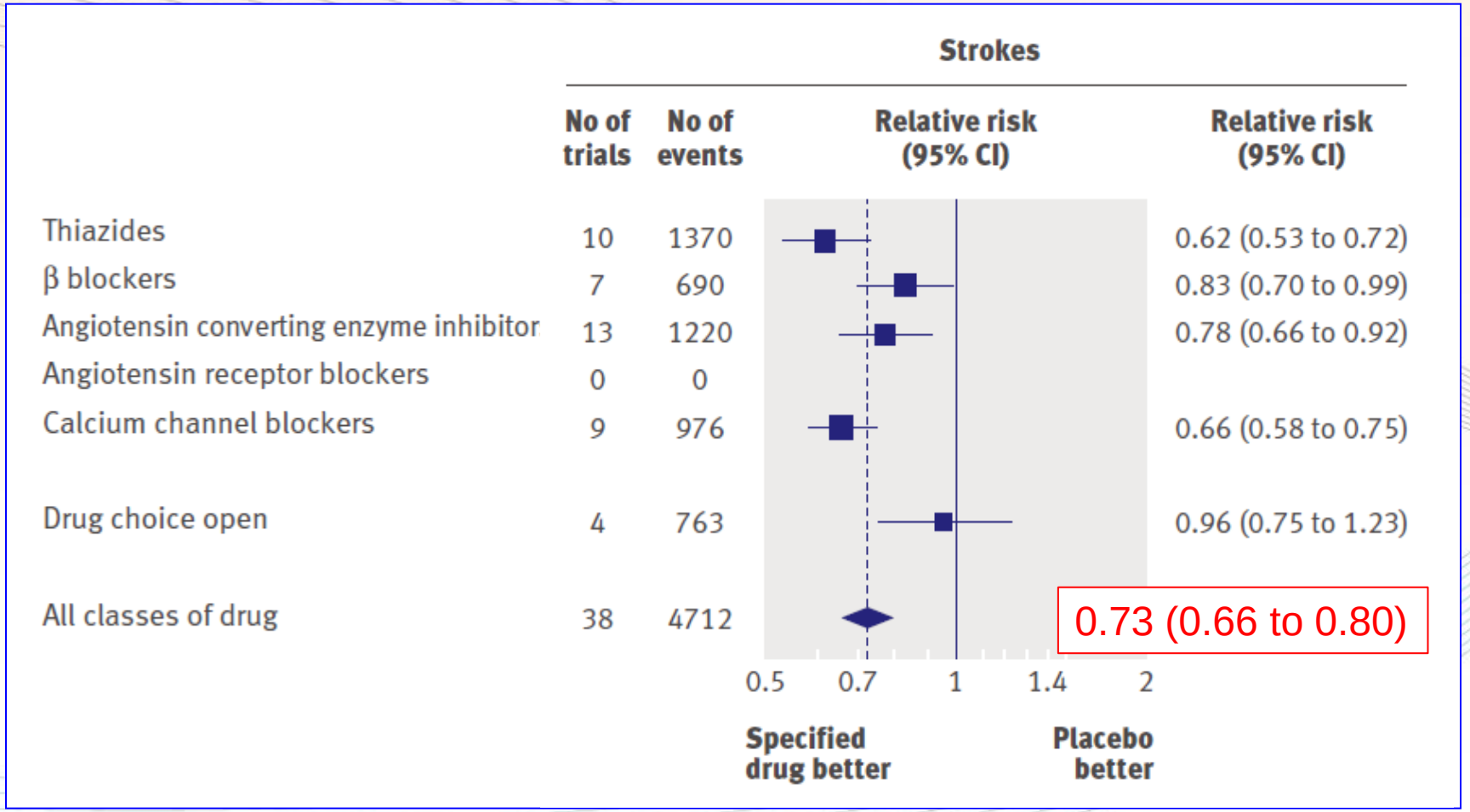
Mancia et al J Hypertens 2006

Relative risk estimates of CHD in single drug blood pressure difference trials according to class of drug



Law MR *et al.* BMJ 2009;338:b1665

Relative risk estimates of Stroke in single drug blood pressure difference trials according to class of drug



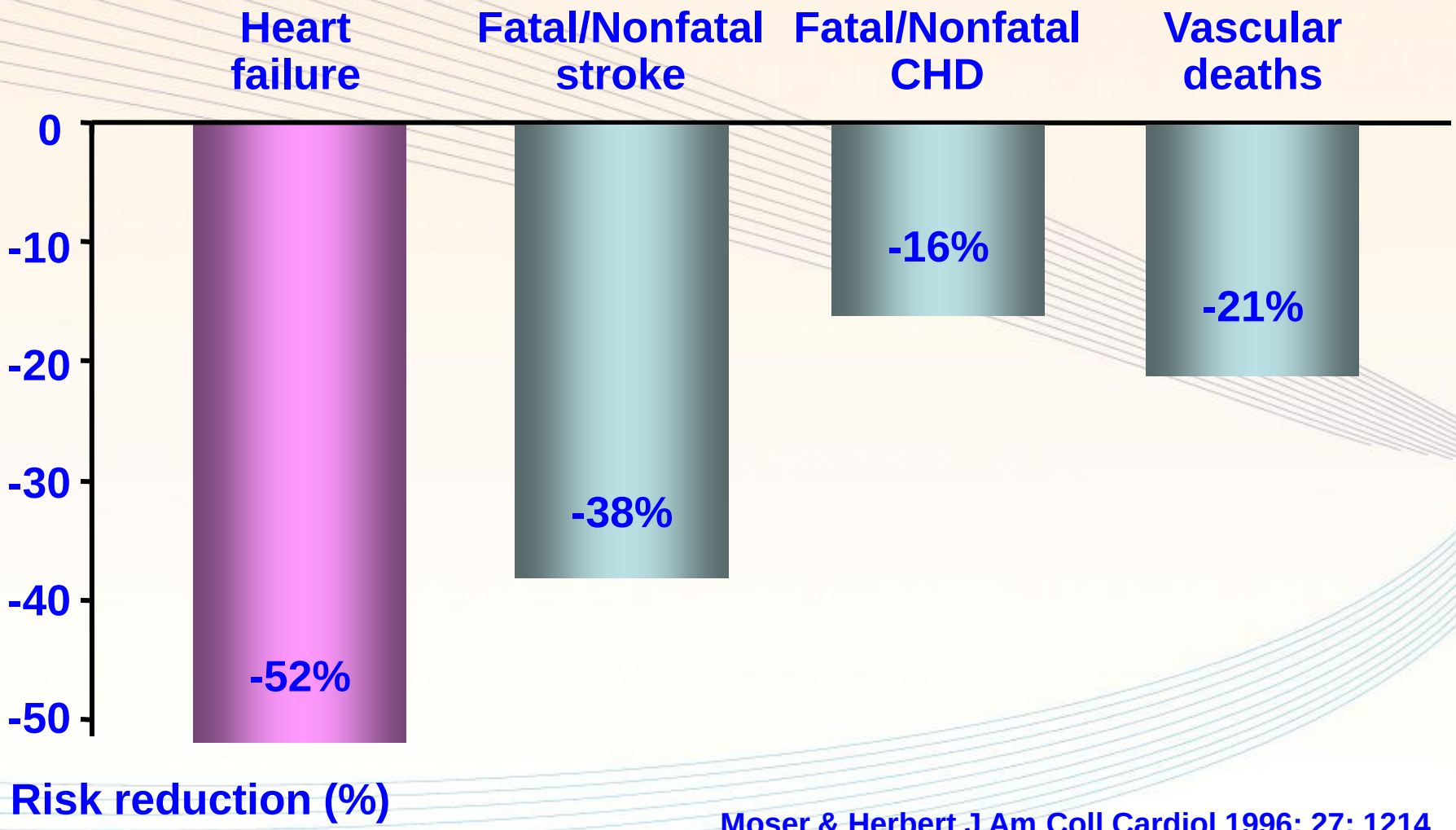
Law MR *et al.* BMJ 2009;338:b1665

Relative risk estimates of HF in single drug blood pressure difference trials according to class of drug

Class of drug	Relative risk* (95% CI)
Single drug therapy:	
Calcium channel blockers	0.81 (0.69 to 0.94)
Thiazides	0.59 (0.45 to 0.78)
β blockers	0.77 (0.69 to 0.87)
Angiotensin converting enzyme inhibitors	0.74 (0.68 to 0.81)
Angiotensin receptor blockers	0.82 (0.73 to 0.92)
All drug classes except calcium channel blockers	0.76 (0.72 to 0.81)
Combination drug therapy	0.57 (0.36 to 0.92)

Law MR *et al.* BMJ 2009;338:b1665

Results of randomised trials of antihypertensive drug therapy



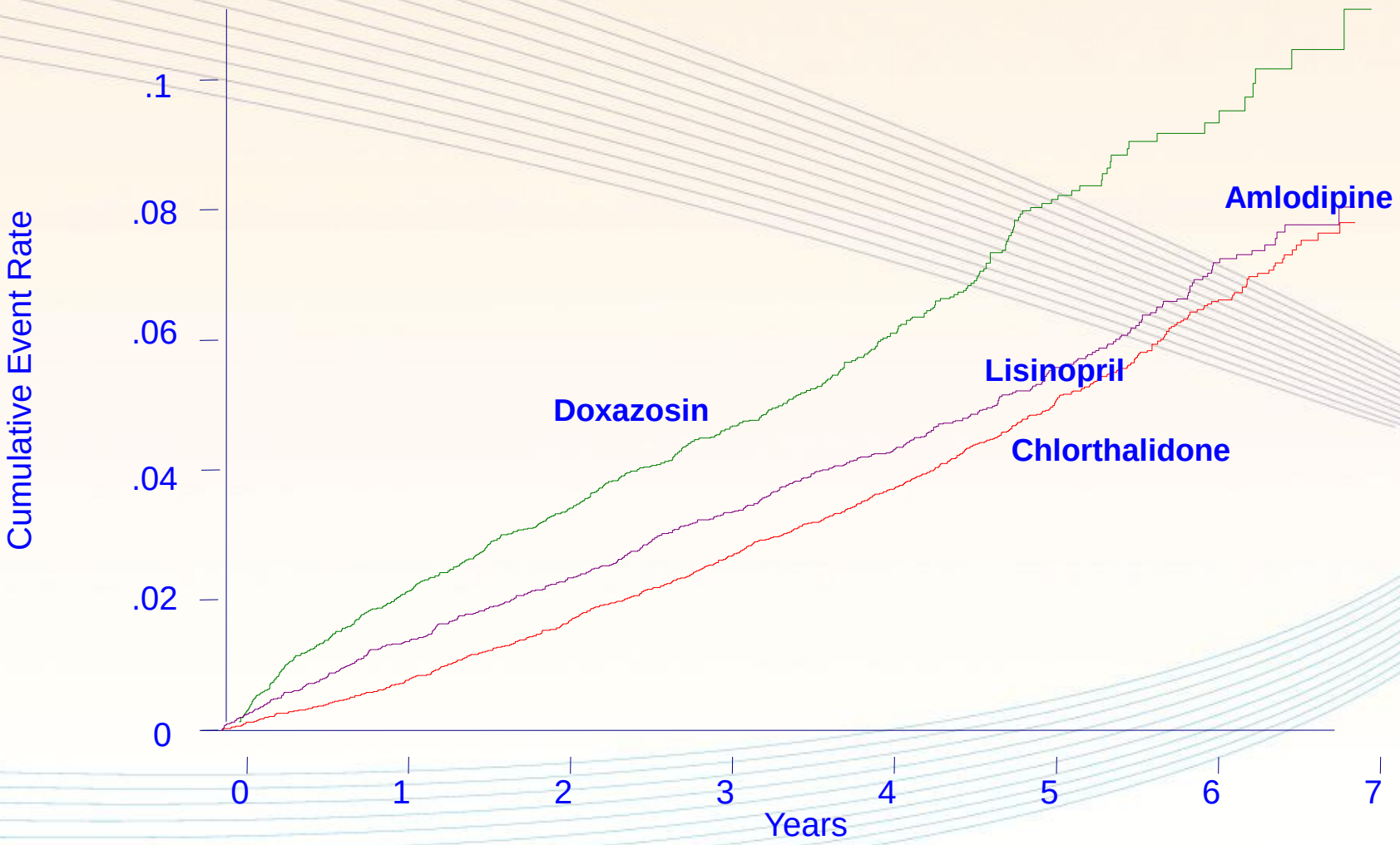
Moser & Herbert J Am Coll Cardiol 1996; 27: 1214
Collins R Lancet 1990; 8693: 827

Relative risk reduction in the development of heart failure in hypertensives: Results of placebo-controlled trials

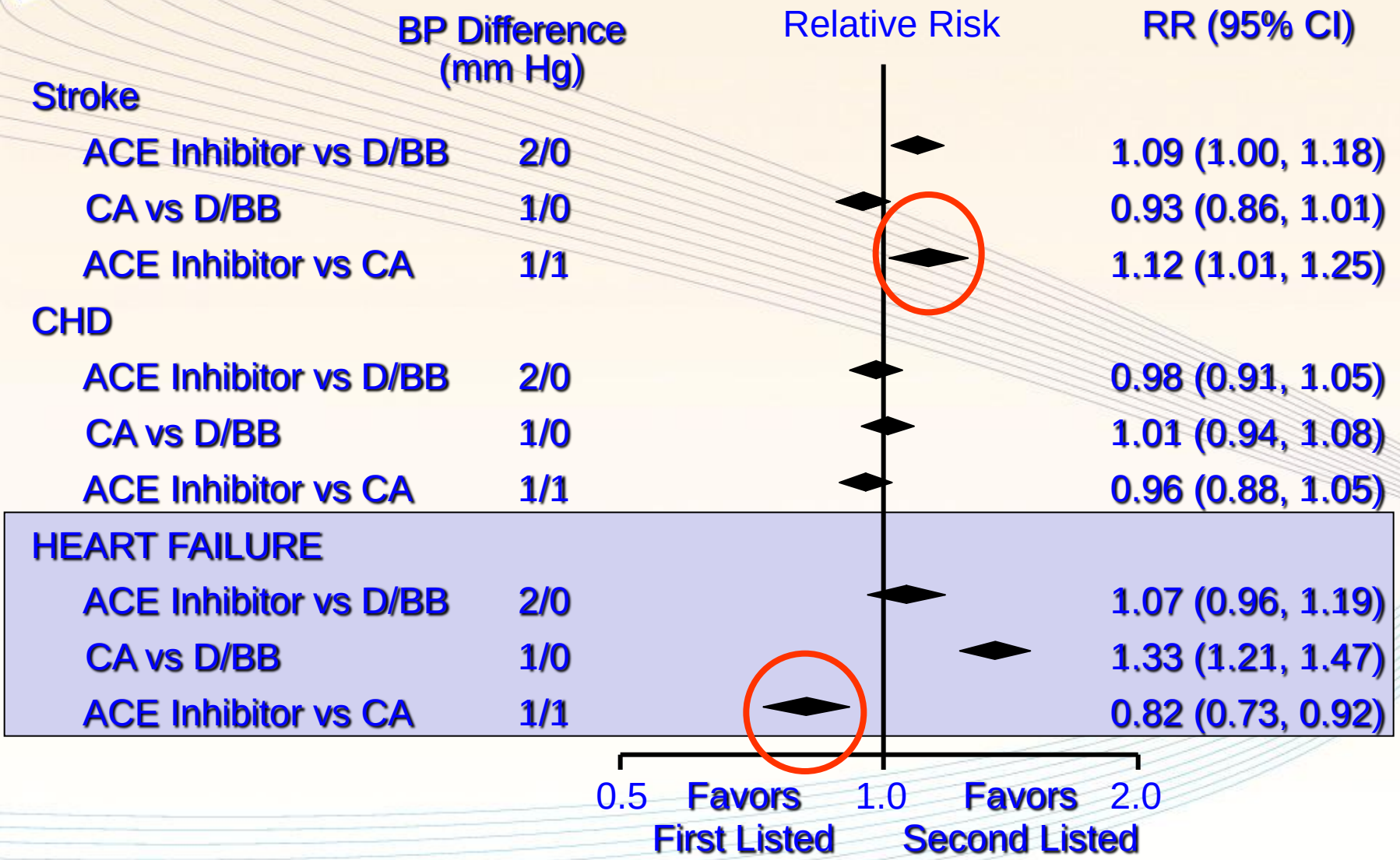
Study	N	Age yrs	Medication	BP	BP-reduction	RRR (%)	ARR (%)
STOP	1627	76	BB + HCTZ	195/102	22/10	51	2.4
SHEP	4736	72	Chlor-thalidone (+ atenolol + reserpine)	171/77	12/4	53	2.3
Syst-Eur	4695	70	Nitrendipine (+enalapril + HCTZ)	174/86	10/5	29	2.5

RRR= relative risk reduction
ARR= absolute risk reduction

Cumulative Event Rates for Hospitalized/ Fatal Heart Failure by ALLHAT Treatment Group



BP-Lowering Treatment Trialists



Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2003;362:1527-1535.

Development of heart failure according to antihypertensive strategies

Drug	Heterogeneity	HR	95% CI	p
CCB/ DIU-BB	0.09	1.15	1.02-1.19	0.01
ACEi/ DIU-BB	0.0001	1.11	0.75-1.62	0.55
ACEi/ CCB	0.51	0.83	0.75-0.92	0.0005
ARB/ Diu-BB	0.15	0.85	0.70-1.03	0.02
ARB/ CCB		0.88	0.76-1.01	0.07

Tocci G at al Hypertension 2008

ONTARGET: Key results

Outcome	Ramipril, n=8576 (%)	Telmisartan, n=8542 (%)	Combination, n=8502 (%)
CV death/MI/ stroke/ CHF hospitalization[a]	16.5	16.7	16.3
CV death/MI/stroke[b]	14.1	13.9	14.1
MI	4.8	5.2	5.2
Stroke	4.7	4.3	4.4
CHF hospitalization	4.1	4.6	3.9
CV death	7.0	7.0	7.3
Any death	11.8	11.6	12.5
Renal impairment	10.2	10.6	13.5

a. Primary end point
b. Primary end point in the HOPE trial

Yusuf S et al. *N Engl J Med* 2008: 358:1547-1559.

ONTARGET: Key results

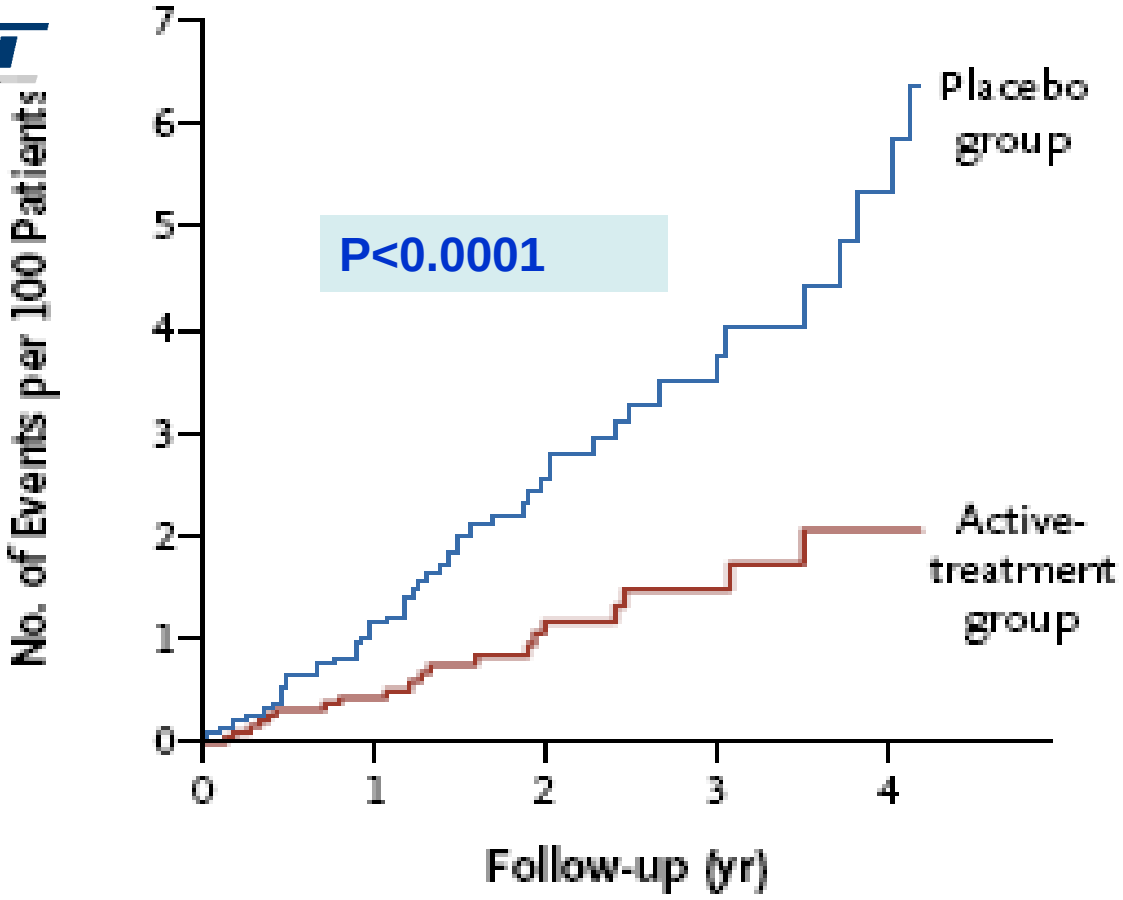
Outcome	Risk ratio (95% CI), telmisartan vs ramipril	Risk ratio (95% CI), combination therapy vs ramipril
CV death/MI/ stroke/ CHF hospitalization[a]	1.01 (0.94–1.09)	0.99 (0.92–1.07)
CV death/MI/stroke[b]	0.99 (0.91–1.07)	1.00 (0.93–1.09)
MI	1.07 (0.94–1.22)	1.08 (0.94–1.23)
Stroke	0.91 (0.79–1.05)	0.93 (0.81–1.07)
CHF hospitalization	1.12 (0.97–1.29)	0.95 (0.82–1.10)
CV death	1.00 (0.89–1.12)	1.04 (0.93–1.17)
Any death	0.98 (0.90–1.07)	1.07 (0.98–1.16)
Renal impairment	1.04 (0.96–1.14)	1.33 (1.22–1.44)

a. Primary end point
b. Primary end point in the HOPE trial

Yusuf S et al. *N Engl J Med* 2008: 358:1547-1559.

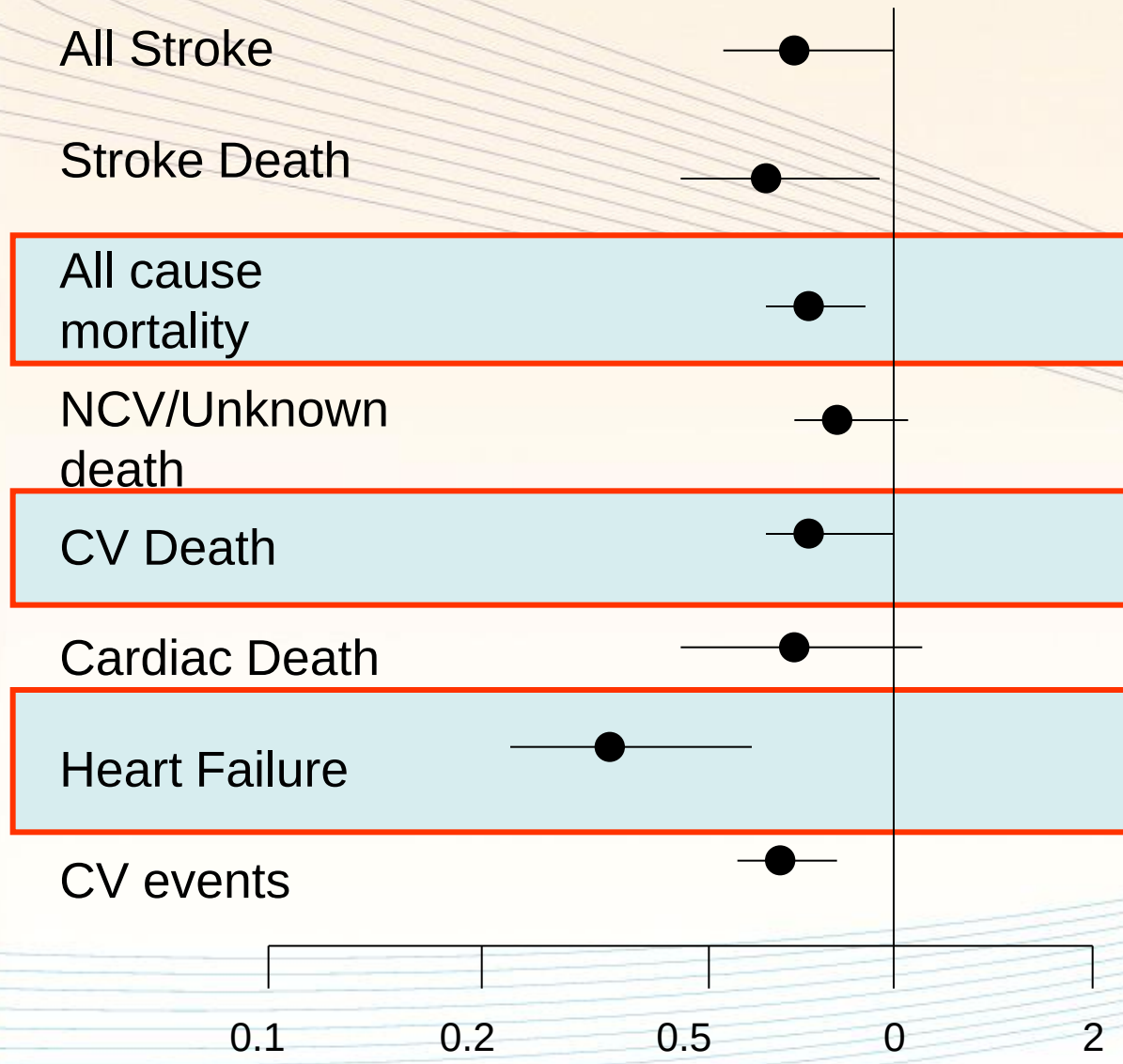
Lowering BP in healthy octogenarians reduces the risk of HF by 64%

HYVET
HYPERTENSION IN THE VERY ELDERLY TRIAL



No. at Risk					
Placebo group	1912	1480	794	367	188
Active-treatment group	1933	1559	872	416	228

Risk reduction associated with lowering blood pressure is highest for heart failure

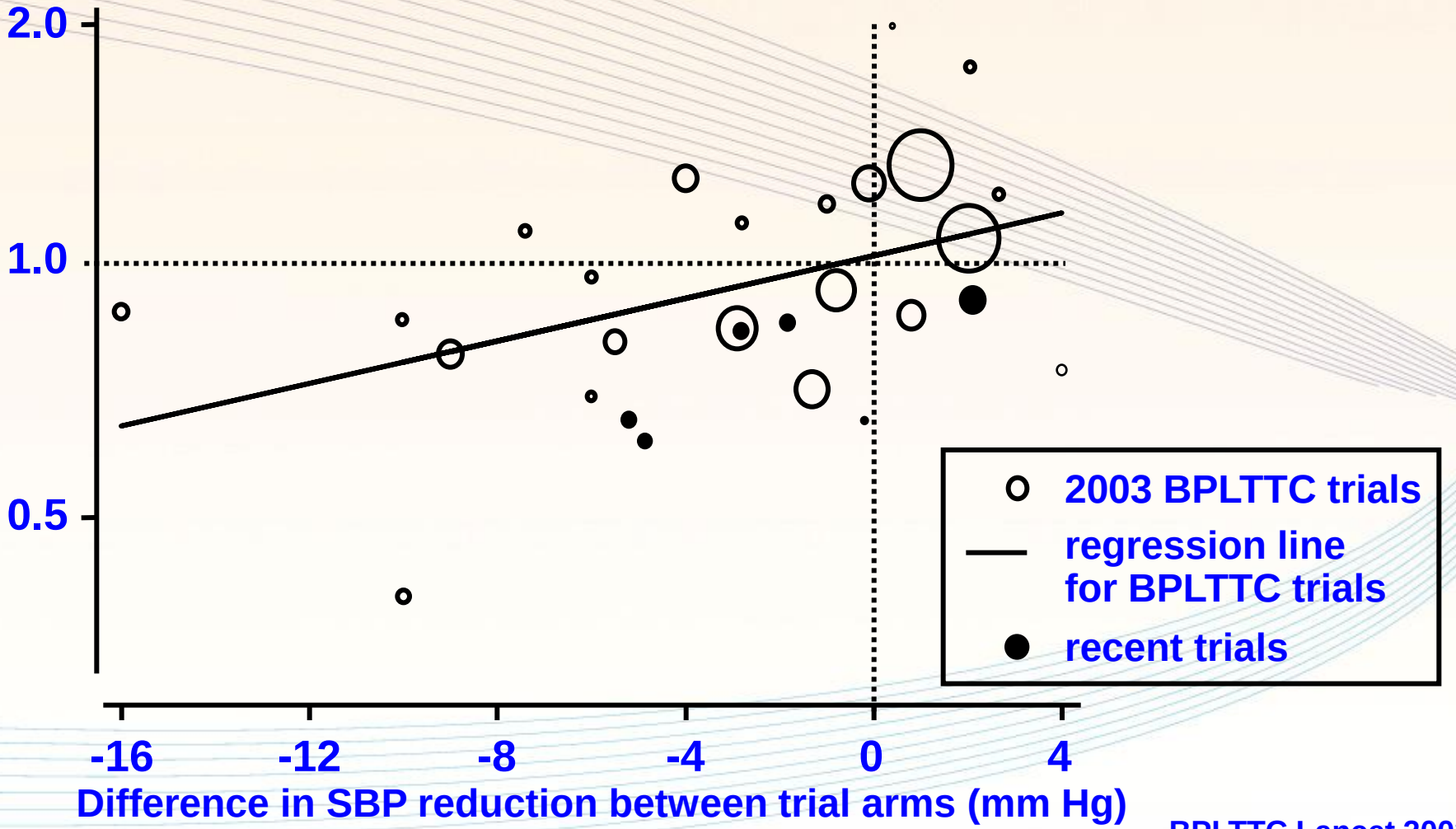


	HR	95% CI
All Stroke	0.70	(0.49, 1.01)
Stroke Death	0.61	(0.38, 0.99)
All cause mortality	0.79	(0.65, 0.95)
NCV/Unknown death	0.81	(0.62, 1.06)
CV Death	0.77	(0.60, 1.01)
Cardiac Death	0.71	(0.42, 1.19)
Heart Failure	0.36	(0.22, 0.58)
CV events	0.66	(0.53, 0.82)

HYVET
HYPERTENSION IN THE VERY ELDERLY TRIAL

Reduction in heart failure risk by SBP reduction

slope = 26% risk reduction per 10 mmHg decrease in SBP p<0.001



BPLTTC Lancet 2003

CONCLUSION

- Hypertension is the most common risk factor for CHF
- Lifetime risk for CHF doubles for subjects with BP> 160/100 mmHg
- Systolic and pulse pressures confer greater risk than diastolic pressure

- Hypertensive vasculopathy (atherosclerosis, endothelial dysfunction, increased artery stiffness) and hypertensive cardiopathy (LVH & cardiac fibrosis) are the main mechanisms responsible for the progression from hypertension to heart failure.

Conclusion

- Other (non-barometric) factors may contribute to the clinical benefit of RAAS inhibitors

- Treating hypertension, most likely and mainly through effective and strict BP lowering is the most efficient way to prevent HF