The importance of heart rate in heart failure

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EDITORIAL

Rest Heart Rate and Life Expectancy

HERBERT J. LEVINE, MD, FACC

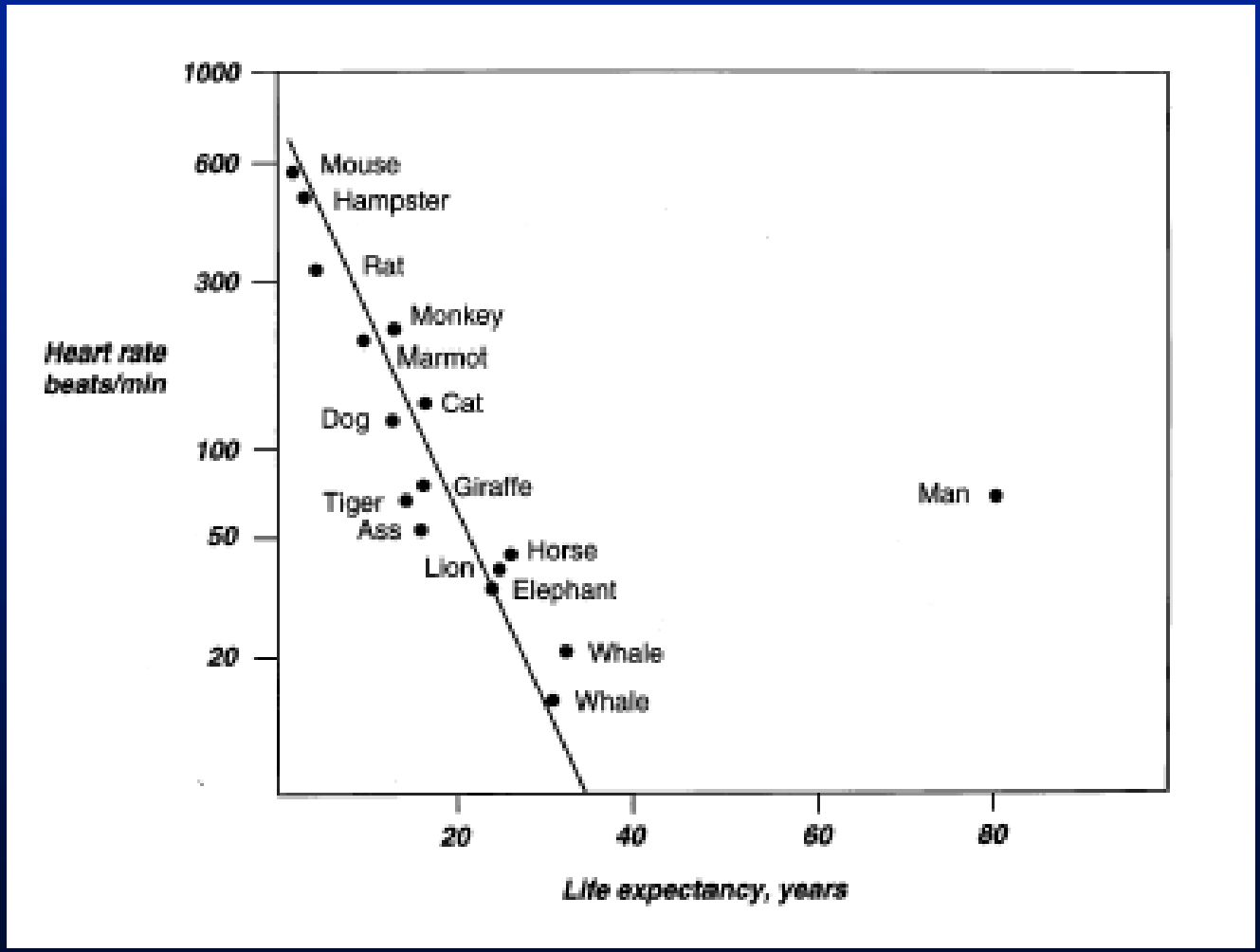
Boston, Massachusetts

Among mammals, there is an inverse semilogarithmic relation between heart rate and life expectancy. The product of these variables, namely, the number of heart beats/lifetime, should provide a mathematical expression that defines for each species a predetermined number of heart beats in a lifetime. Plots of the calculated number of heart beats/lifetime among mammals against life expectancy and body weight (allometric scale of 0.5 × 10^6) are, within an order of magnitude, remarkably constant and average 7.3 ± 5.6 × 10^8 heart beats/lifetime. A study of universal biologic scaling and mortality suggests that the basal energy consumption/body atom per heart beat is the same in all animals (~10^{-8} O_2 molecules/heart beat). These data yield a mean value of 10 × 10^8 heart beats/lifetime and suggest that life span is predetermined by basic energetics of living cells and that the apparent inverse relation between life span and heart rate reflects an epiphenomenon in which heart rate is a marker of metabolic rate. Thus, the question of whether human life can be extended by cardiac slowing remains moot and most likely will only be resolved by retrospective analyses of large populations, future animal studies and clinical trials using bradycardic therapy.

(J Am Coll Cardiol 1997;30:1104–6)

Rest Heart Rate and Life Expectancy

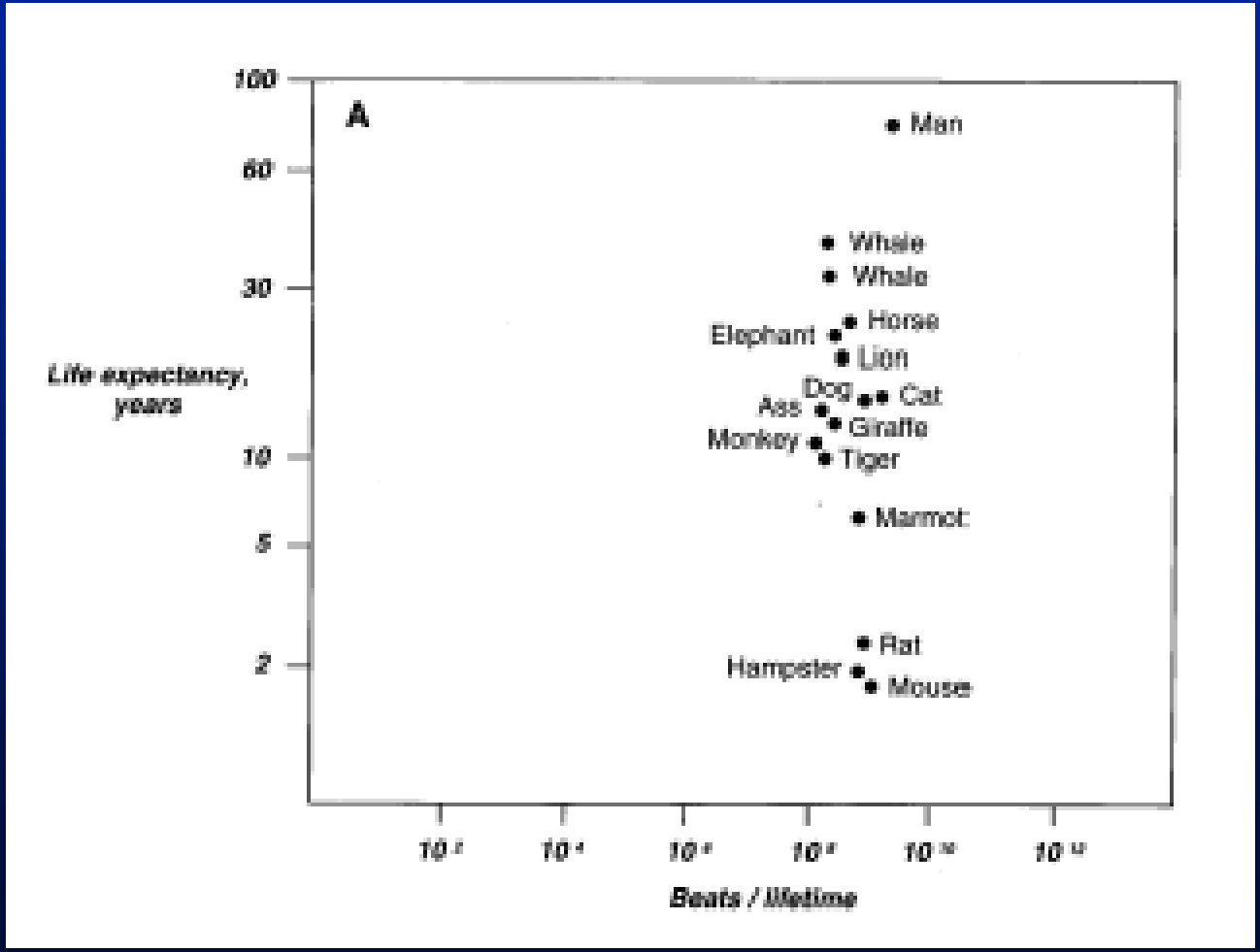
Semilogarithmic relation between rest heart rate and life expectancy



Levine HJ JACC 1997

Rest Heart Rate and Life Expectancy

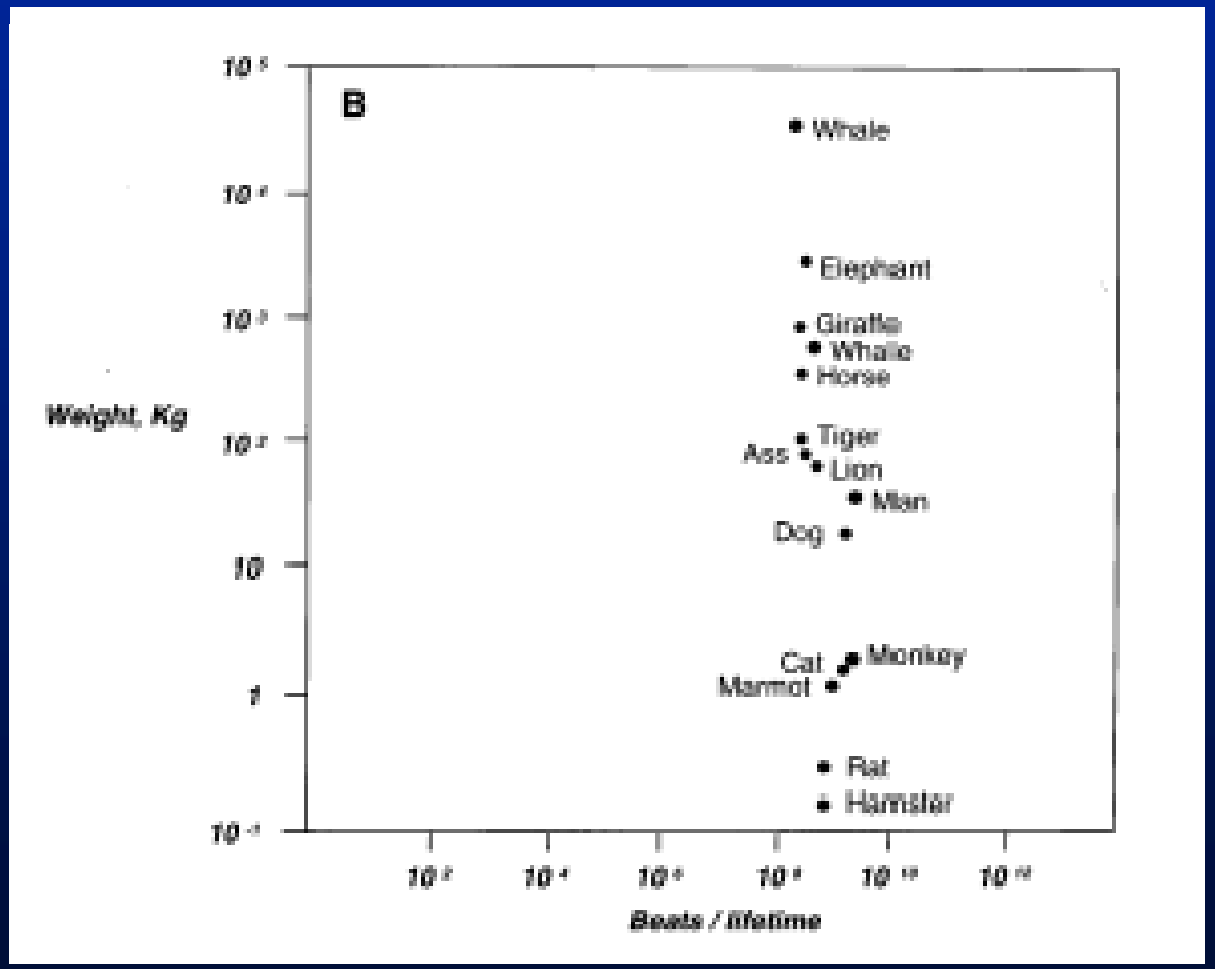
Logarithmic life-time number of beats and life expectancy



Levine HJ JACC 1997

Rest Heart Rate and Life Expectancy

Logarithmic lifetime beats and weight

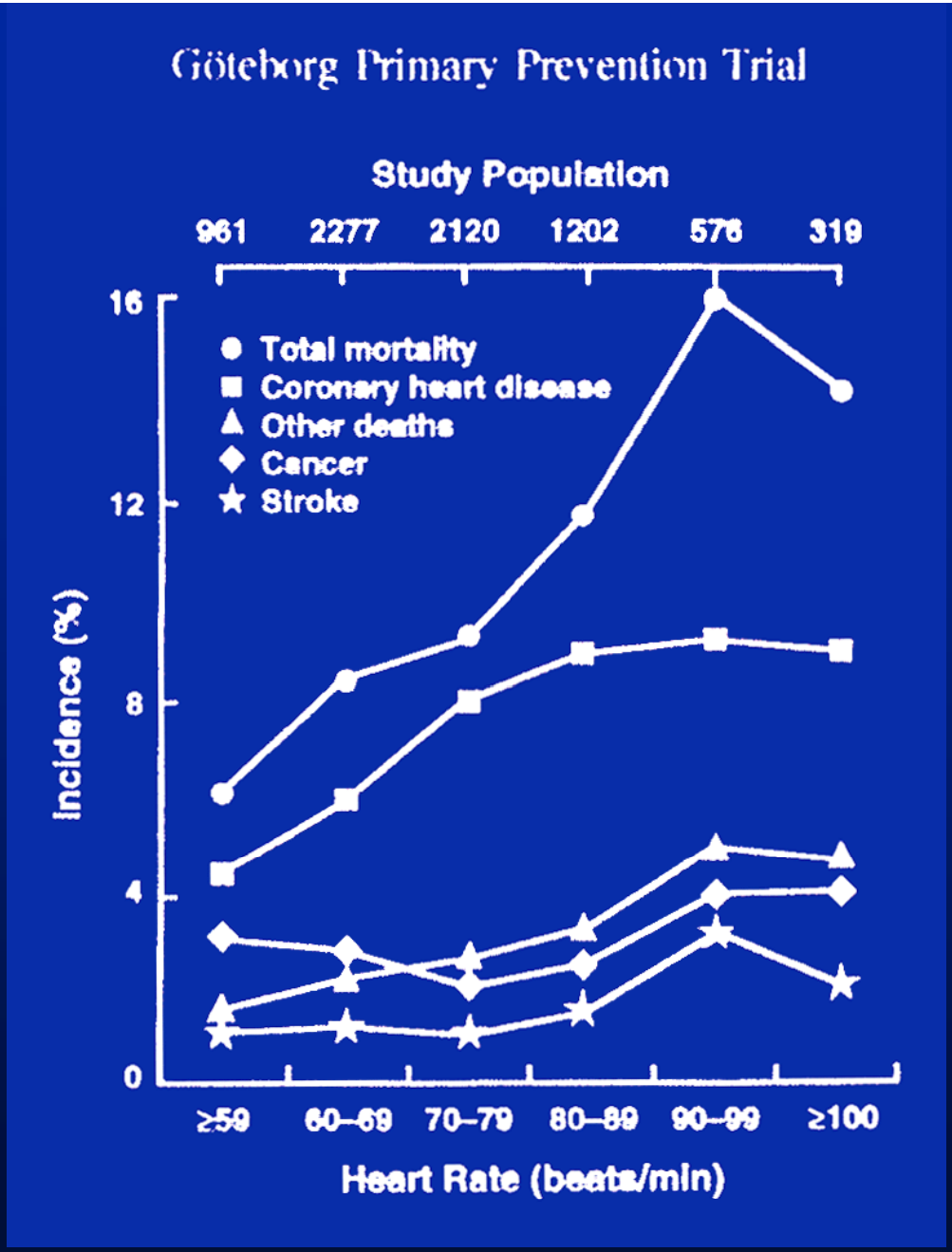


Levine HJ JACC 1997

Göteborg Primary Prevention Study

- 7495 men 45-55 years randomly selected
- examined 1970-73 and followed for 27 years
- Risk factors collected at baseline
- Hypertension defined as BP >175/115 or treated

Wilhelmsen et al JIM 2001



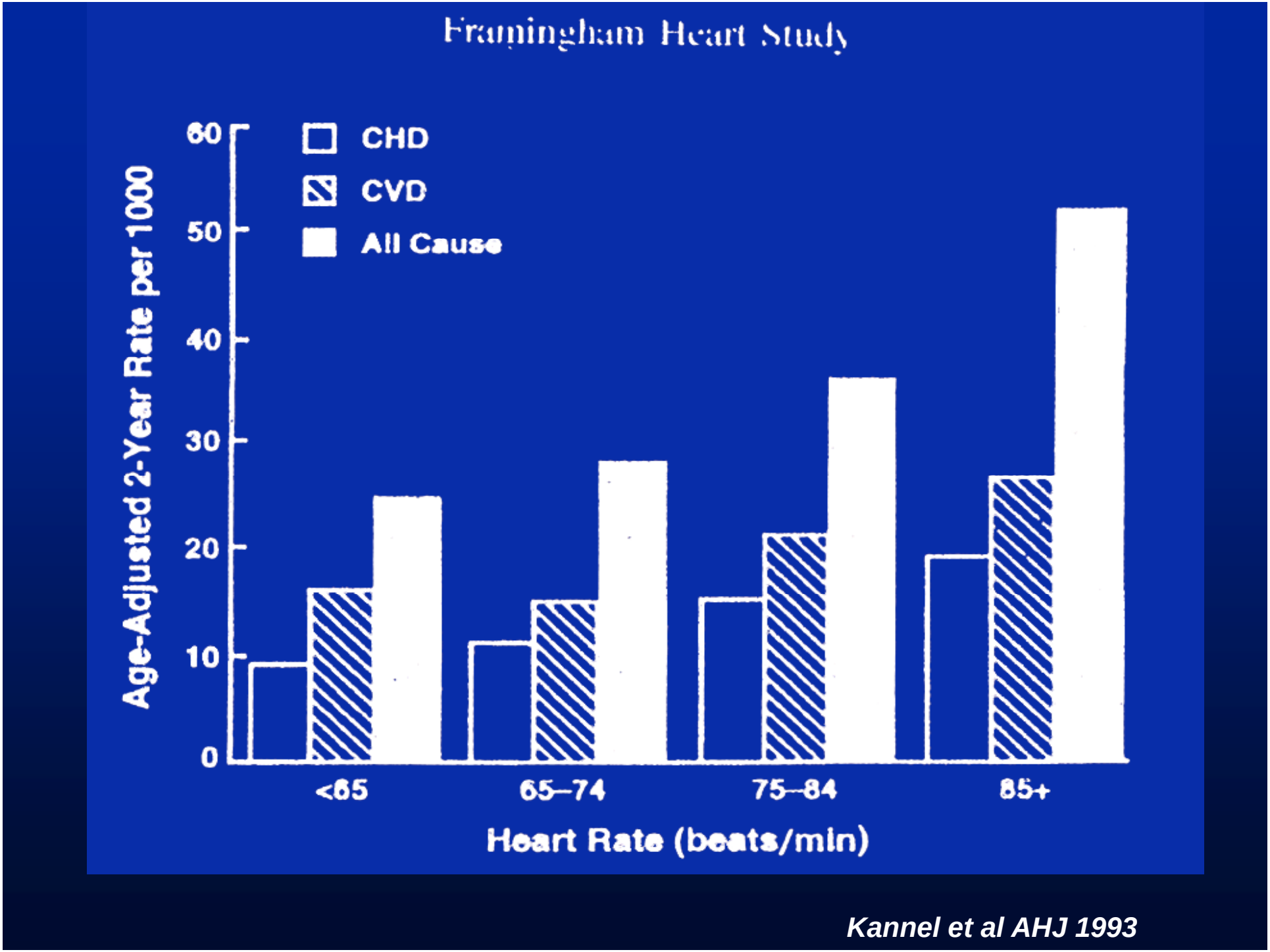
Wilhelmsen, Berglund EHJ 1986

Heart Rate as Risk Factor

Variable	n[a]	Heart failure %	OR (95% CI)	P
Body height (cm)				
≤ 172	2340	13.6	1	0.02
173–179	3165	12.4	0.90 (0.77–1.05)	
≥ 180	1971	11.6	0.83 (0.70–1.00)	
Body weight (kg)				
≤ 72.9	2294	11.0	1	0.001
73.0–83.9	3010	12.0	1.10 (0.93–1.31)	
≥ 84.0	2170	15.1	1.43 (1.20–1.71)	
Weight change from age 20				
Weight loss or increase ≤ 4%	1181	10.7	1	0.01
Increase 5–25%	4662	12.0	1.02 (0.86–1.22)	
Increase ≥ 26%	1176	16.2	1.45 (1.17–1.80)	
Body mass index (kg m^{-2})				
≤ 23.99	2678	11.1	1	0.001
24.0–26.99	2922	11.7	1.06 (0.90–1.25)	
≥ 27.00	1837	15.7	1.50 (1.26–1.78)	
Heart rate (beats min^{-1})				
≤ 65	2235	11.3	1	0.003
66–80	3336	12.9	1.17 (0.99–1.38)	
≥ 81	1884	13.4	1.22 (1.01–1.47)	
Systolic blood pressure (mmHg)				
≤ 145	3629	10.5	1	0.001
146–175	2974	13.4	1.31 (1.13–1.53)	
≥ 176	881	18.4	1.92 (1.57–2.35)	
Treatment for hypertension or screening blood pressure ≥ 175/115				
Yes	1228	18.6	1.79 (1.52–2.11)	0.0001
No	6267	11.3	1	

[a]Numbers that do not add up to 7495 are due to missing information.

Wilhelmsen et al JIM 2001



Kannel et al AHJ 1993

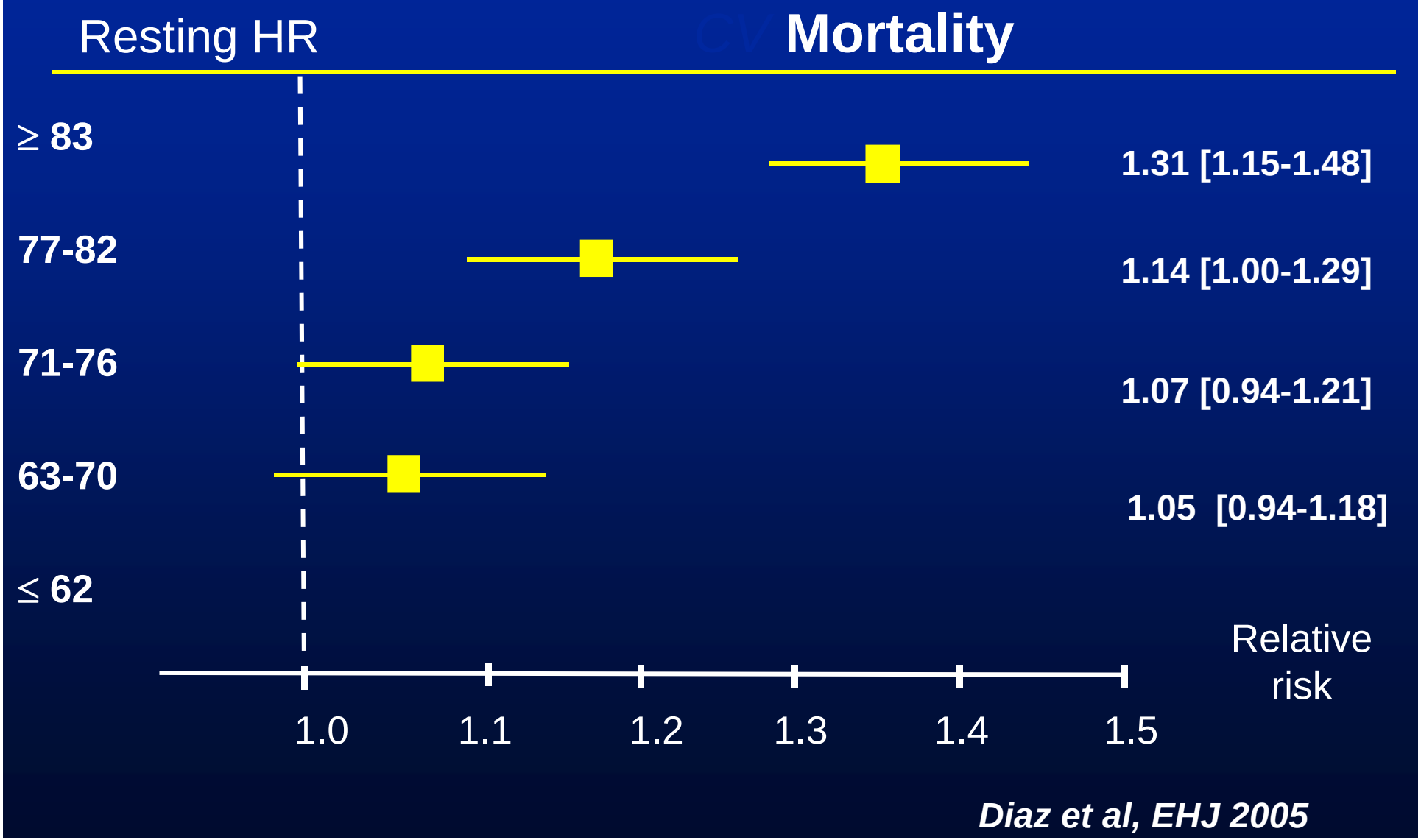
Overall Deaths by Resting Heart Rate According to Age and Sex:
30 Year Follow-up Framingham Study (N=5070)

Resting heart rate (beats/min)	Age-adjusted annual rate/1000			
	Men		Women	
	36-64	65-94	35-64	65-94
30-67	6	35	3	22
68-75	8	43	4	28
76-83	11	46	6	25
84-91	13	61	8	30
92-220	24	64	9	35

Kannel et al. *Am Heart J* . 1987;113:1489-494

Increase of CV risk with baseline HR at rest

24913 patients with CAD (CASS registry), follow up 14.7 years

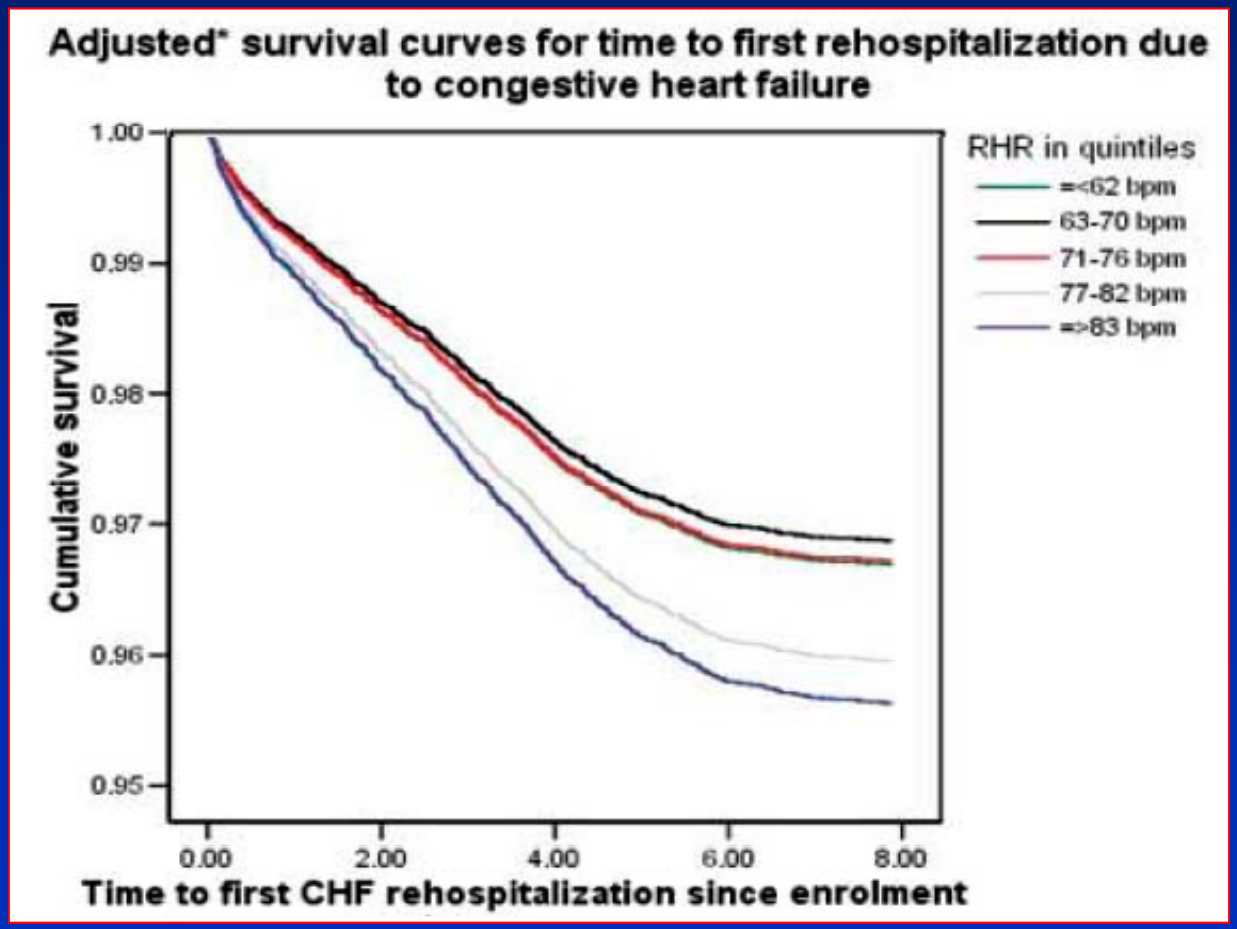


Diaz et al, EHJ 2005

Increased HR increase risk of heart failure

24.913
Men/women suspected or proved CAD

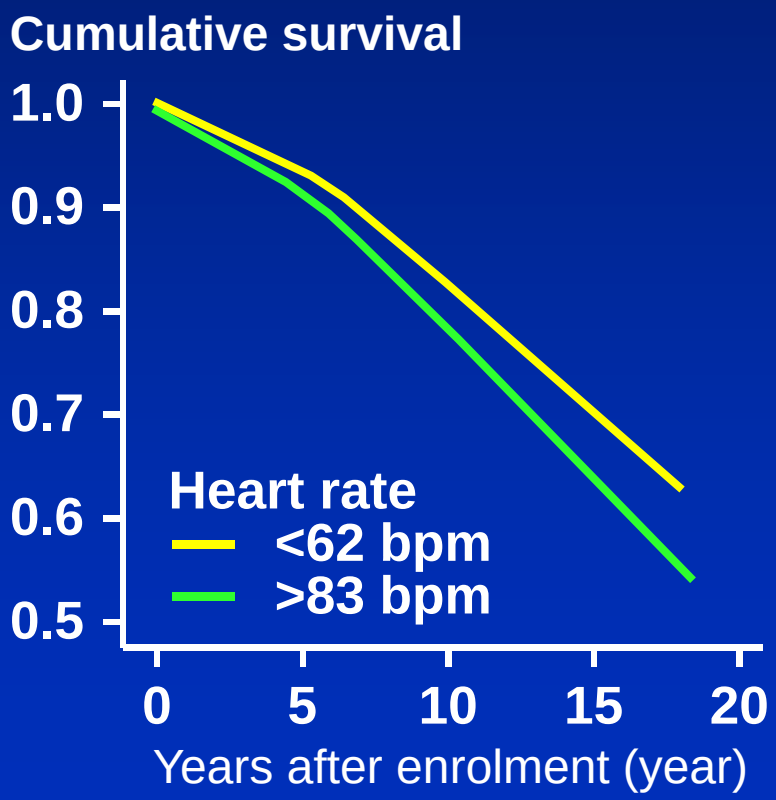
14.7 years
Follow-up



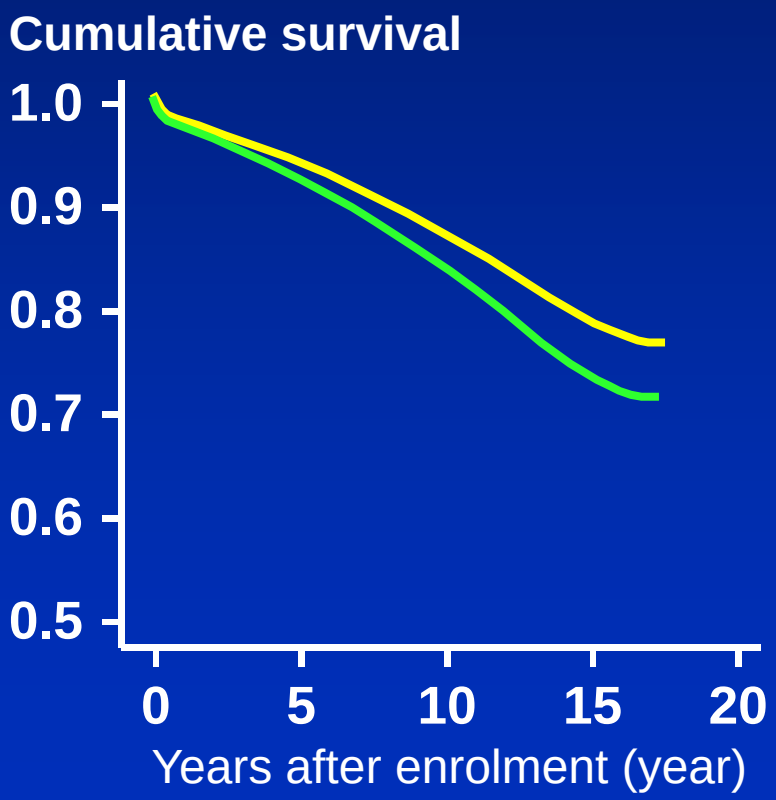
Diaz et al *Eur Heart J.* 2005

Prognostic value of HR in Patients with Suspected or proven CAD (n=24913)

Adjusted survival curves for overall mortality



Adjusted survival curves for cardiovascular mortality



Diaz et al. *Eur Heart J.* 2005;26:967-74

Increased HR increases risk of death

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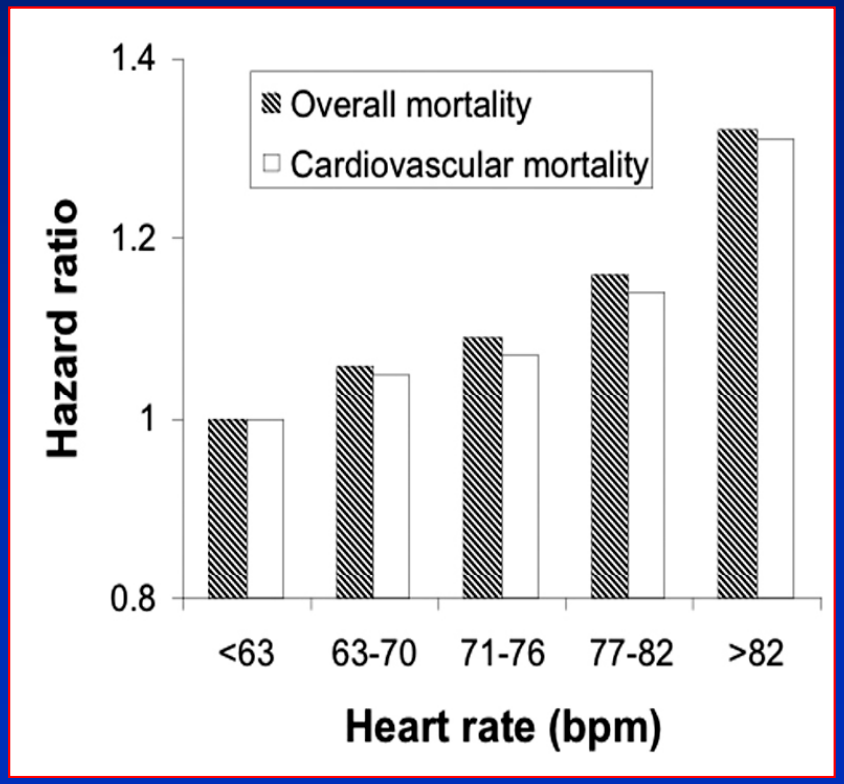
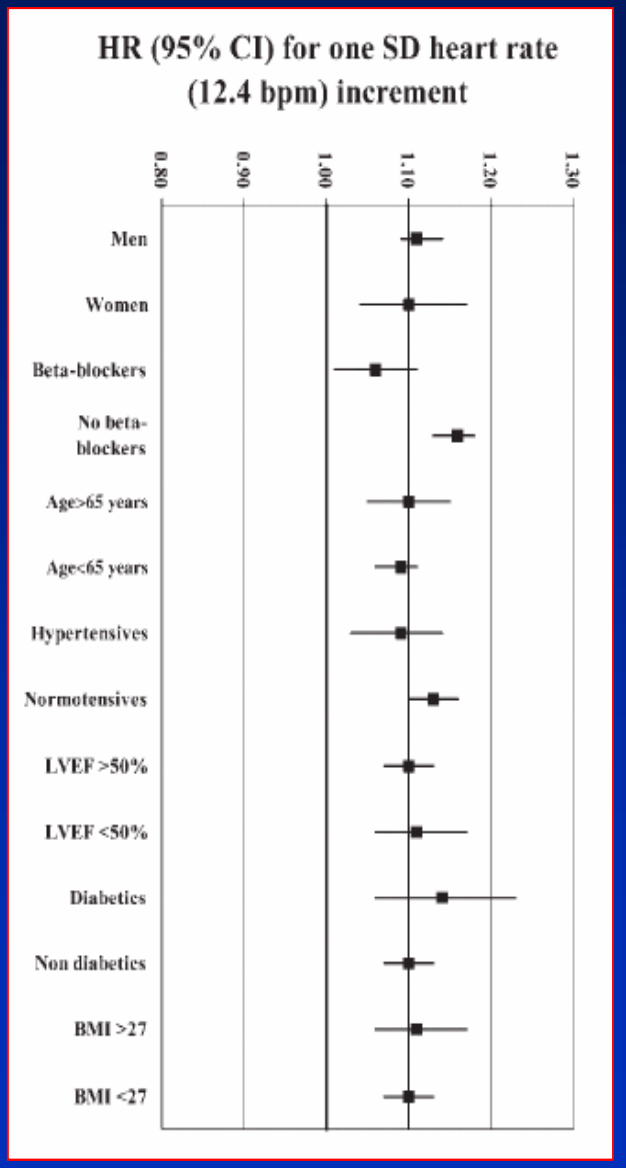
Men/women suspected or proved CAD

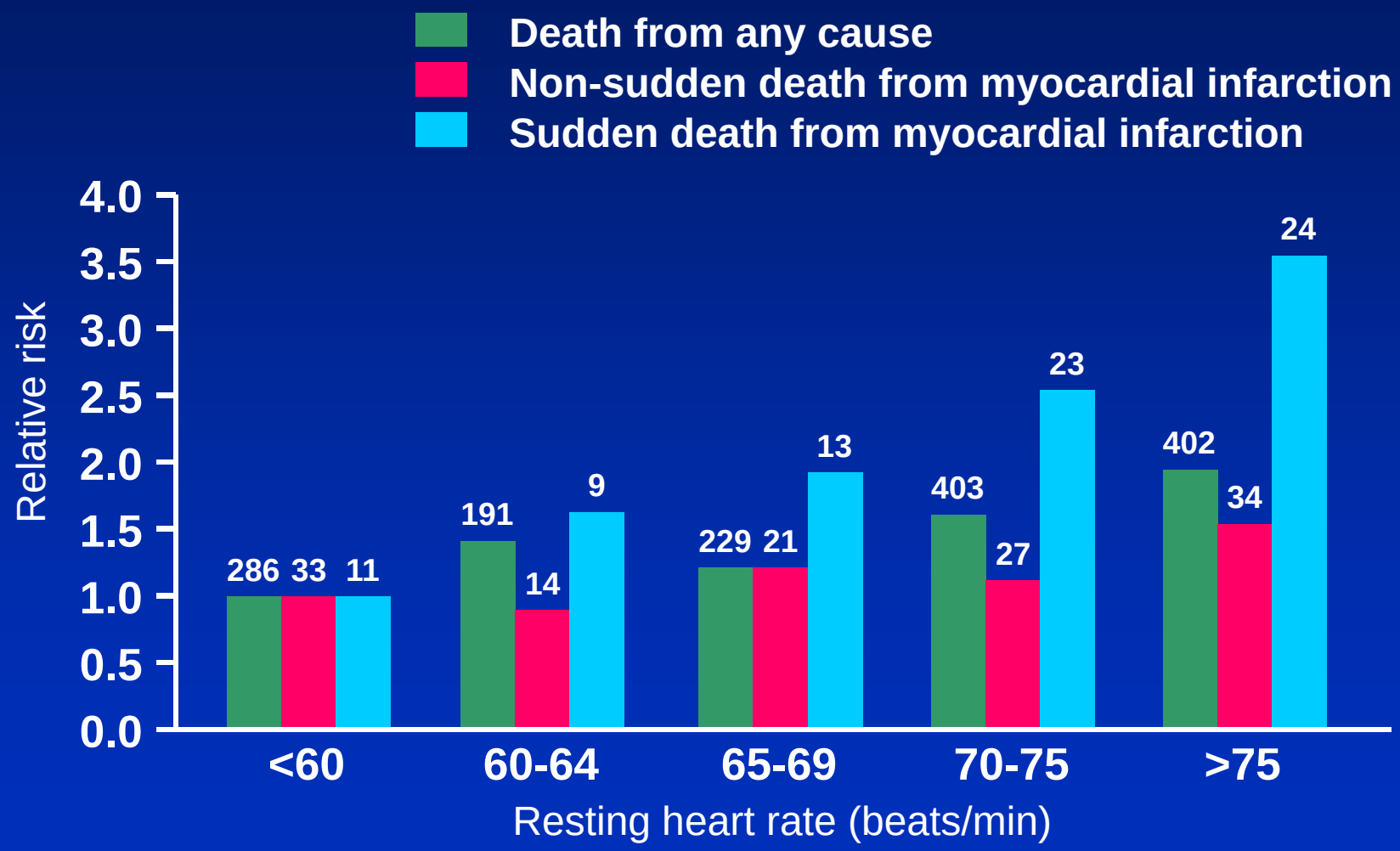
14.7 y
Follow-up





CASS *Eur Heart J.* 2005;26:967

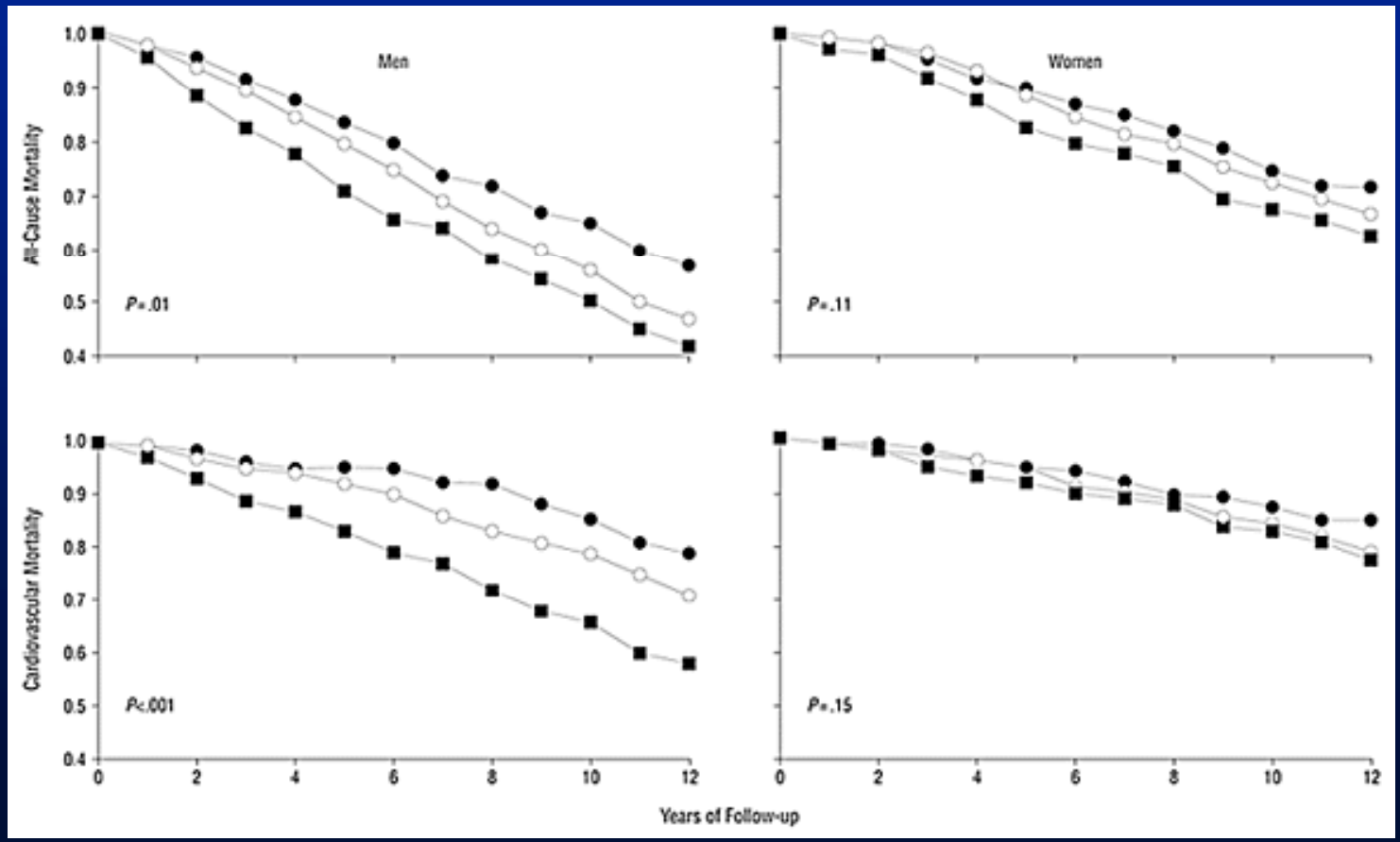
Relative Risks of Death According to the Quintile of Resting Heart Rate (n=5713)



Jouven et al. *N Engl J Med*. 2005;352:1951-1958

Heart Rate and Risk in Elderly Men

- 763 men >65 years in the Cardiovascular Study in the Elderly
- Risk by quintiles
- Top quintile (squares) >80 bpm
- Low quintile (black dots) <64 bpm



Palatini et al Arch Int Med 1999

Heart Rate and Risk in Elderly Men

Table 5. Multivariate Cox Analysis of Risk Function for Cardiovascular Survival in 763 Men

Independent Variable	Improvement, χ^2 Test	*P*
Age, y	58.56	<.001
Coronary artery disease (yes or no)	25.69	<.001
Quintiles of heart rate*	17.30	<.001
Congestive heart failure (yes or no)	11.17	.001
Diabetes mellitus (yes or no)	10.22	.001
History of stroke (yes or no)	7.36	.007
Intermittent claudication (yes or no)	6.68	.01
Arterial hypertension (yes or no)	5.20	.02
Serum triglycerides, mmol/L	4.05	.04
FEV_1, % theoretical value†	3.13	.08

**From the mean of the last 2 measurements.*
†FEV indicates forced expiratory volume in 1 second.

Palatini et al Arch Int Med 1999

Rationale for benefits of heart rate reduction beyond angina prevention

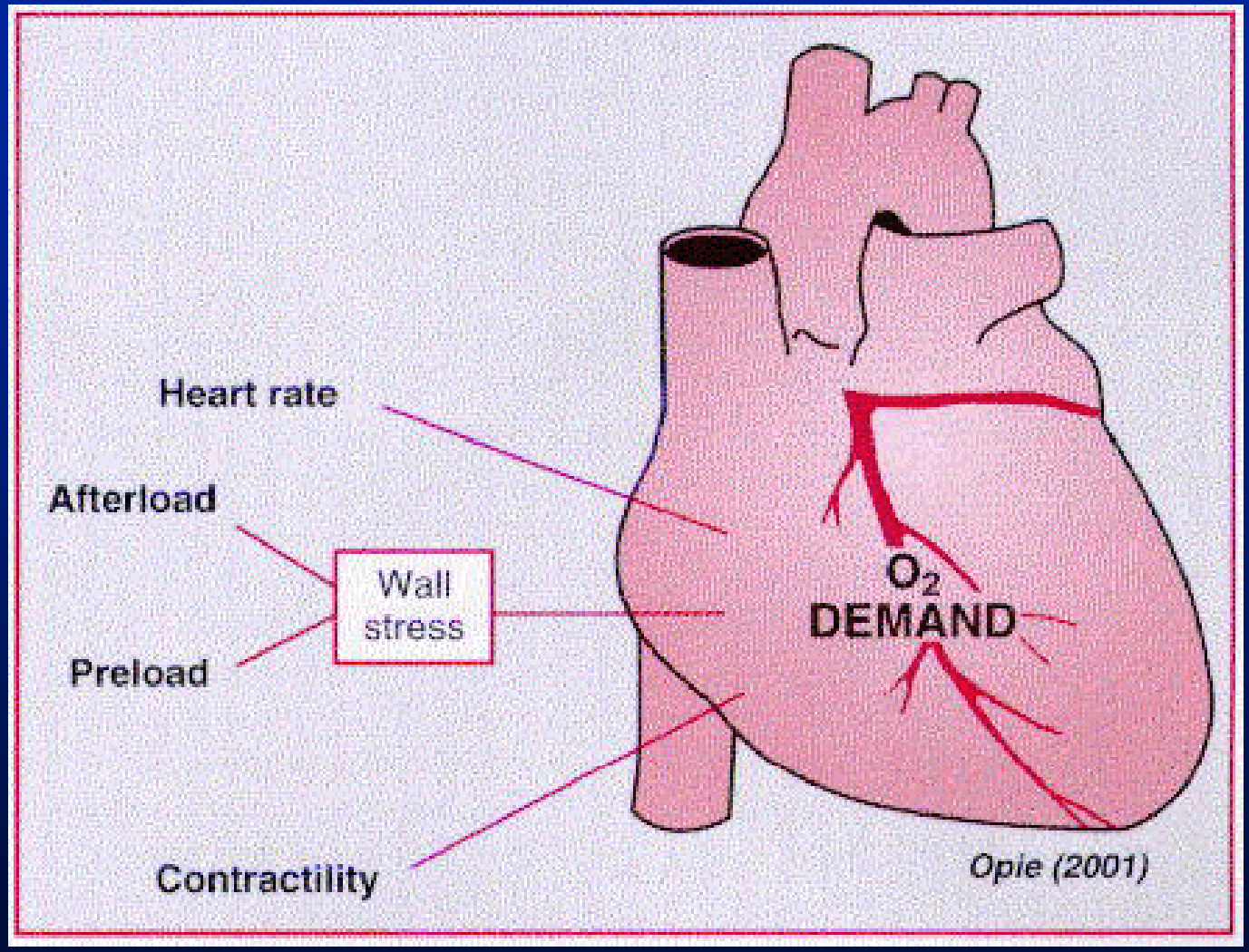
- The natural history of CAD includes progression towards acute MI, LV systolic dysfunction, heart failure, and cardiovascular death
- Increased HR is an independent prognostic factor in general population and patients with CAD or HF

Why is Level of Heart Rate a Risk Factor

- Reflects adrenergic drive
- Reflects vagal tone

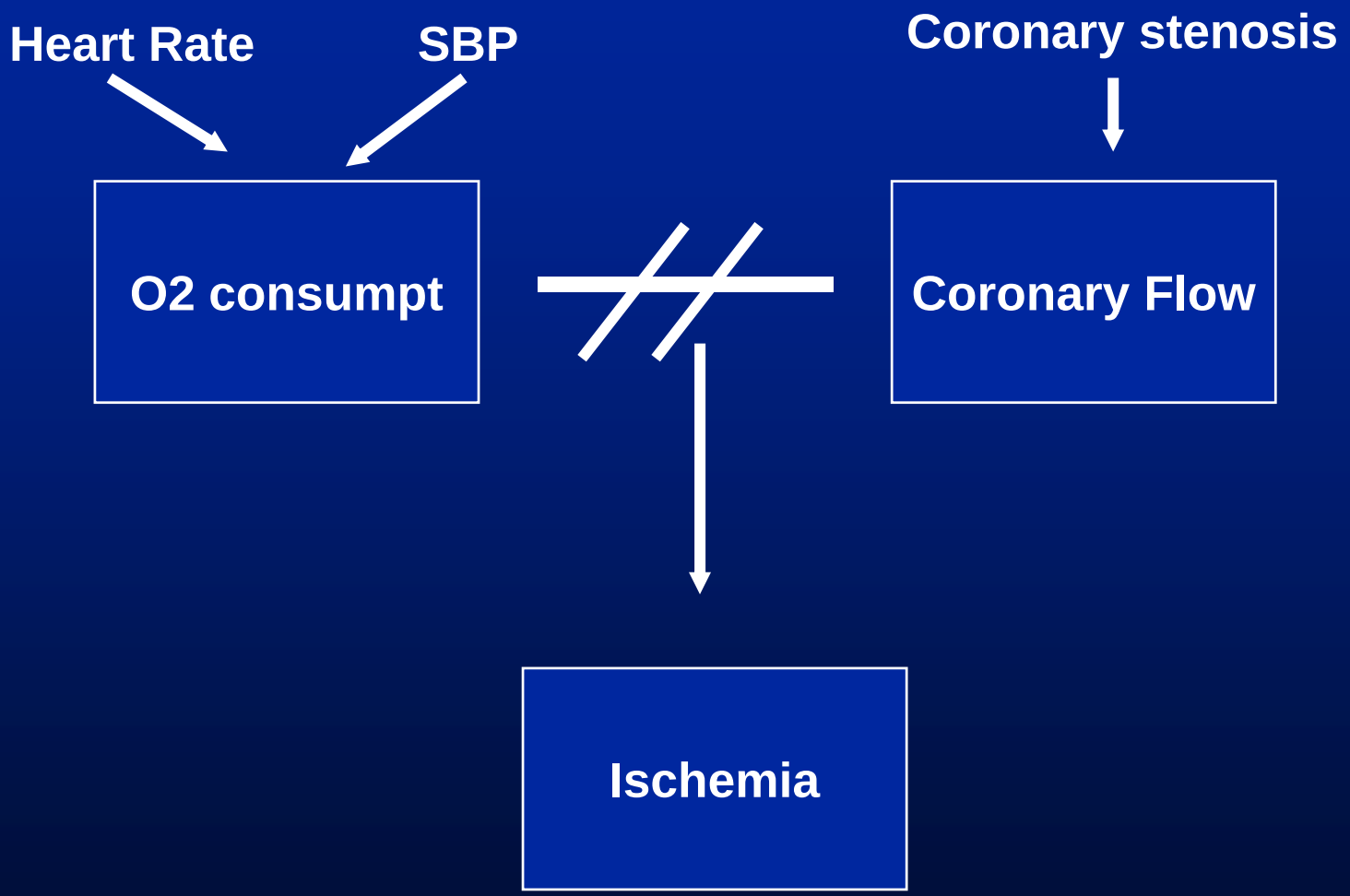
Both these autonomic systems influence atherogenesis and/or ventricular fibrillation threshold

Myocardial Oxygen Consumption



From Opie 2001

Myocardial Metabolic Balance and Heart Rate



Benficial Effects of Heart Rate Reduction

- Angina pectoris
- Acute coronary syndromes
- Myocardial infarction
- Atrial tachyarrhythmias
- Heart failure
  - Systolic dysfunction
  - Diastolic dysfunction
- Palpitations

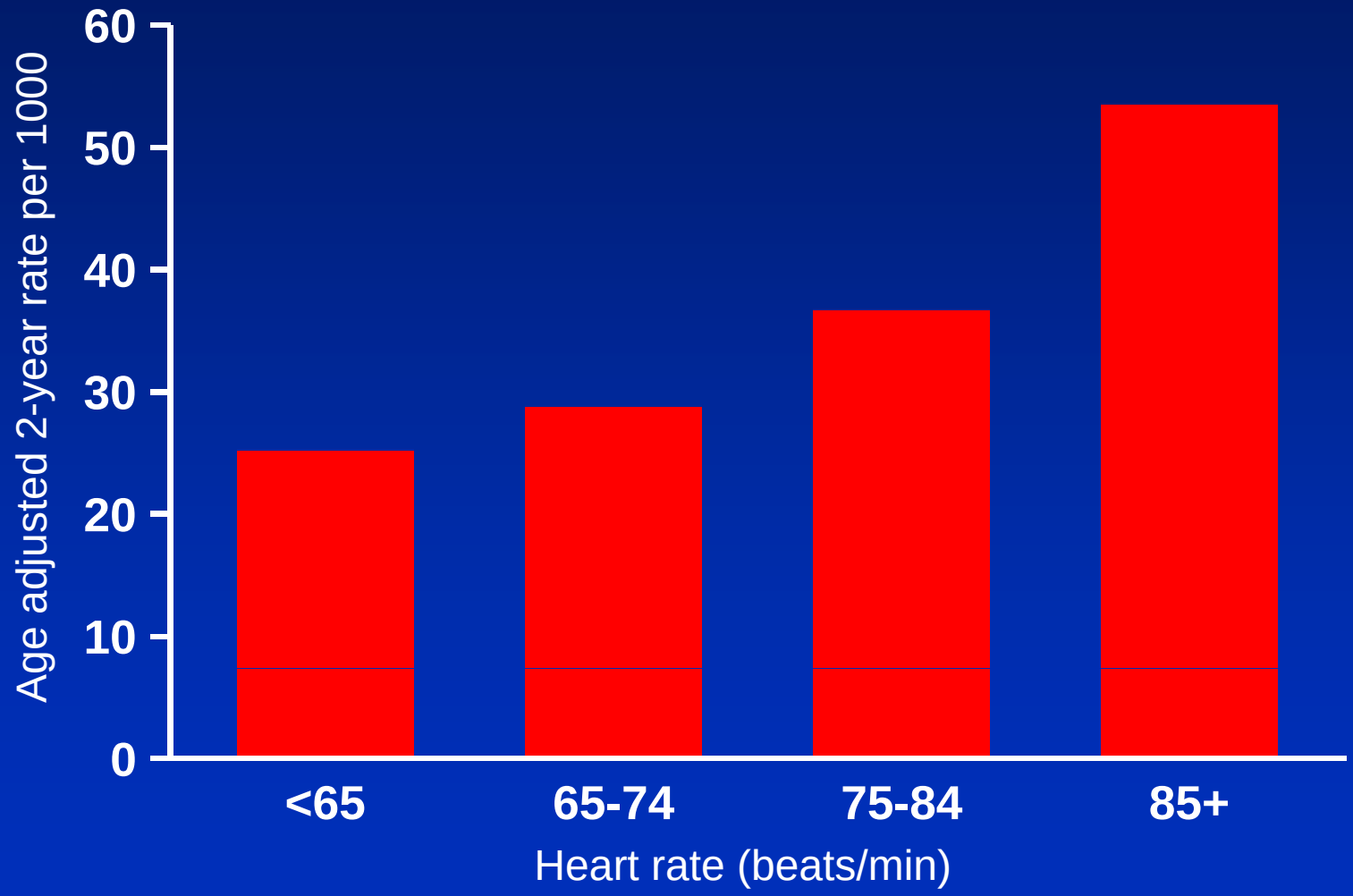
Epidemiological studies on the relationship between HR and CV mortality (general population and HTN)

Study	Population	Follow-up	Cardiovascular mortality RR	
Chicago Gas Company ‘80	1,233 M	15 y	>94 vs. ≤60 bpm	2.3
Chicago Heart Ass.Project ’80	33,781 M&W	22 y	≥90 vs. <70 bpm	M: 1.6 W: 1.1 (ns)
Framingham ‘93	4,530 M&W HTN	36 y	>100 vs. <60 bpm	M: 1.5 W: 1.4 (ns)
British Regional Heart ’93	735 M	8 y	>90 vs. ≤90 bpm	IHD death 3.3
Spandau ’97	4,756 M&W	12 y	Sudden death	5.2 per 20 bpm
Benetos ’99	19,386 M&W	18.2 y	>100 vs. <60 bpm	M: 2.2 W: 1.1 (ns)
Castel ’99	1,938 M&W	12 y	5th vs. 3rd quintile	M: 1.6 W: 1.1
Cordis ’00	3,257 M	8 y	≥90 vs. <70 bpm	2.0
Reunanen ’00	10,717 M&W	23 y	M: 1.4 (>84 vs. <60)	W: 1.5 (>94 vs.<66)
Thomas ’01	60,343 M HTN	14 y	>80 vs. ≤80 bpm	<55y:1.5 >55y:1.3
Matiss ’01	2,533 M	9 y	per 20 bpm: 1.5	≥90 vs. <60 bpm: 2.7
Ohasama ‘04	1,780 M&W	10 y	M: 1.2 W: 1.1 (ns) per 5 bpm	
Okamura ‘04	8,800 M&W	16.5 y	per 11 bpm (1 SD) M: 1.3 W: 1.2	
Jouven ’05	5 713 M	23 y	Sudden death from AMI 3.92 (>75 bpm)	

Adapted from V. Aboyans et al. *Journal of Clinical Epidemiology* . 59 (2006) 547–558

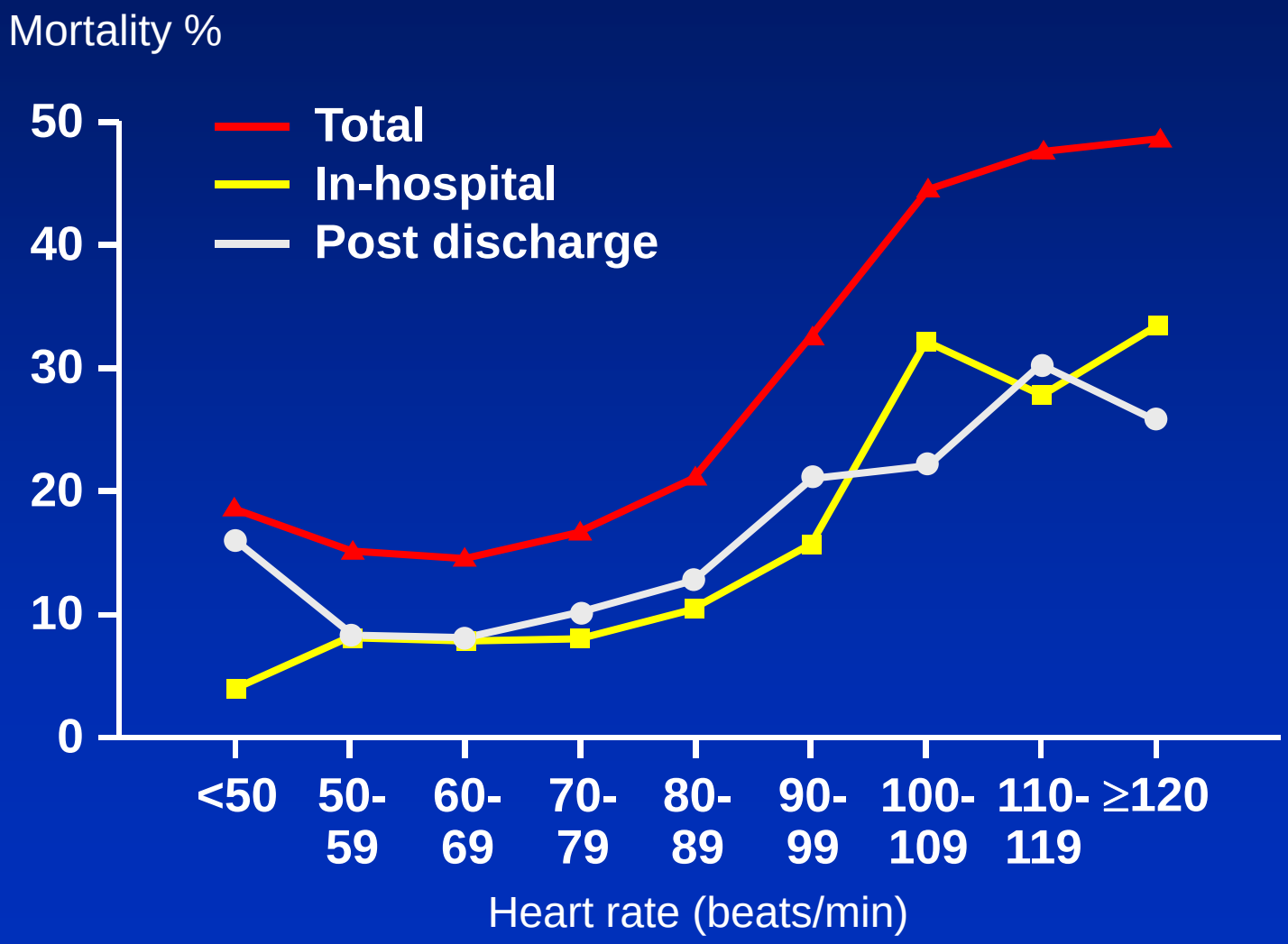
All Cause Mortality - men With Hypertension

36 Year Follow-up Framingham Study (n=2037)



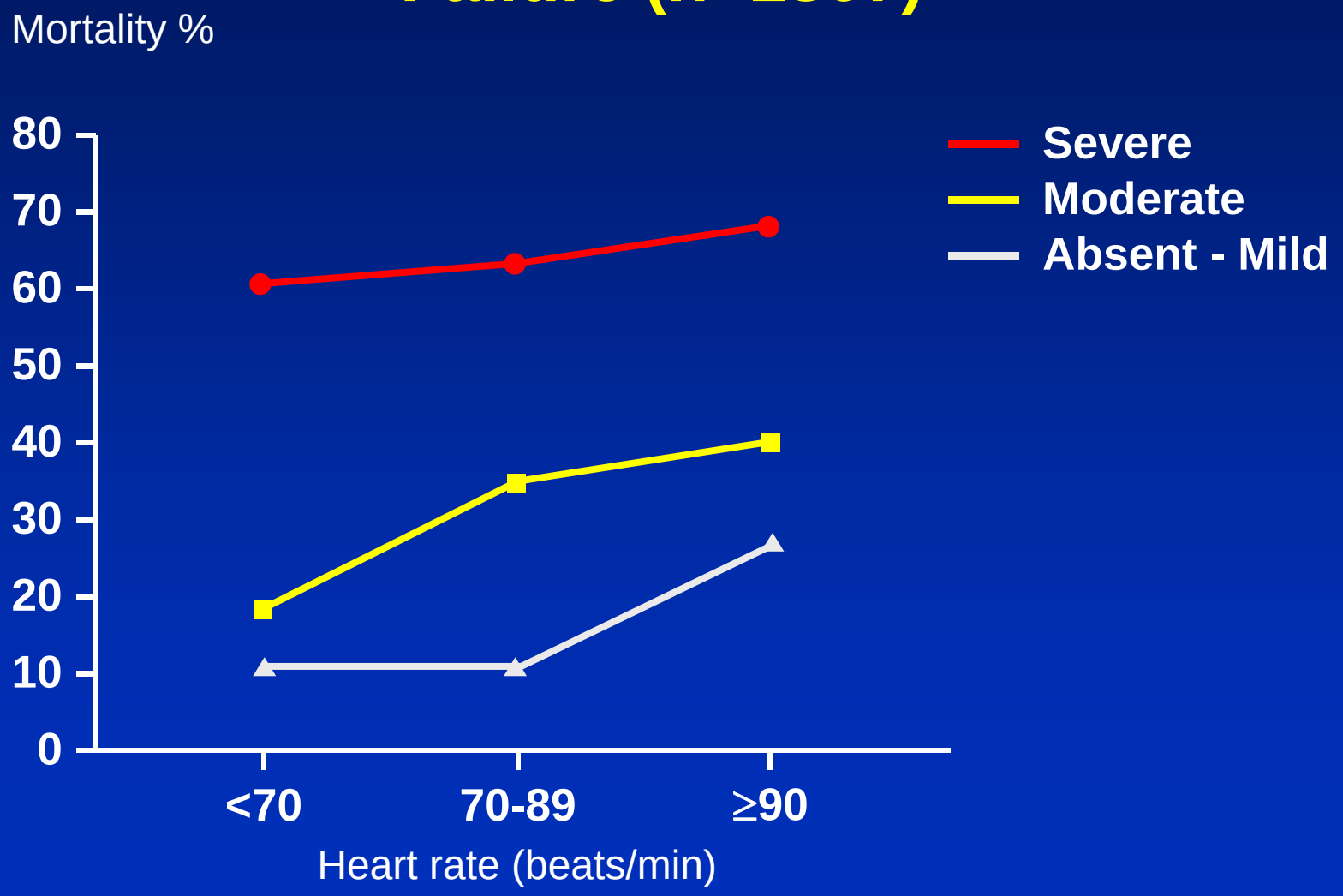
Gillman et al. *Am Heart J*. 1993;125:1148-1154

Mortality With Different Heart Rate on Hospital Admission for AMI (n=1807)



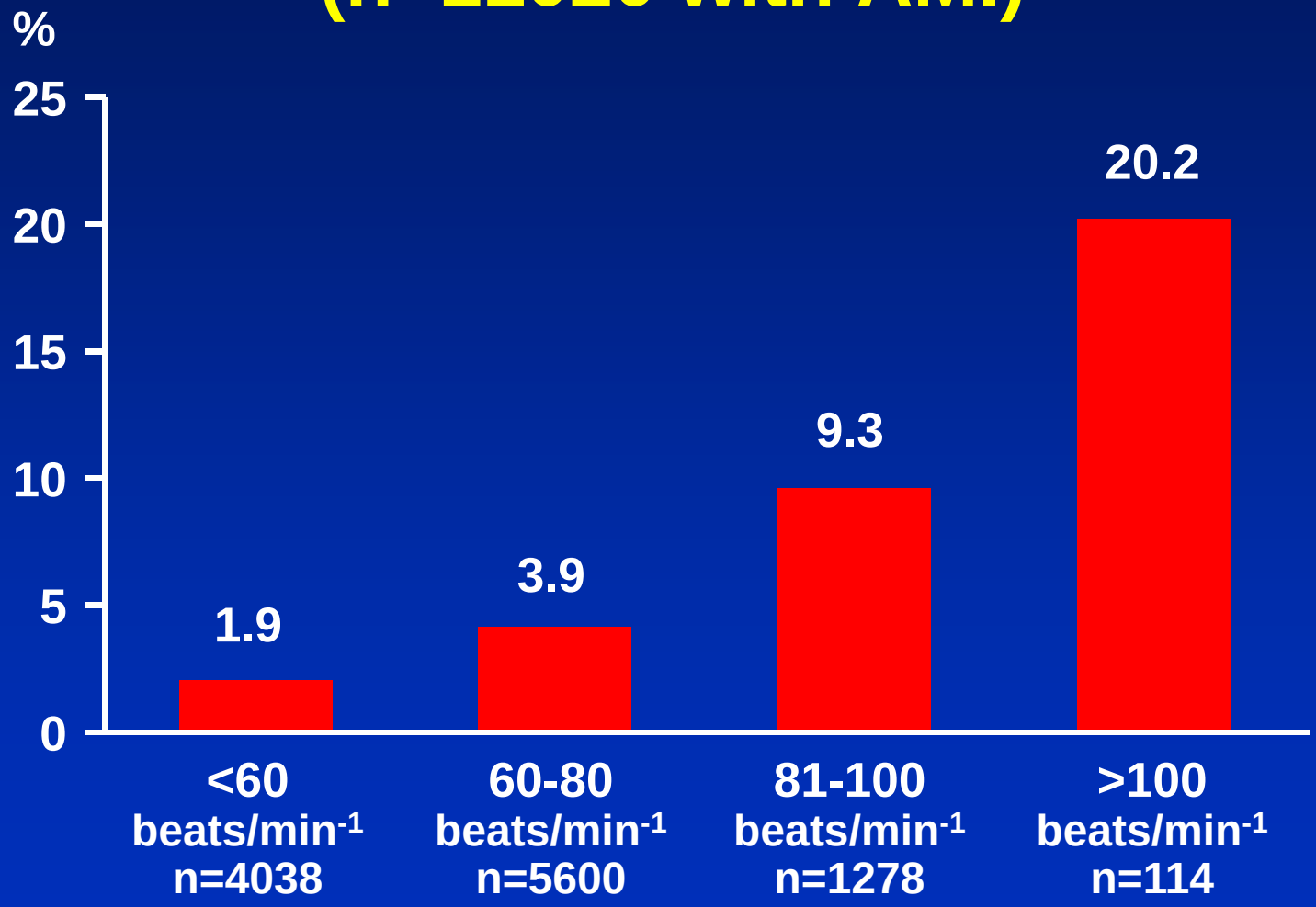
Hjalmarson et al. *Am J Cardiol*. 1990;65:547-553

Total Mortality From Day 2 to 1 Year Related to Admission HR in Patients With or without Heart Failure (n=1807)



Hjalmarson et al. *Am J Cardiol*. 1990;65:547-553

Heart Rate at Discharge and 6-month Mortality in the GISSI-3 Study (n=11020 with AMI)

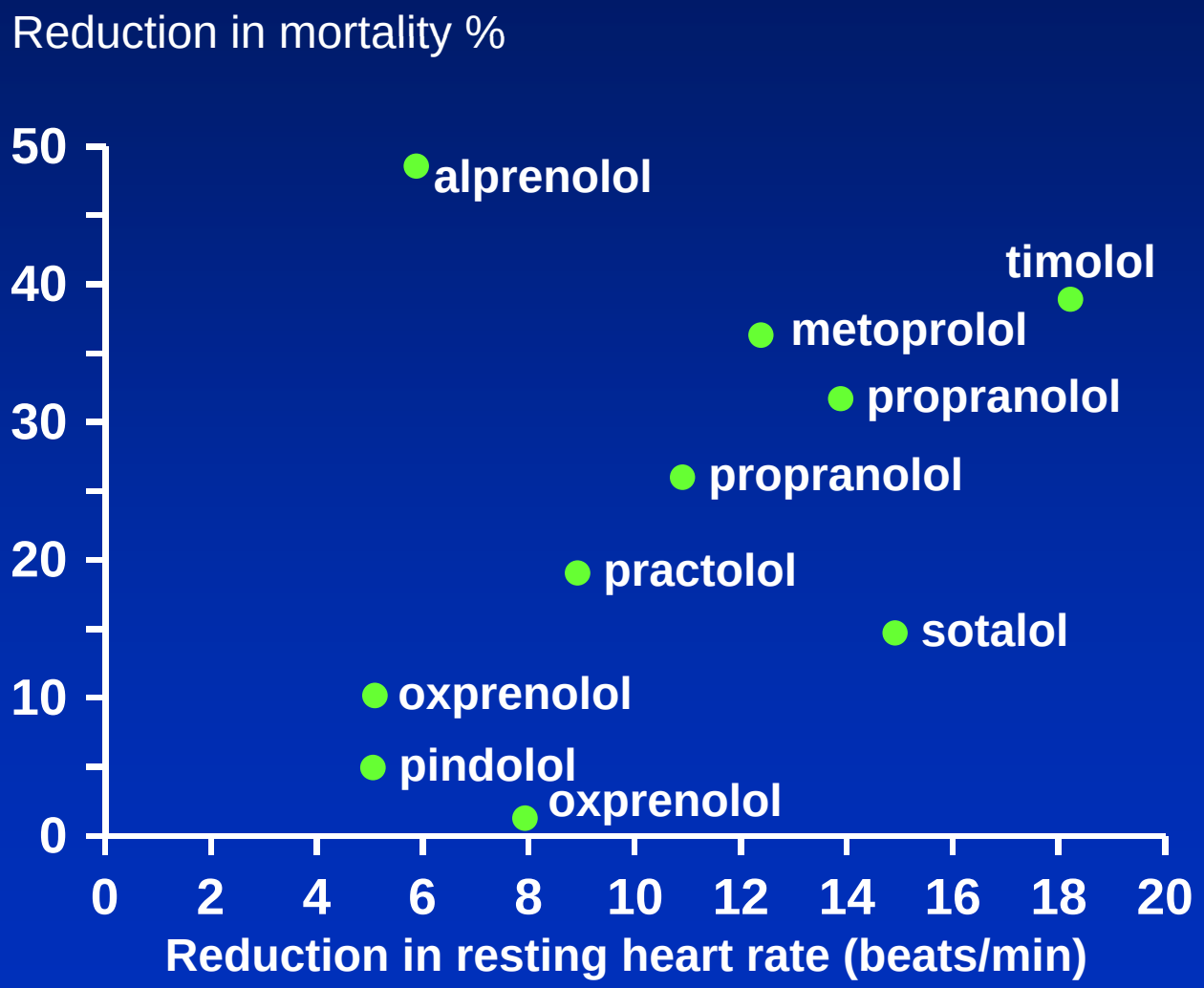


Zuanetti et al. *Eur Heart J.* Supplements 1999, Vol. 1 (Suppl H):H52-H57

Baseline HR as Independent Risk Factor in the MERIT-HF Trial (n=3991Cox adjusted)

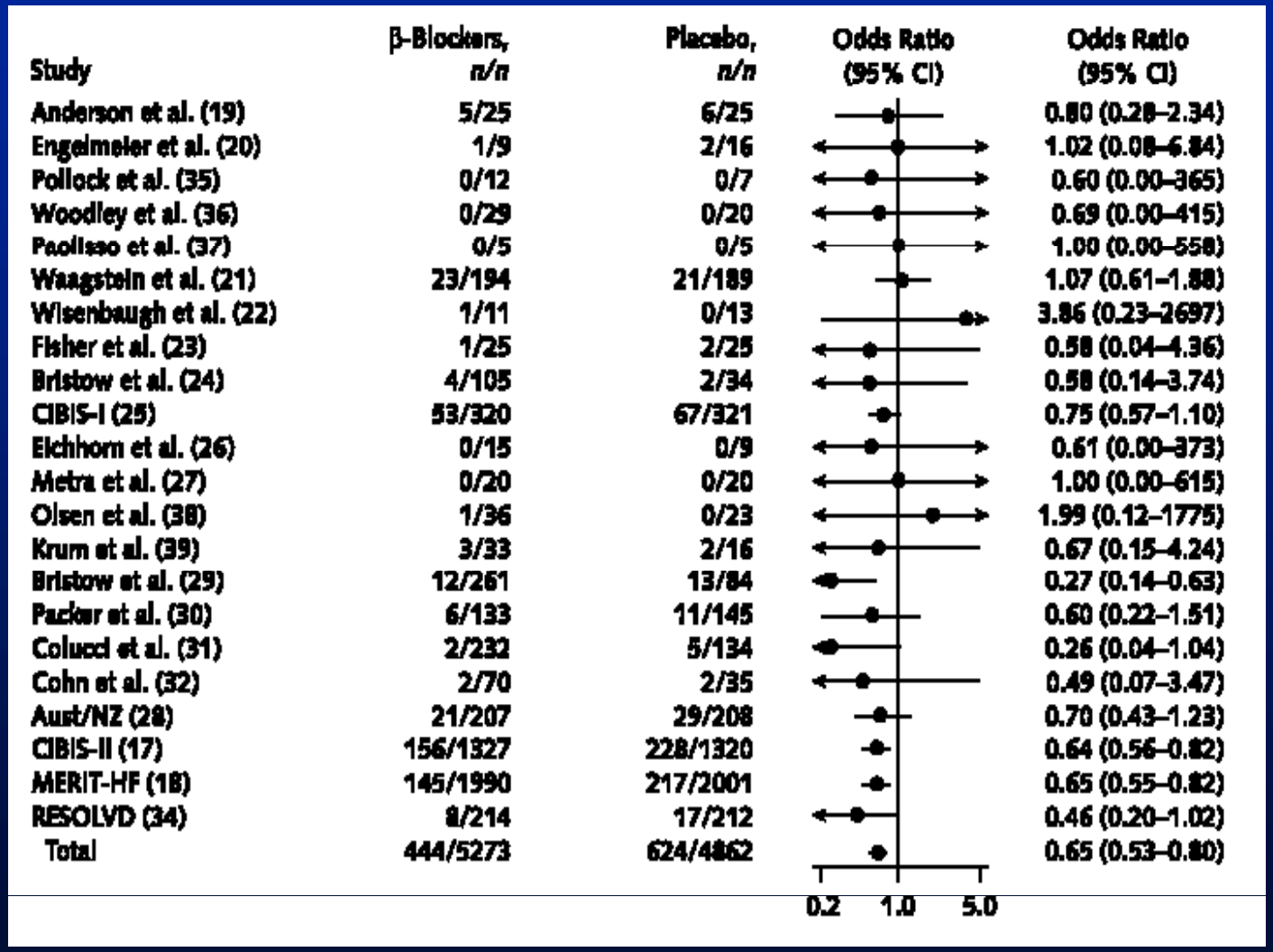
Endpoint	Placebo n=2001 p-value (No of events)		Metoprolol CR/XL n=1990 p-value (No of events)	
All-cause mortality	0.003	(217)	ns	(145)
CV mortality	0.006	(203)	ns	(128)
Pts hospitalized (CHF)	<0.0001	(294)	ns	(200)

Relationship Between Reduction of Resting Heart Rate and Reduction in Mortality From Beta-blocker Trials



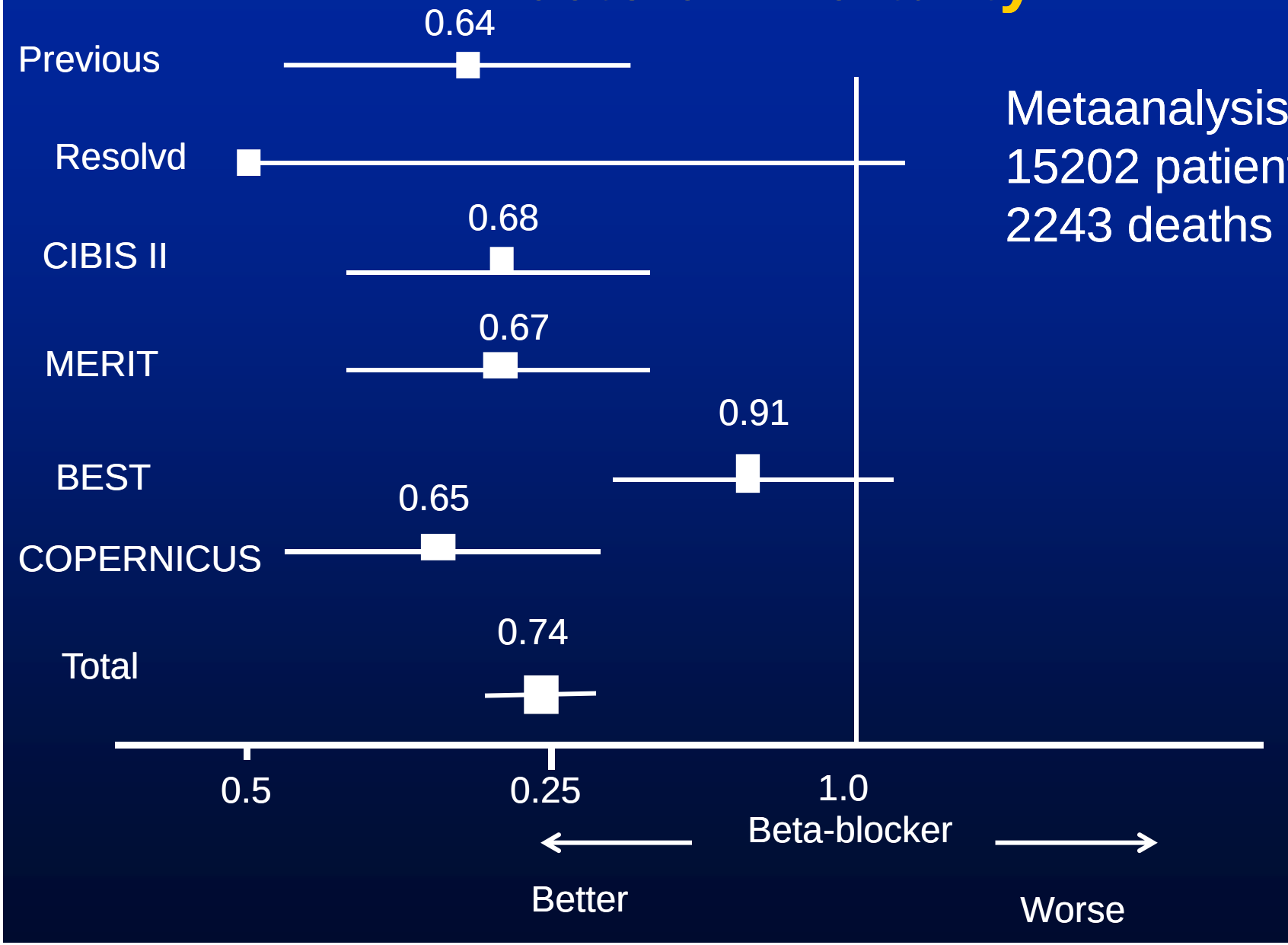
Kjekshus and Gullestad. *Eur Heart J* Supplements 1999, Vol. 1 (Suppl H):H64-H69

Metaanalysis Mortality



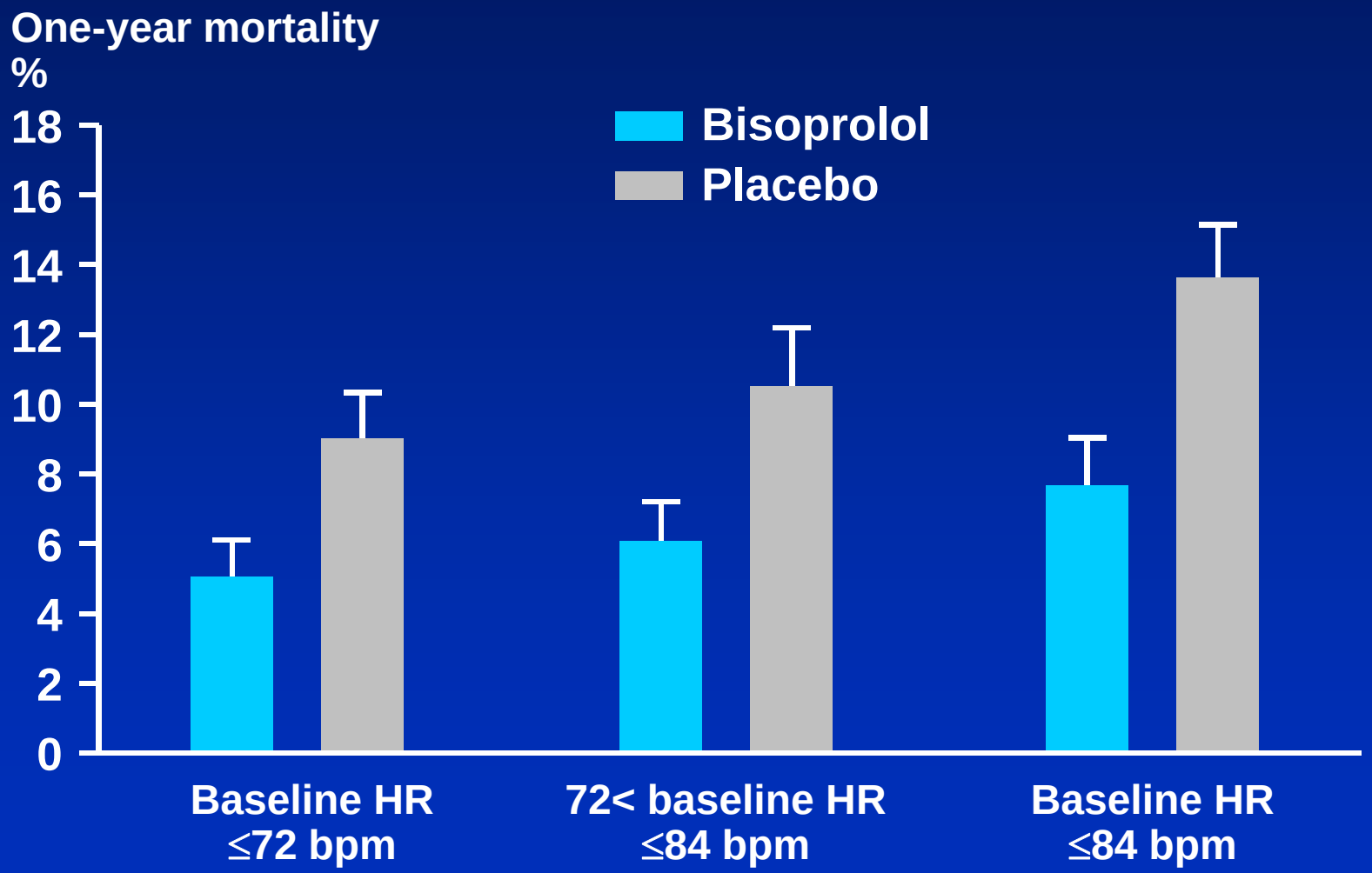
Brophy et al Ann Int Med 2001

Beta-blocker Trials in Heart Failure
Effects on Mortality



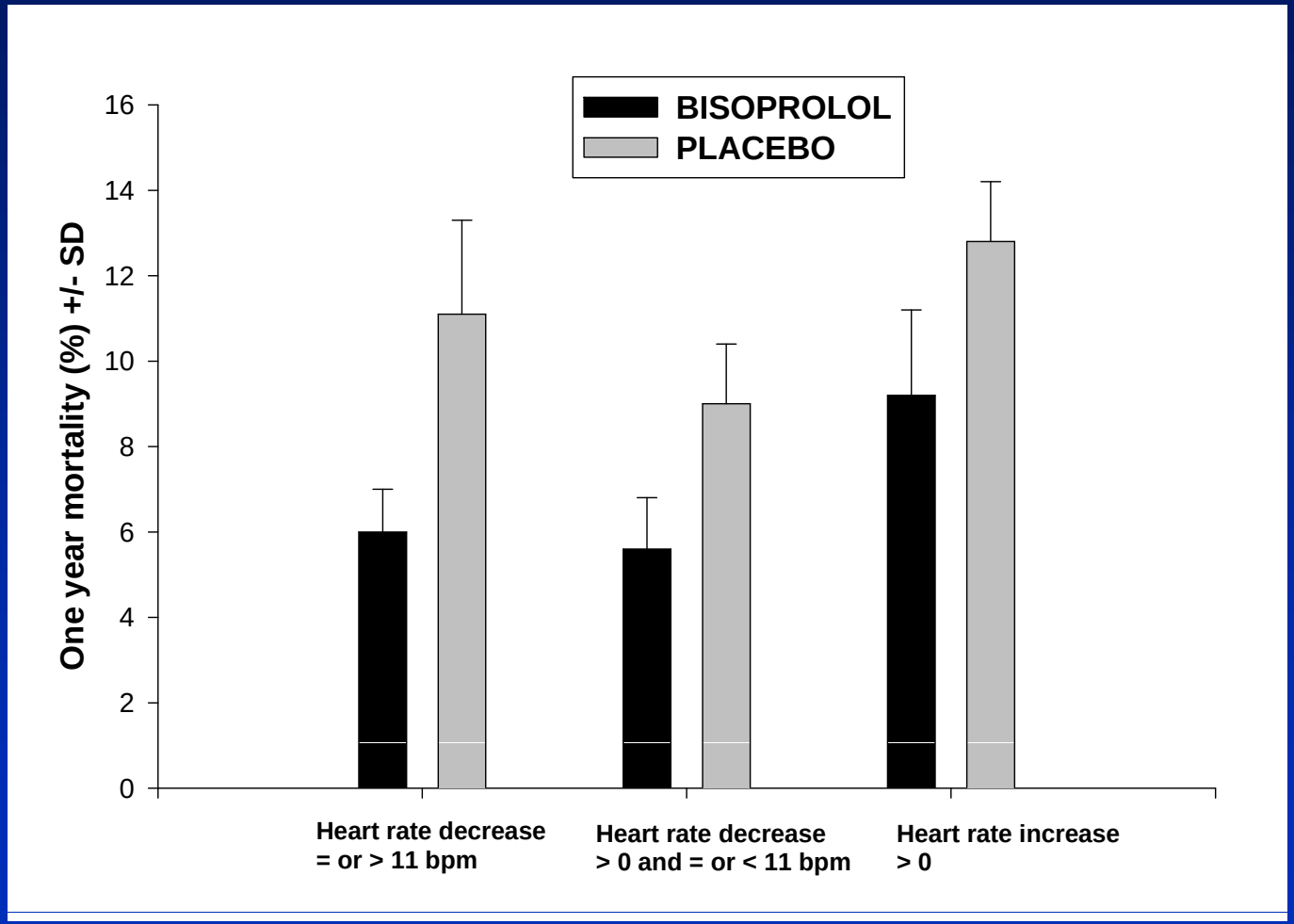
Metaanalysis incl.
15202 patients
2243 deaths

One-year Mortality According to Baseline Heart Rate in the CIBIS-II Trial (n=2539 with CHF)



Lechat et al. *Circulation* 2001;March 13:1428-1433

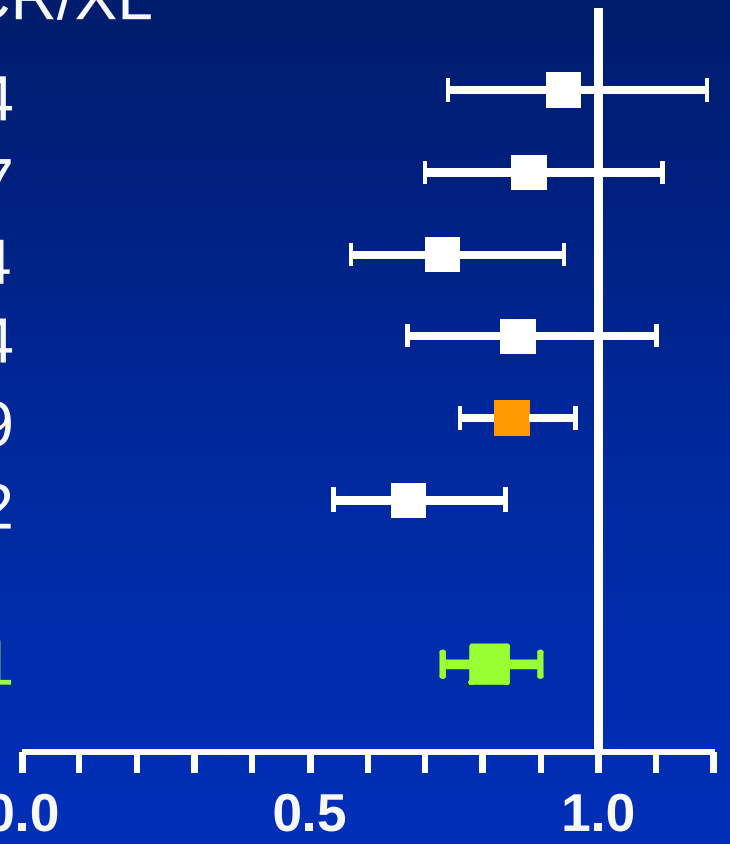
One year Mortality in CIBIS II by Changes in HR



Lechat et al Circ 2001

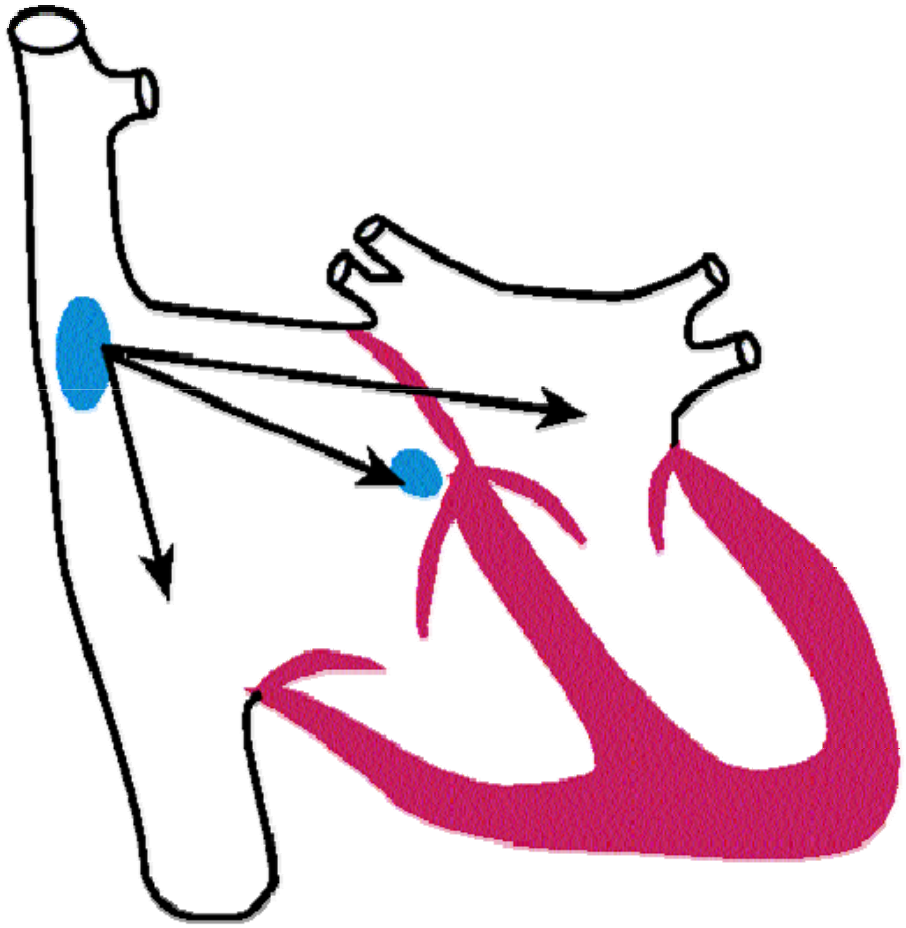
All-cause Mortality/All-cause Hospitalization in the MERIT-HF Trial (n=3991)

	No. of events Plac/Meto CR/XL
Q1	152/134
Q2	146/137
Q3	141/114
Q4	133/124
Q1-4	572/509
Q5	195/132
All randomized	767/641



Gullestad L et al, for the MERIT-HF Study Group *JACC* 2005; 45: 252-259

Sinus node inhibition



Mor*B*idity-mortality *E*v*A*l*U*ation of *T*he I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventric*UL*ar Dysfunction

SERVIER

BEAUTIFUL

Population

≥ 55 years or diabetics > 18years

Documented CAD

LV Ejection Fraction < 40%

HR ≥ 60 bpm

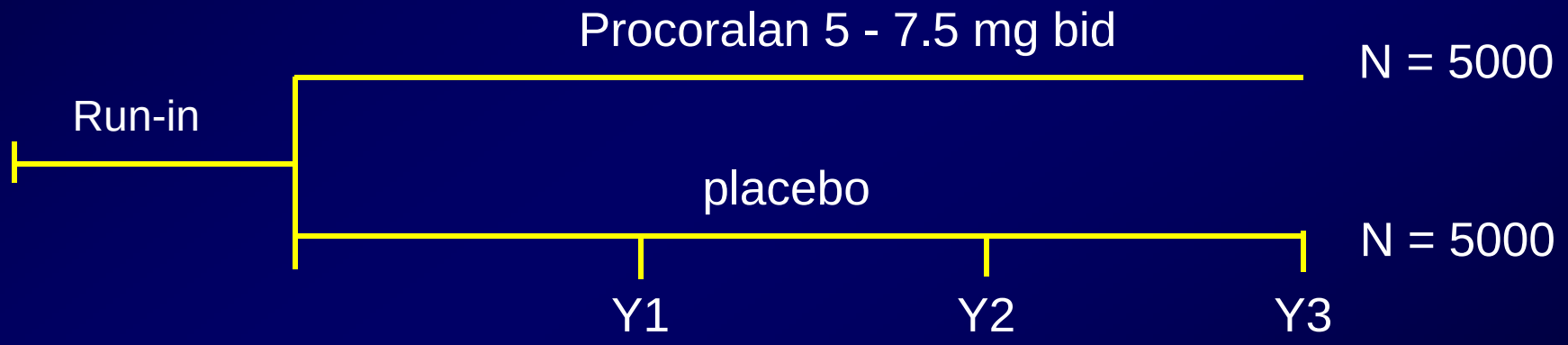
Methods

Events 11%, n=950, RRR: 19%

Power: 90%; alpha bilateral 5%

Mean follow-up: 2.25 years

850 centers in 33 countries



Combined primary endpoint

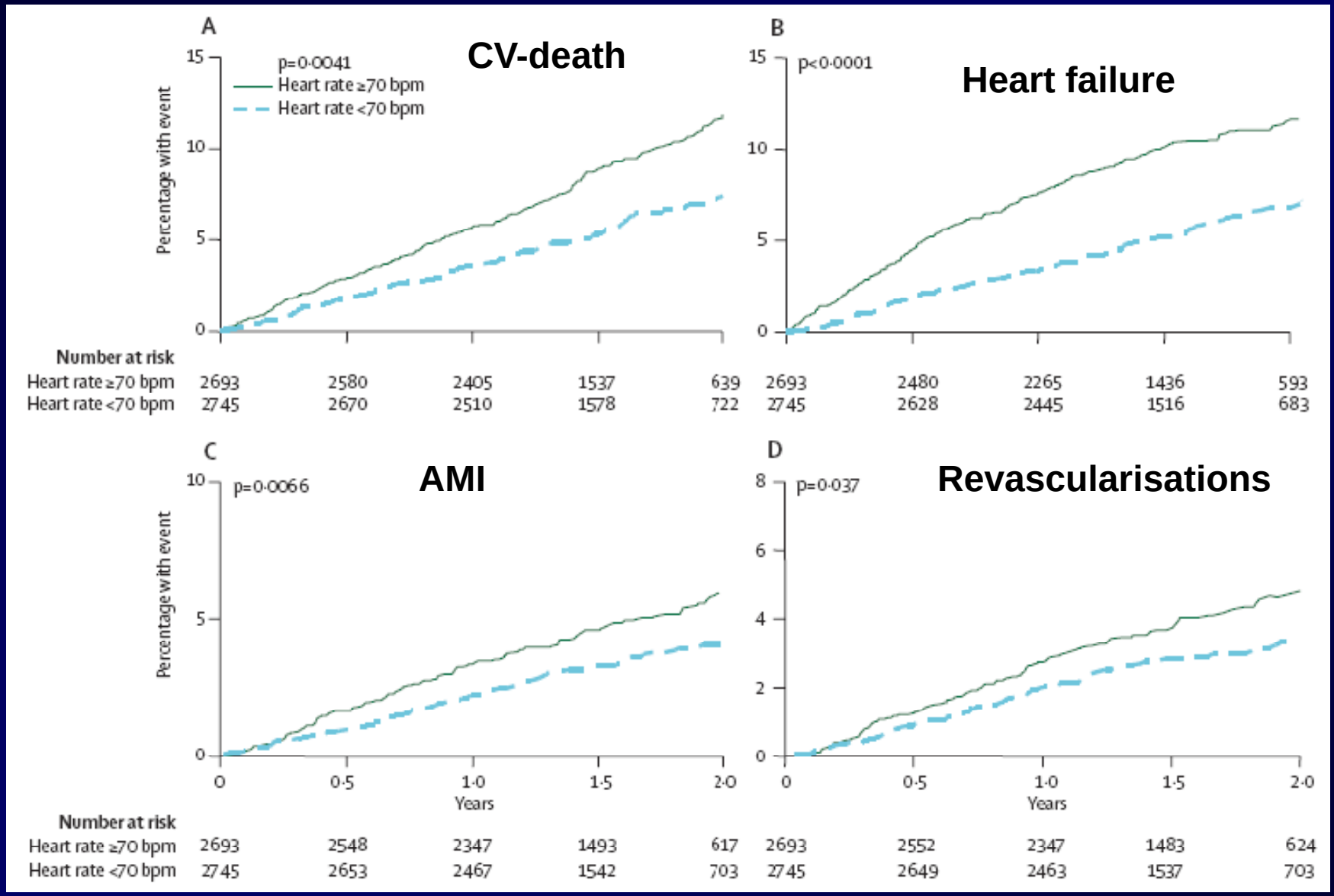
Cardiovascular death

Hospitalisation for acute myocardial infarction (MI)

Hospitalisation for new onset or worsening heart failure (HF)

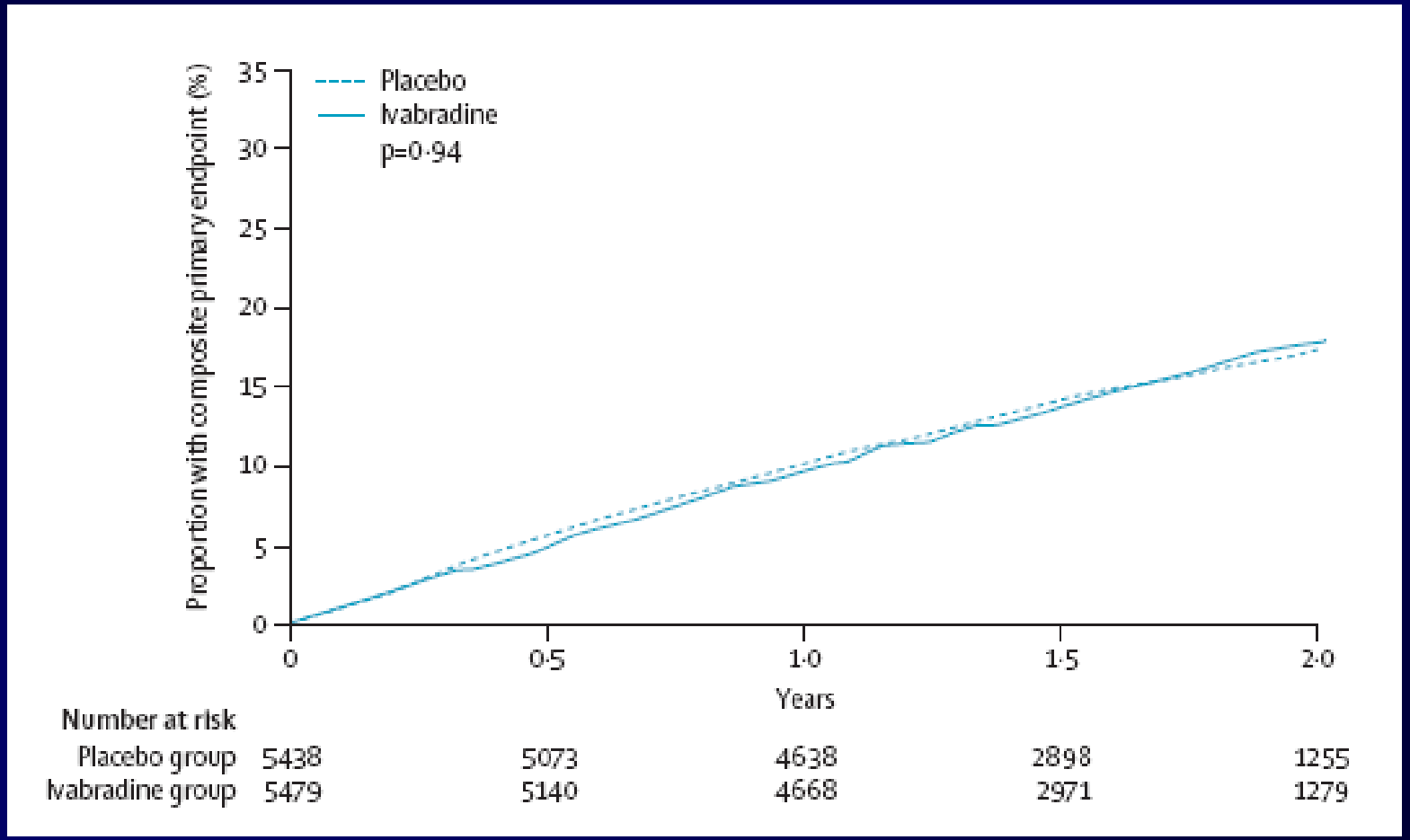
SERVIER

Heart rate



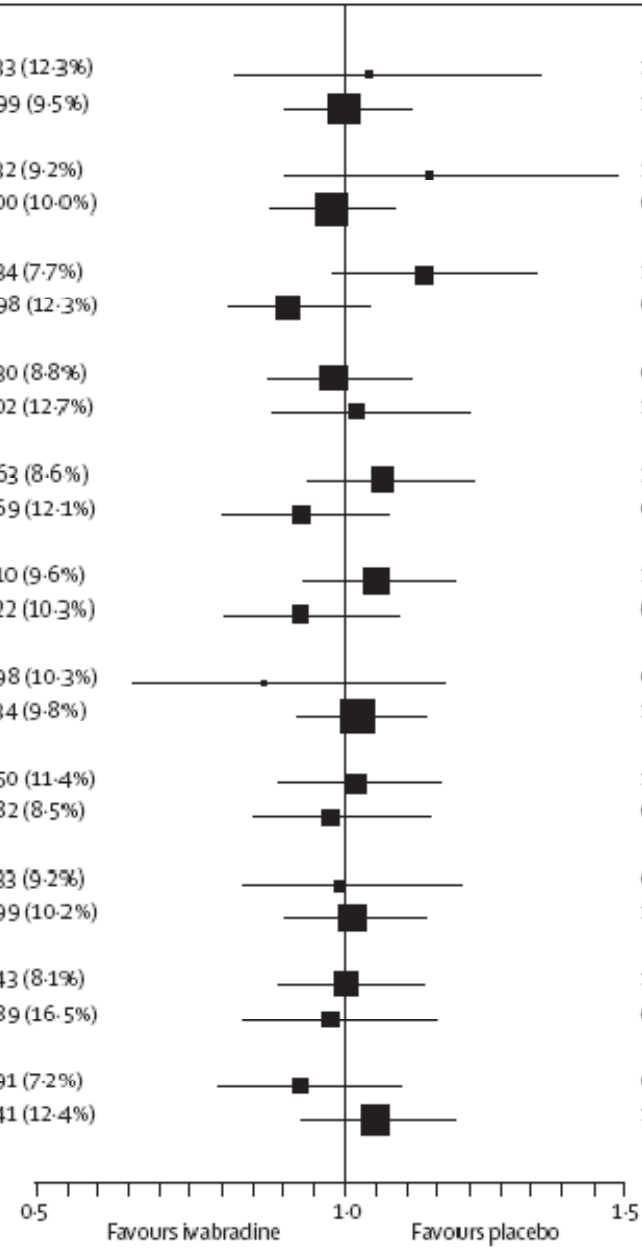
Fox et al Lancet 2008

Primary outcome
CV-death or hospitalisation for AMI or heart failure



Fox et al Lancet 2008

	Ivabradine group	Placebo group	Hazard ratio	p value
β blockers				
No β blocker intake (N=1430)	144 (12·8%)	133 (12·3%)	1·04	
β blocker intake (N=9487)	700 (9·5%)	699 (9·5%)	1·00	0·763
Sex				
Female (N=1870)	152 (10·5%)	132 (9·2%)	1·14	
Male (N=9047)	692 (9·8%)	700 (10·0%)	0·98	0·226
Baseline heart rate				
<70 bpm (N=5525)	381 (8·7%)	334 (7·7%)	1·13	
≥70 bpm (N=5392)	463 (11·3%)	498 (12·3%)	0·91	0·030
Age				
<70 years (N=7657)	517 (8·6%)	530 (8·8%)	0·98	
≥70 years (N=3260)	327 (13·0%)	302 (12·7%)	1·02	0·681
Diabetes				
No history of diabetes (N=6881)	500 (9·2%)	463 (8·6%)	1·06	
History of diabetes (N=4036)	344 (11·3%)	369 (12·1%)	0·93	0·169
Metabolic syndrome				
No history of metabolic syndrome (N=6834)	533 (10·1%)	510 (9·6%)	1·05	
History of metabolic syndrome (N=4083)	311 (9·6%)	322 (10·3%)	0·93	0·257
Myocardial infarction				
No previous myocardial infarction (N=1272)	89 (9·0%)	98 (10·3%)	0·87	
Previous myocardial infarction (N=9645)	755 (10·0%)	734 (9·8%)	1·02	0·276
Revascularisation				
No previous revascularisation (N=5274)	470 (11·6%)	450 (11·4%)	1·02	
Previous revascularisation (N=5643)	374 (8·4%)	382 (8·5%)	0·98	0·740
Hypertension				
No history of hypertension (N=3197)	232 (9·1%)	233 (9·2%)	0·99	
History of hypertension (N=7720)	612 (10·3%)	599 (10·2%)	1·01	0·884
Heart failure				
NYHA class I and II heart failure (N=8385)	544 (8·2%)	543 (8·1%)	1·00	
NYHA class III heart failure (N=2532)	300 (16·2%)	289 (16·5%)	0·98	0·779
Ejection fraction				
Left-ventricular ejection fraction ≥35% (N=5118)	275 (6·7%)	291 (7·2%)	0·93	
Left-ventricular ejection fraction <35% (N=5791)	569 (13·0%)	541 (12·4%)	1·05	0·247



Results

- ✓ N= 10 917 patients, median follow up 19 months
- ✓ Treatment with ivabradine was not shown to improve the primary composite endpoint of cardiovascular mortality, hospitalisation for MI, and HF in this study population *
- ✓ In patients with HR ≥ 70 bpm, ivabradine reduces the composite of fatal and non-fatal MI and reduces the need for revascularisation*
- ✓ Ivabradine can be safely used in combination with beta blockade in those patients

** Fox et al, Lancet 2008*

SHIFT

Population

≥ 18 years

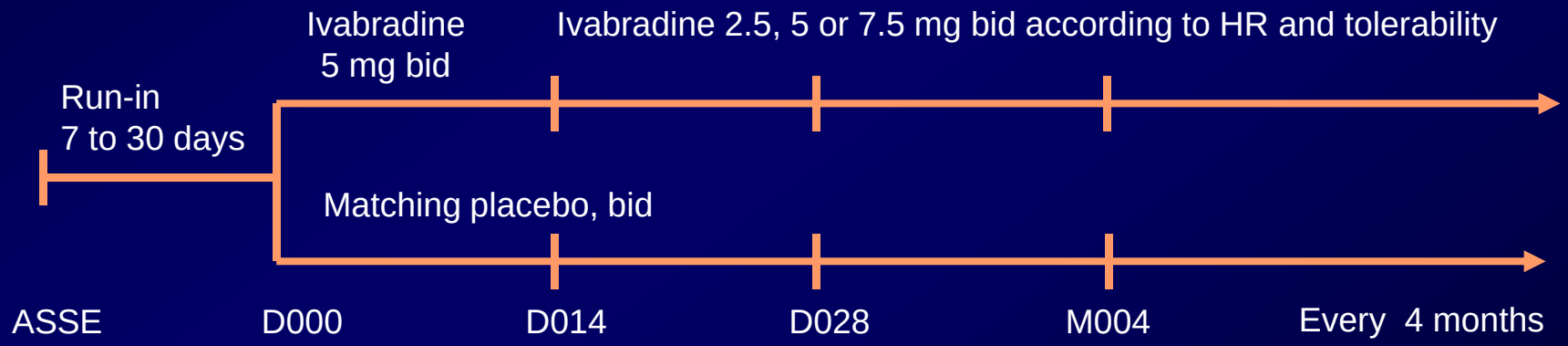
Symptomatic CHF, class II to IV NYHA

All etiologies of CHF

Documented hospital admission for worsening heart failure ≤ 12 months

LV systolic dysfunction (EF) ≤ 35%

HR ≥ 70 bpm



Composite primary endpoint

Cardiovascular death

Hospitalisation for worsening heart failure

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BEAUTIFUL Implications of the results on SHIFT

- ✓ SHIFT is specifically designed for a severe HF population
- ✓ With a different study treatment schedule
- ✓ With different study population characteristics
- ✓ Different background treatment

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BEAUTIFUL Implications of the results on SHIFT

- ✓ Executive Committee SHIFT :
  - no reason to change the inclusion or evaluation criteria
  - Statistical hypothesis revised

    1) to re-evaluate the estimated RRR (15% vs 17%)

    → 1600 expected primary endpoints (vs 1220)

    → 7000 patients (vs 5500)

    and

    2) to ensure a sufficient power in the population of interest of patients receiving at least half of the target daily dose of beta-blockers

⇒ amendment n°5 (dated 10th Sep 08)

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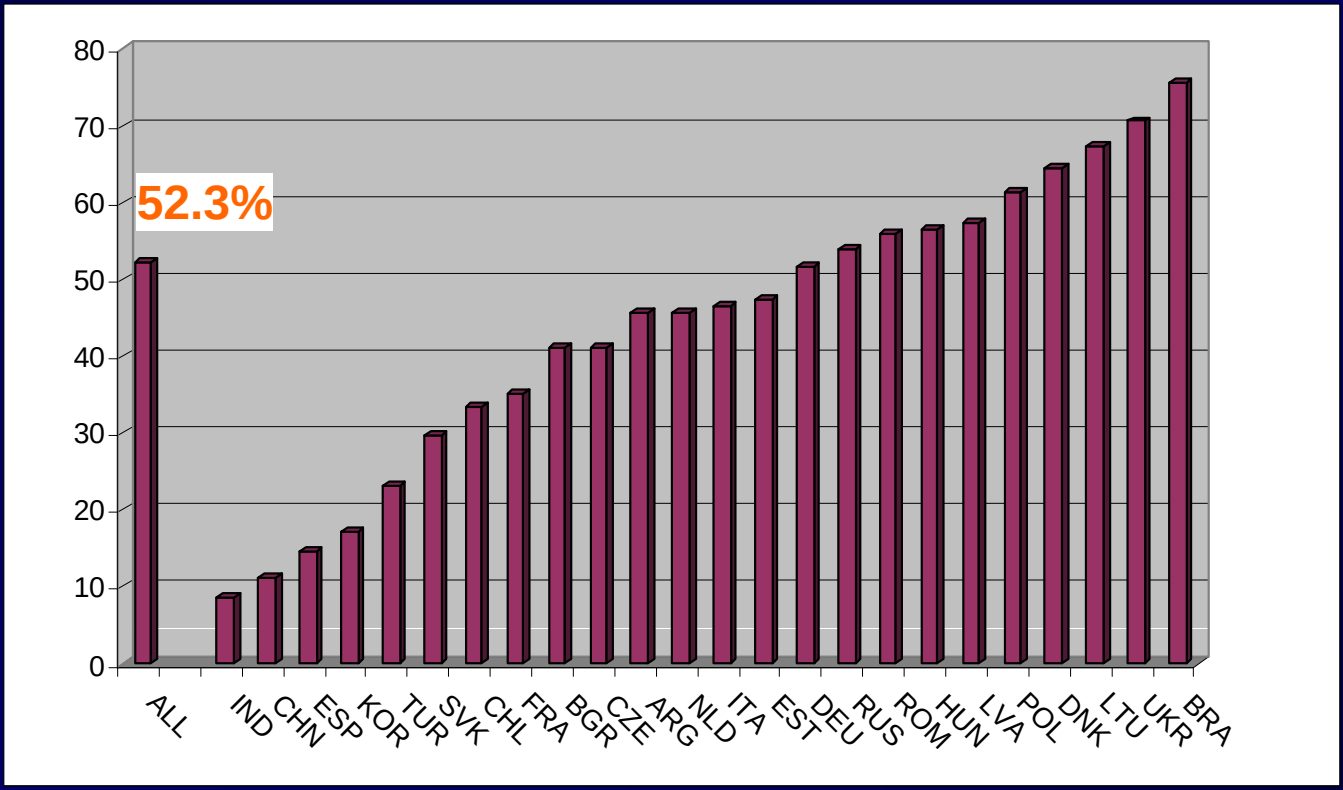
50% BB target daily dose

(RS = 5618 -03/10/08)

- ✓ Among patients treated with BB* (n=4911), 52.3 % receive at least 50% of the target daily dose

(*:Carvedilol, bisoprolol, nebivolol, metoprolol tartrate, metoprolol succinate;

393 (8.4%) patients with missing data)



- ✓ Overall, 45.7% of all randomised patients (n=5618) receive at least 50% of the BB target daily dose

Study status

- ✓ **Study follow-up ended March 31 2010**
- ✓ **Presentation in a Hot Line session at ESC congress in Stockholm August 29**
- ✓ **Simultaneous publication in Lancet**

CONCLUSIONS

- Heart rate is an independent predictor of mortality/morbidity in a general population as well as in patients with CAD or heart failure
- Reduction of heart rate by a beta-blocker is associated with improved outcome
- Can direct reduction of elevated heart rate in heart failure improve outcomes?