Heart rate reduction in heart failure and angina: A paradox?

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Disclosures:
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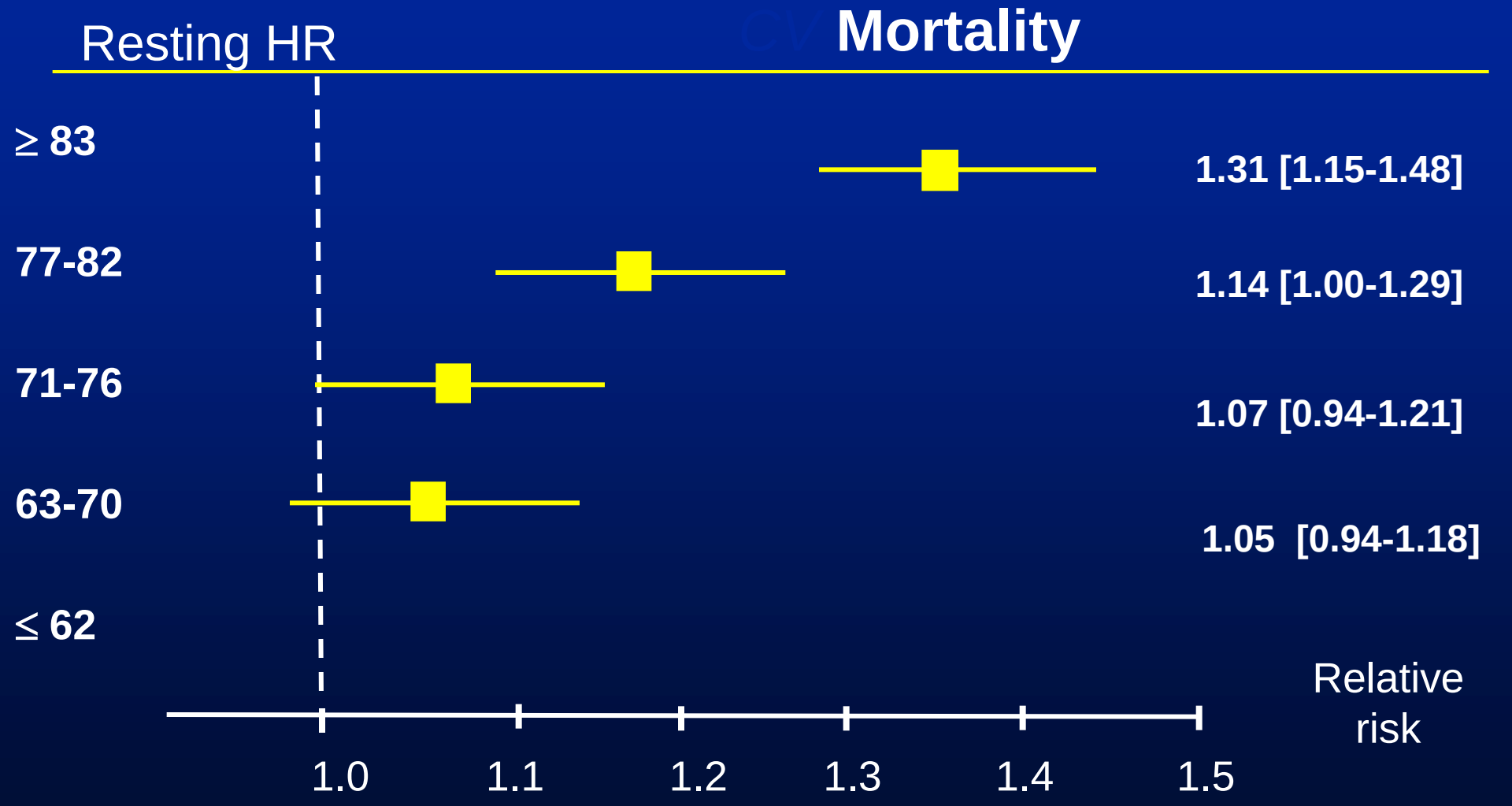
Consultant: Amgen, Medicines Company, Novartis, Respicardia, Roche

Increase of CV risk with baseline HR at rest

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



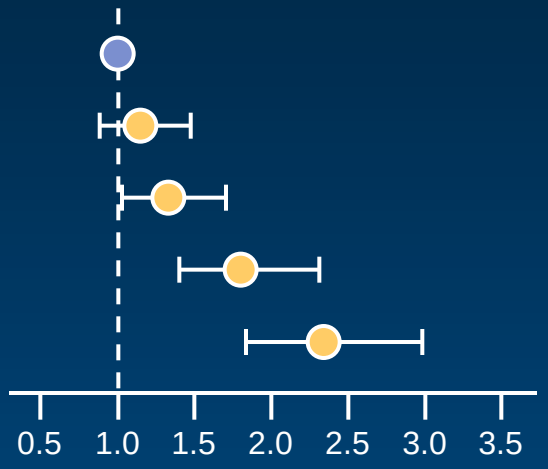
Diaz et al, EHJ 2005

Relative risk of primary composite endpoint in the placebo group divided by quintiles of heart rate

Böhm et al Lancet 2010

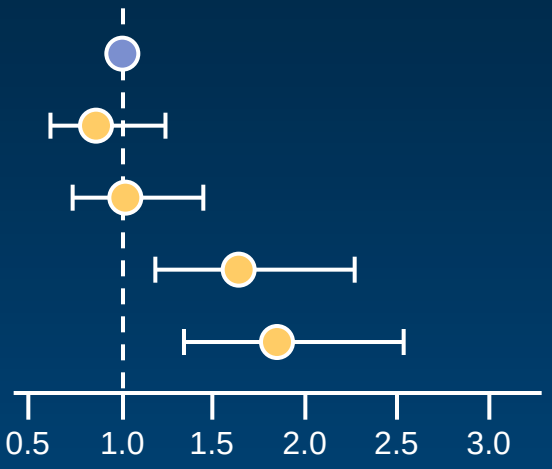
Primary composite endpoint

Heart rate at baseline (bpm)	HR
70 - <72	1.00
72 - <75	1.15
75 - <80	1.33
80 - <87	1.80
≥ 87	2.34



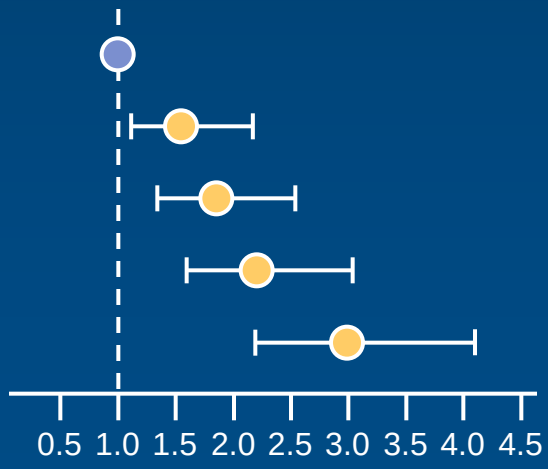
CV death

HR
1.00
0.87
1.03
1.64
1.85



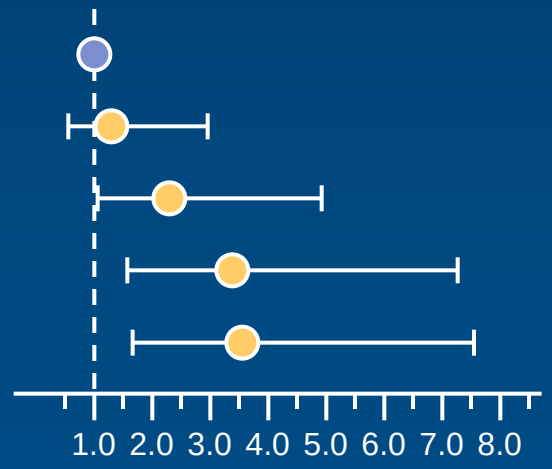
HF hospitalisation

Heart rate at baseline (bpm)	HR
70 - <72	1.00
72 - <75	1.55
75 - <80	1.85
80 - <87	2.20
≥ 87	2.99



Death from HF

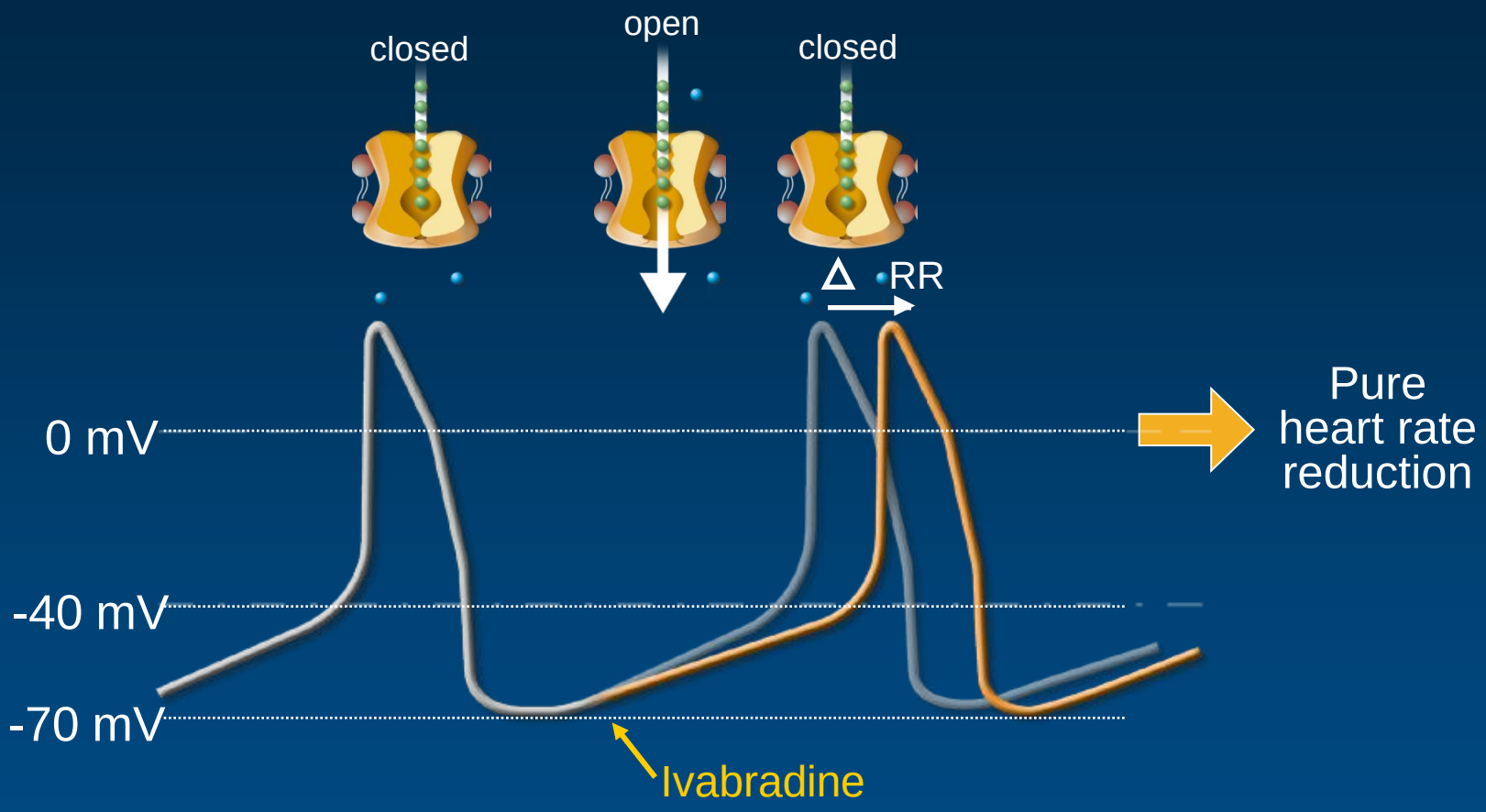
HR
1.00
1.29
2.29
3.40
3.56



Heart rate reduction in sinus rhythm

- Digoxin
- Verapamil
- Betablockade
- Sinus node inhibition

Ivabradine: pure heart rate reduction



I_f inhibition reduces the diastolic depolarization slope, thereby lowering heart rate

Thollon et al. *Br J Pharmacol*. 1994;112:37-42.

BEAUTIFUL

Population

≥ 55 years or diabetics > 18years

Documented CAD

LV Ejection Fraction < 40%

HR ≥ 60 bpm

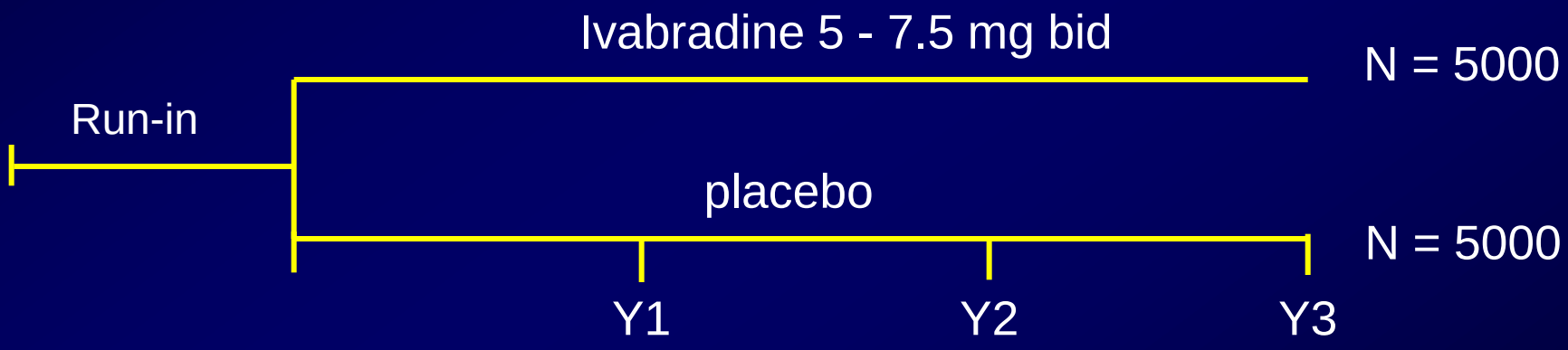
Methods

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)

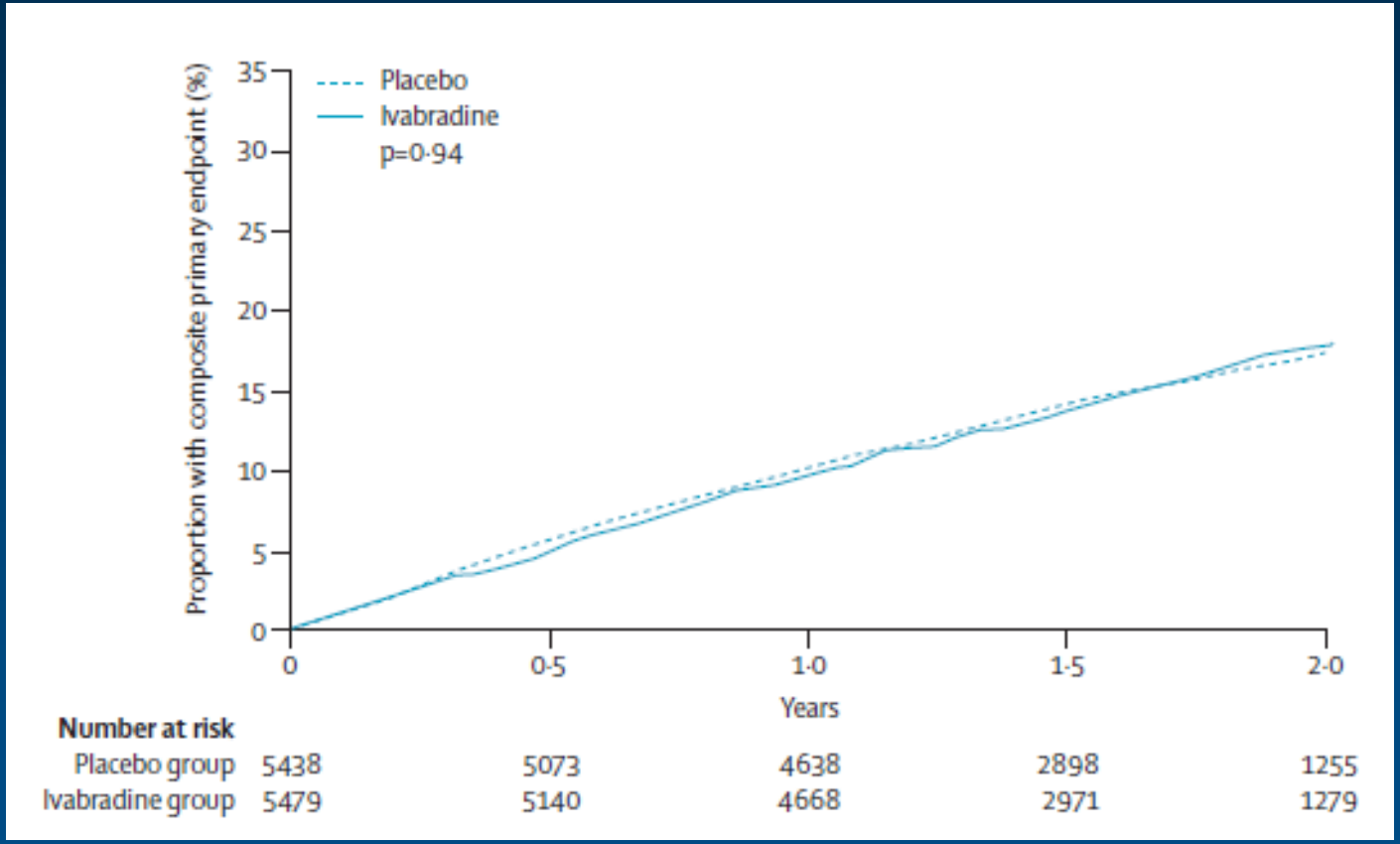
Hospitalisation for new onset or worsening heart failure (HF)

SERVIER

BEAUTIFUL

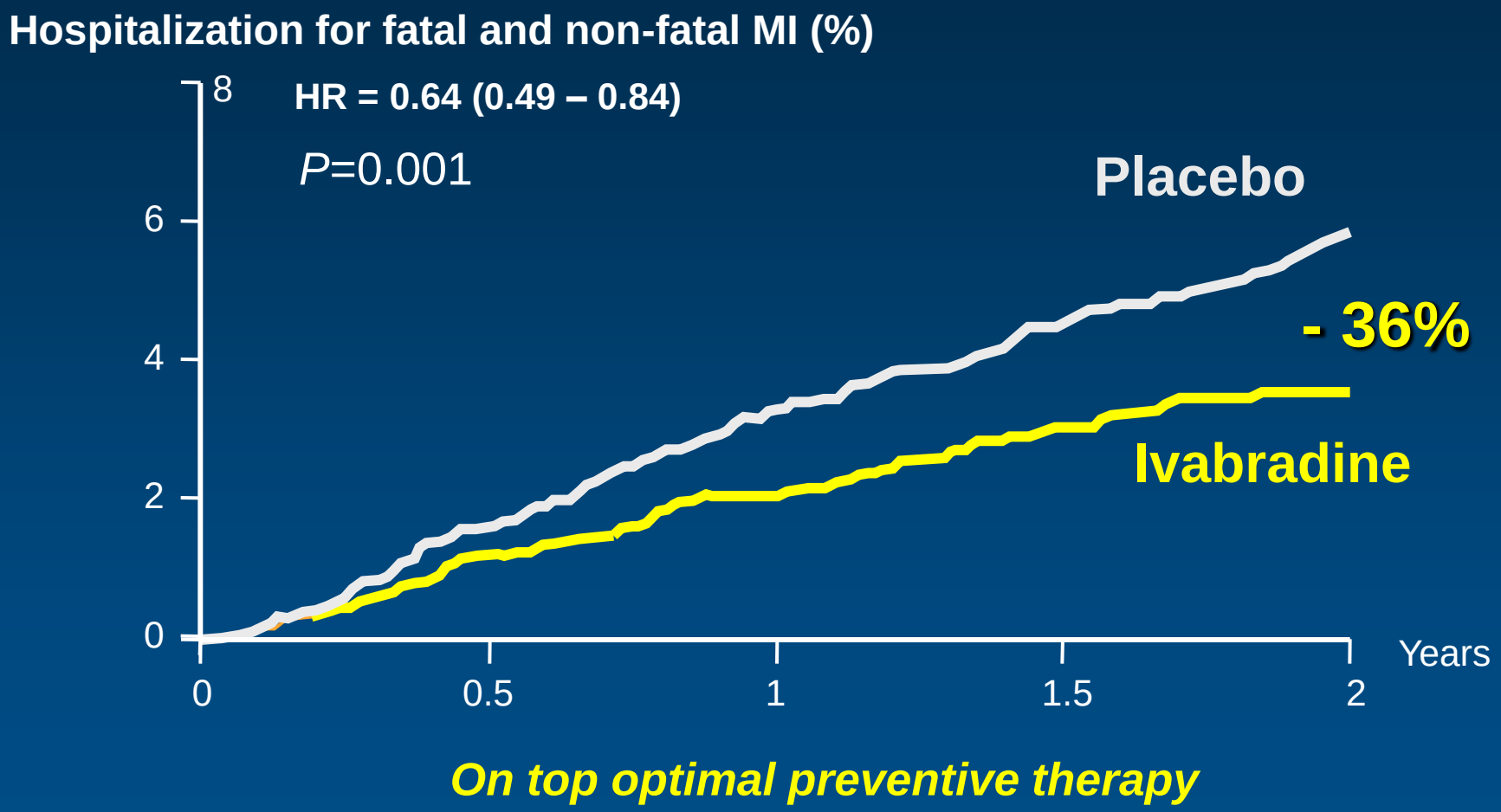
Outcome of primary endpoint

Cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure



Fox K, et al. *Lancet*. 2008.

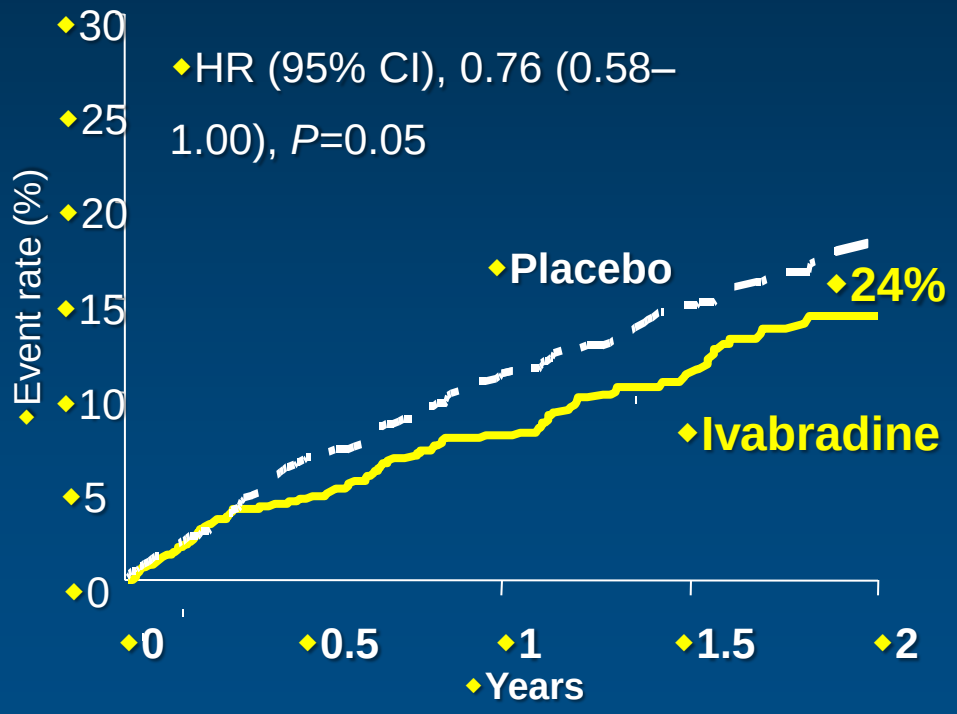
Ivabradine reduces MI in CAD with LVSD (HR ≥ 70 bpm)



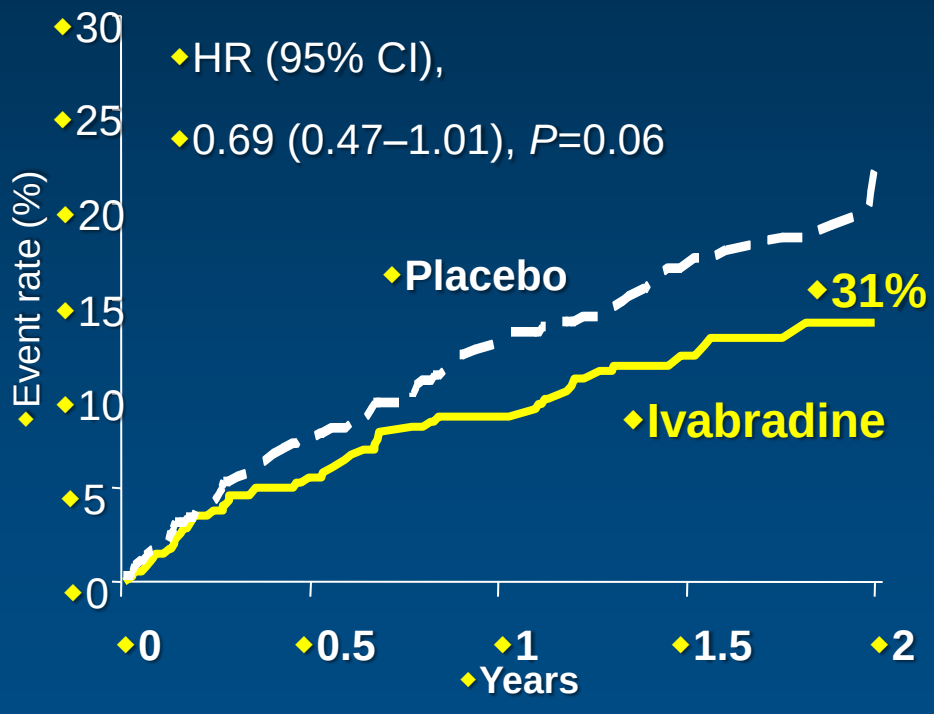
Fox K, et al. *Lancet*. 2008;372:817-821.

Ivabradine reduces composite of CV death, non-fatal MI or CHF hospitalization in CAD with angina and LVSD

- Angina
- (n = 1507)



- Angina and HR ≥70 bpm
- (n = 712)



Fox K, et al. *Eur Heart J.* 2009; 30:2337-2345 .

Study Conduct

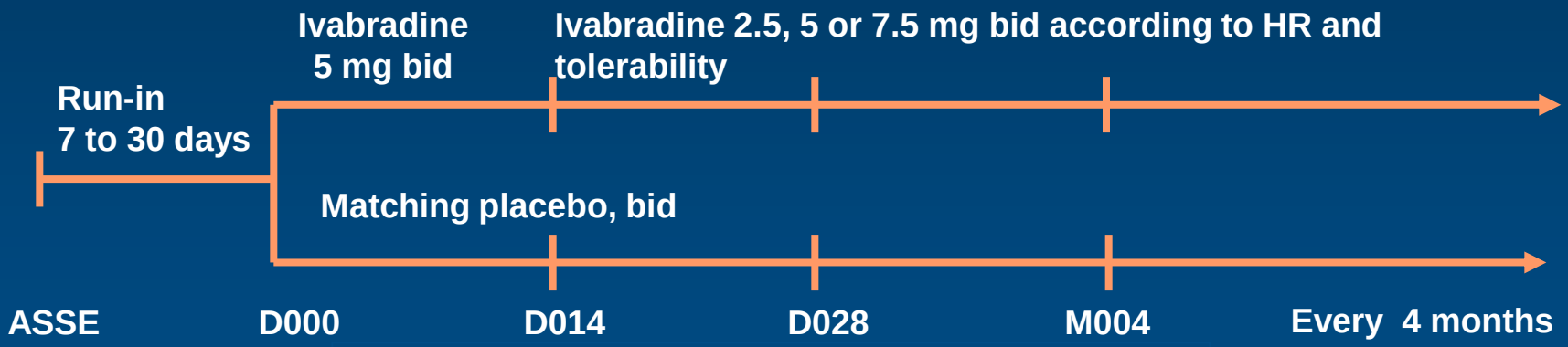
Symptomatic CHF, class II to IV NYHA

All etiologies of CHF

Documented hospital admission for worsening heart failure ≤ 12 months

LV systolic dysfunction (EF) ≤ 35%

HR ≥ 70 bpm



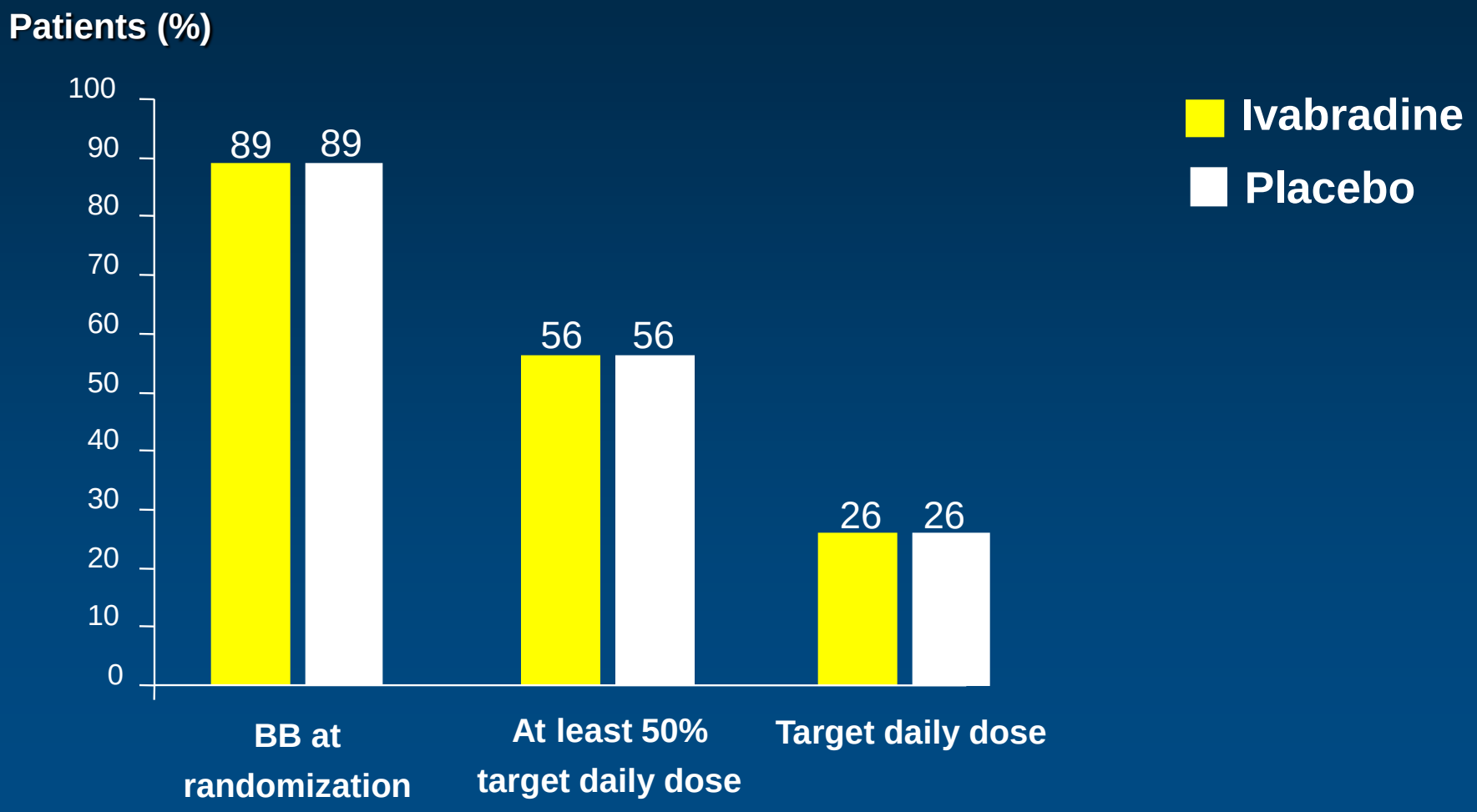
Composite primary endpoint

Cardiovascular death OR

Hospitalisation for worsening heart failure

Swedberg K, et al. *Lancet*. 2010.

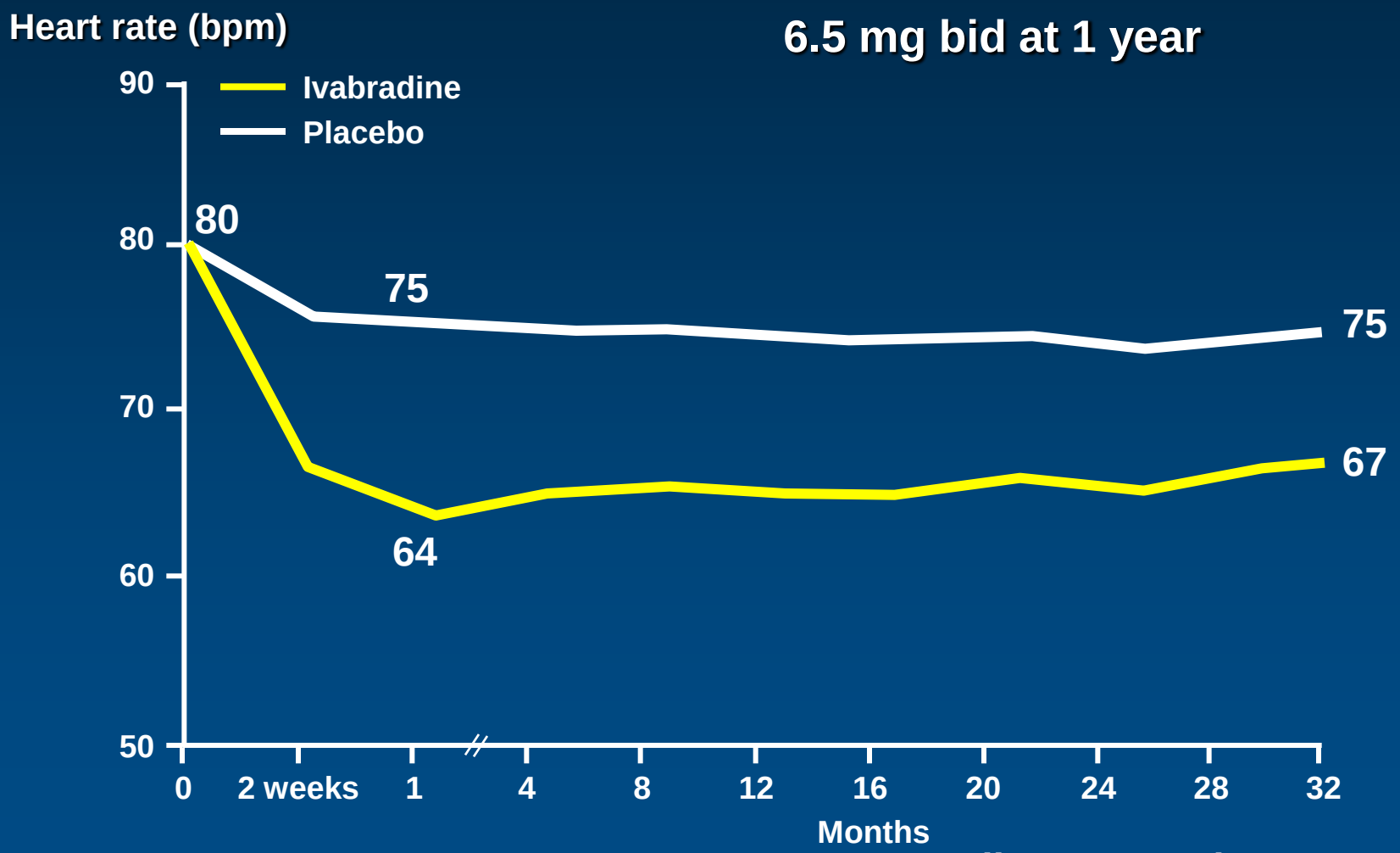
Background beta-blocker treatment



Swedberg K, et al. *Lancet*. 2010.

Mean heart rate reduction

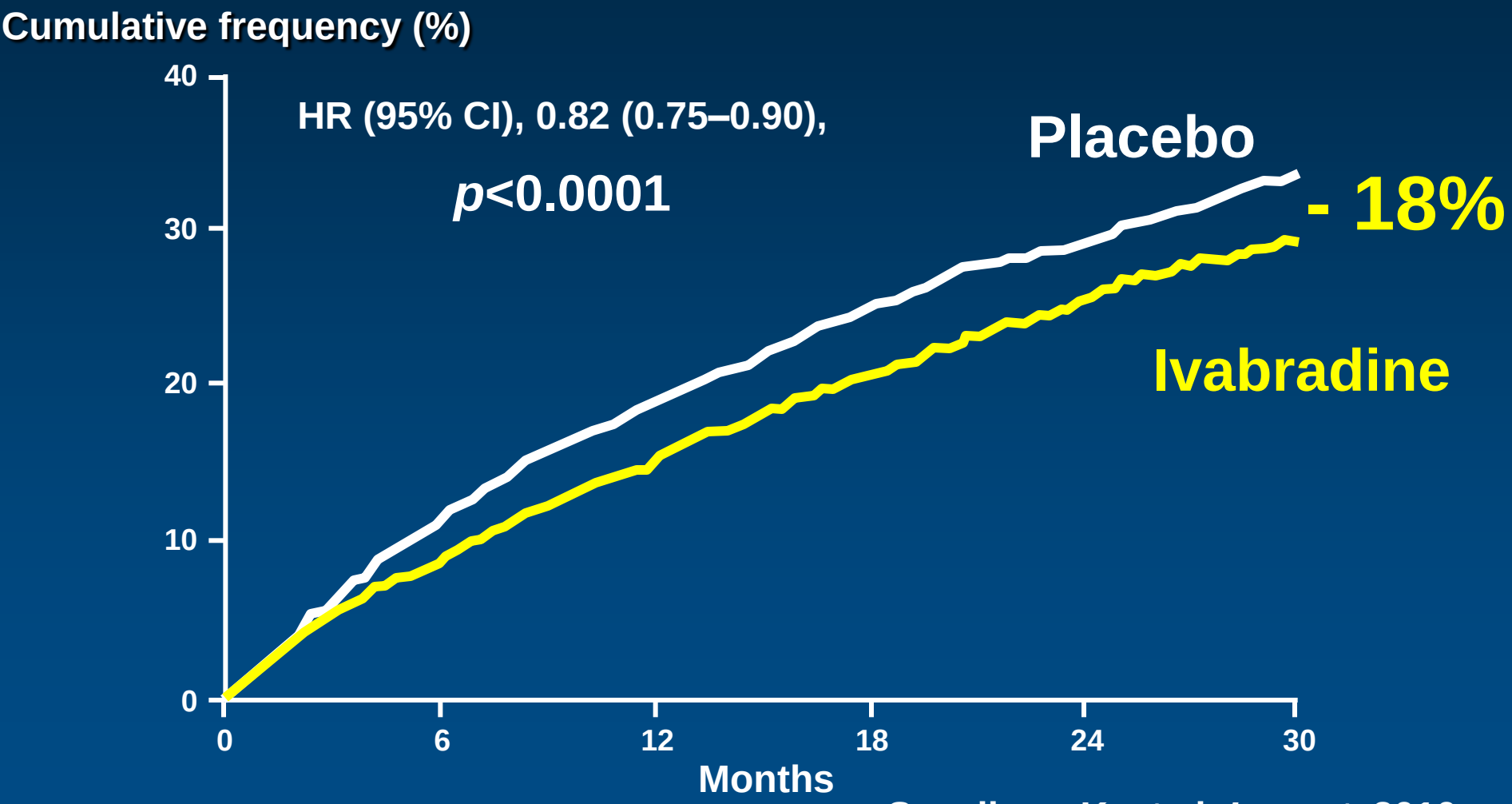
Mean ivabradine dose: 6.4 mg bid at 1 month
6.5 mg bid at 1 year



Swedberg K, et al. *Lancet*. 2010.

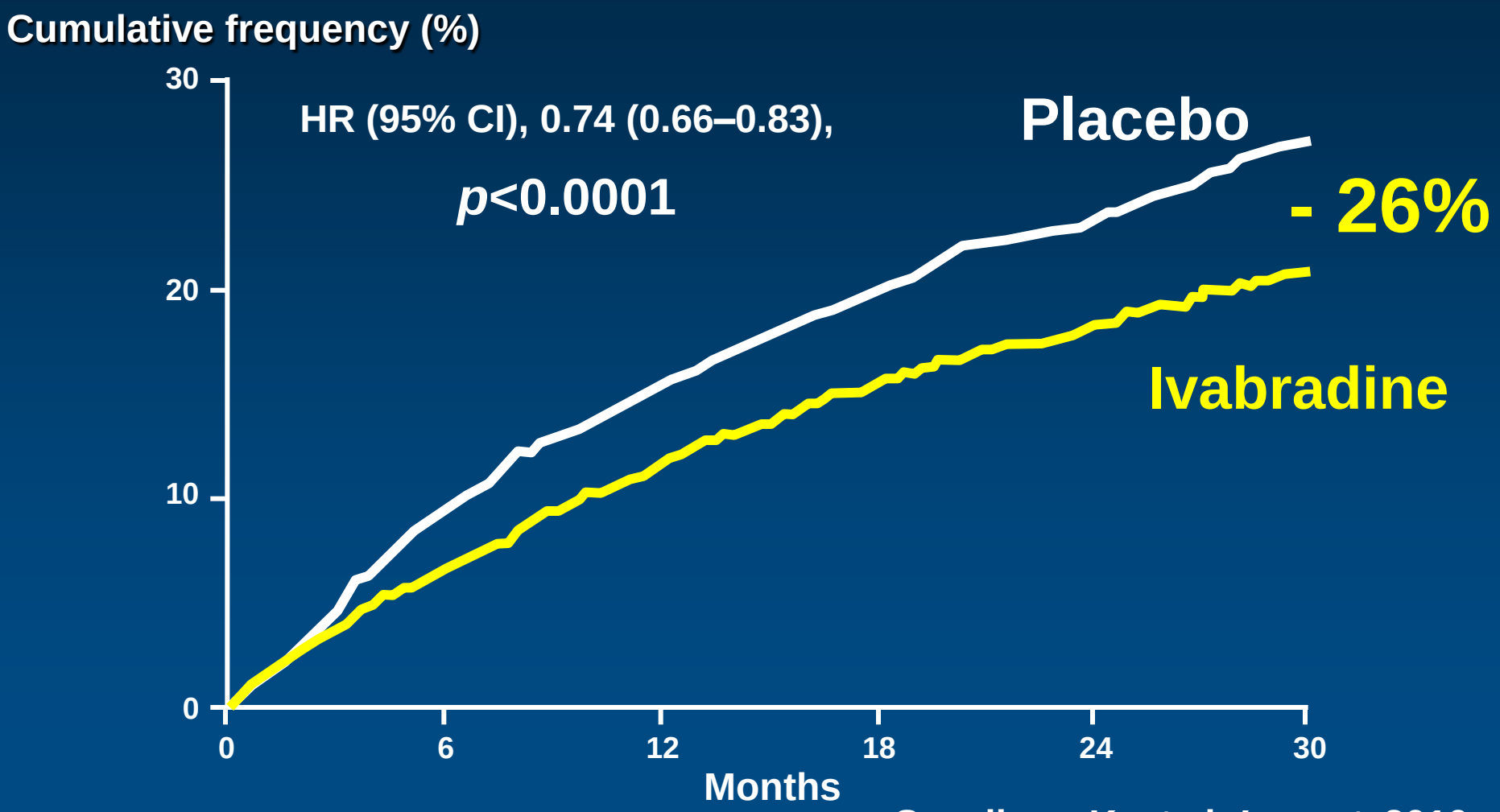
Primary composite endpoint

(CV death or hospital admission for worsening HF)



Swedberg K, et al. *Lancet*. 2010.

Hospitalization for worsening HF



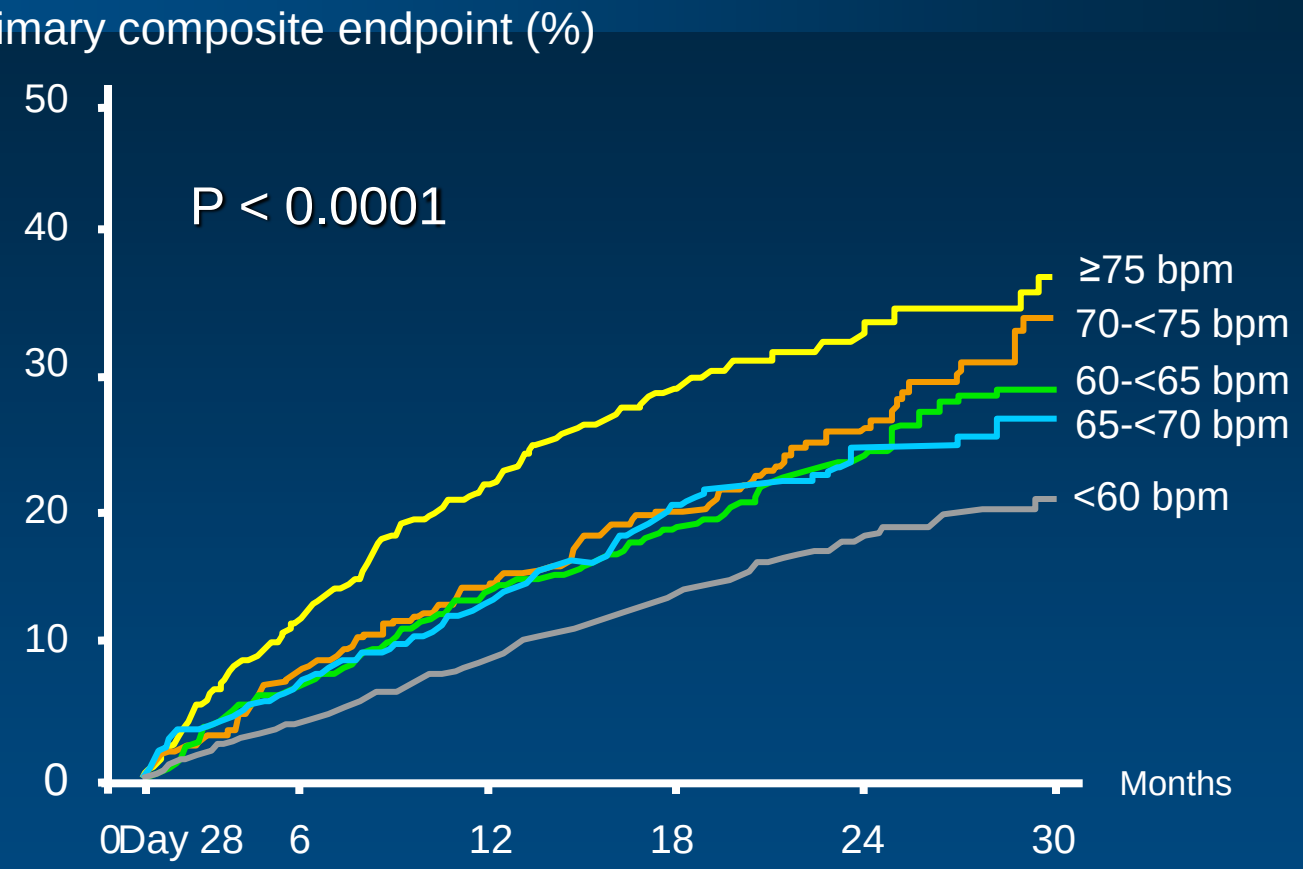
Swedberg K, et al. *Lancet*. 2010.

Effect of ivabradine on outcomes

Endpoints	Hazard ratio	95% CI	*p* value
Primary composite endpoint	0.82	[0.75;0.90]	*p*<0.0001
All-cause death	0.90	[0.80;1.02]	*p*=0.092
Death from HF	0.74	[0.58;0.94]	*p*=0.014
Hospitalisation for any cause	0.89	[0.82;0.96]	*p*=0.003
Hospitalisation for CV reason	0.85	[0.78;0.92]	*p*=0.0002
CV death/hospitalisation for HF or non-fatal MI	0.82	[0.74;0.89]	*p*<0.0001

Swedberg K, et al. *Lancet 2010*.

Primary composite endpoint according to heart rate achieved at D28* in the ivabradine group



After Adjustment of Ivabradine Effect for Change in Heart Rate at 28 days:

HR 0.95 (0.85 – 1.06), P = 0.352

Böhm et al, *Lancet,* 2010.

Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. *N Eng J Med.* 2014 August 31. DOI:10.1056/NEJMoa1406430.

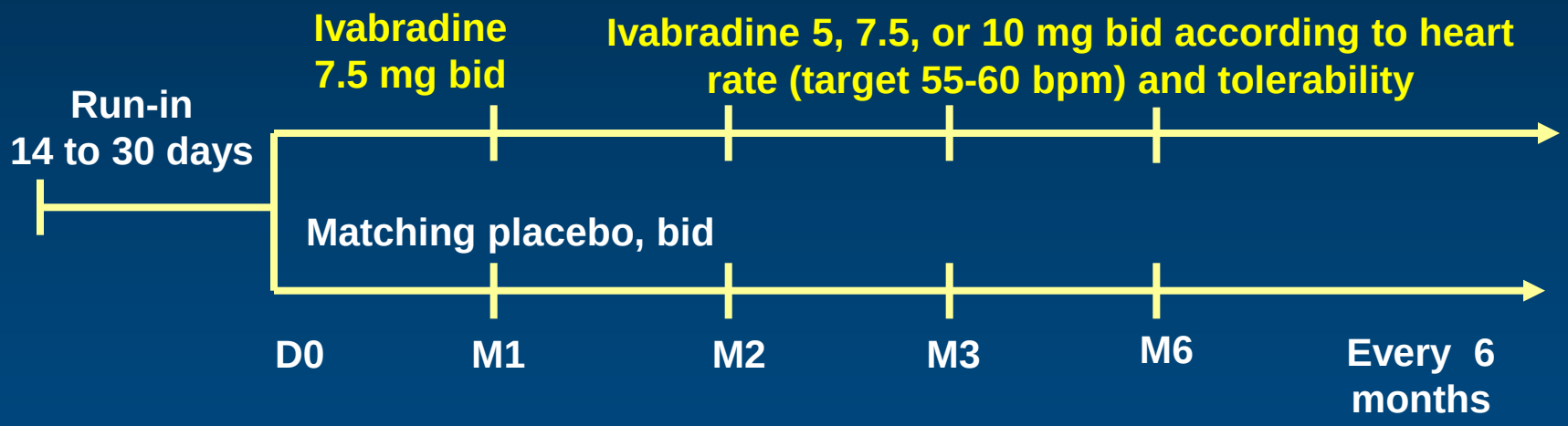
Study design

Study outcomes

- Events: 2.8% PY placebo, N=19 102
- Median follow-up: 27.8 months
- 51 countries - 1139 centres

Population

- ≥55 years, stable CAD
- With at least one other CV risk factor (including angina CCS class ≥II)
- Without clinical heart failure (LVEF >40%)
- HR ≥70 bpm



***Primary composite end point**: cardiovascular death or nonfatal myocardial infarction*

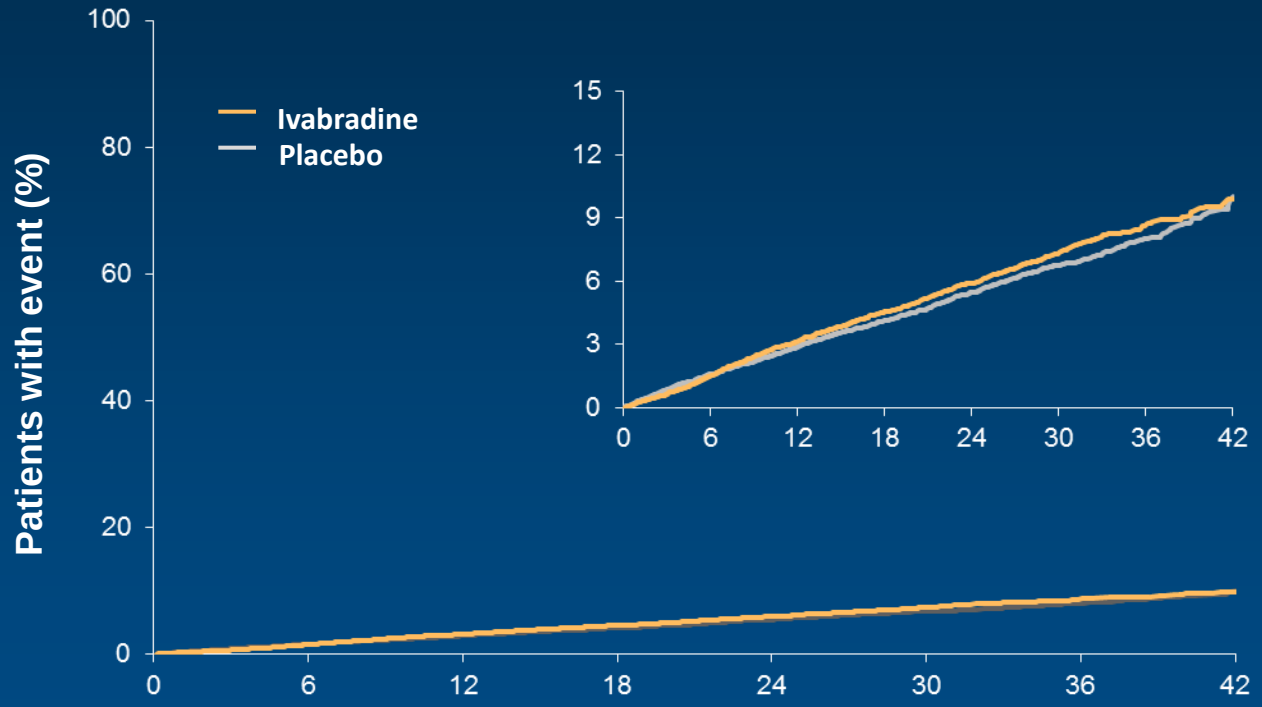
- *Primary analysis: ivabradine versus placebo on primary end point*
- *Prespecified analysis: in patients with angina CCS class ≥II on primary end point*

Fox K et al. *Am Heart J.* 2013;166:654-661.

Primary composite end point

Ivabradine n=654 (3.03% PY) **Placebo n=611 (2.82% PY)**

HR = 1.08 [95% CI 0.96-1.20] *P*=0.20



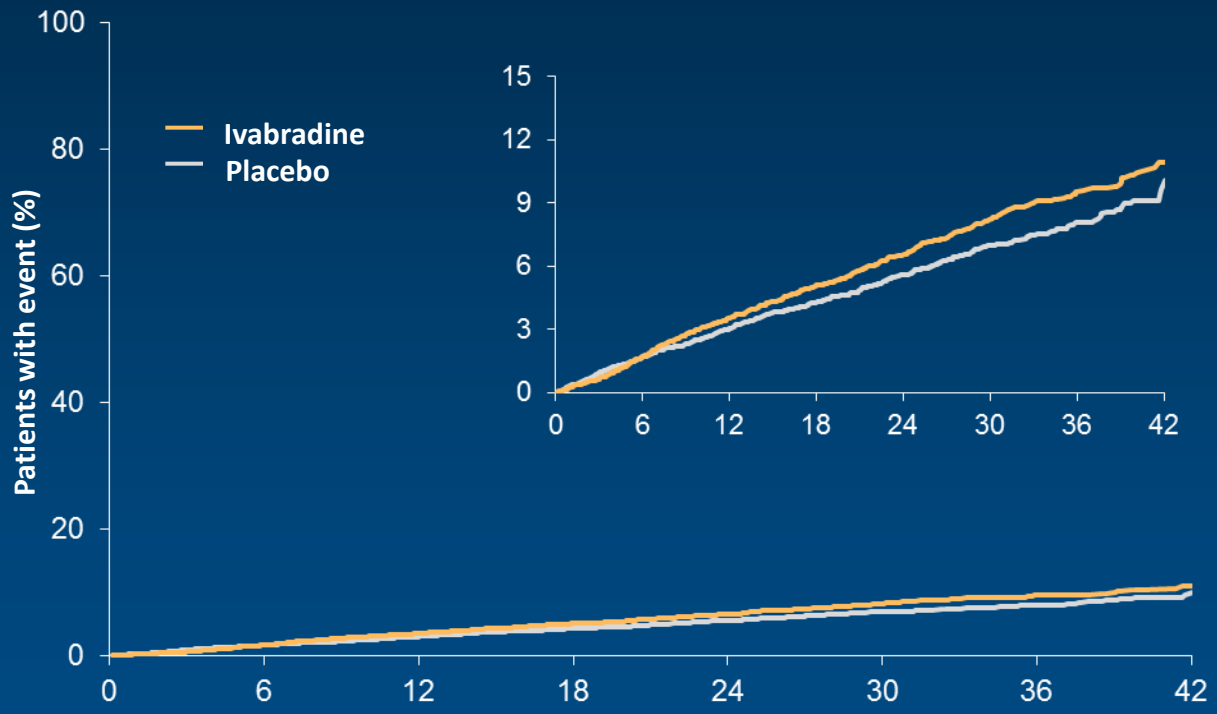
Numbers at risk								
Ivabradine	9550	9297	9077	8611	5570	3776	1832	349
Placebo	9552	9311	9130	8656	5649	3749	1836	365

Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. *N Eng J Med.* 2014 August 31. DOI:10.1056/NEJMoa1406430.

Primary composite end point (angina population: CCS class ≥II, n=12 049)

Ivabradine n=459 (3.37% PY) **Placebo n=390 (2.86% PY)**

HR = 1.18 [95% CI 1.03-1.35] *P*=0.018



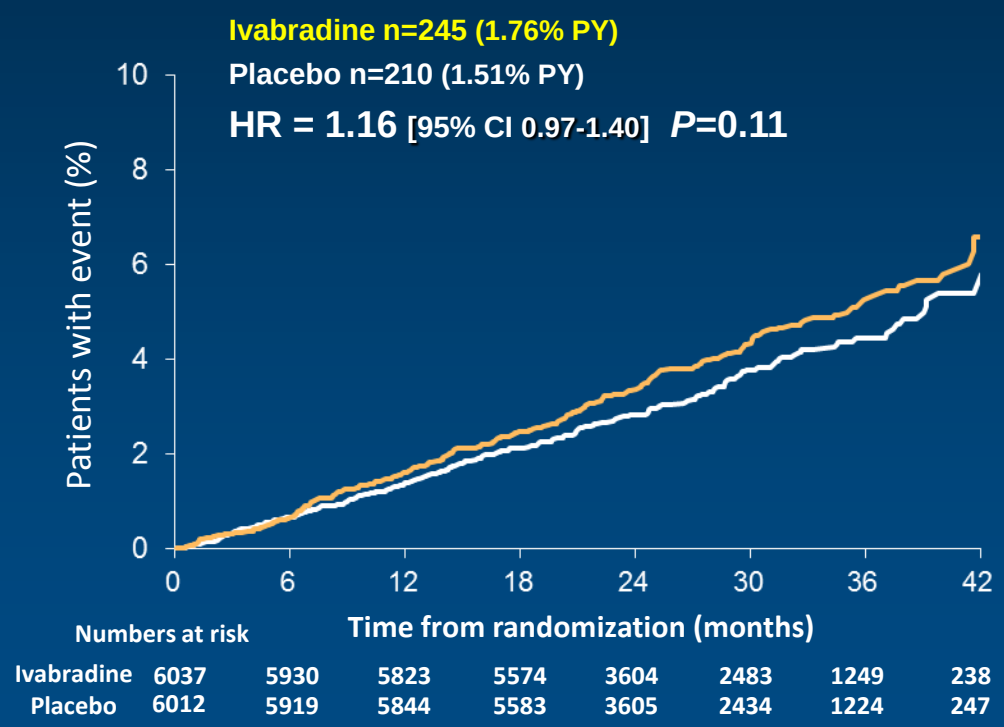
Numbers at risk

Ivabradine	6037	5869	5712	5428	3483	2387	1197	227
Placebo	6012	5859	5747	5463	3502	2350	1178	232

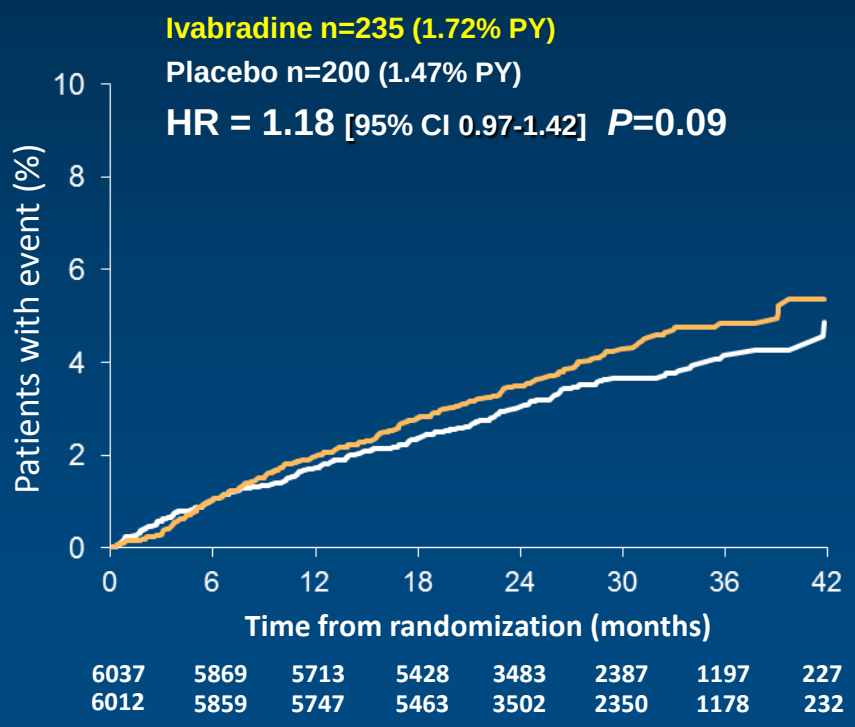
Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. *N Eng J Med.* 2014 August 31. DOI:10.1056/NEJMoa1406430.

Components of primary composite end point (angina population: CCS class ≥II, n=12 049)

Cardiovascular death



Nonfatal myocardial infarction

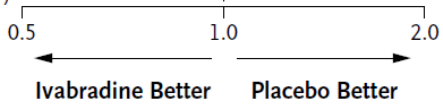


Ivabradine Placebo

Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. *N Eng J Med.* 2014 August 31. DOI:10.1056/NEJMoa1406430.

Impact of ivabradine on PEP in prespecified subgroups

Subgroup	No. of Patients	Ivabradine	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/total no. (%)			
Angina class at baseline					0.02
Class I or no symptoms	7,053	195/3513 (5.6)	221/3540 (6.2)	0.89 (0.74–1.08)	
Class ≥II	12,049	459/6037 (7.6)	390/6012 (6.5)	1.18 (1.03–1.35)	
Beta-blocker use at randomization					0.98
Yes	15,878	543/7934 (6.8)	506/7944 (6.4)	1.08 (0.95–1.21)	
No	3,224	111/1616 (6.9)	105/1608 (6.5)	1.07 (0.82–1.40)	
Heart rate					0.69
<75 beats/min	9,170	289/4589 (6.3)	263/4581 (5.7)	1.10 (0.93–1.30)	
≥75 beats/min	9,931	365/4960 (7.4)	348/4971 (7.0)	1.05 (0.91–1.22)	
Age					0.35
<65 yr	10,205	309/5109 (6.1)	272/5096 (5.3)	1.14 (0.97–1.34)	
≥65 yr	8,897	345/4441 (7.8)	339/4456 (7.6)	1.02 (0.88–1.19)	
Sex					0.46
Male	13,839	485/6949 (7.0)	460/6890 (6.7)	1.05 (0.92–1.19)	
Female	5,263	169/2601 (6.5)	151/2662 (5.7)	1.16 (0.93–1.44)	
History of diabetes					0.83
Yes	8,230	324/4103 (7.9)	301/4127 (7.3)	1.09 (0.93–1.27)	
No	10,872	330/5447 (6.1)	310/5425 (5.7)	1.06 (0.91–1.24)	
Previous myocardial infarction					0.84
Yes	14,002	519/7009 (7.4)	487/6993 (7.0)	1.07 (0.94–1.21)	
No	5,100	135/2541 (5.3)	124/2559 (4.9)	1.10 (0.86–1.41)	
Previous coronary revascularization					0.66
Yes	12,949	397/6453 (6.2)	380/6496 (5.8)	1.05 (0.92–1.21)	
No	6,153	257/3097 (8.3)	231/3056 (7.6)	1.11 (0.93–1.32)	



The explanation for this surprising finding is uncertain, although it should be treated with caution since the results of the primary efficacy analysis were not significant.

Fox K, et al. *New Engl J Med*. 2014;371:1091-9.

Adverse events of ivabradine in stable CAD patients without HF

Table 3. Adverse Events during the Study.*

Event	Ivabradine (N = 9539)	Placebo (N = 9544)	P Value
	no. of patients with event (%)		
Any adverse event	6990 (73.3)	6382 (66.9)	<0.001
Selected adverse events†			
Bradycardia	1718 (18.0)	223 (2.3)	<0.001
Symptomatic	757 (7.9)	110 (1.2)	<0.001
Asymptomatic	1047 (11.0)	126 (1.3)	<0.001
Phosphenes	512 (5.4)	52 (0.5)	<0.001
Blurred vision	117 (1.2)	37 (0.4)	<0.001
Atrioventricular block			
Second degree	44 (0.5)	31 (0.3)	0.13
Third degree	20 (0.2)	19 (0.2)	0.87
Atrial fibrillation	508 (5.3)	362 (3.8)	<0.001
QT-interval prolongation‡	171 (1.8)		
Supraventricular tachyarrhythmia	137 (1.4)		
Immune disorder	22 (0.2)		
Severe ventricular arrhythmia	79 (0.8)		

Bradycardia occurred more often in SIGNIFY than in previous ivabradine trials, most likely owing to the dose regimen in SIGNIFY, which included higher initiation and maintenance doses than those that are currently recommended.

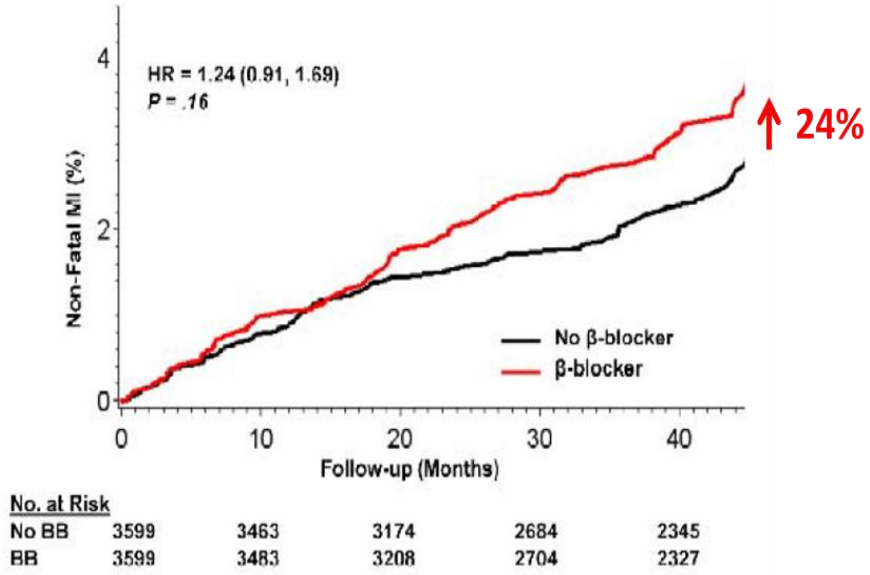
Fox K, et al. *New Engl J Med*. 2014;371:1091-9.

Are the effects in SIGNIFY in contrast to other heart rate lowering interventions?

In stable CAD there is no impact of HR lowering by beta-blockade on outcomes

REACH REGISTRY
REduction of Atherothrombosis for Continued Health

eFigure 9. Cumulative incidence curve for the risk of non-fatal myocardial infarction in the known CAD without MI matched cohort by ß-blocker status

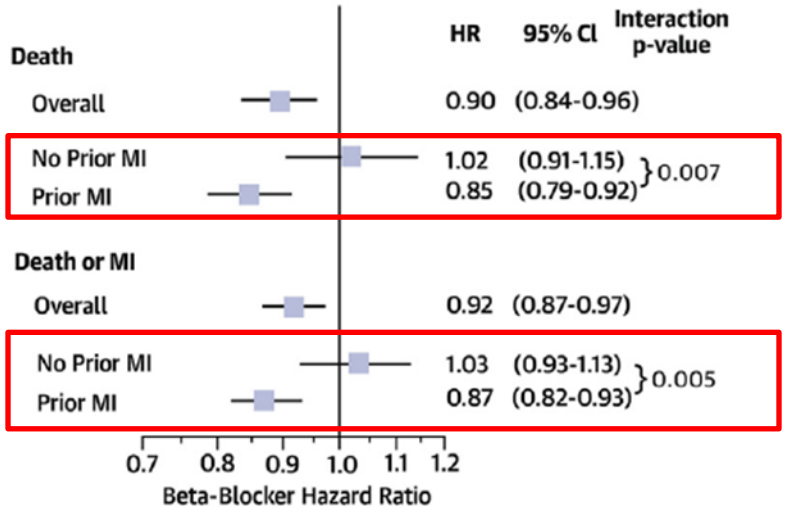


Conclusion In this observational study of patients with either CAD risk factors only, known prior MI, or known CAD without MI, the use of β-blockers was not associated with a lower risk of composite cardiovascular events.

JAMA. 2012;308(13):1340-1349 www.jama.com

Bangalore S, et al. *JAMA*. 2012;308:1340-1349.

Beta-Blocker Therapy and Cardiac Events Among Patients With Newly Diagnosed Coronary Heart Disease



CONCLUSIONS Use of beta-blockers among patients with new-onset CHD was associated with a lower risk of cardiac events only among patients with a recent MI. (J Am Coll Cardiol 2014;64:247-52) © 2014 by the American College of Cardiology Foundation.

Andersson C, et al. *J Am Coll Cardiol.* 2014;64:247-52.

How to explain discrepancies between Signify, BEAUTIFUL and SHIFT?

- Spurious finding. Subgroup in a neutral study.
- Reduction of heart rate in patients with angina on top of beta-blockade (87%) is ineffective.
- Myocardial metabolism in stable CAD and LV-dysfunction very different and heart rate sensitive

Heart rate reduction in angina and systolic heart failure –a paradox?

- In angina – heart rate is reduced to adapt energy production to oxygen delivery
- In heart failure – heart rate is reduced to adapt energy consumption to ATP-synthesis

MECHANISMS OF DISEASE

FRANKLIN H. EPSTEIN, M.D., *Editor*

CARDIOMYOPATHY OF OVERLOAD

A Major Determinant of Prognosis in Congestive Heart Failure

ARNOLD M. KATZ, M.D.

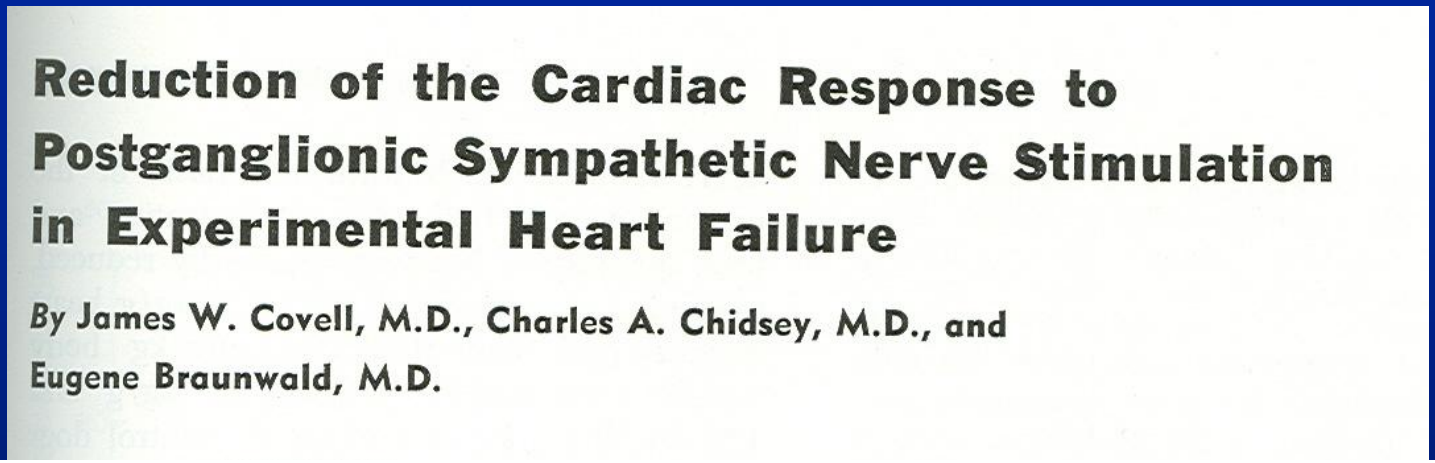
ward failure) and through reduced ejection of blood under pressure into the aorta and pulmonary artery (forward failure). However, the response of the body to these abnormalities is complex and varies from person to person. Furthermore, because blood flows in a circle, forward failure and backward failure generally coexist, although the highly variable circulatory adjustments in response to impaired pump performance may cause one or the other to dominate the clinical picture in any given patient.

In patients with left ventricular dysfunction, by far the most common cause of heart failure, an increase in

Adaptations to systolic heart failure

- Hypertrophy
- ATP-synthesis per myofibrill decreases
- Increased sympathetic activity
- Myocardial norepinephrine depletion
- Protein synthesis abnormal and more fetal
- Increase in heart rate

Myocardial norepinephrine depletion



Reduction of the Cardiac Response to Postganglionic Sympathetic Nerve Stimulation in Experimental Heart Failure

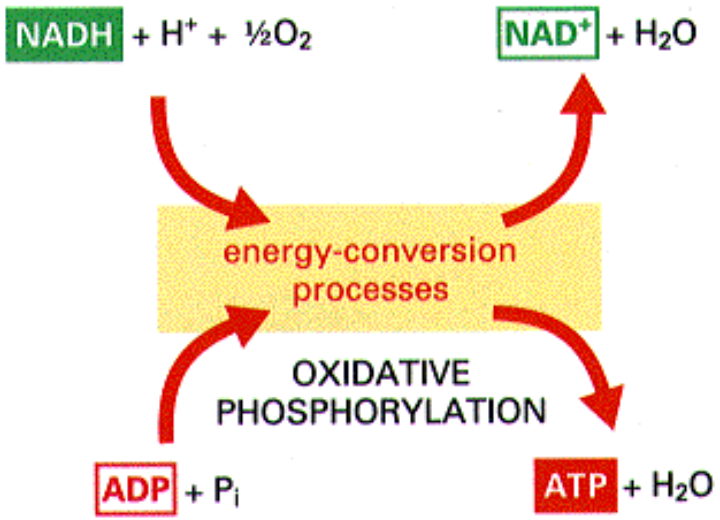
By James W. Covell, M.D., Charles A. Chidsey, M.D., and Eugene Braunwald, M.D.

Thus, norepinephrine depletion interferes with the ability of the adrenergic nervous system to support the failing myocardium and in this manner it may intensify the congestive heart failure state.

per nerve impulse. Thus, norepinephrine depletion interferes with the ability of the adrenergic nervous system to support the failing myocardium and in this manner it may intensify the congestive heart failure state.

Circ Research 1966; 21:51

ATP-synthesis



Focus on myocardial energy balance 1966-73

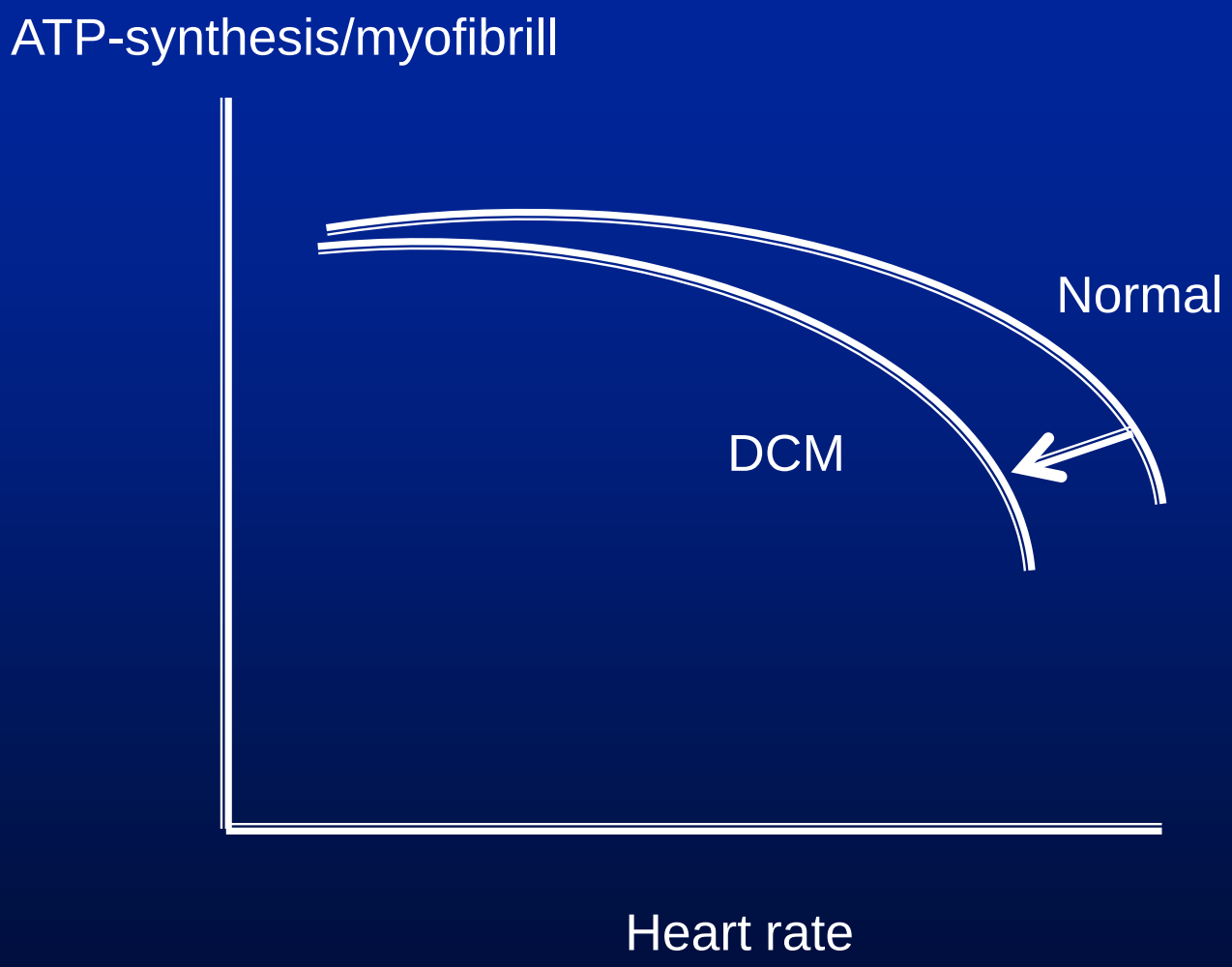
- **There is a biochemical defect in the failing heart due to impairment of oxidative phosphorylation**

  Chidsey et al J Clin Invest 1966

- **Positive inotropy can *increase* the amount of ischemic damage and negative inotropy *reduces* the extent of necrosis**

- **The depression of myocardial contractility in the chronically overloaded heart might prolong life**

  Katz AM; Circulation 1973

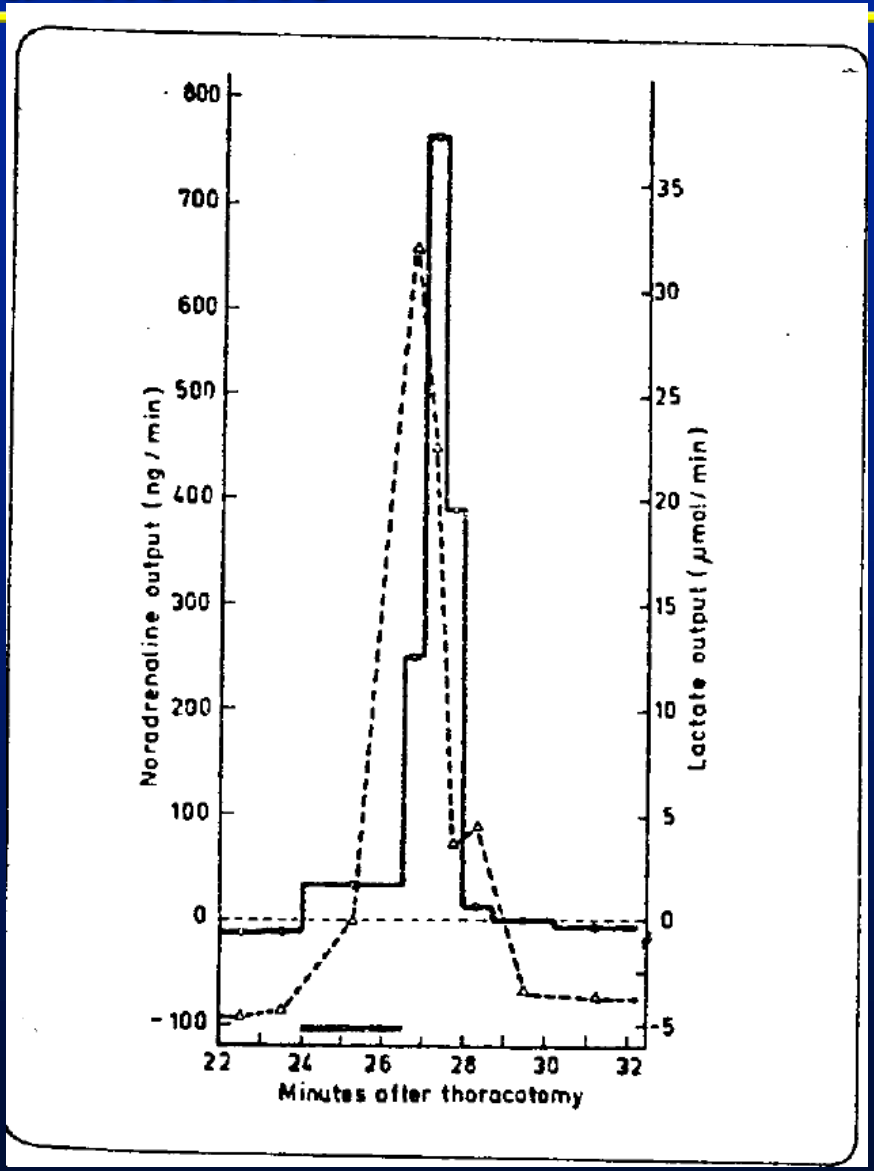

ATP-synthesis/myofibrill
Normal
DCM
Heart rate

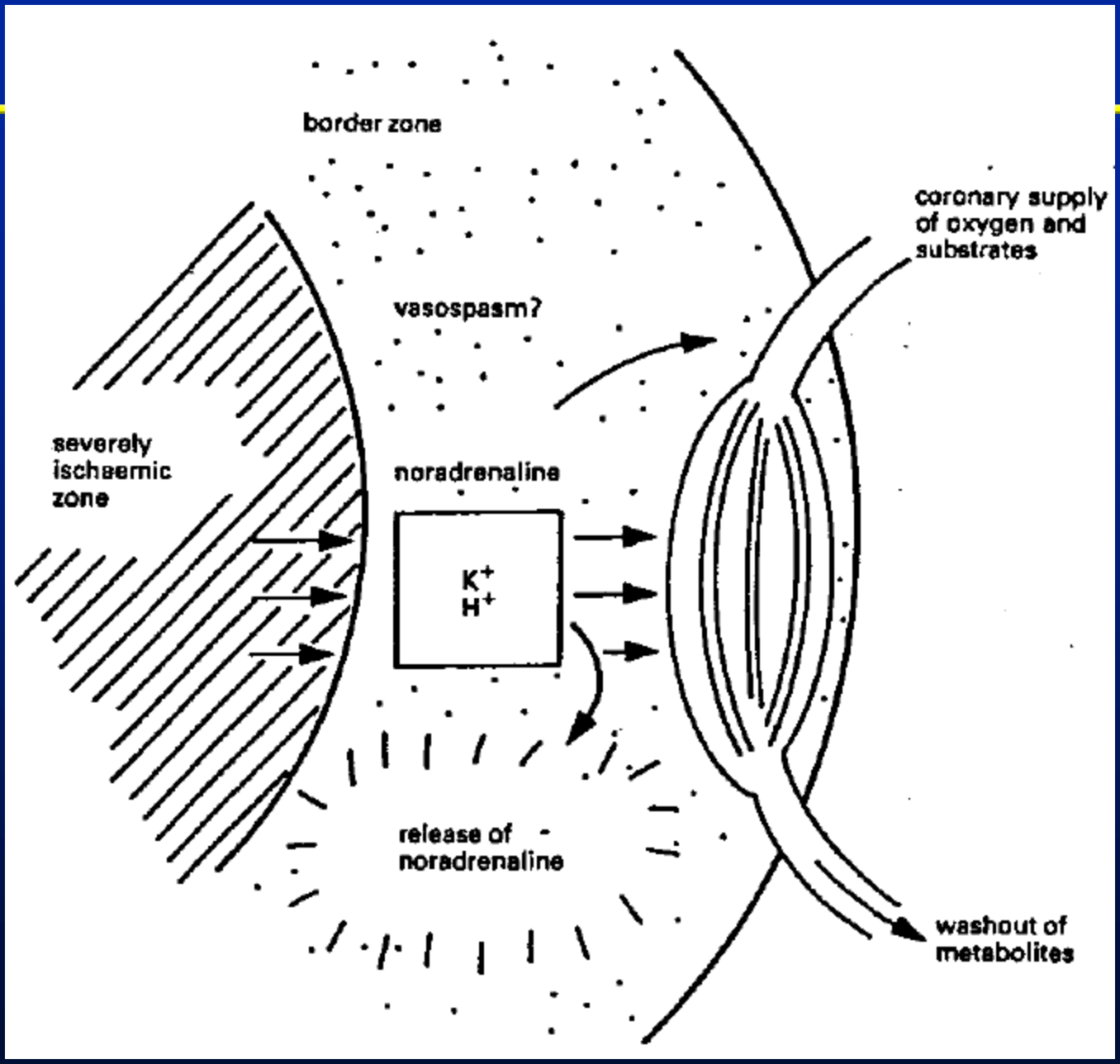
Myocardial release of noradrenaline and lactate

Release of noradrenaline and lactate from dog hearts after coronary occlusion

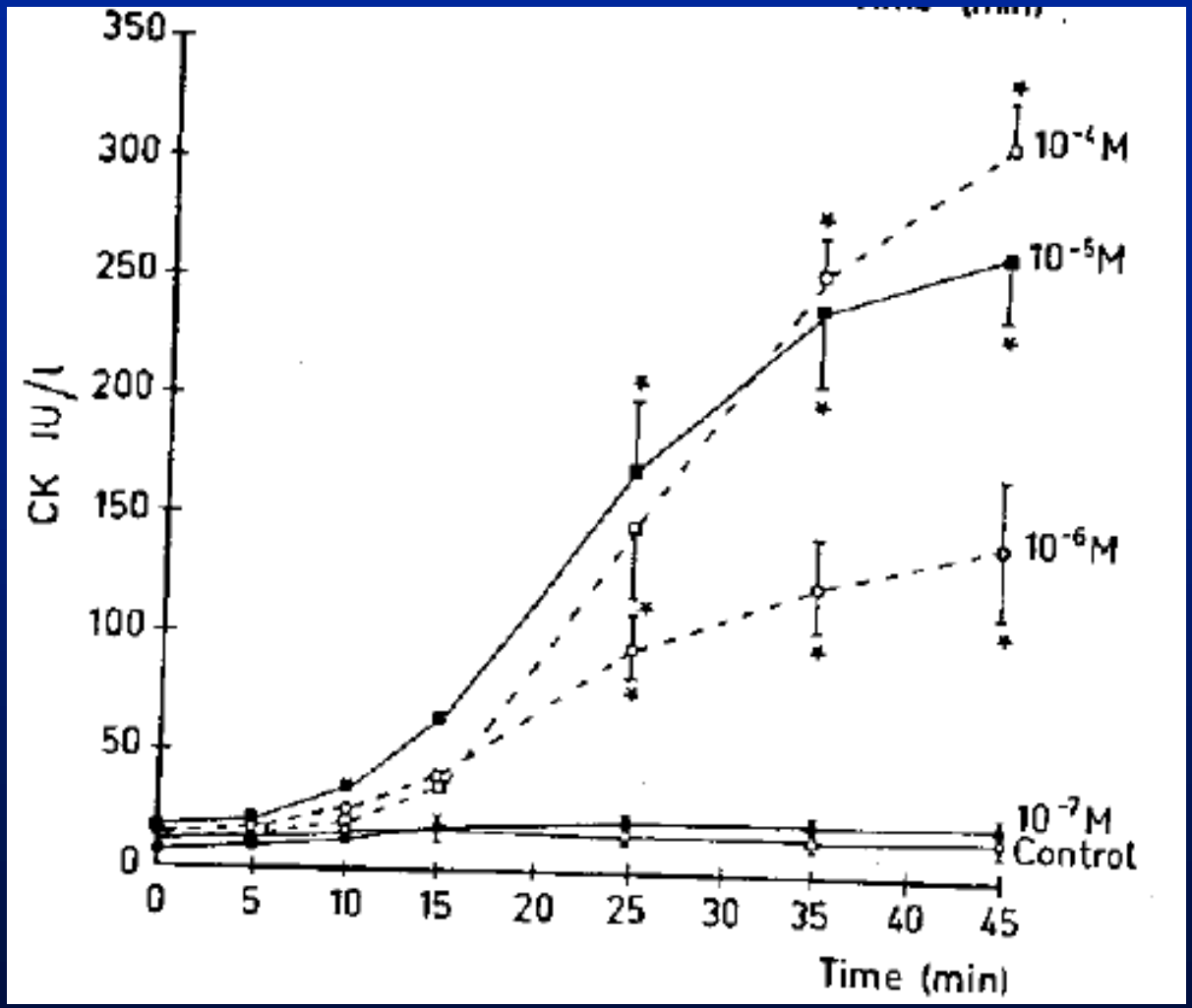
Wollenberger et al:

Proceedings 1967




border zone
coronary supply of oxygen and substrates
vasospasm?
severely ischaemic zone
noradrenaline
K^+
H^+
release of noradrenaline
washout of metabolites

CK release from rat heart perfused with various concentrations of noradrenaline



Waldenstrom AP, et al: *Am Heart J. 1978*

Release of ASAT from ischemic rat-hearts with and without noradrenaline

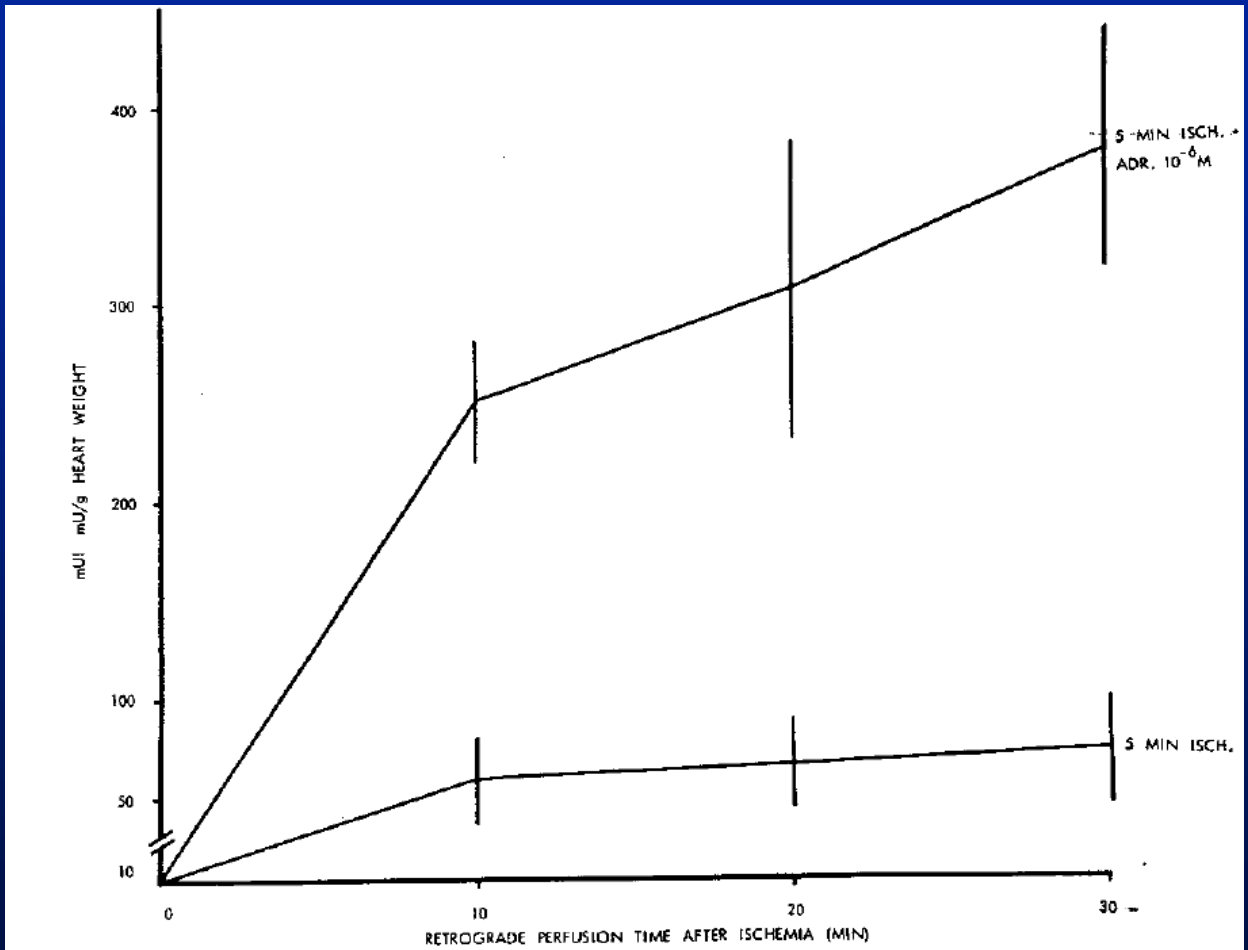


Fig. 1. Release of myocardial ASAT from hearts being ischemic for 5 min and thereafter reperfused for 30 min. Adrenaline 10^{-6} *M* was added to the perfusion-buffer of one group of hearts. There were 6 hearts in each group.

Waldenstrom AP et al: Journal of Molecular Medicine 1977

Worsening heart failure (WHF) or ACS in SHIFT

- During follow-up of 22.9 months of 6588 patients in SHIFT

	N	%
Worsening heart failure	1154	17.7
Acute coronary syndrome	134	2.1

Abrahamsson et al EHJ 2013

Adverse effects of heart rate reduction in SIGNIFY

- Can bradycardia induce ischemia and myocardial infarction?
- Unlikely as bradycardia reduce oxygen demand and allows longer coronary perfusion.

Changes in myocardial metabolism in chronic systolic heart failure Potential mechanisms

- Myocardial cathecolamine depletion protects the myocardium from ischemia and infarction
- ATP-synthesis is more rate dependant than in normal myocardium
- More prolonged diastole allows the ATP-synthesis to recover

Conclusions

- In LV-dysfunction with or without CAD, elevated heart rate is a modifiable risk factor.
- In stable CAD with preserved EF, elevated heart rate is a risk marker
- The myocardial metabolic adaptation in heart failure is very different to a normal situation
- Heart rate reduction in angina and heart failure results in two different situations which are actually explained by different metabolic backgrounds

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