Betablokkere: Indikasjon, titrering og dosering

Lars Gullestad

Norsk hjertesviktforum

7/11-2017

Oslo University Hospital

UNIVERSITY OF OSLO
FACULTY OF MEDICINE

7 ulike indikasjoner :

Metoprolol Sandoz Depot/Selo-Zok
(metoprololsuksinat)

- Hjertesvikt *
- Hypertensjon
- Angina Pectoris
- Sekundærprofylakse etter hjerteinfarkt
- Arytmier
- Migreneprofylakse
- Hypertyreose

Carvedilol

- Hjertesvikt *
- Angina pectoris

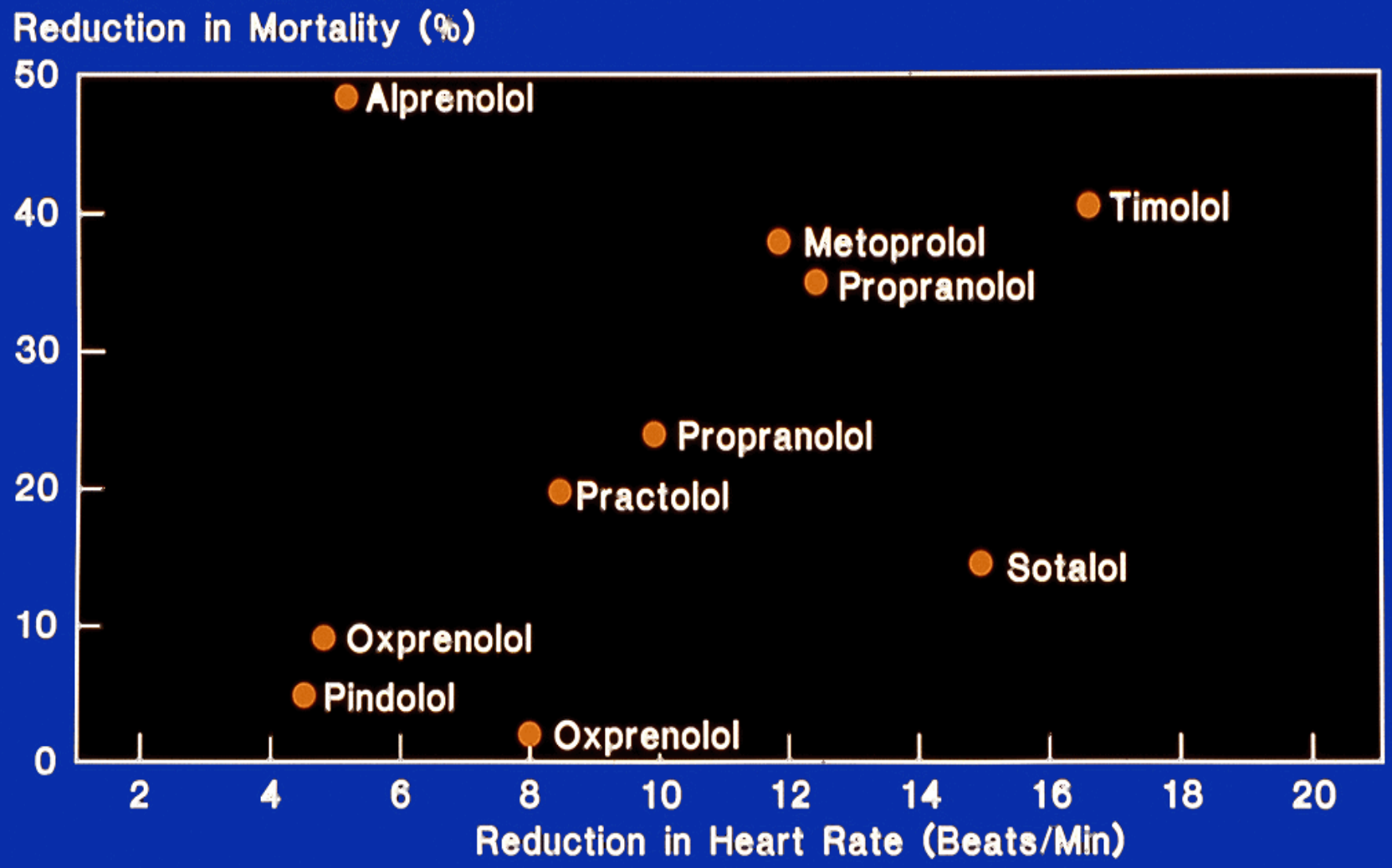
Bisoprolol

- Hjertesvikt *
- Hypertensjon
- Angina Pectoris

- *Som tilleggs behandling ved hjertesvikt
- Preparatomtale 2017

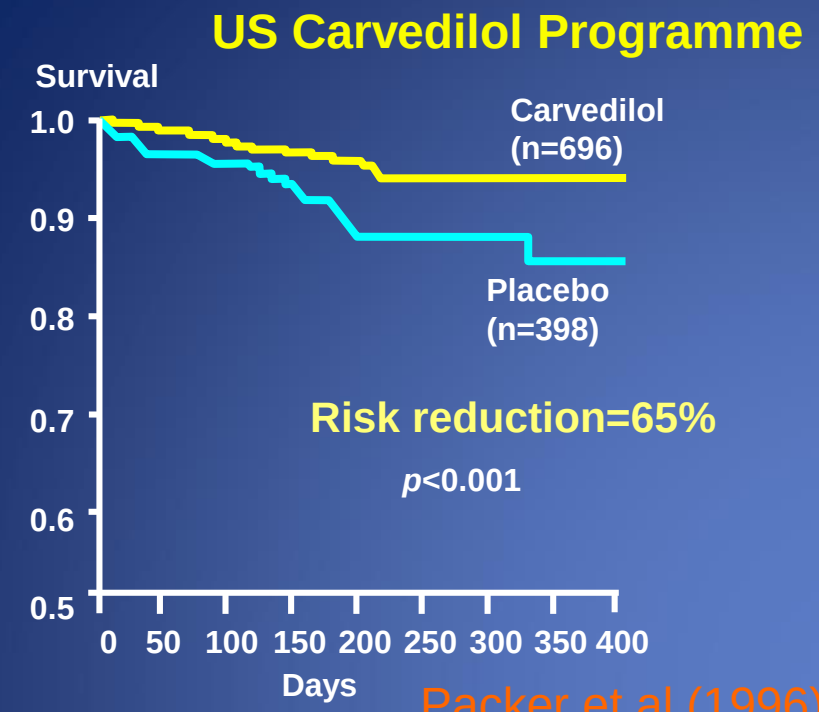
Justert Morten

BETA BLOCKERS AFTER MI: RELATIONSHIP BETWEEN REDUCTION IN HEART RATE AND REDUCTION IN MORTALITY

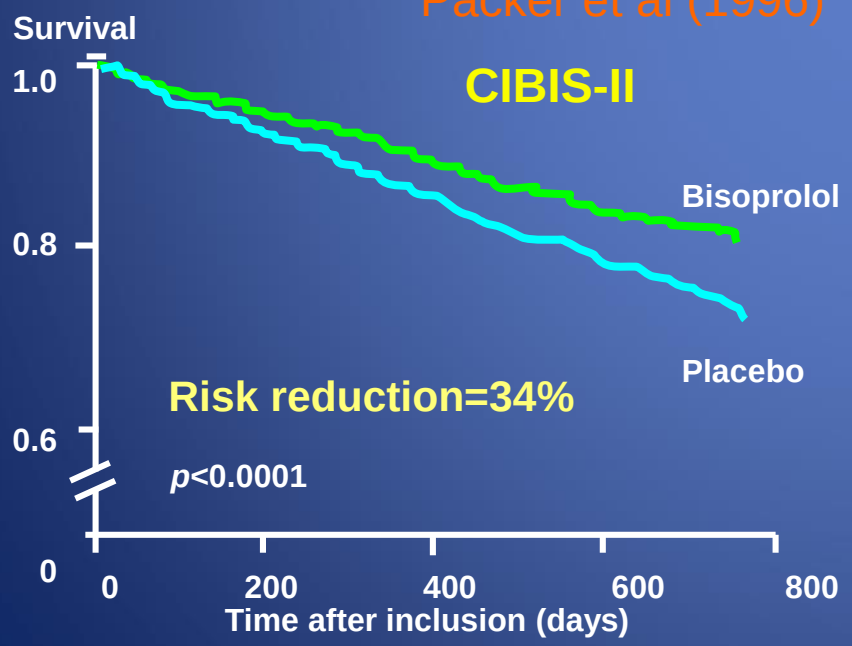


Kjekshus J. Eur Heart J. 1985.

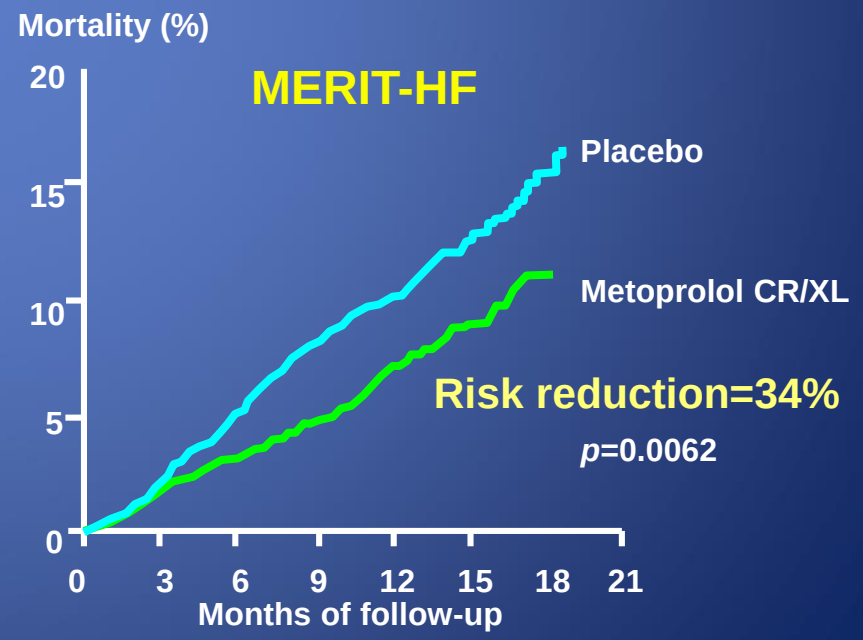
b blockers in heart failure – all-cause mortality



Packer et al (1996)



CIBIS-II Investigators



The MERIT-HF Study Group

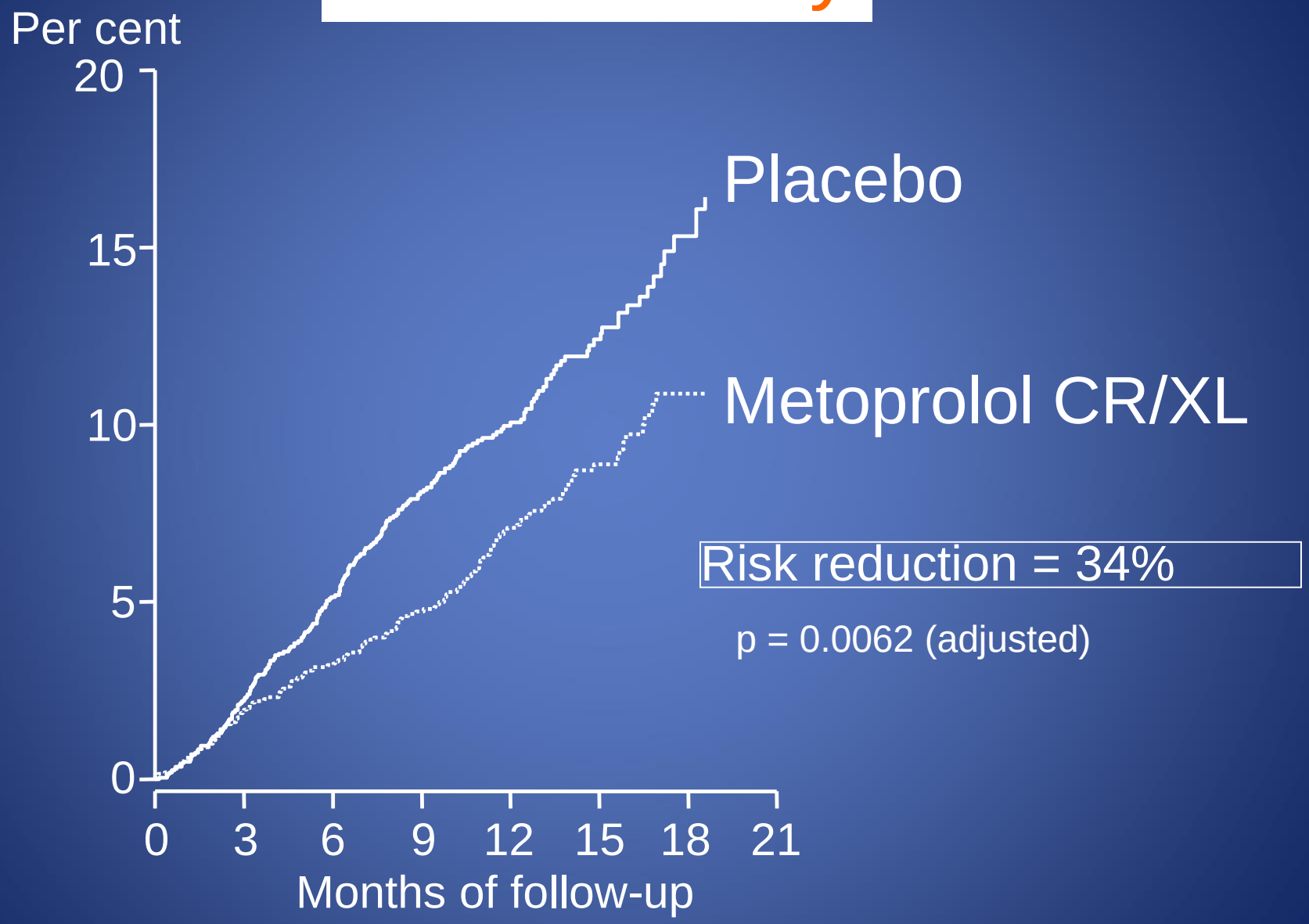
Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure

MERIT-HF

A Double-Blind, Placebo Controlled Survival Study with Metoprolol CR/XL in Patients with EF ≤ 0.40 % and Symptoms of Heart Failure (NYHA II-IV)

The International Steering Committee on Behalf of the MERIT-HF Study Group
Am J Cardiol 1997;80(9B):54J-58J, Lancet 1999;353:2001-07

Total Mortality

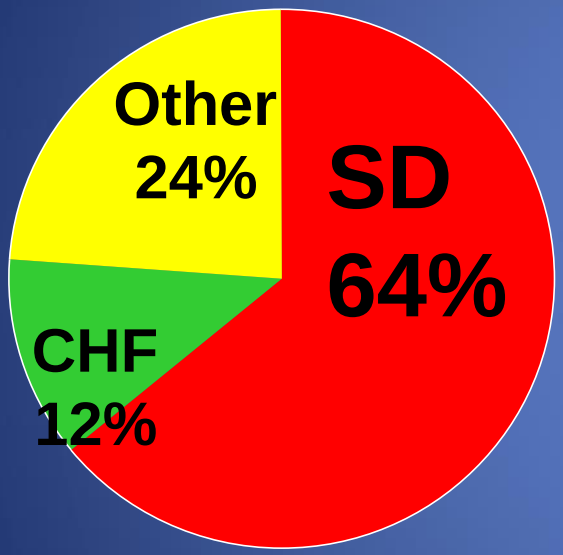


The MERIT-HF Study Group, Lancet 1999;353:2001-07

MERIT- HF

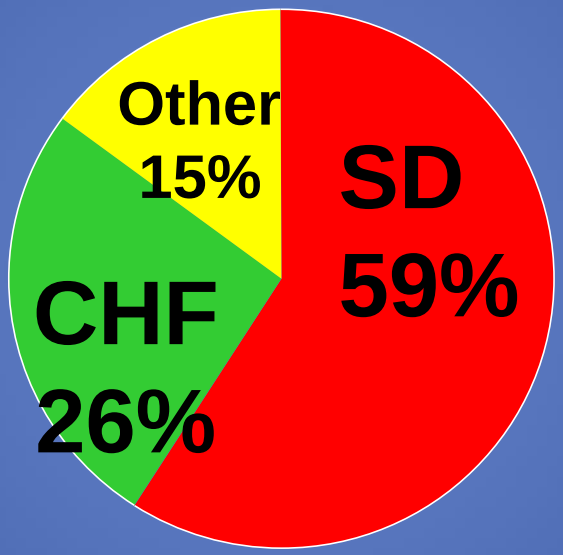
Mode of Death by NYHA Class

NYHA II



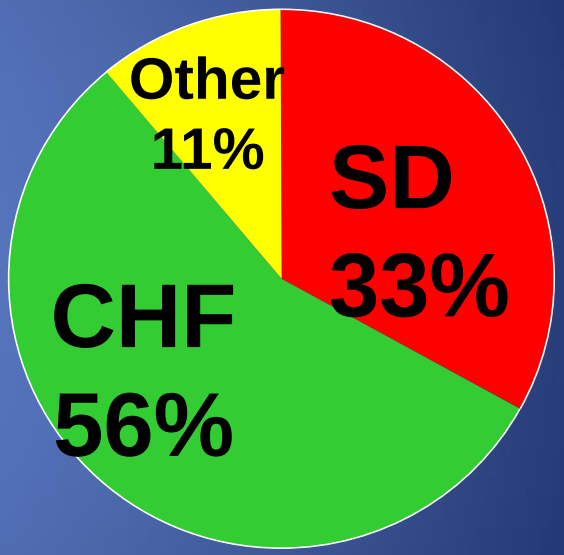
No. of deaths
n=103

NYHA III



No. of deaths
n=232

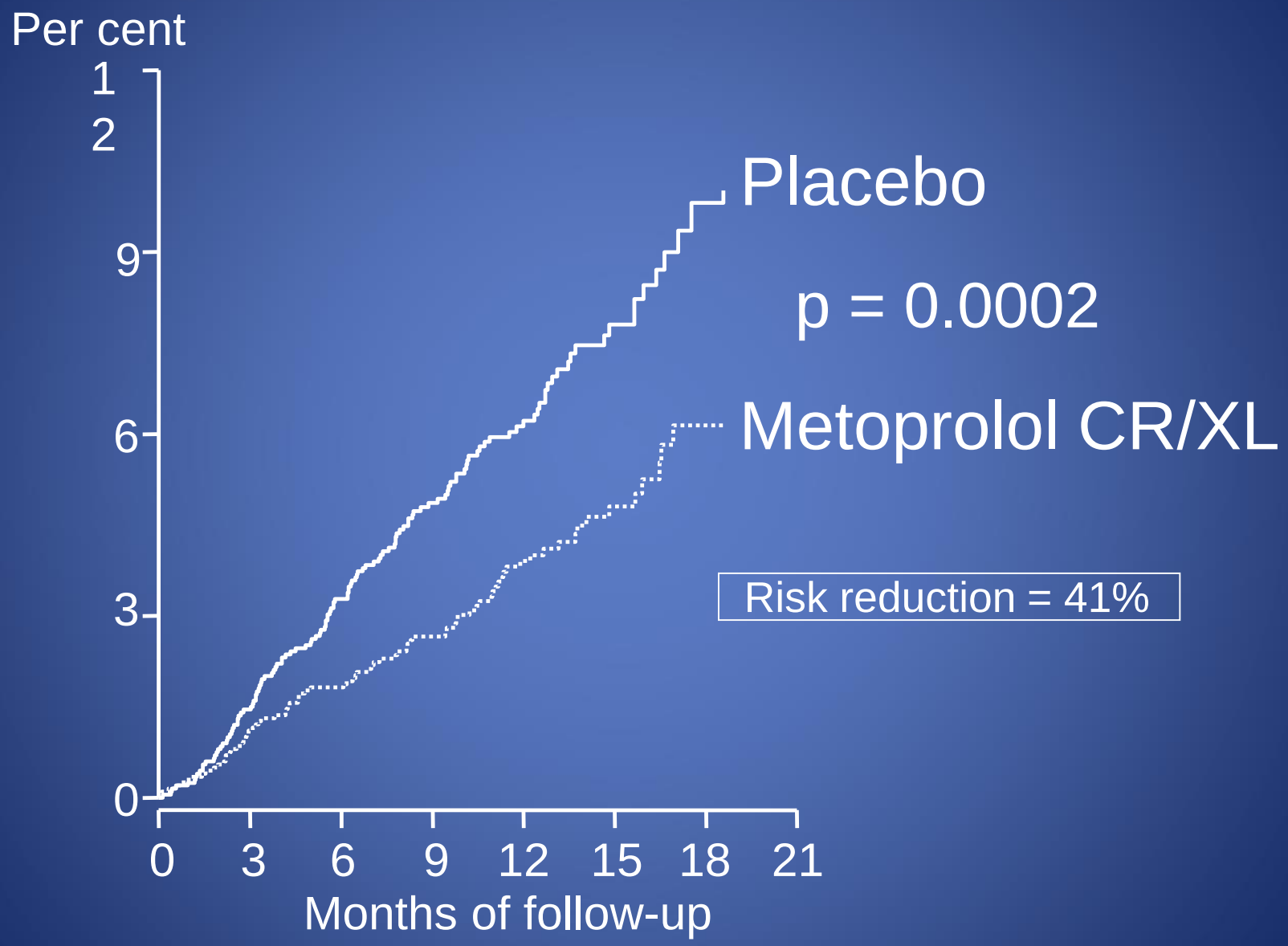
NYHA IV



No. of deaths
n=27

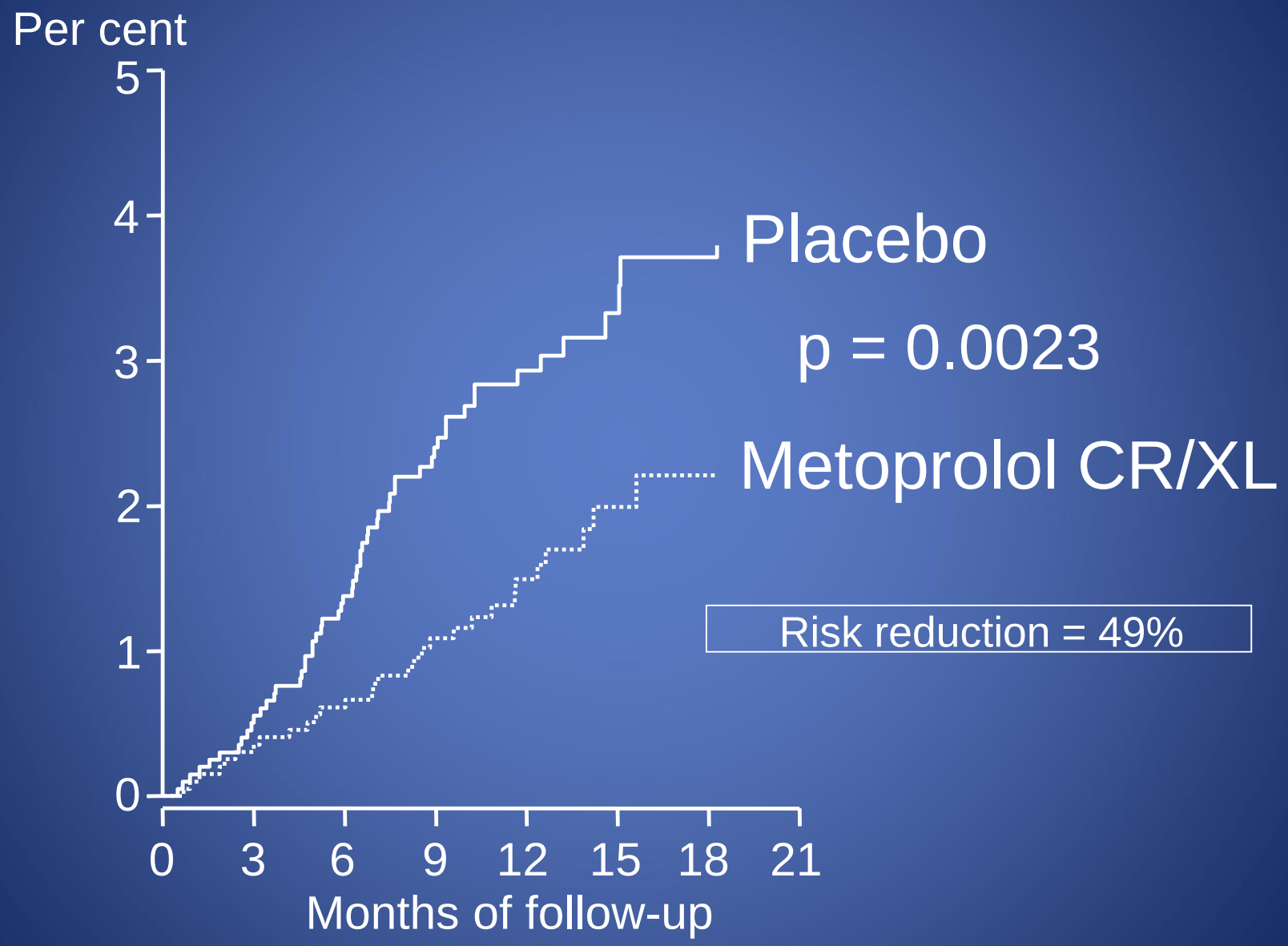
The MERIT-HF Study Group, Lancet 1999;353:2001-07

Sudden Death



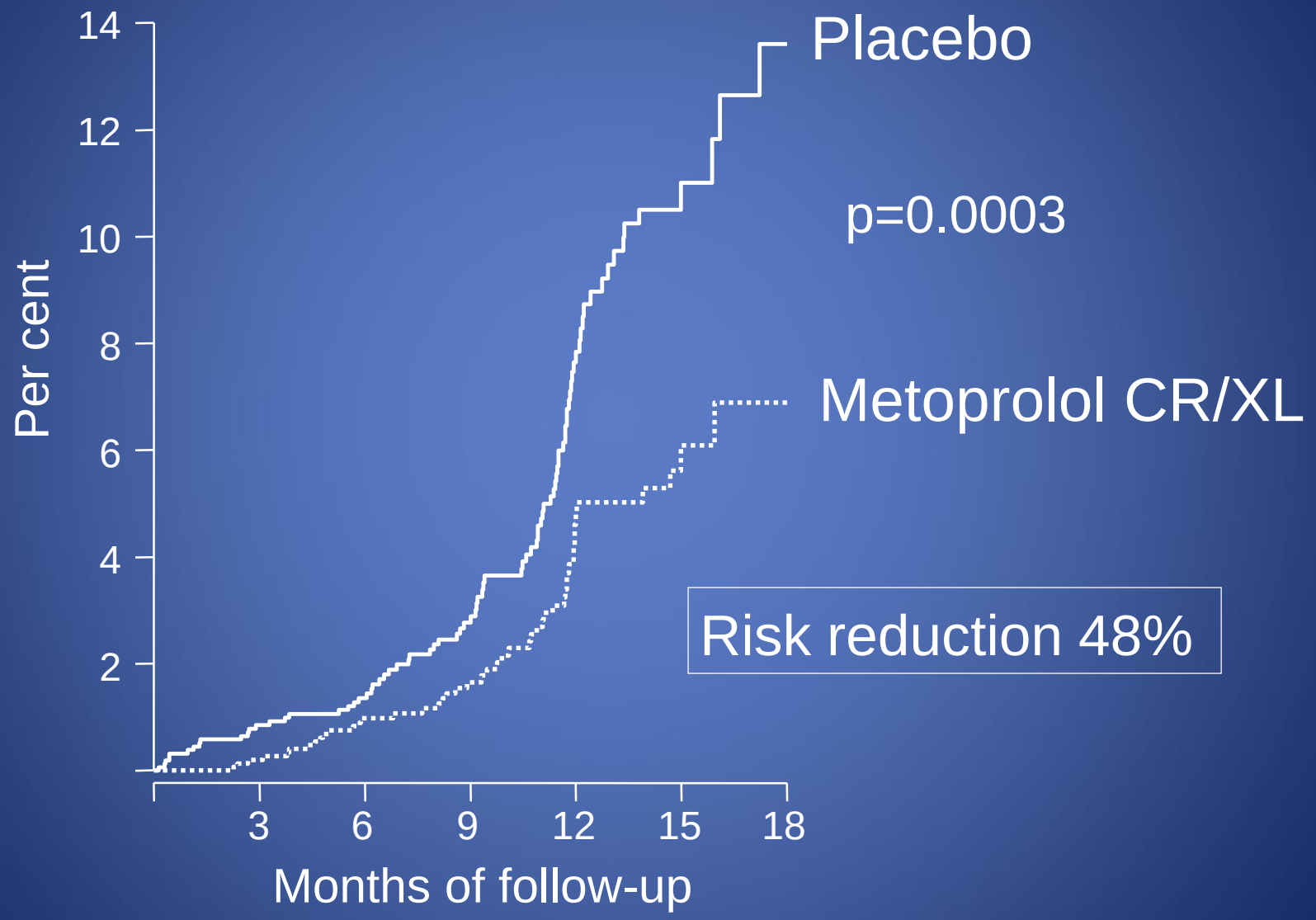
The MERIT-HF Study Group, Lancet 1999;353:2001-07

Death from Worsening Heart Failure



The MERIT-HF Study Group, Lancet 1999;353:2001-07

Newly Developed Atrial Fibrillation

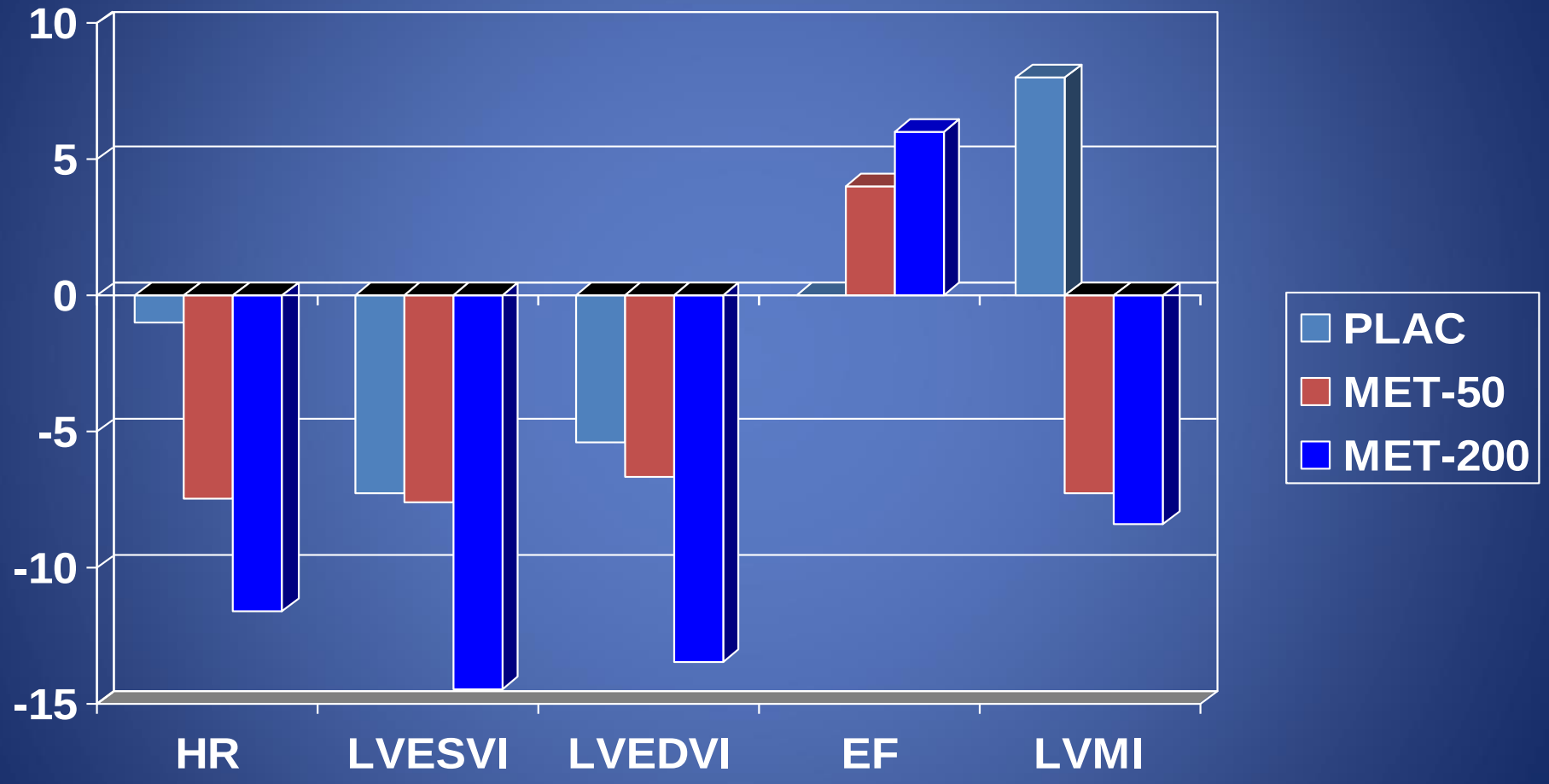


Veldhusien D et al. MERIT-HF Study Group

Hvilken dose skal vi sikte mot?

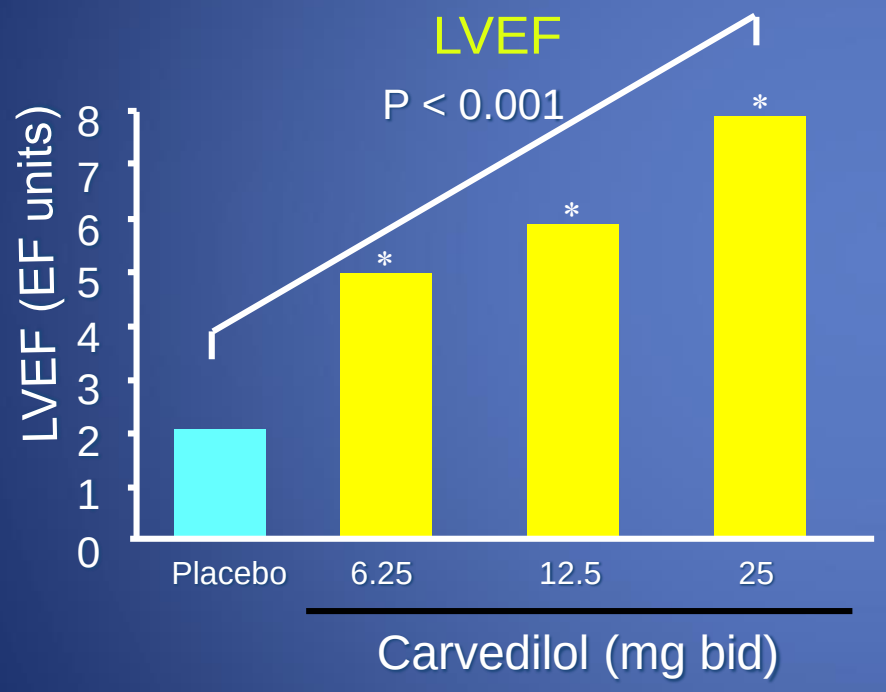
REVERT

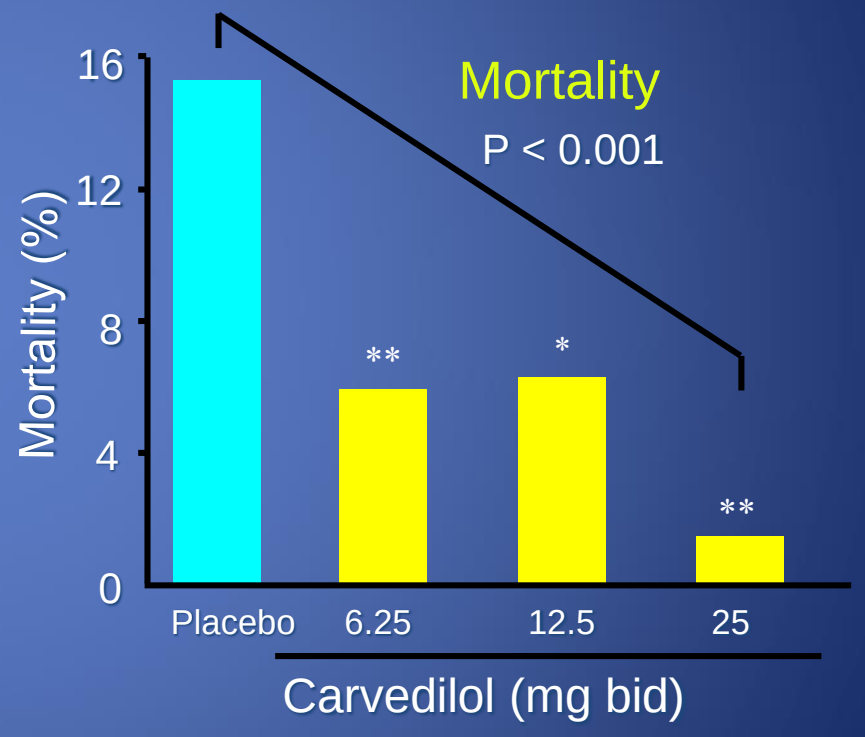
n=164, dobbelt blind, 12 mnd, NYHA I/Asymp



Starting β Blockade in CHF
Dose-response to Carvedilol (MOCHA)

Effect on LVEF and mortality





Placebo (n = 84); carvedilol (n = 261)
Patients receiving diuretics, ACE inhibitors ± digoxin; follow-up 6 months

Bristow MR et al. Circulation 1996

A metaanalysis of effect of betablockers in HFrEF

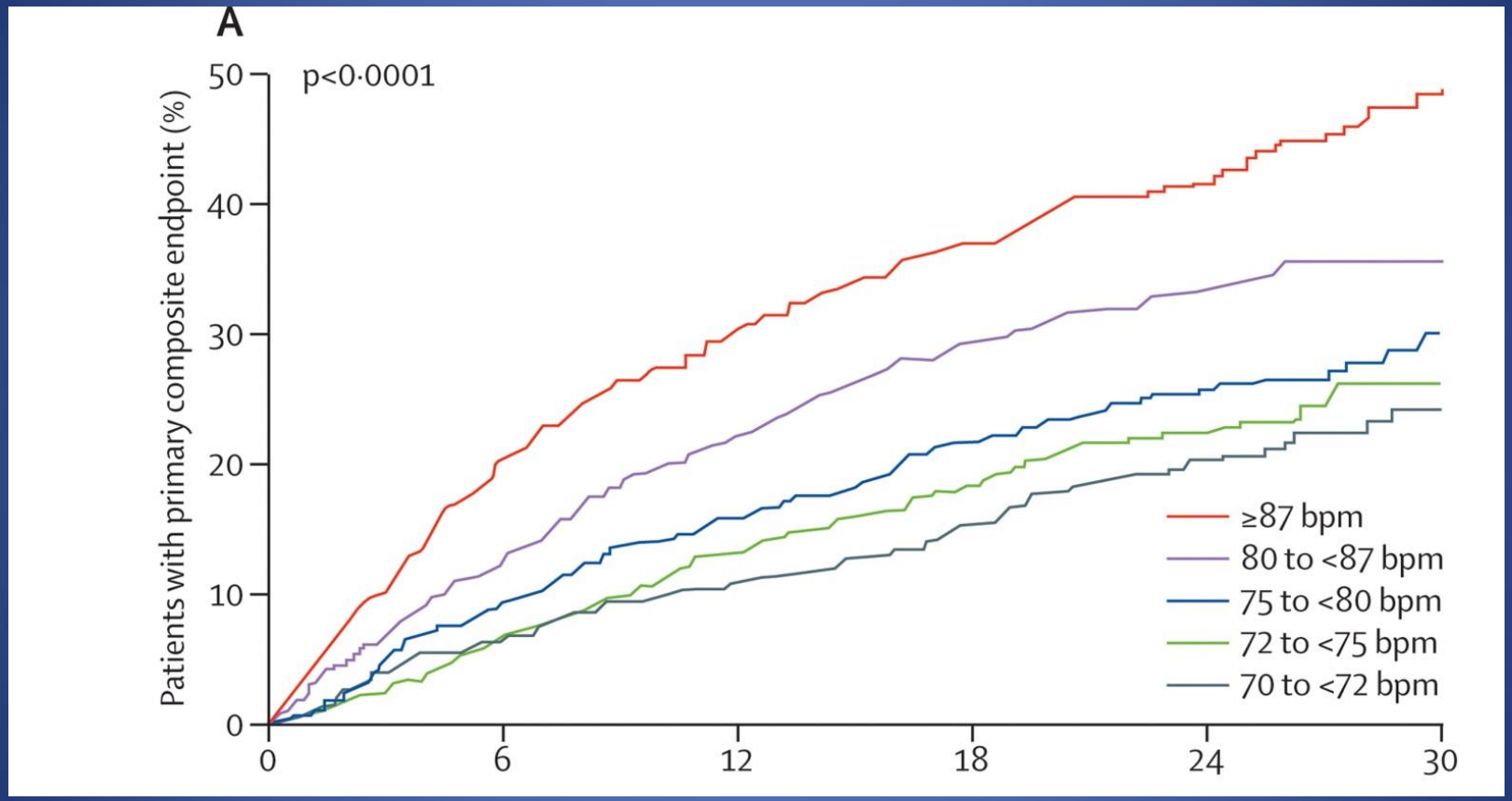
Resultat fra 17 studier med 17831 pasienter:

Hver reduksjon av HR med 5 bpm gir 18 % redusert mortalitet

Mc Alister Ann Intern Med 2009;150:784

Hvilken hjertefrekvens skal vi sikte mot?

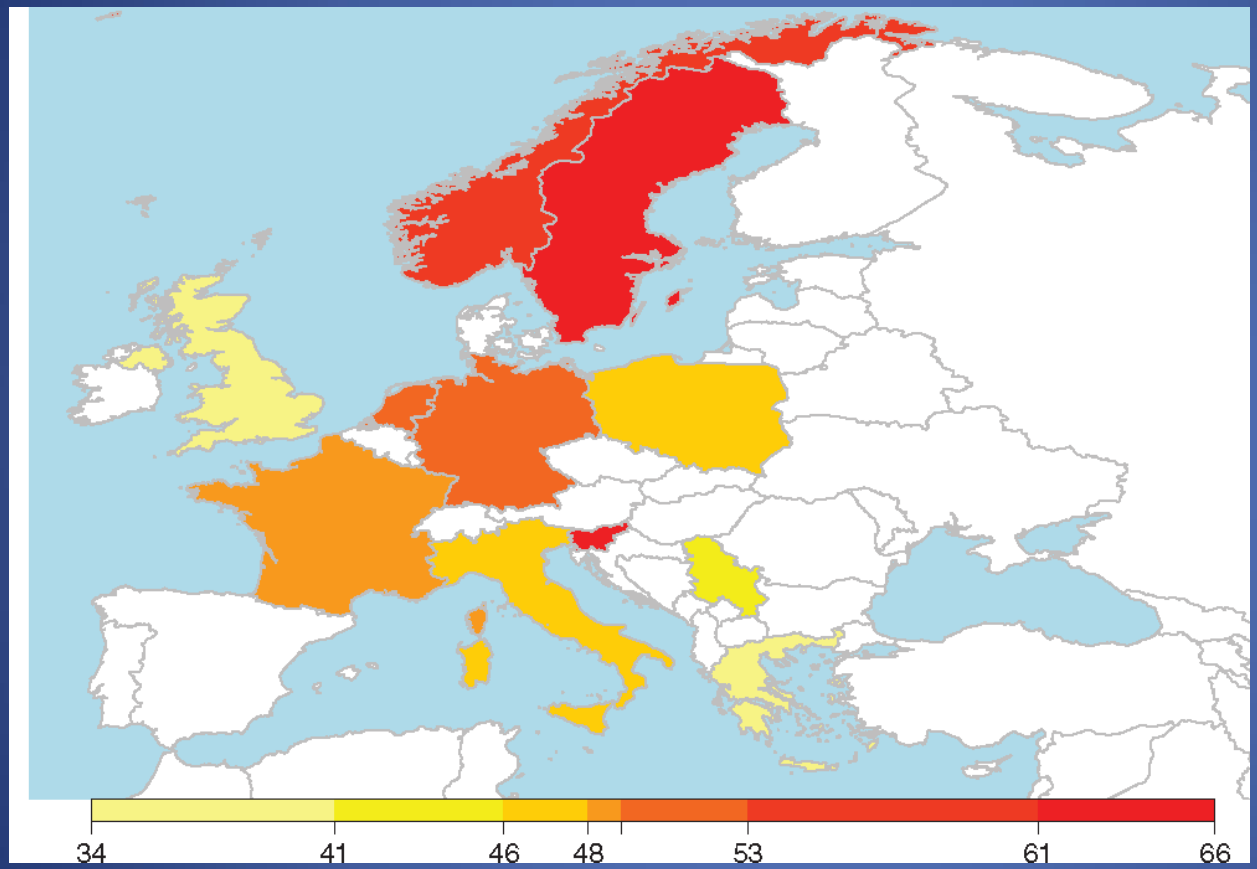
Heart rate as a determinant of outcome in HFrEF
The SHIFT trial: primary outcome:CV death and HF hosp



Risk of primary composite endpoint events increased by 16 % for every 5-bpm increase.

M Bøhn Lancet 2010;376:886

Prosent oppnådd måldose av betablocker i Europa: BIOSTAT CHF

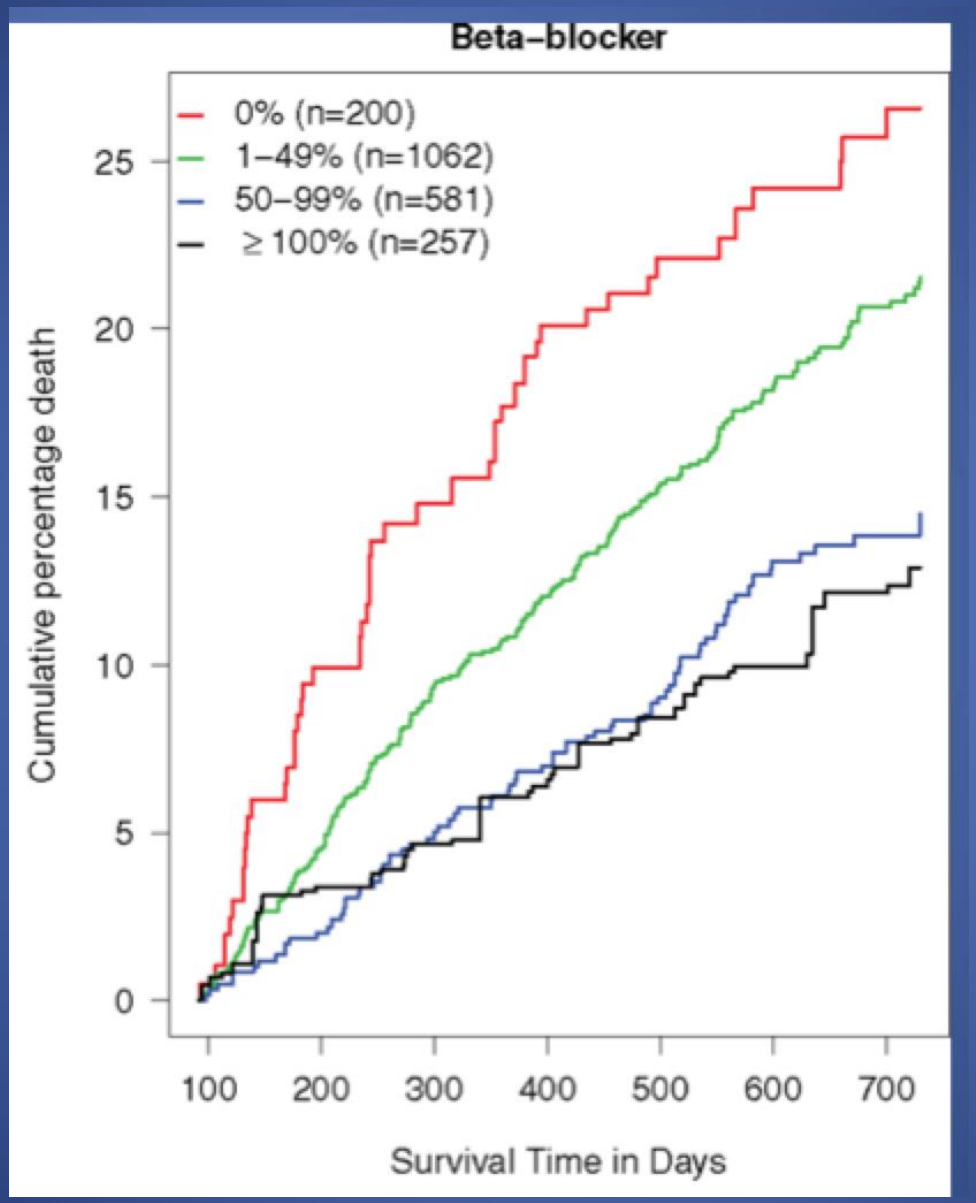


69 sentra
11 Europeiske land
N=2516

Oppnådd måldose
ACE-I: 22%
BB: 12%

W Ouwerverker EHJ 2017;38:1883

Adjustet mortality according to achieved betablocker dose: BIOSTAT CHF



69 sentra
11 Europeiske land
N=2516

Oppnådd måldose
BB: 12%

W Ouwerverker EHJ 2017;38:1883

MERIT-HF Titration Schedule

Recommended starting dose

- 12.5 mg in NYHA III/IV
- 25 mg in NYHA II

Target dose

- Titration period 6-8 weeks with a target dose of 200 mg CR/XL once daily

Janosi A et al. for the MERIT-HF Study Group. Am J Cardiol 1997;80(9B):54J-58J; Lancet 1999;353:2001-07; JAMA 2000;283:1295-1302

MERIT-HF

Subgroup Analysis of Post-MI Patients

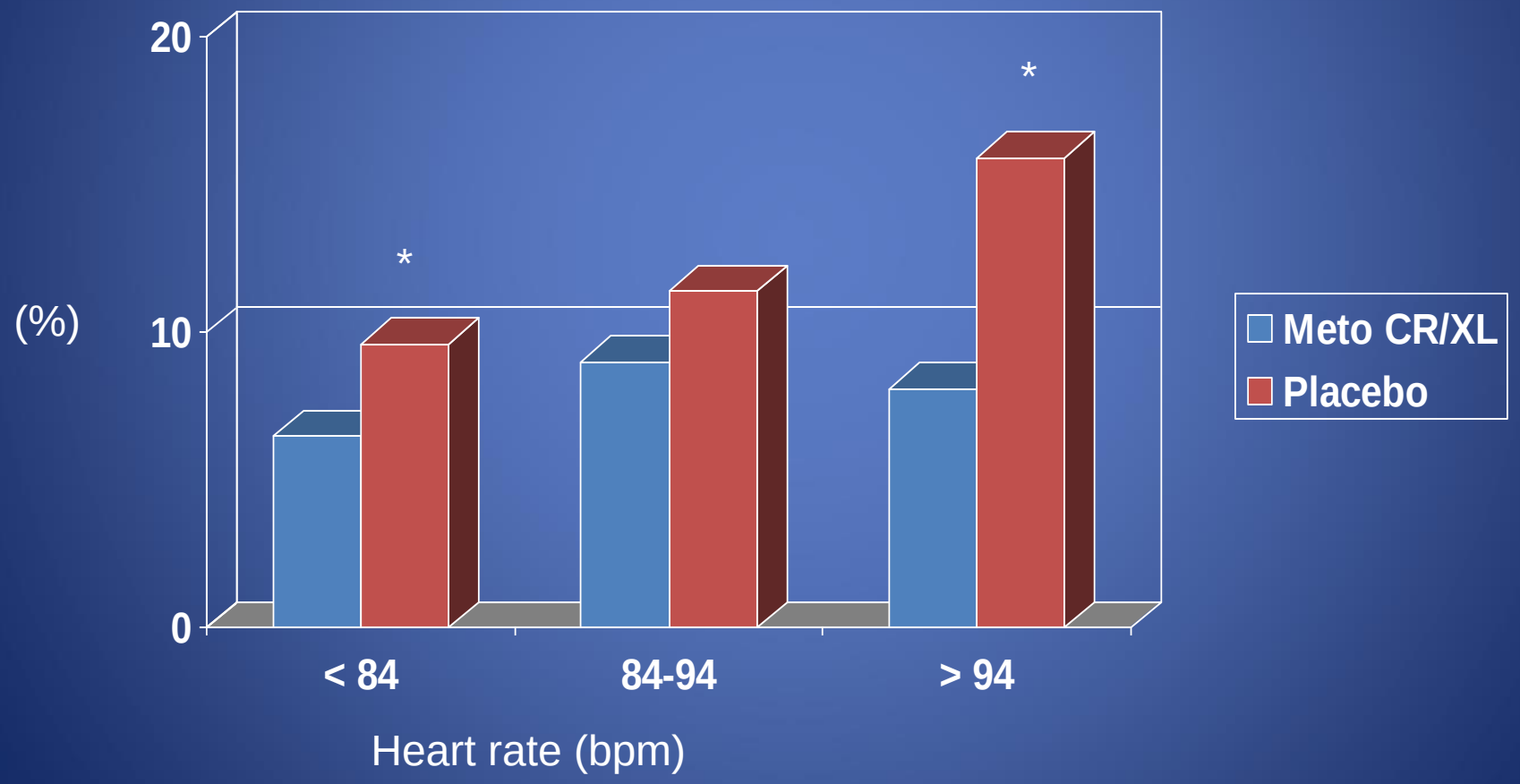
Dose at Study Closure

Mean and % in patients on treatment

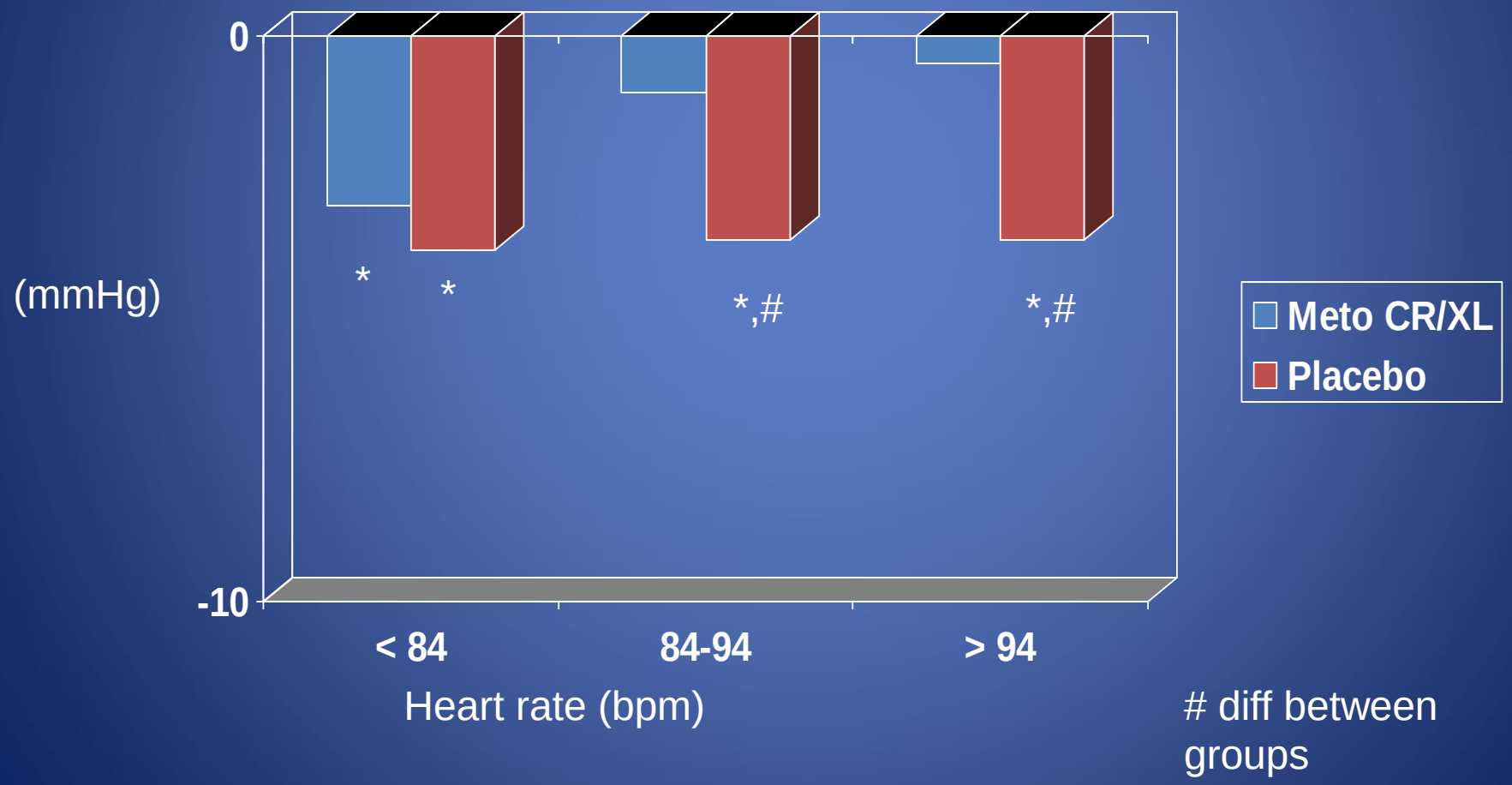
	Placebo	Meto CR/XL
Mean (mg)	173	149
≥ 100 mg (%)	91	82
On 200 mg (%)	77	57

Janosi A et al. for the MERIT-HF Study Group

All cause mortality according to baseline heart rate



Change in systolic BP from baseline to end of study



What resting heart rate should one aim for?

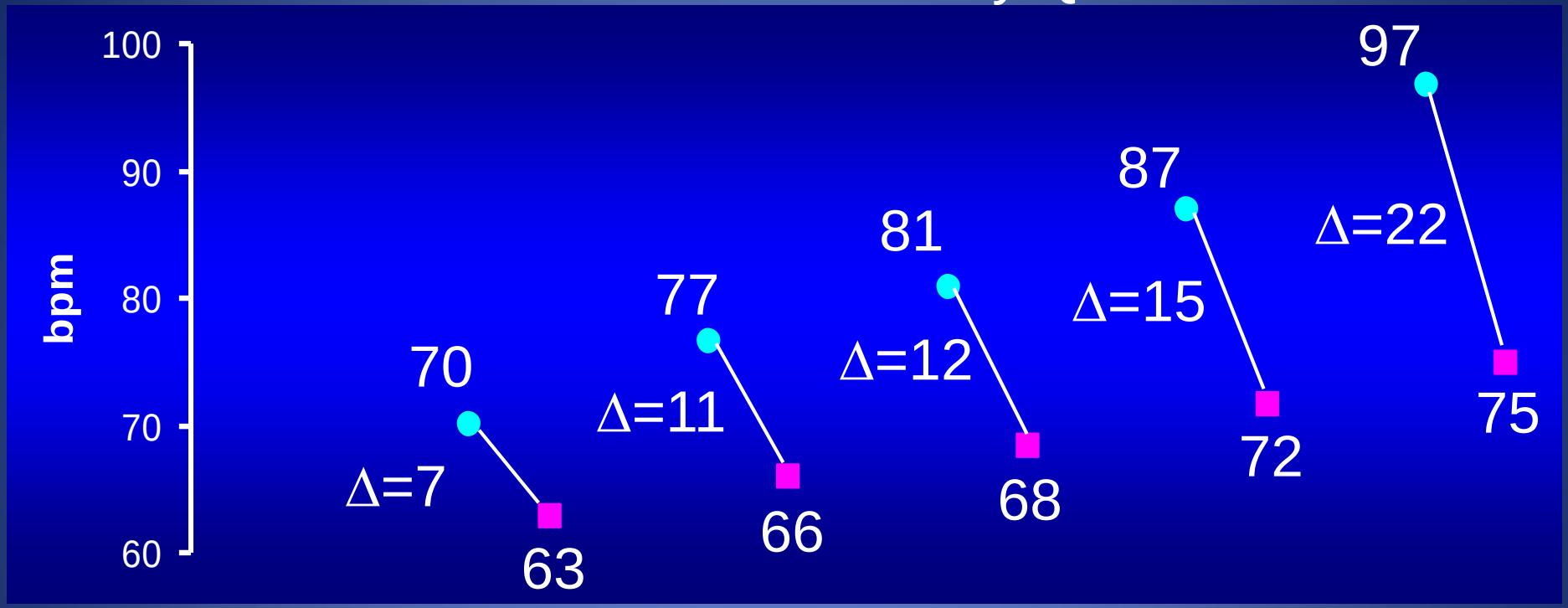
Five Subgroups Defined by Baseline HR

Mean Heart Rate in the 5 Quintiles (Q):

- Q1 71 bpm
- Q2 76 bpm
- Q3 81 bpm
- Q4 87 bpm
- Q5 98 bpm (> 90 bpm)

Gullestad L et al, JACC 2005;45:252-9

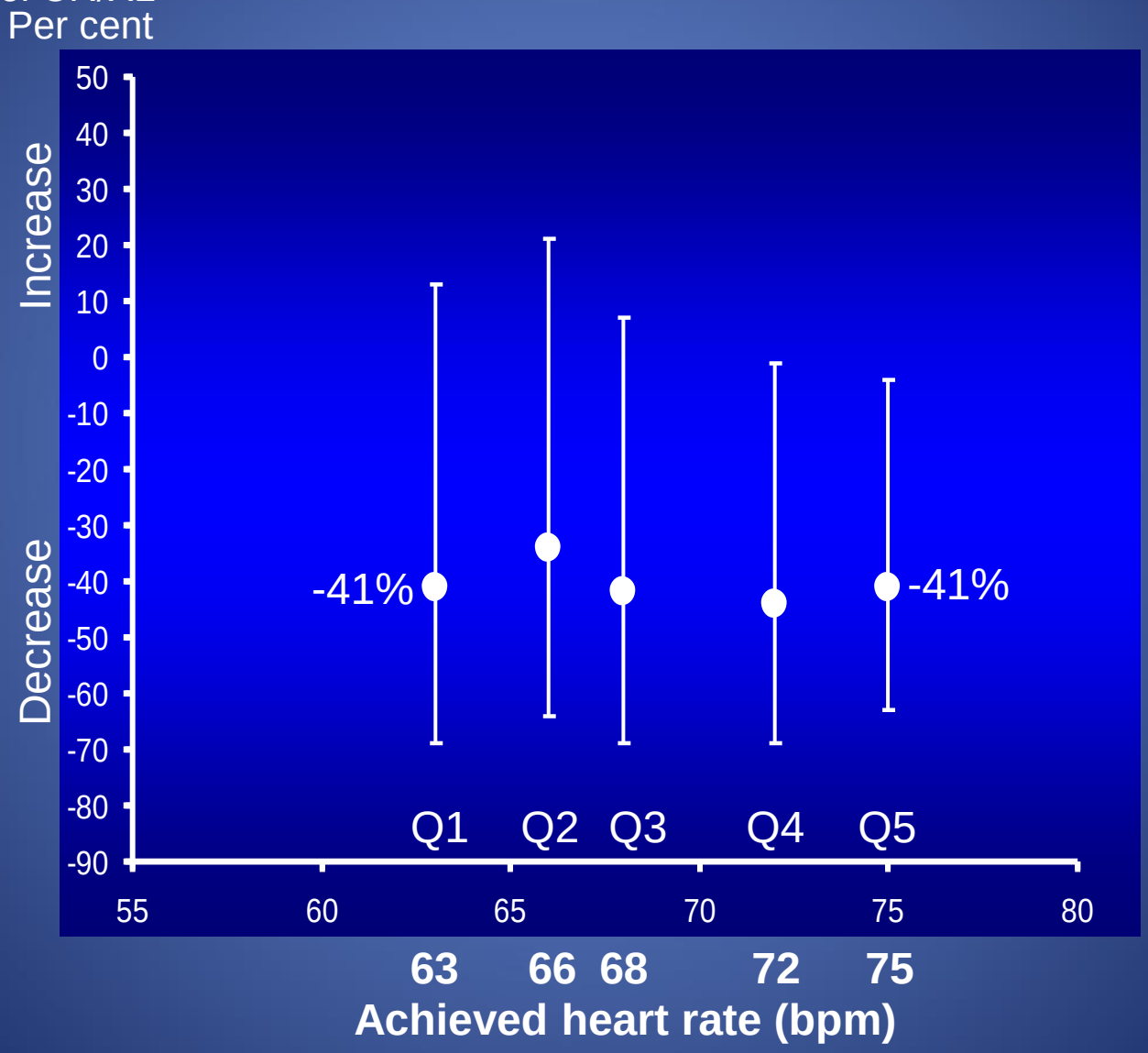
Baseline Heart Rate, Dose of Metoprolol CR/XL, and Achieved Heart Rate by Quintiles



Quintile (Q)	Q1	Q2	Q3	Q4	Q5
Meto CR/XL dose (mg)	146	149	163	167	166
Net reduction (bpm)	8	10	11	13	14
% reduction (bpm)	10	14	16	18	23

Gullestad L et al, JACC 2005;45:252-9

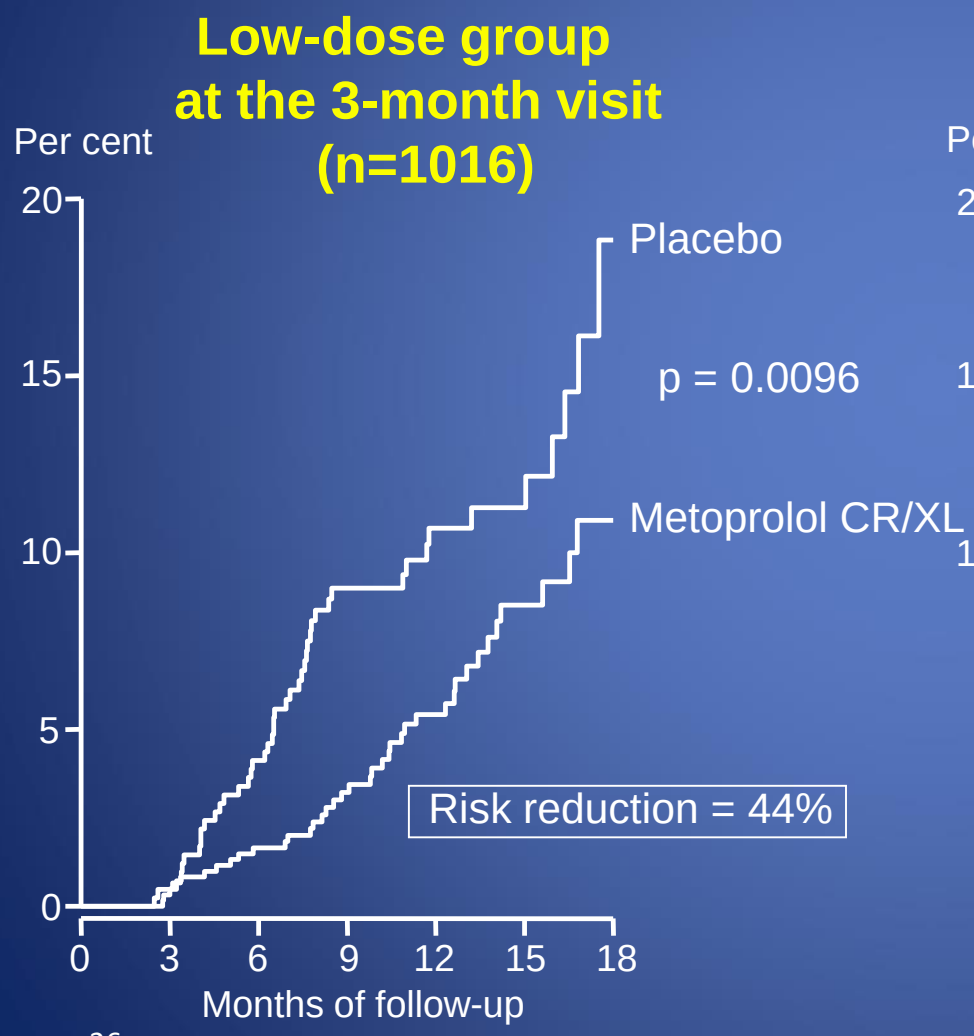
Total Mortality vs Achieved Heart Rate

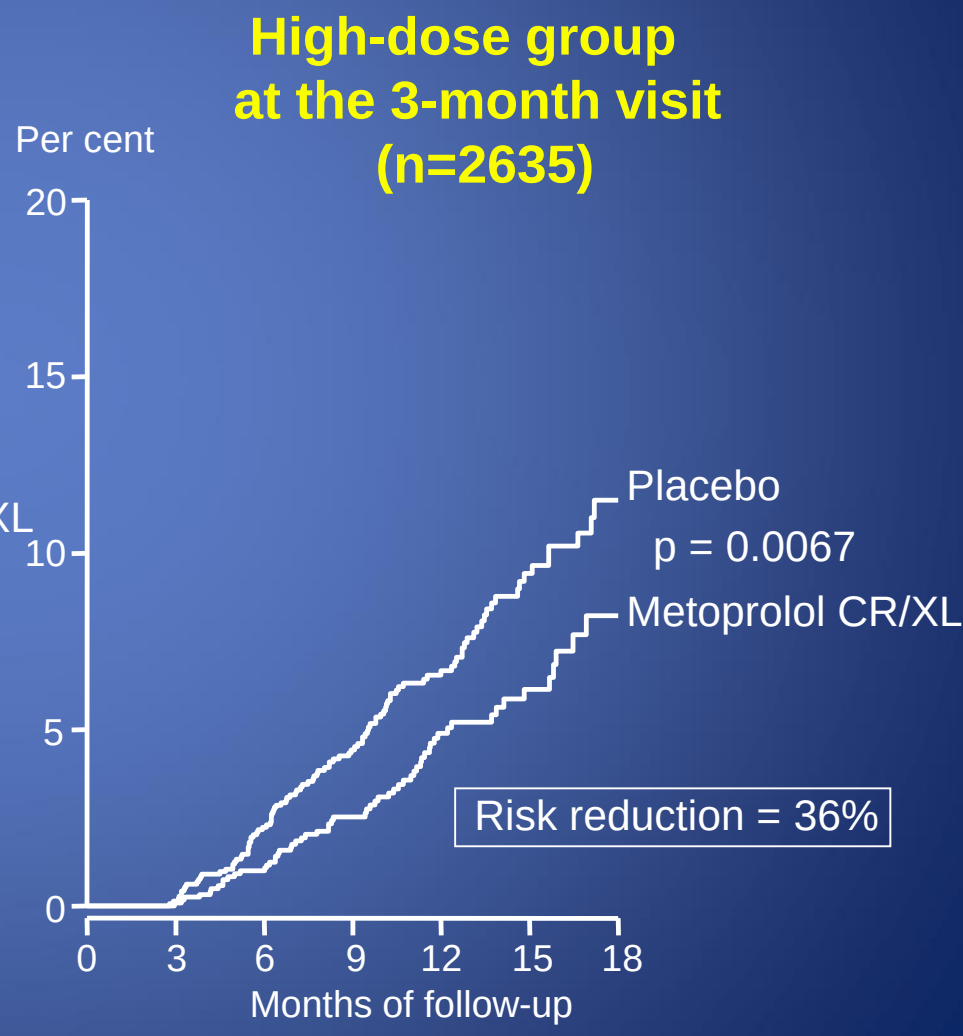


Gullestad L et al, JACC 2005;45:252-9

Post-hoc Subgroup Analysis in Relation to Dose of Study Medicine after 3 Months

Total Mortality





Wikstrand J et al. for the MERIT-HF Study Group

Comment

- Metoprolol CR/XL significantly reduced mortality and hospitalizations independently of achieved heart rate and change in heart rate
- Achieved heart rate and change in heart rate during follow-up were closely related to baseline heart rate. Therefore a common target heart rate can not be defined for all patients with heart failure
- Aim for the highest tolerated dose in all patients with heart failure regardless of baseline and achieved heart rate

Trenger alle oppnå mål dose betablokker for å dra nytte?

Dose vs Outcome

Mean Dose and Median Plasma Concentration of Metoprolol Succinate at 3-month Visit

Dose group	Meto CR/XL	Plasma conc.
Low-dose group	76 mg	95 nmol/l
High-dose group	192 mg	247 nmol/l

Wikstrand J et al, JACC 2002;40:491-8

Dose vs Outcome

Baseline Characteristics by Dose Group

Dose group	Placebo (n=1845)	Metoprolol CR/XL Low-dose (n=604)	Metoprolol CR/XL High-dose (n=1202)
Mean age (years)	64	66	63
Mean EF	0.28	0.27	0.28
NYHA III/IV (%)	58	67	53
Previous MI (%)	49	54	44
Systolic BP (mm Hg)	130	127	131

Wikstrand J et al, JACC 2002;40:491-8

Dose vs Outcome

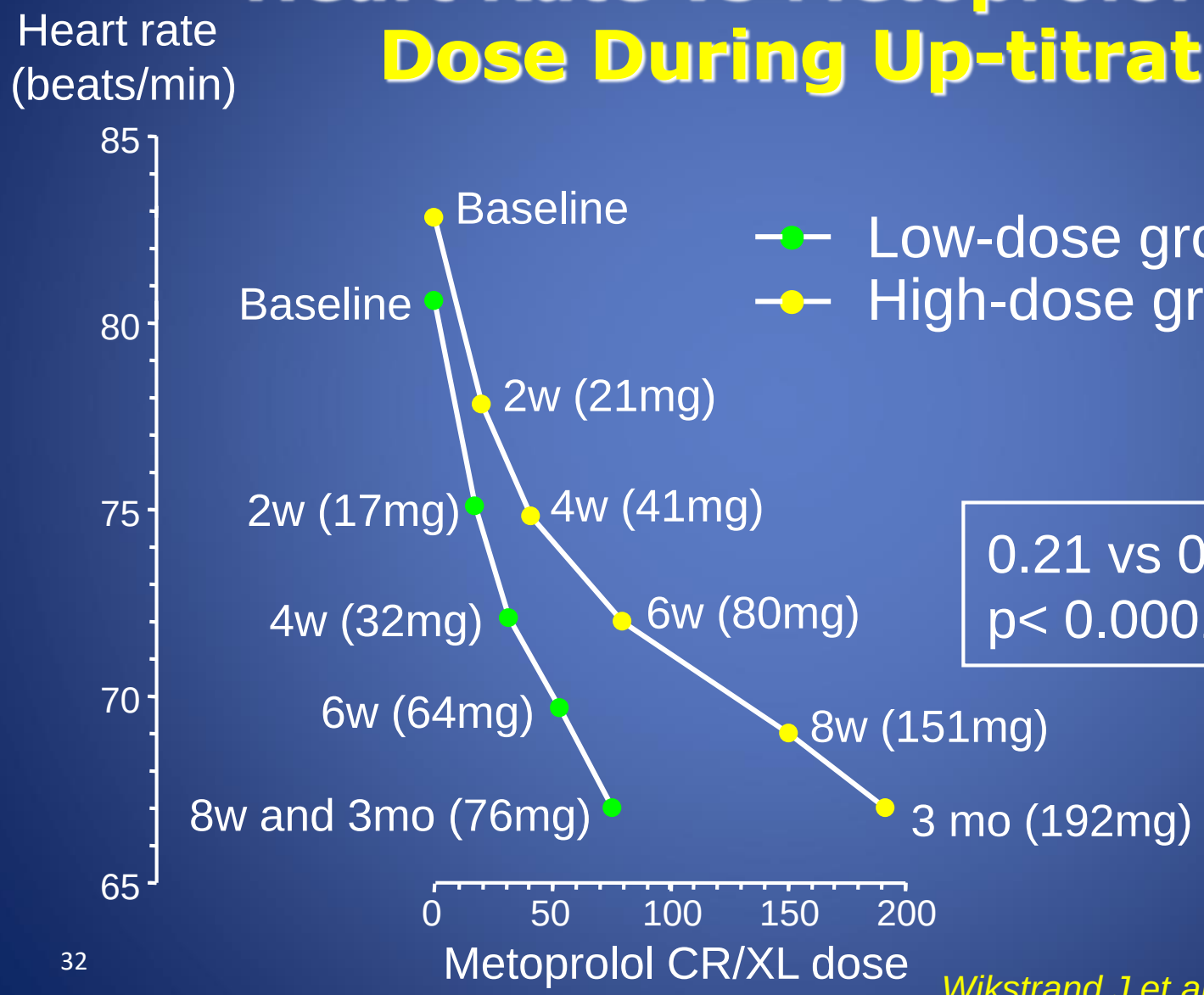
Heart Rate at Baseline and after 3 Months

	Baseline (bpm)	3-months (bpm)
Low-dose group	81	67
High-dose group	83	67

Wikstrand J et al, JACC 2002;40:491-8

Dose vs Outcome

Heart Rate vs Metoprolol CR/XL Dose During Up-titration

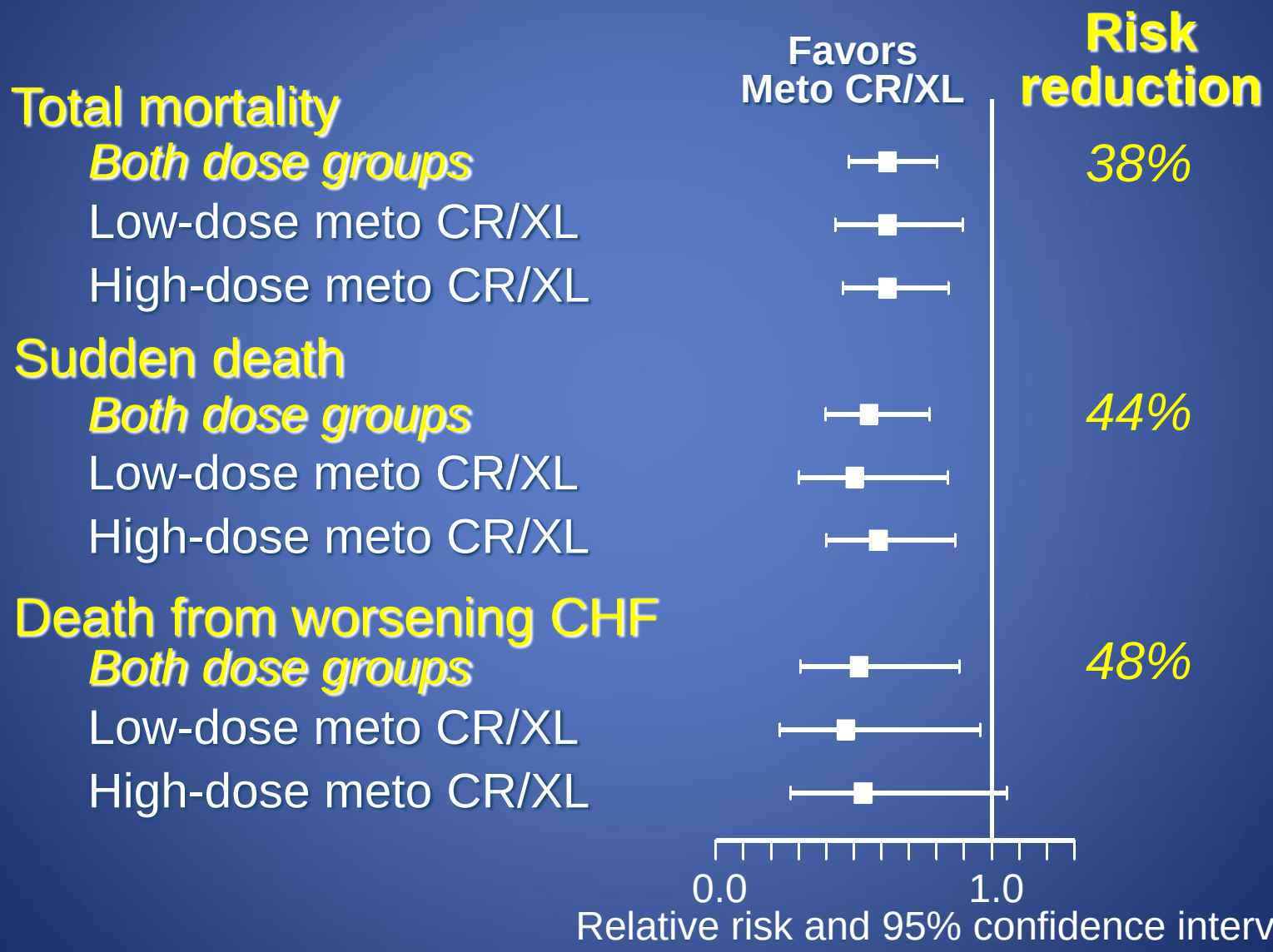


0.21 vs 0.08 bpm/mg
p< 0.0001

Wikstrand J et al, JACC 2002;40:491-8

Dose vs Outcome

Cause-specific Mortality after the 3-Month Visit



Wikstrand J et al, JACC 2002;40:491-8

Dose vs Outcome

Summary (1)

The data taken together clearly show that patients in whom doctors stopped titration at 100 mg are at higher risk than those titrated to more than 100 mg

The heart rate reduction was surprisingly similar in the high-dose and low-dose groups - both reached a mean heart rate of 67 bpm - indicating increased beta-blocker sensitivity in the low-dose group of patients

Wikstrand J et al, JACC 2002;40:491-8

Dose vs Outcome

Summary (2)

Risk reduction was similar in the high-dose and low-dose groups
- a 38% reduction in total mortality

This may be the result of similar beta-blockade as judged from the heart rate response

Wikstrand J et al, JACC 2002;40:491-8

Conclusion

- These data do not imply that the maximum target dose of 200 mg metoprolol CR/XL should be reduced for patients with heart failure, but rather the results support the idea of an individualized, non-forced dose-titration regimen, which is guided by patient tolerability

- Prognosis clearly seems to be improved also for patients not tolerating the maximum target dose of 200 mg metoprolol CR/XL

Wikstrand J et al. for the MERIT-HF Study Group

Hvilken betablokker skal man velge

Survival Studies with Beta-blockers in Heart Failure

Total Mortality

	Plac/Beta	Randomized n	NYHA Class	EF Mean
CIBIS II *Bisoprolol β_1*	228/156	2647	III/IV	0.28
MERIT-HF *Metoprolol CR/XL β_1*	217/145	3991	II-IV	0.28
COPERNICUS *Carvedilol β_1 β_2 (α)*	190/130	2289	(III/IV)[1]	0.20
All pooled	635/431	8927		

Relative risk and 95% CI

[1] Not recorded in COPERNICUS, placebo mortality indicates III/IV

Lancet 1999;353:9-13; Lancet 1999;353:2001-7, N Engl J Med 2001;344:1651-8

Conclusion 1(2)

It is not possible to define a common target heart rate or a common final beta-blocker dose for all patients with heart failure.

Analyses performed support the idea of an individualized dose-titration regimen, which is guided by patient tolerability only.

Wikstrand J et al, JACC 2002;40:491-8, Gullestad L et al, JACC 2005;45:252-9

Conclusion 2(2)

The first line target dose should be any of the following:

- 200 mg metoprolol CR/XL once daily
- 10 mg bisoprolol once daily
- 25 mg carvedilol twice daily

aiming for the highest tolerated dose.

Lancet 1999;353:9-13; Lancet 1999;353:2001-7, N Engl J Med 2001;344:1651-8
Wikstrand J et al, JACC 2002;40:491-8, Gullestad L et al, JACC 2005;45:252-9