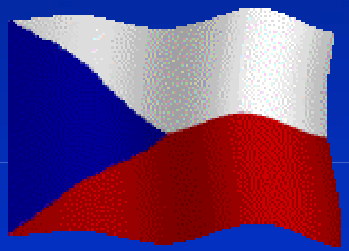
Acute heart failure

Spinar J.
Brno, Czech republic



European Heart Journal
doi:10.1093/eurheartj/ehi044

ESC Guidelines

Executive summary of the guidelines on the diagnosis and treatment of acute heart failure

The Task Force on Acute Heart Failure of the European Society of Cardiology

Endorsed by the European Society of Intensive Care Medicine (ESICM)

Authors/Task Force Members, Markku S. Nieminen, Chairperson* (Finland), Michael Böhm (Germany), Martin R. Cowie (UK), Helmut Drexler (Germany), Gerasimos S. Filippatos (Greece), Guillaume Jondeau (France), Yonathan Hasin (Israel), José Lopez-Sendon (Spain), Alexandre Mebazaa[+] (France), Marco Metra (Italy), Andrew Rhodes[+] (UK), Karl Swedberg (Sweden)

Acute heart failure - definition

Acute heart failure is:

- Acute signs and symptoms of HF
- Left ventricle dysfunctiuon (systolic and/or diastolic)
- Urgent treatment needed

Notice: AHF in Mi stenosis can have normal LV function

Acute heart failure - definition

De novo AHF

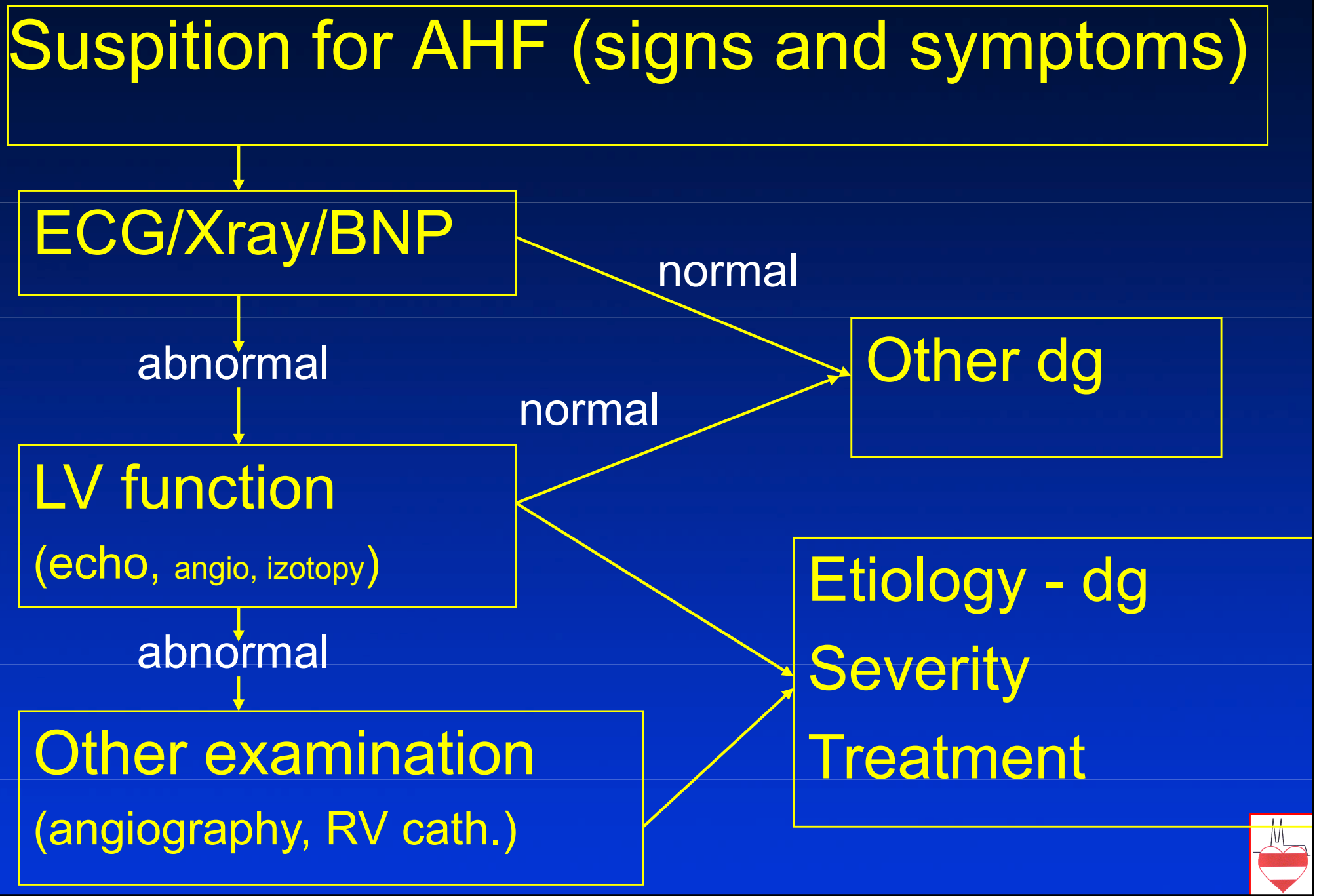
CHF decompensation

Lung oedema
Cardiogenic schock
Combination

Acute heart failure - clinics

1. Acute CHF decompensation without lung oedema or schock
2. Hypertension crisis with AHF
3. Lung oedema (saturation < 90%)
4. Cardiogenic schock (BPs < 90mmHg, CI < 0,5ml/kg/h, HR > 100)
5. AHF with high output (thyreotoxikósis, anemia, sepsis)
6. Right HF with low CI

Acute heart failure - diagnosis



Acute heart failure - diagnostics

ECHO – must be done

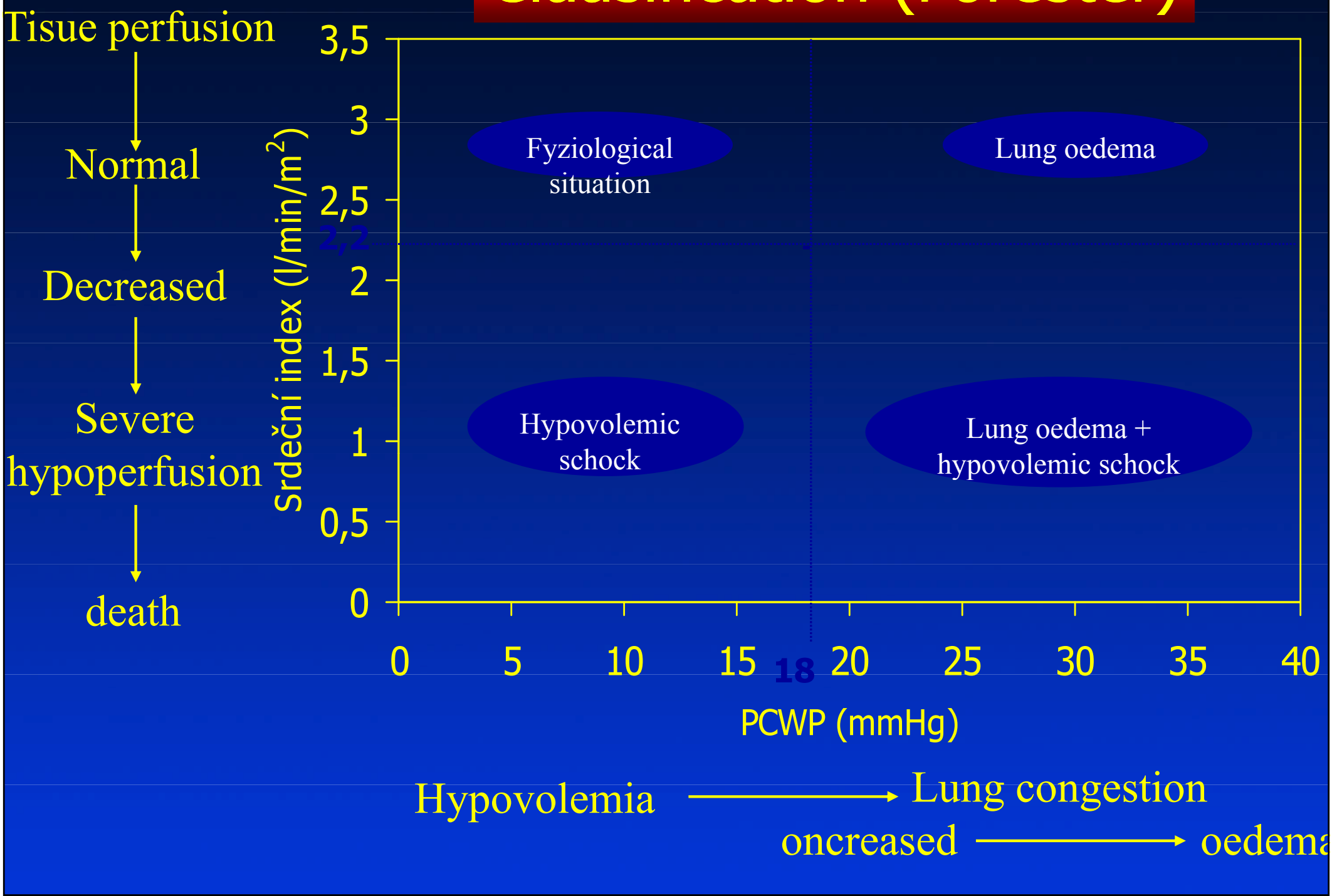
- systolic function of LV
- diastolic function of LV
- regional wall motion
- valves
- pericardial fluid
- infiltrativ process
- hypertension crises - 50% normal systolic function (EF > 45%), intermittent diastolic dysfunction

Acute heart failure - diagnostics

BNP - doporučené pro dg

- Increased in CHF
- Increased in AHF
- Normal value excludes AHF
- Prognosis
- Admition – discharge value
- BNP > 500 pg/ml (100-500 ???)
- Nt-proBNP > 1 800 pg/ml (300-1 800)

Claasification (Forester)



Acute heart failure - diagnostics
(Killip and Kimbal)

Grade 1

- **Wtihout HF**

Grade 2

- **Light dyspnoe**
- **Basal rales**
- **Gallop**
- **Lung congestionon chest X ray**

Grade 3

- **Lung oedema**

Grade 4

- **Cardiogenic schock – vasoconstrikction**
- **- hypotension**
  - oligouria

X ray (Mezsaros)

- CTR > 50%
- Lung congestion

0 = fyziological finding
I = hyeremia of upper lung
II = intestitial lung oedema
III = alveolar lung oedema

Acute heart failure - epidemiology USA 1997

	AHF	AMI
No hospitalisation	957 000	800 000
Hospit. mortality	10%	3%
Rehospitalisation	many	few
Guidelines for dg.	2004	1984
Guidelines for th.	2004	1984
No of random. studies	100	5 000
No of pts in studies	10 000	10 000 000

Nieminen ESC 2004

Acute heart failure - etiology

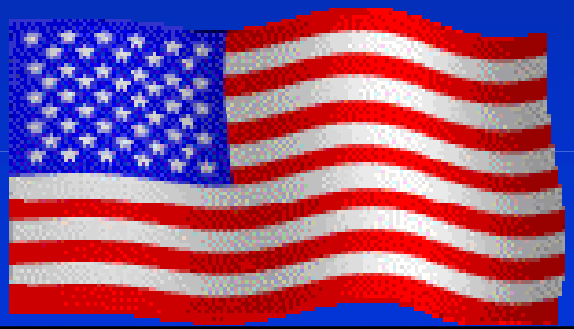
CHF decompensation	65%
Acute HF de novo	35%
ACS (EKG, troponin)	30%

Nieminen AHF registry EUROPE – ESC - 2005

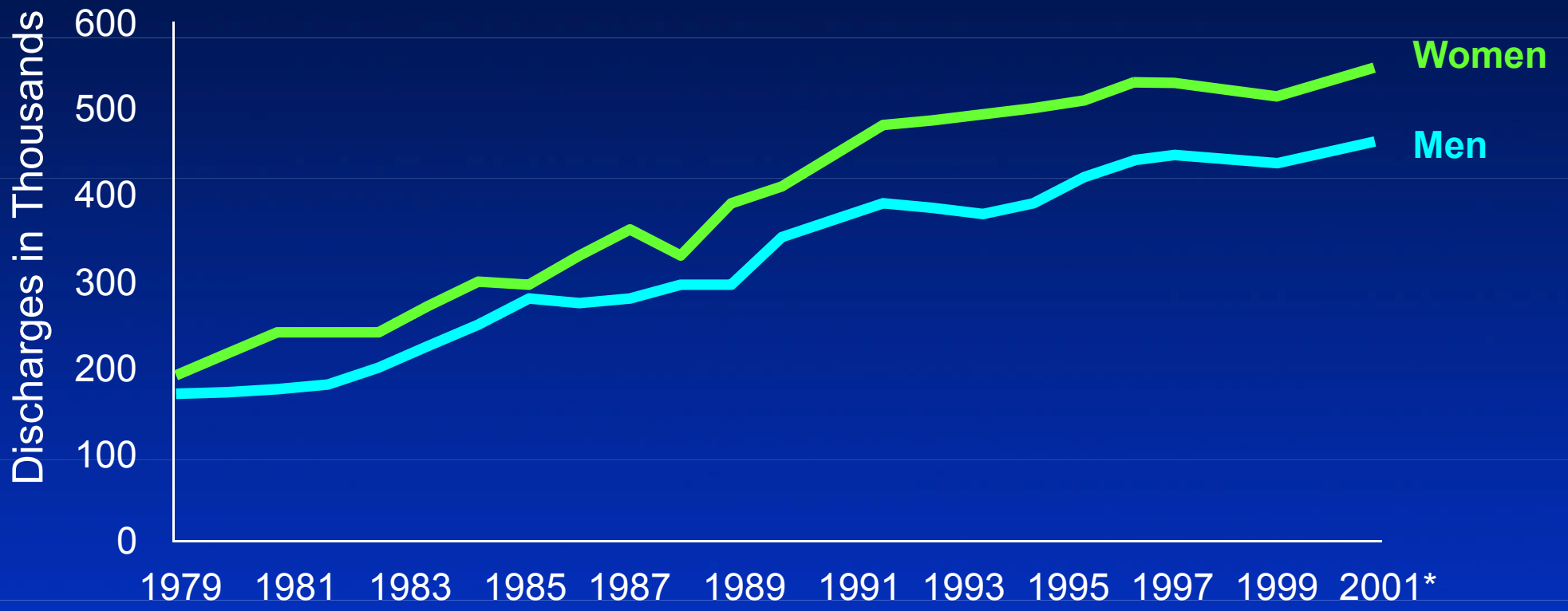
ADHERE registry AHF
100 000 patients in USA

1. 48% patients with AHF had EF > 40%
2. 63% patients with EF > 40% were female

1. 2% patients had BPs < 90 mmHg
2. 48% patients had BPs 90-140 mmHg
3. 50% patients had BPs > 140 mmHg



Heart Failure Hospitalizations: US

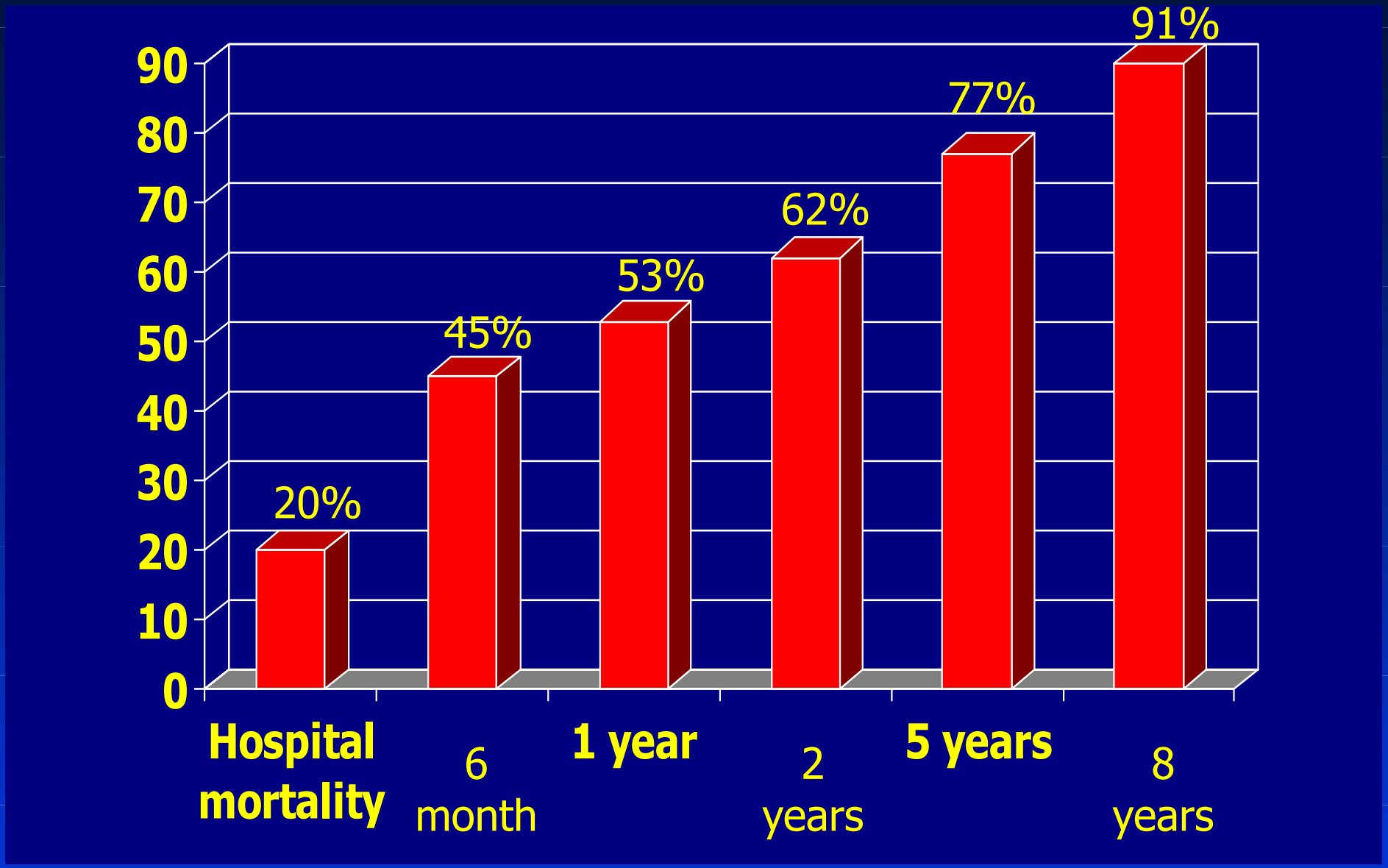


*Data includes heart failure and shock.

Healthcare Cost and Utilization Project 2001 National Statistics. Rockville, MD: Agency for Healthcare Research and Quality; 2002.

Heart and Stroke Statistics–2005 Update. Dallas, TX: American Heart Association; 2005.

AHF - prognosis



Sasin EJHF 2004; 6: 669-72

Acute heart failure – prognosis

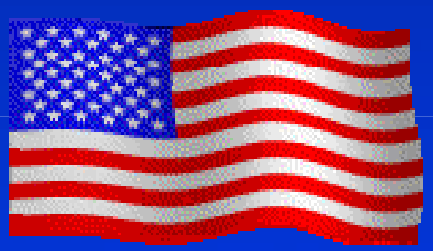
Hospit. mortality	9%
Discharge - 1. month	3%
1. – 3. month	3%
3. – 6. month	3%
6. – 12. month	3%
1 year mortality	21%

Nieminen AHF registry - ESC 2005

Acute heart failure – conflicting information

CHF decompensation	65%
ACS (ECG, troponin)	30%
EF > 40%	48%
BPs > 140 mmHg	50%
1 year mortality	21 – 53 %

ESC AHF registry 2005



ADHERE registry 2005

Heart Failure Treatment Gaps

- Heart failure affects at at least 10 million people in Europe and at least 4.9 million people in the US
- Approximately 550 000 new cases are diagnosed each year in the US
- Heart failure is a major and growing health care problem worldwide
- There are currently no drugs that improve long-term survival in patients treated for heart failure
- Current therapies provide short-term benefits but there are unmet needs for long-term outcomes

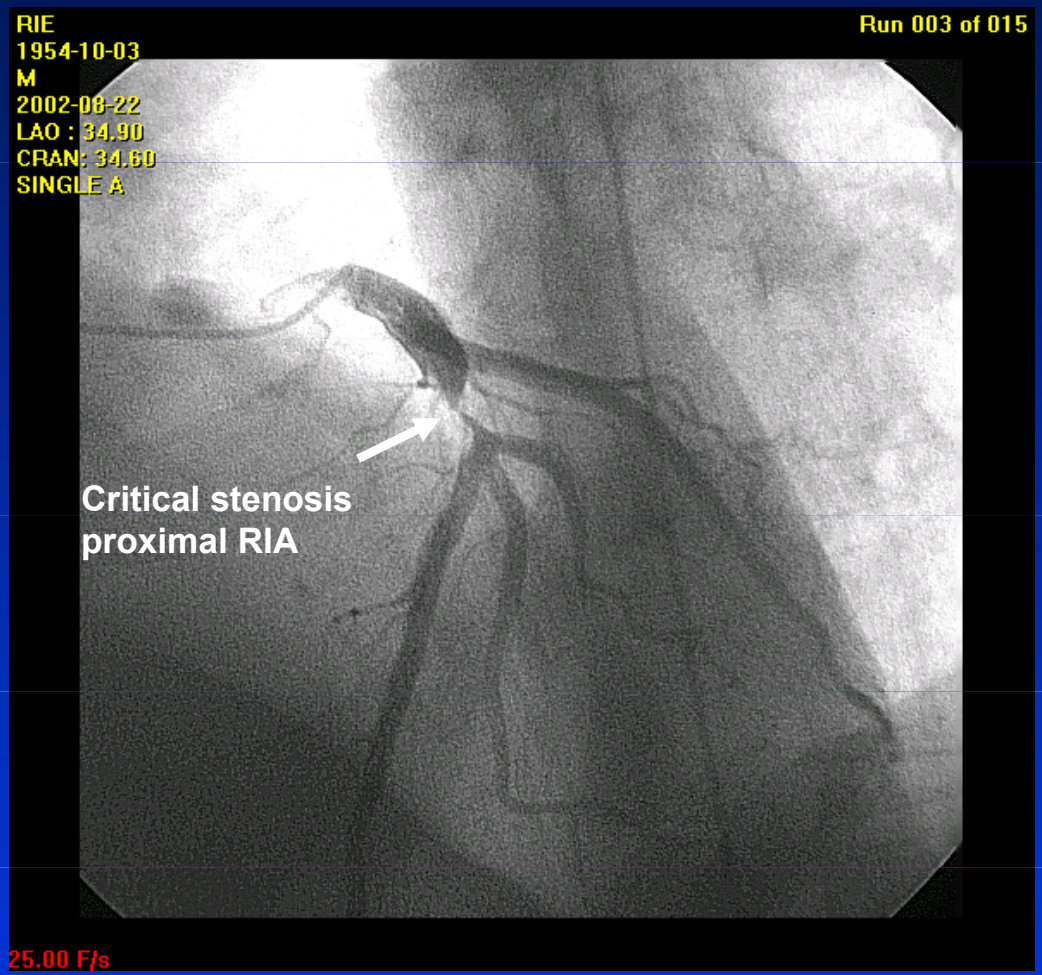
Remme WJ, et al. *Eur Heart J.* 2001;22:1527-1560.
McBride BF, et al. *Pharmacotherapy*. 2003;23:997-1020.
Heart Disease and Stroke Statistics — 2005 Update.
Dallas: American Heart Association; 2005.

Goals of AHF Management

- Immediate – Improve symptoms and prevent morbidity and mortality
  - Restore oxygenation
  - Improve organ perfusion (kidney, brain, heart)
  - Treat volume overload
- Intermediate – Stabilize patient and optimize treatment
  - Initiate maintenance regimen
  - Minimize ICU time
  - Minimize length of stay
- Longer term disease management
  - Prevent early readmission
  - Improve long-term medical regimen, symptoms, and survival

McBride BF, et al. *Pharmacotherapy*. 2003;23:997-1020.

What Characteristics Would be Ideal in a Treatment for AHF?



Characteristics of an Ideal Treatment for AHF

- Offers early symptom relief
- Promotes diuresis
- Provides vasodilation (venous and arterial)
- Improves end-organ function (eg, renal function)
- Does not exacerbate arrhythmias
- Does not exacerbate ischemia
- Does not interfere with other AHF therapies (eg, β-blockers)
- Decreases length of stay
- Reduces hospitalizations and mortality

Jain P, et al. *Am Heart J*. 2003;145:S3-S17.
Nohria A, et al. *JAMA*. 2002;287:628-640.
Brewster UC, et al. *Am J Med Sci*. 2003;326:15-24.

Current IV Therapies for AHF

IV Diuretics	Vasodilators	Inotropes
Reduce Volume Overload	**Decrease Preload and Afterload**	**Augment Contractility**
Loop Diuretics	**Nitroglycerin Nitroprusside Nesiritide**	**Dobutamine Milrinone**

McBride BF, et al. *Pharmacotherapy*. 2003;23:997-1020.

Loop Diuretics

- Mechanism of action
  - Inhibition of $Na^+/K^+/2Cl^-$ symporter in the thick ascending limb of the Loop of Henle
- Clinical Benefits
  - Rapid symptomatic improvement
  - Decreased volume overload
- Clinical Drawbacks
  - Increased neurohormonal activation
  - Electrolyte disturbances and/or arrhythmias
  - Potentially worsened renal function

McBride BF, et al. *Pharmacotherapy.* 2003;23:997-1020.

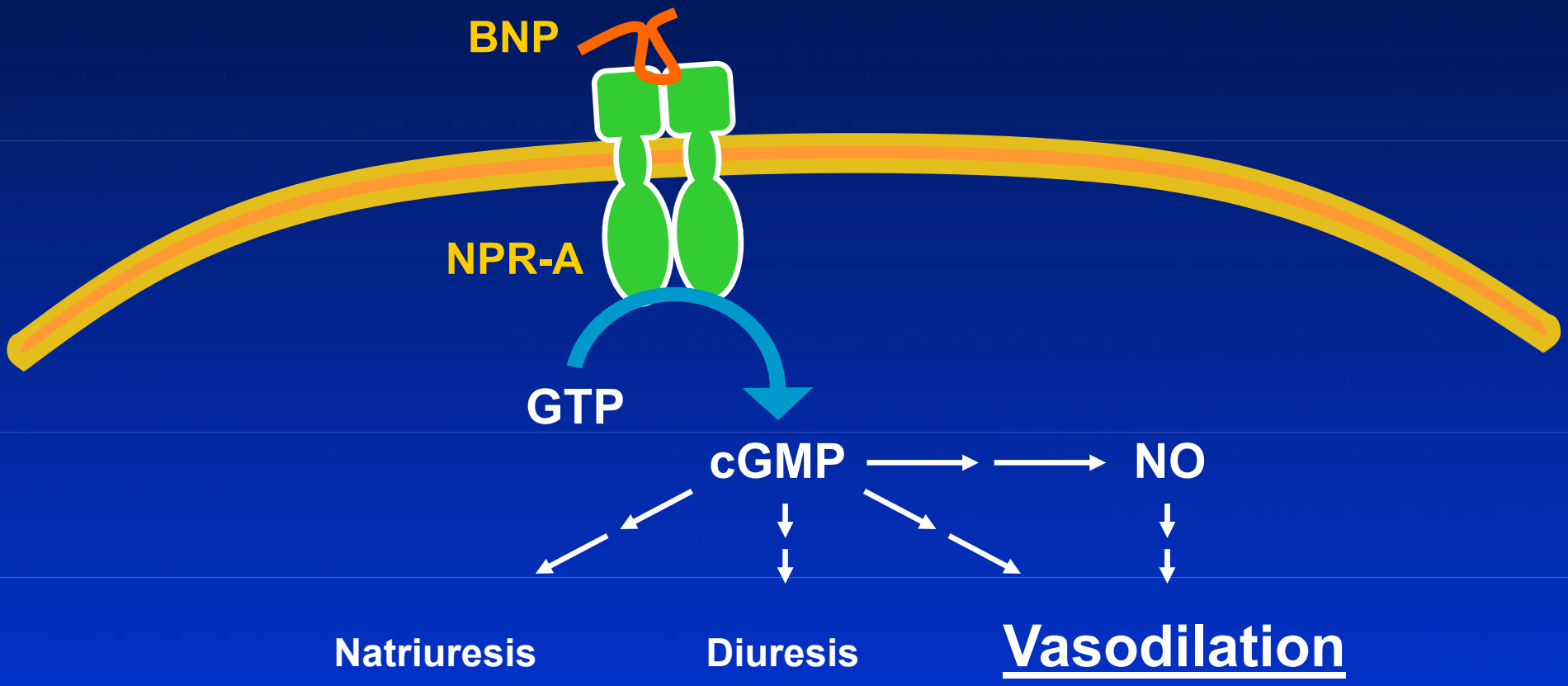
Nitrovasodilators

- Mechanism of action
  - cGMP-mediated venous and arterial vasodilation
- Clinical Benefits
  - Reduce PCWP
  - Rapid symptomatic improvement
- Clinical Drawbacks
  - Minimal indirect effect in increasing cardiac output
  - Hypotension, headache
  - Tolerance, tachyphylaxis (frequent titration)
  - Invasive monitoring
  - Rare cyanide toxicity (nitroprusside)

McBride BF, et al. *Pharmacotherapy.* 2003;23:997-1020.

Nesiritide Mechanism of Action

- Recombinant human B-type natriuretic peptide (BNP)



Kuhn M. *Circ Res.* 2003;93:700-709.

Nesiritide

- Clinical Benefits
  - Rapid symptomatic improvement
  - Improvement in hemodynamic factors
  - No clinical evidence of tachyphylaxis
- Clinical Drawbacks
  - Minimal indirect effect in increasing cardiac output
  - Incompatibilities; cannot be infused through same IV catheter as heparin (no heparin-coated catheters), insulin, bumetanide, enalaprilat, hydralazine, or furosemide
  - May cause hypotension
  - Associated with increased serum creatinine levels
  - Impact on hospitalization and mortality remains uncertain

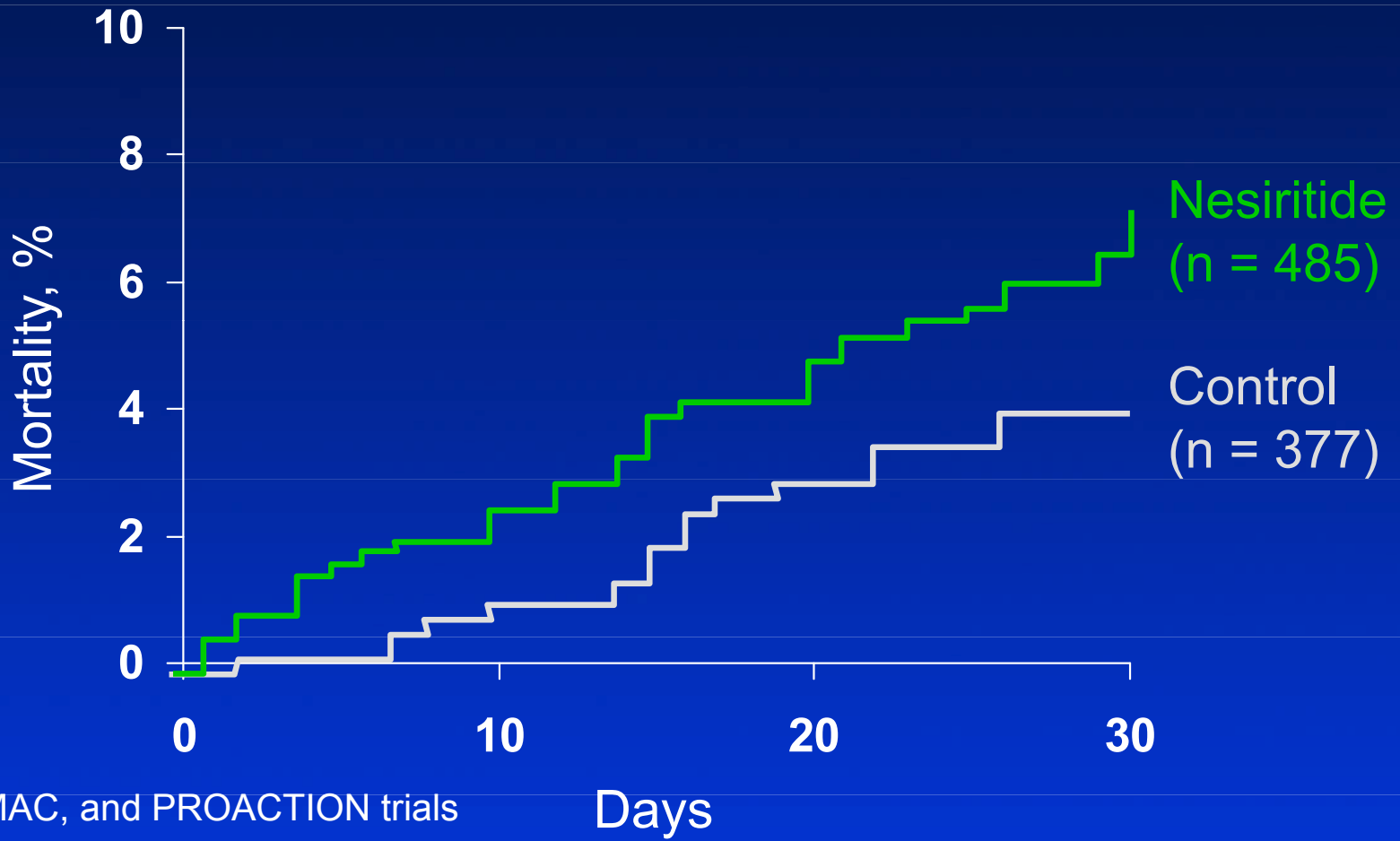
Keating GM, et al. *Drugs.* 2003;63:47-70.
Natrecor [package insert]. Fremont, Calif: Scios Inc; 2004.
Noviasky JA, et al. *Pharmacotherapy*. 2003;23:1081-1083.
Sackner-Bernstein JD, et al. AHA Scientific Sessions 2004. New Orleans, Louisiana. Abstract 2413.

Effect of Nesiritide on Mortality

Meta-Analysis of 3 Nesiritide Trials*

Unadjusted: hazard ratio 1.86 (95% CI, 1.02-3.41), *P*=0.04

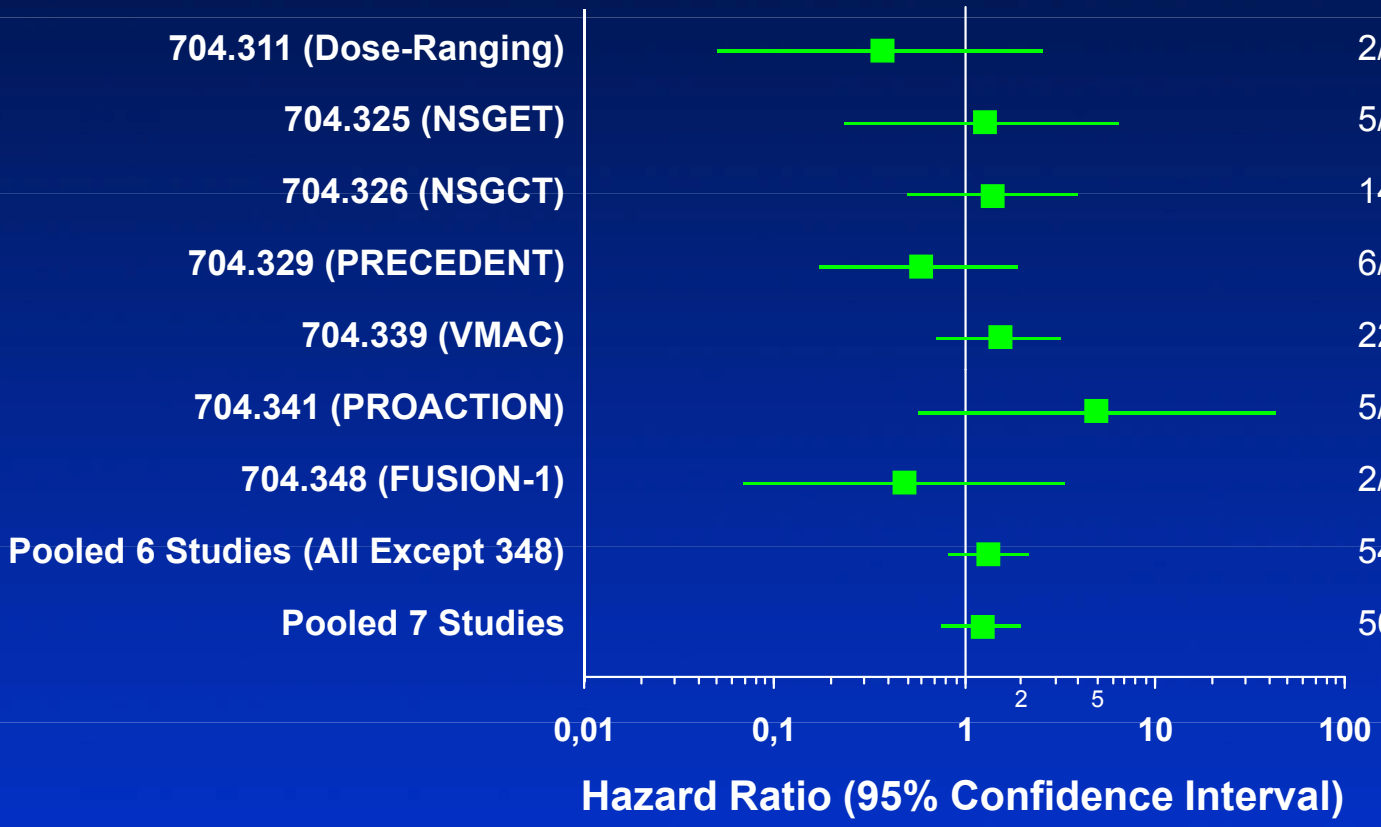
Adjusted for study: hazard ratio 1.80 (95% CI 0.98-3.31), *P*=0.057



*NSGET, VMAC, and PROACTION trials

Sackner-Bernstein JD, et al. *JAMA*. 2005;293:1900-1905.

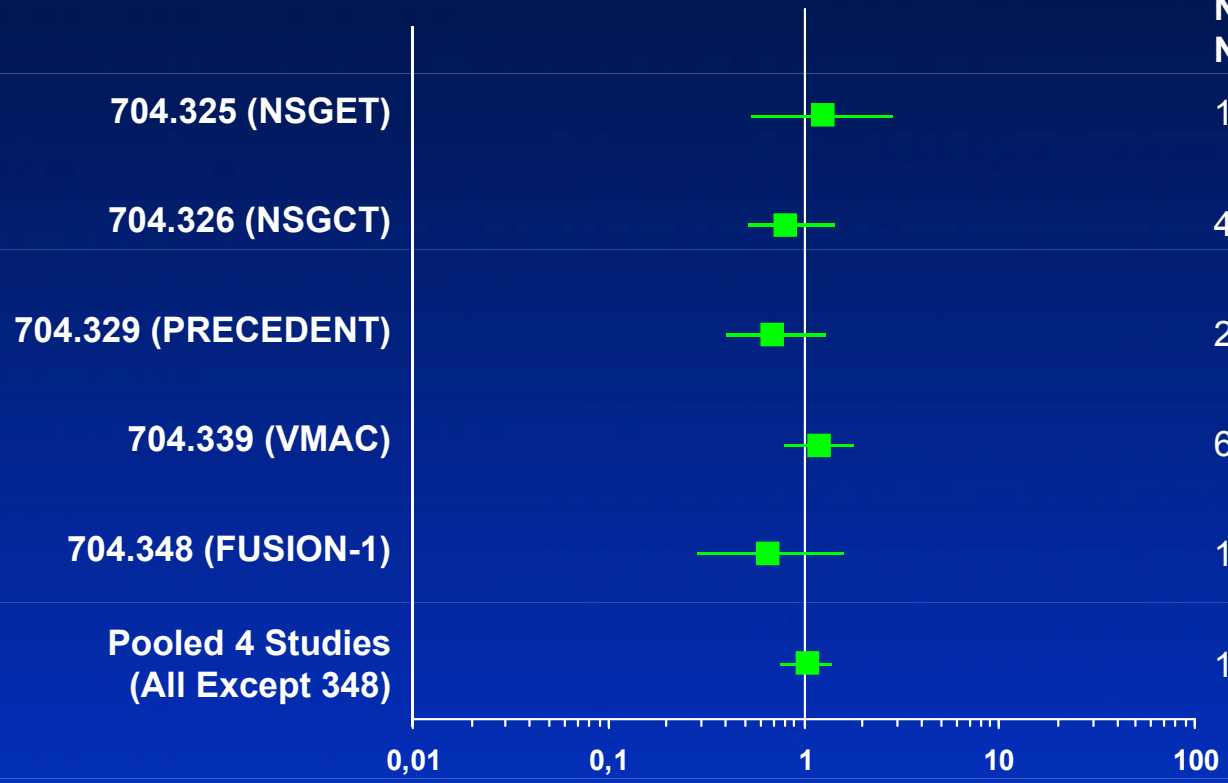
Effect of Nesiritide on Mortality at 30 Days



	Nesiritide N (%)	Control N (%)
704.311 (Dose-Ranging)	2/74 (2.7%)	2/29 (7.5%)
704.325 (NSGET)	5/85 (5.9%)	2/42 (4.8%)
704.326 (NSGCT)	14/203 (6.9%)	5/102 (4.9%)
704.329 (PRECEDENT)	6/163 (3.7%)	5/83 (6.1%)
704.339 (VMAC)	22/273 (8.1%)	11/216 (5.1%)
704.341 (PROACTION)	5/120 (4.2%)	1/117 (0.9%)
704.348 (FUSION-1)	2/141 (1.4%)	2/69 (2.9%)
Pooled 6 Studies (All Except 348)	54/918 (5.9%)	26/589 (4.4%)
Pooled 7 Studies	56/1059 (5.3%)	28/658 (4.3%)

Natrecor [package insert]. Fremont, Calif: Scios Inc; 2005.

Effect of Nesiritide on Mortality at 180 Days

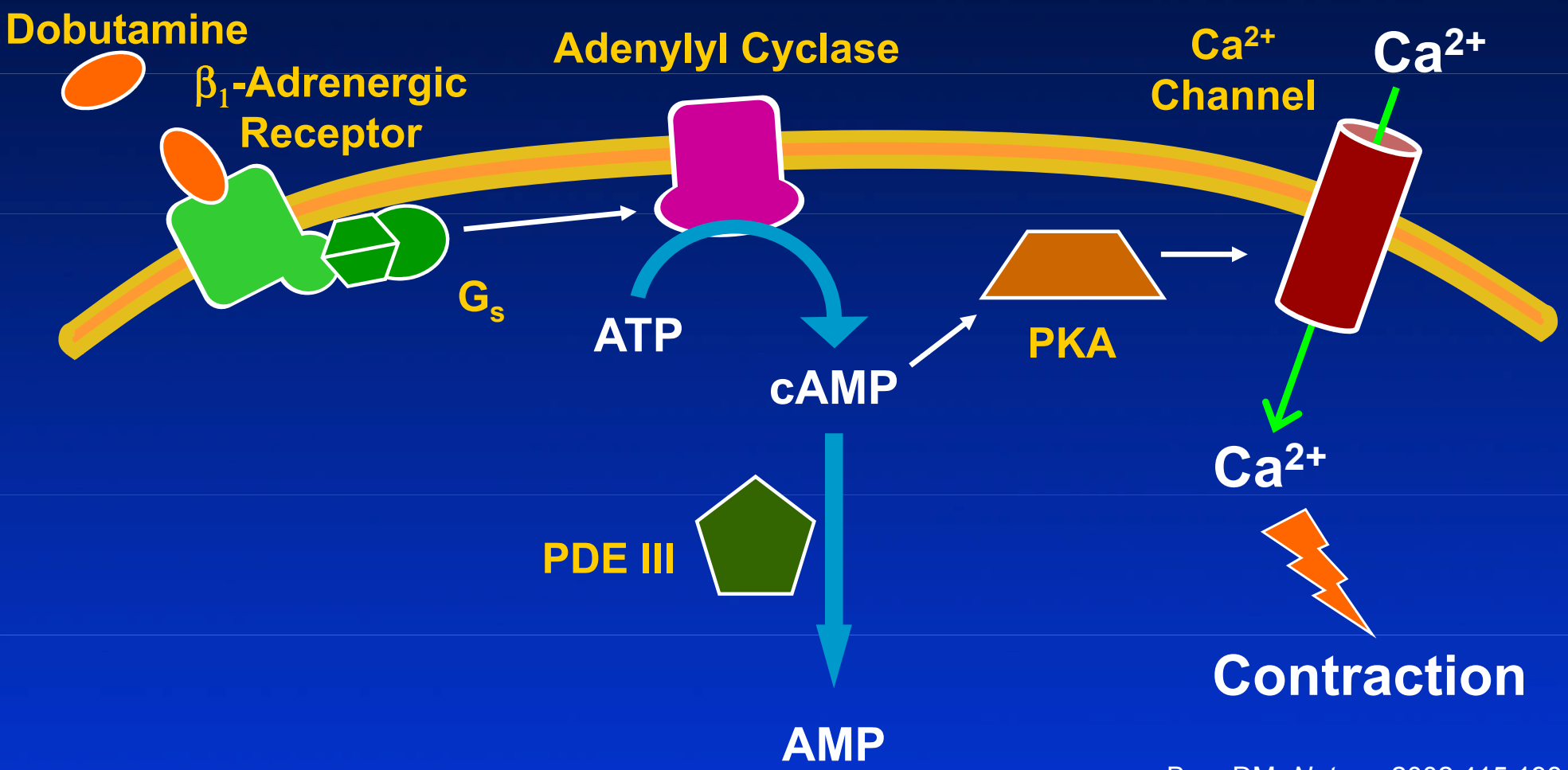


	Nesiritide N (%)	Control N (%)
704.325 (NSGET)	19/85 (23.1%)	8/42 (19.3%)
704.326 (NSGCT)	42/203 (20.8%)	24/102 (23.5%)
704.329 (PRECEDENT)	26/163 (16.3%)	18/83 (22.2%)
704.339 (VMAC)	67/273 (25.1%)	44/216 (20.8%)
704.348 (FUSION-1)	13/141 (9.4%)	9/69 (13.5%)
Pooled 4 Studies (All Except 348)	154/724 (21.7%)	94/443 (21.5%)

Hazard Ratio (95% Confidence Interval)

Natrecor [package insert]. Fremont, Calif: Scios Inc; 2005.

Dobutamine Mechanism of Action



Bers DM. *Nature.* 2002;415:198-205.
Movsesian MA. *J Card Fail.* 2003;9:475-480.
McBride BF, et al. *Pharmacotherapy.* 2003;23:997-1020.

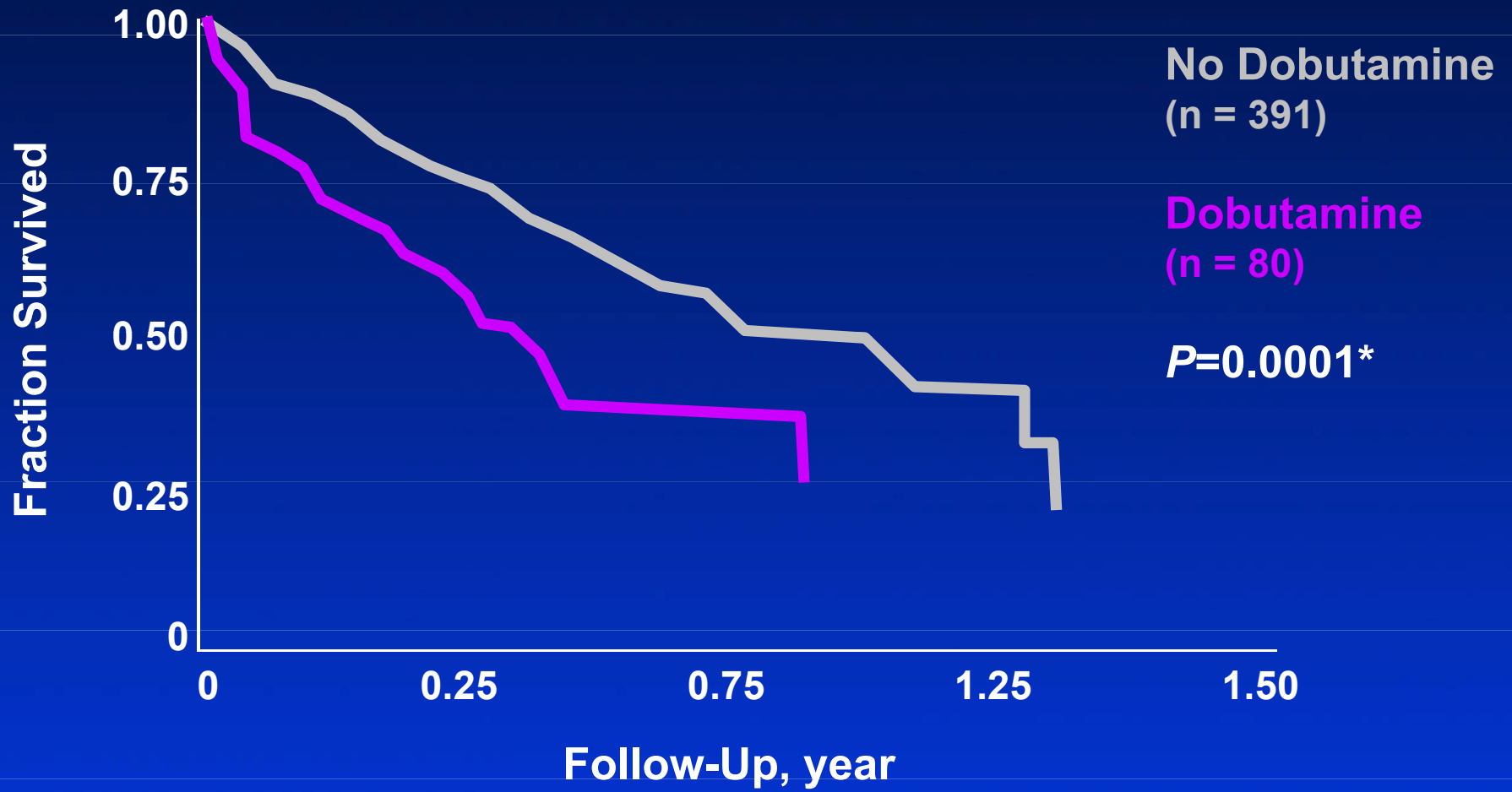
Dobutamine

- Clinical Benefits
  - Increased cardiac output and organ perfusion
  - Improves hemodynamics
  - Arteriolar and venous dilation
  - Slightly decreases preload and afterload
- Clinical Drawbacks
  - Increased myocardial oxygen consumption
  - Tolerance over a period of days
  - Difficult to use with β-blockers
  - Increased arrhythmias
  - Possible or potential increased mortality

McBride BF, et al. *Pharmacotherapy.* 2003;23:997-1020.

Effect of Dobutamine on Survival

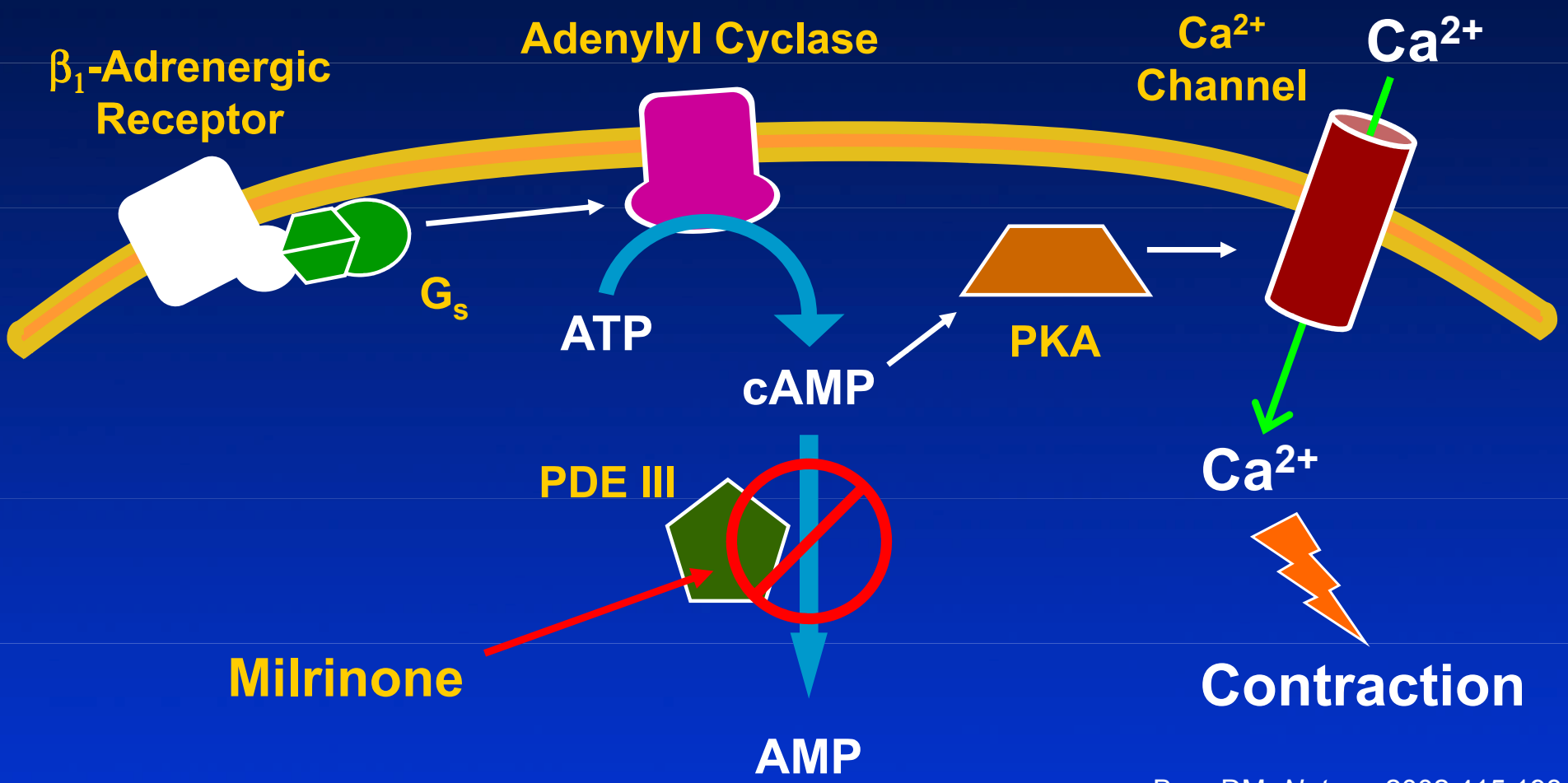
FIRST Trial: Adjusted Survival



*For NYHA III-IV patients.

O'Connor CM, et al. *Am Heart J*. 1999;138:78-86.

Milrinone Mechanism of Action



Bers DM. *Nature.* 2002;415:198-205.
Movsesian MA. *J Card Fail.* 2003;9:475-480.
McBride BF, et al. *Pharmacotherapy.* 2003;23:997-1020.

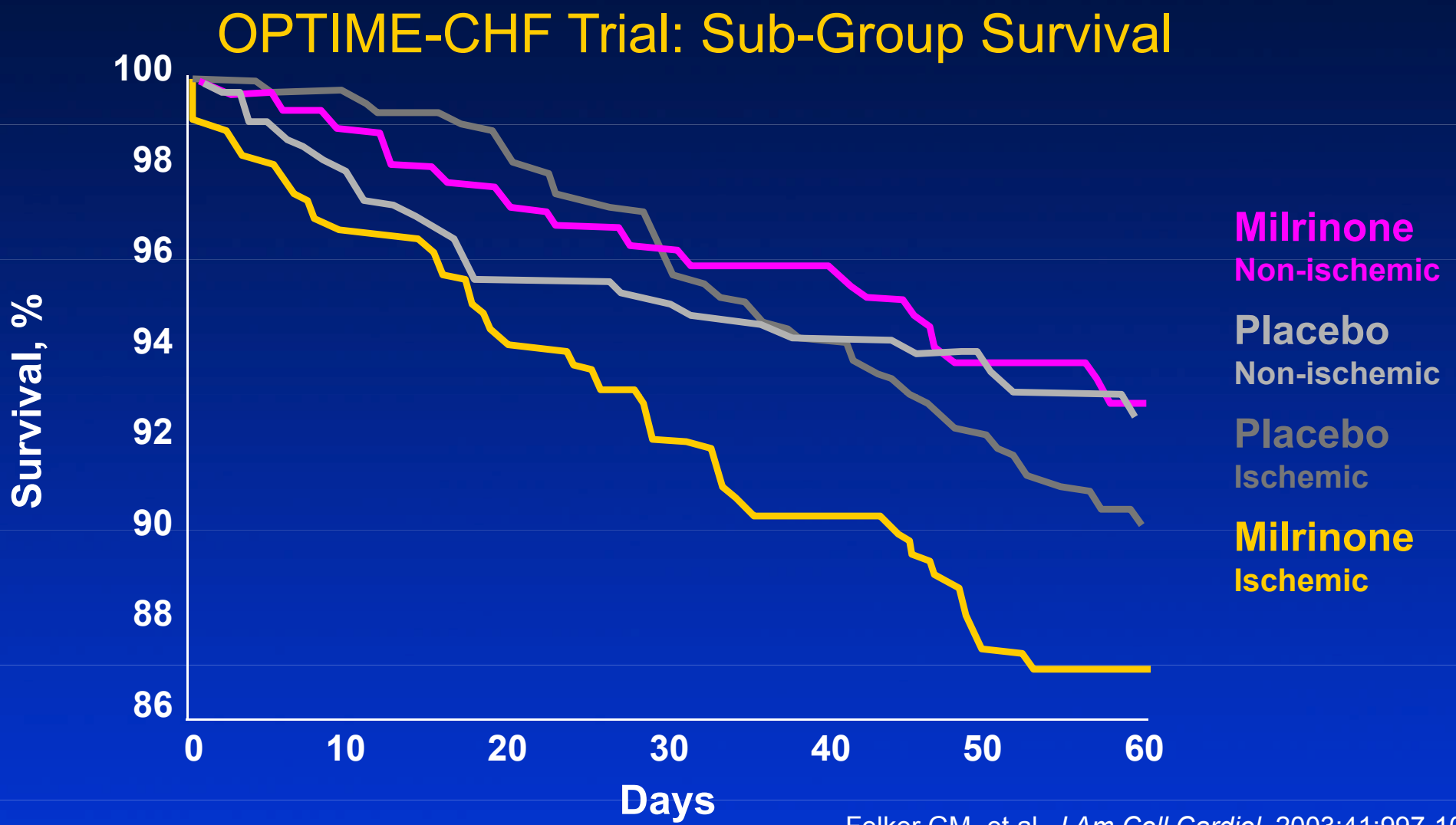
Milrinone

- Clinical Benefits
  - Increased cardiac output and organ perfusion
  - Decreased PCWP
  - Decreased vascular resistance
  - Improvement of hemodynamic function
  - Left ventricular function improvement in ischemic heart disease
- Clinical Drawbacks
  - Increased arrhythmias
  - Increased mortality with long-term use in patients with ischemic heart disease
  - Cannot be administered in same IV catheter as furosemide

McBride BF, et al. *Pharmacotherapy.* 2003;23:997-1020.
Primacor [package insert].
New York, New York: Sanofi-Synthelab Inc.; 2003.

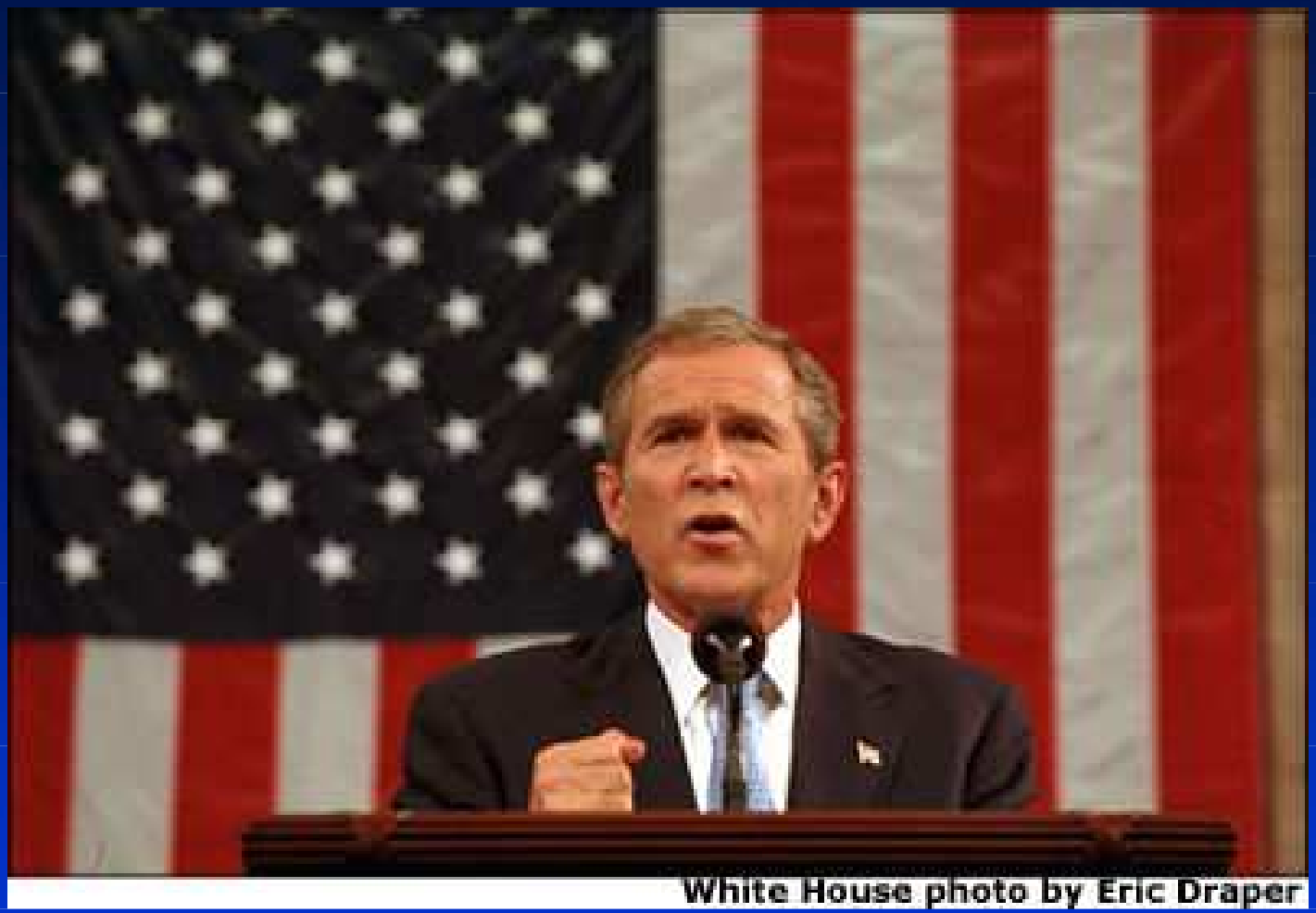
Effect of Milrinone on Survival

Kaplan-Meier Survival Curves to 60 Days by Heart Failure Etiology and Treatment Assignment



Felker GM, et al. *J Am Coll Cardiol*. 2003;41:997-1003.
Cuffe MS, et al. *JAMA*. 2002;287:1541-1547.

Levosimendan

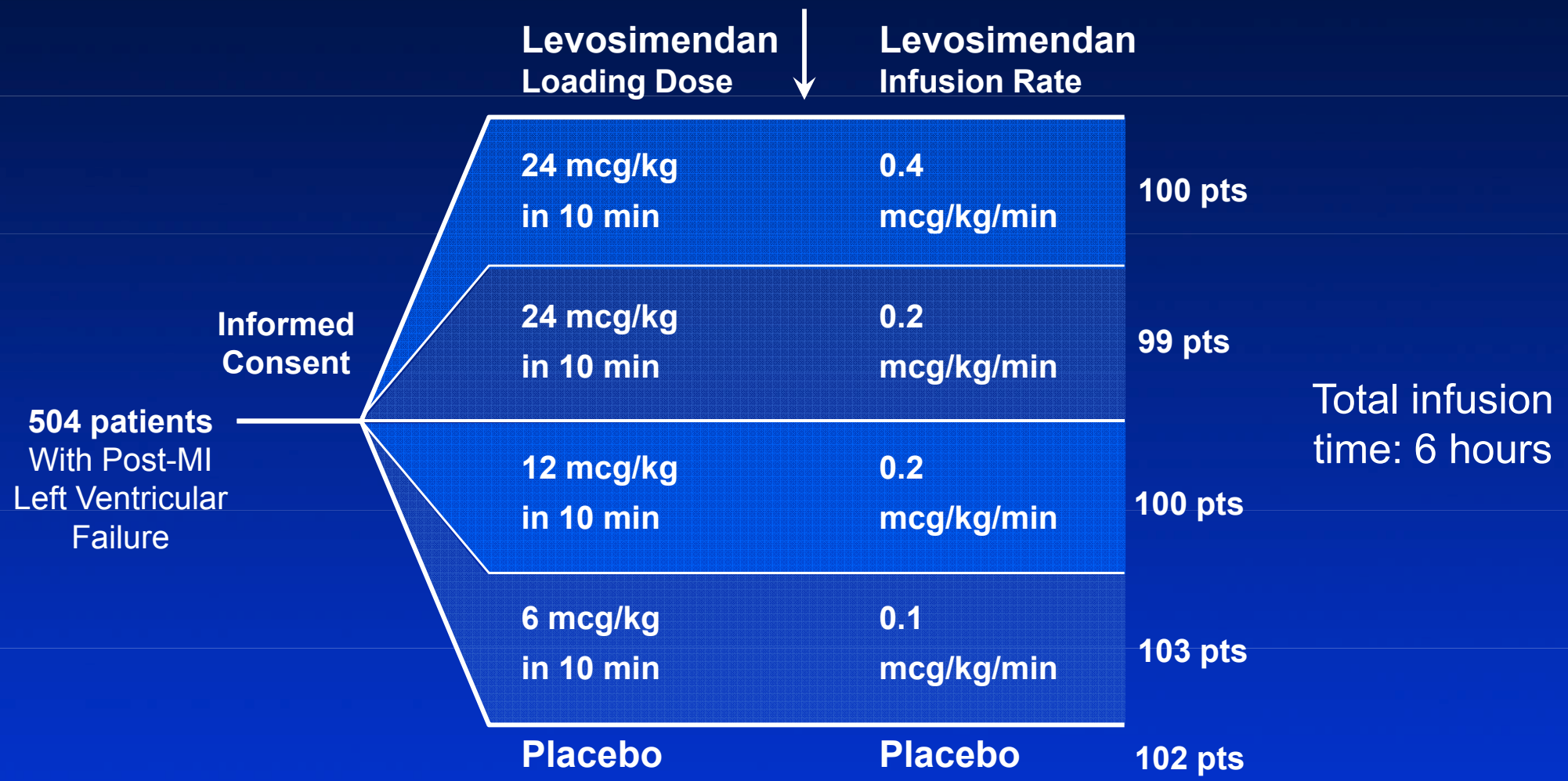


Levosimendan Early Clinical Development

	Study population	Number of patients	NYHA class	Comparator
Dose-Ranging	CHF (ischemic origin)	151	II-IV	Placebo/ Dobutamine
Dose-Escalation	ADHF (LV-systolic dys.)	146	III-IV	Placebo
RUSSLAN	LV failure (post-AMI)	504	III-IV	Placebo
LIDO	Low-output HF	203	III-IV	Dobutamine

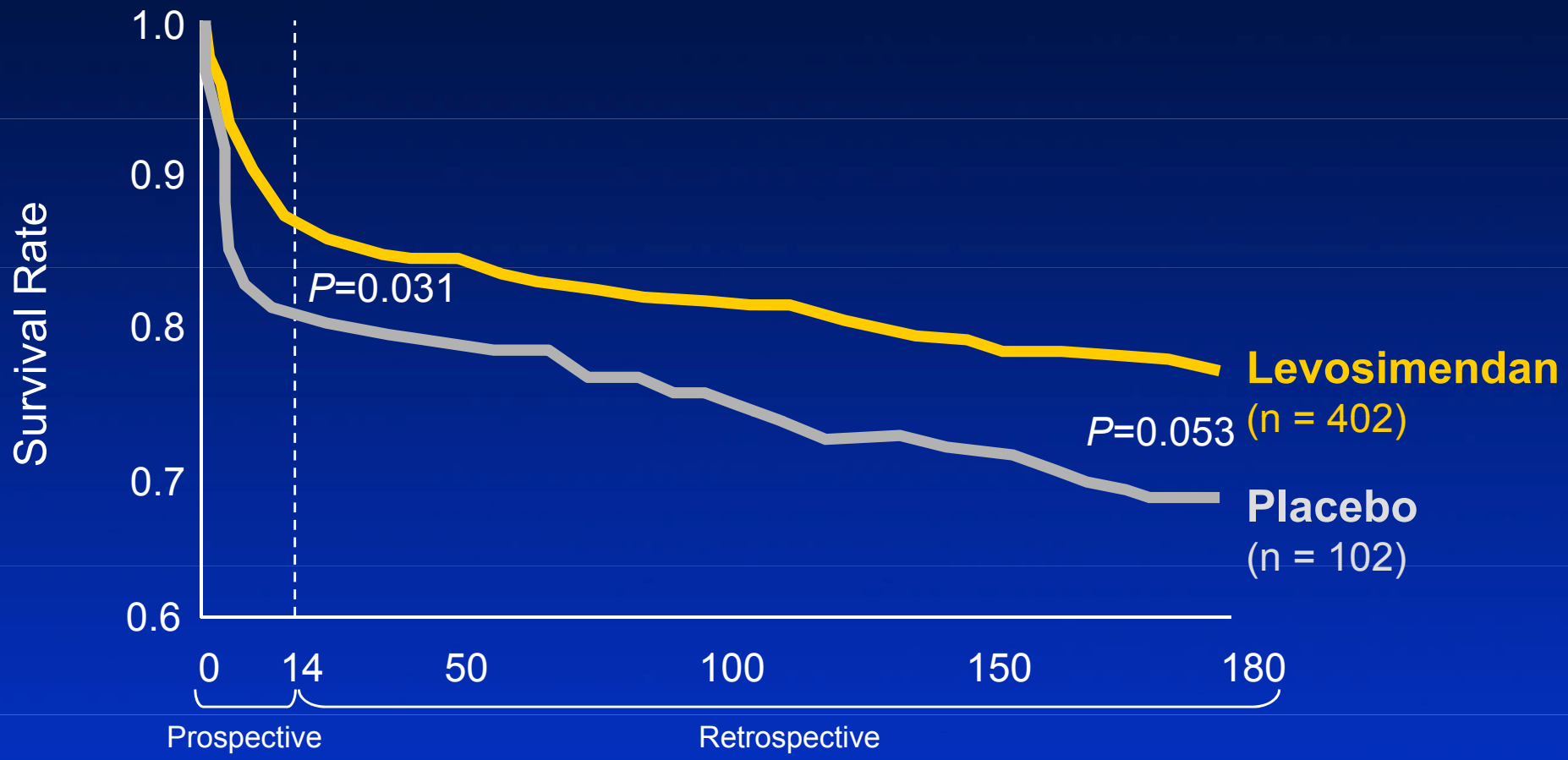
Nieminen MS, et al. *J Am Coll Cardiol*. 2000;36:1903-1912.
Slawsky MT, et al. *Circulation*. 2000;102:2222-2227.
Moiseyev VS, et al. *Eur Heart J*. 2002;23:1422-1432.
Follath F, et al. *Lancet*. 2002;360:196-202.

RUSSLAN Study Design



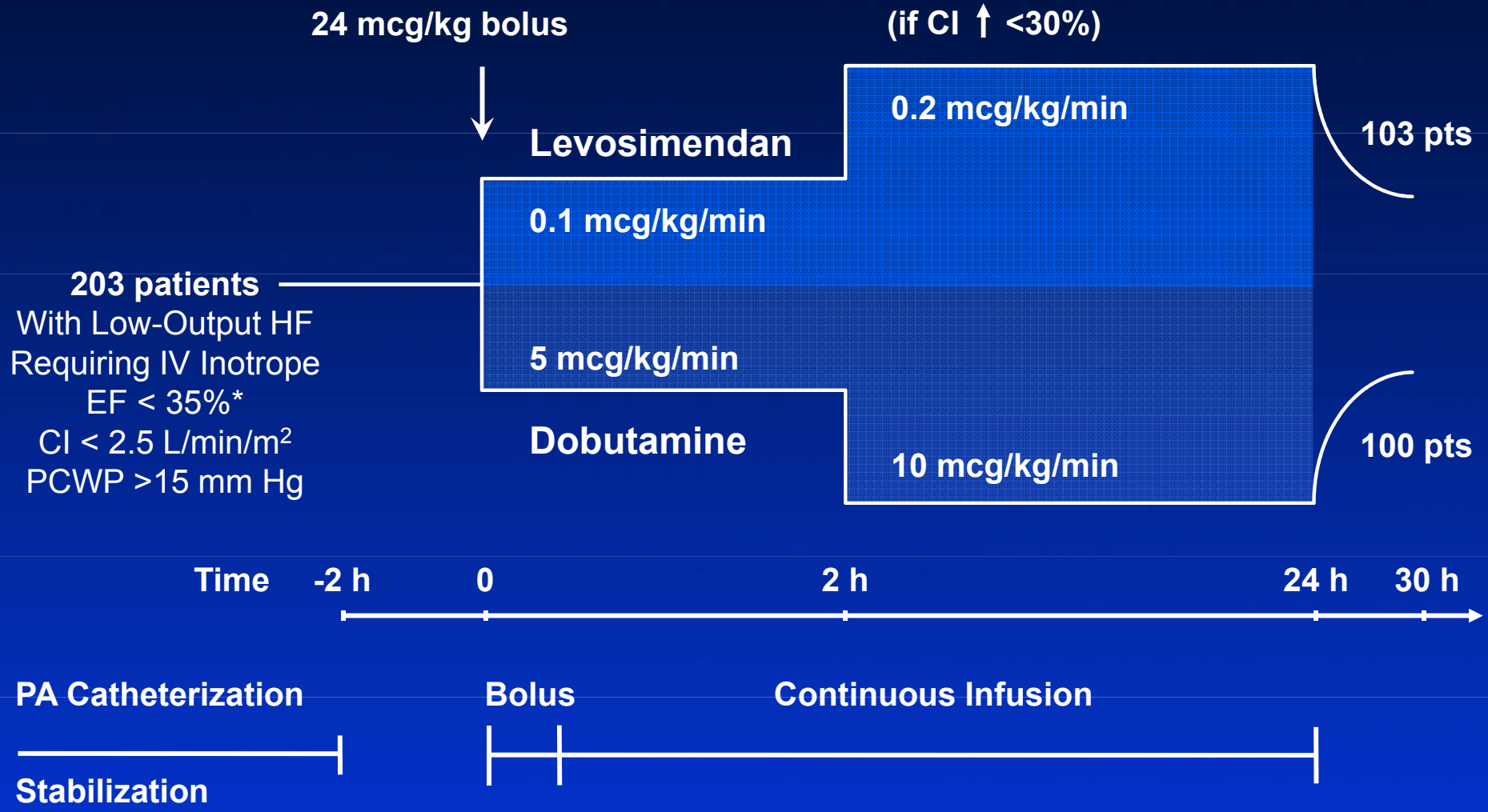
Moiseyev VS, et al. *Eur Heart J*. 2002;23:1422-1432.

RUSSLAN All-Cause Mortality



Moiseyev VS, et al. *Eur Heart J*. 2002;23:1422-1432.

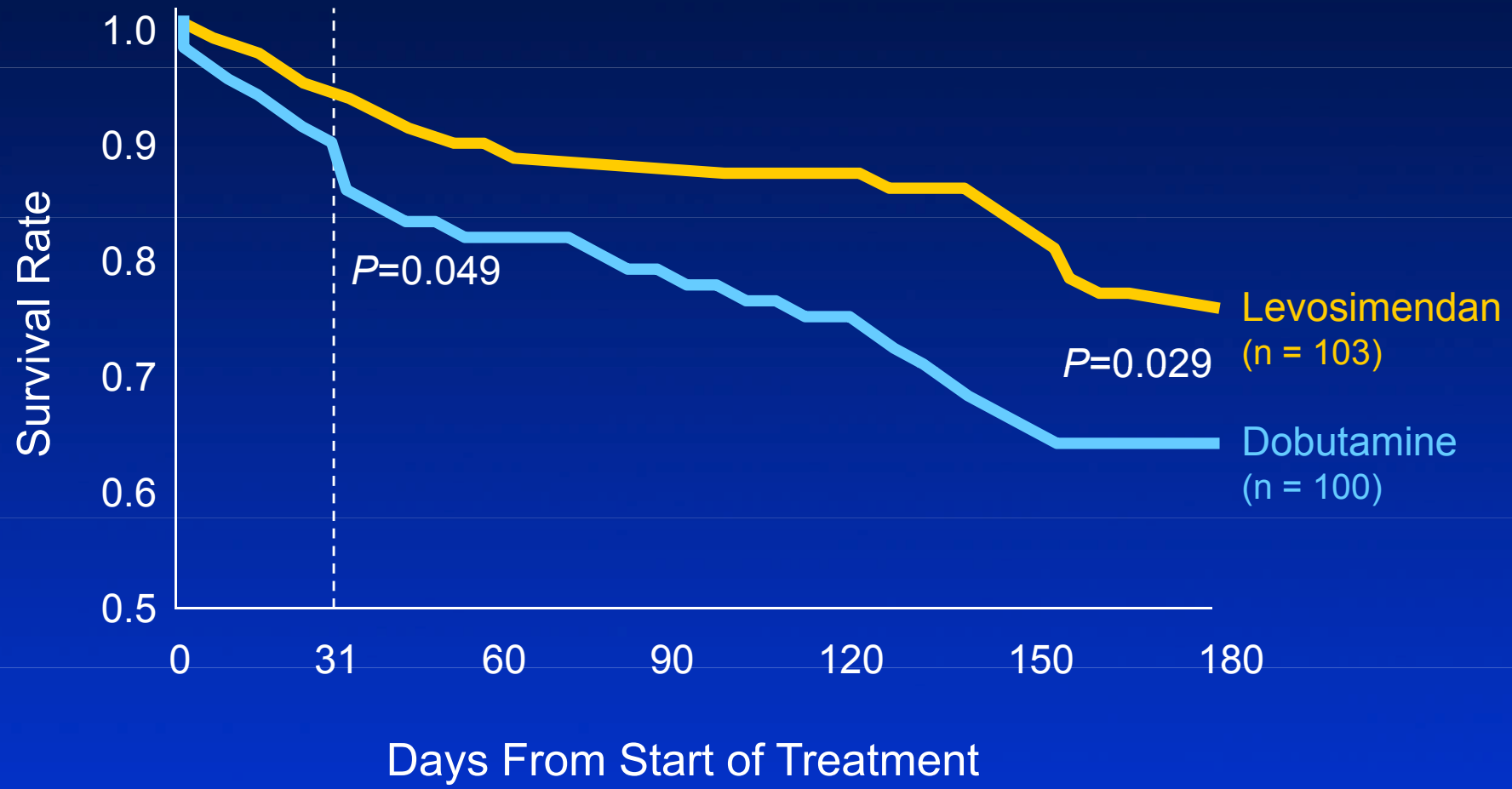
LIDO Study Design



*Within one month of enrollment.

Follath F, et al. *Lancet*. 2002;360:196-202.

LIDO All-Cause Mortality



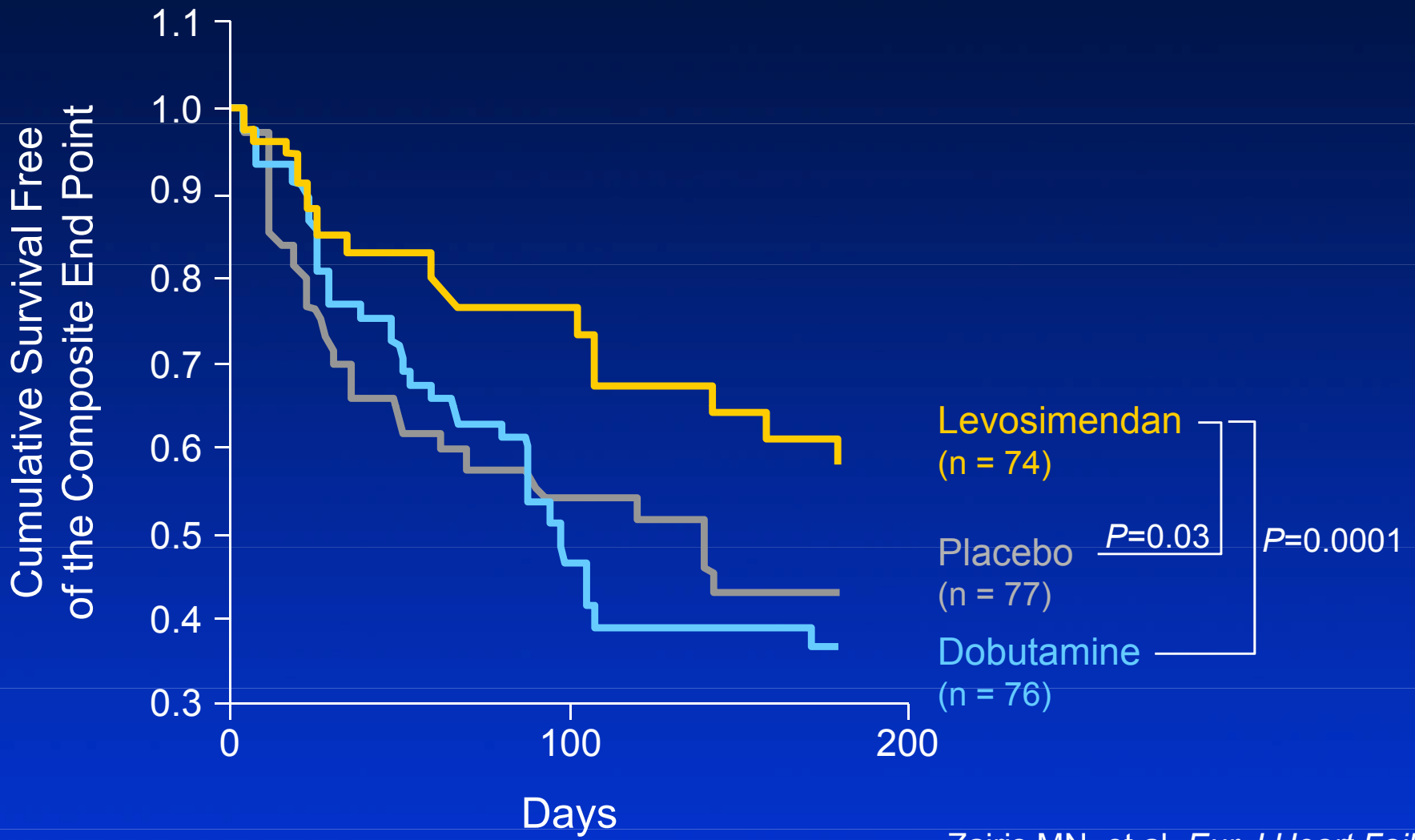
Follath F, et al. *Lancet*. 2002;360:196-202.

CASINO Study

- Purpose was to test effects of levosimendan on long-term prognosis as compared with dobutamine and placebo
- Patients with decompensated low-output chronic heart failure
- Multicenter, randomized, double-blind, double-dummy, placebo-control, parallel-group trial
- Primary end point was the composite of death or rehospitalization due to heart failure deterioration
- Trial was stopped prematurely after 299 patients were enrolled because of a clear mortality benefit in favor of levosimendan

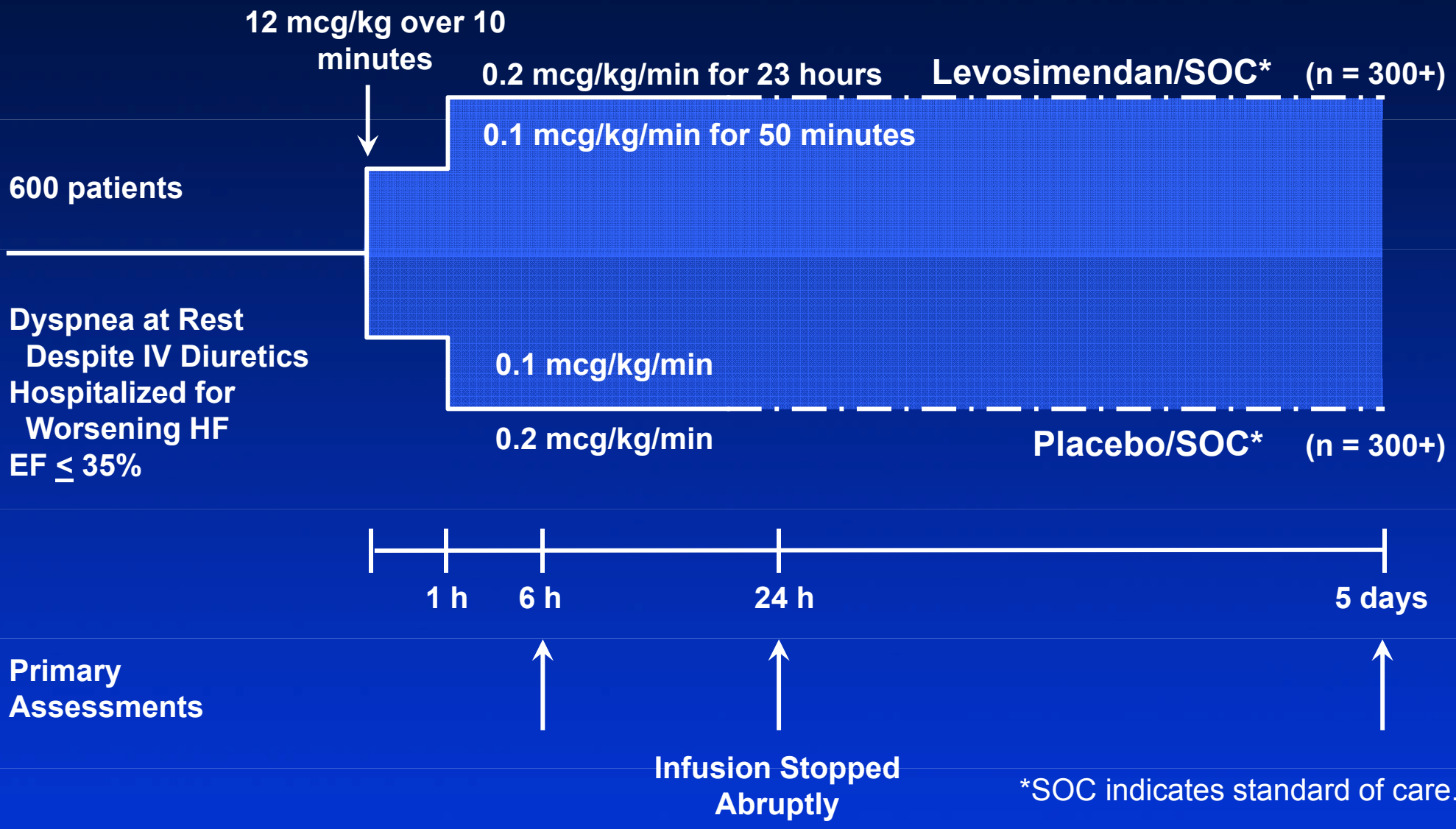
Coletta AP, et al. *Eur J Heart Fail*. 2004;6:673-676.
Zairis MN, et al. *Eur J Heart Fail* 2004;3(suppl 1):66 (abstract 273).

CASINO Study Survival



Zairis MN, et al. *Eur J Heart Fail* 2004;3(suppl 1):66 (abstract 273).

REVIVE II Study Design



*SOC indicates standard of care.

REVIVE II Primary End Point

- Improved
  - If moderate or marked improvement in patient global assessment at each of 6 hours, 24 hours, and 5 days, and not worse at any time within 5 days
- Worse
  - If died or experienced worsening or persistent CHF requiring a rescue therapy for heart failure at any time within 5 days
  - If at least moderate worsening in patient global assessment
- Unchanged
  - If neither improved nor worsened

REVIVE II: Primary Endpoint (n=600)

Duration of Initial Hospitalization

	Levosimendan (n=299)	**Placebo** (n=301)
Days for initial hospitalization		
Mean	7.0 ± 4.6	8.9 ± 8.6
Length of initial hospitalization		
1 to 5 days	129 (45.7%)	108 (37.0%)
6 to 10 days	109 (38.7%)	116 (39.7%)
> 10 days	44 (15.6%)	68 (23.3%)

P=0.006 for REVIVE II

P=0.003 for REVIVE I+II

REVIVE II: Selected Adverse Events

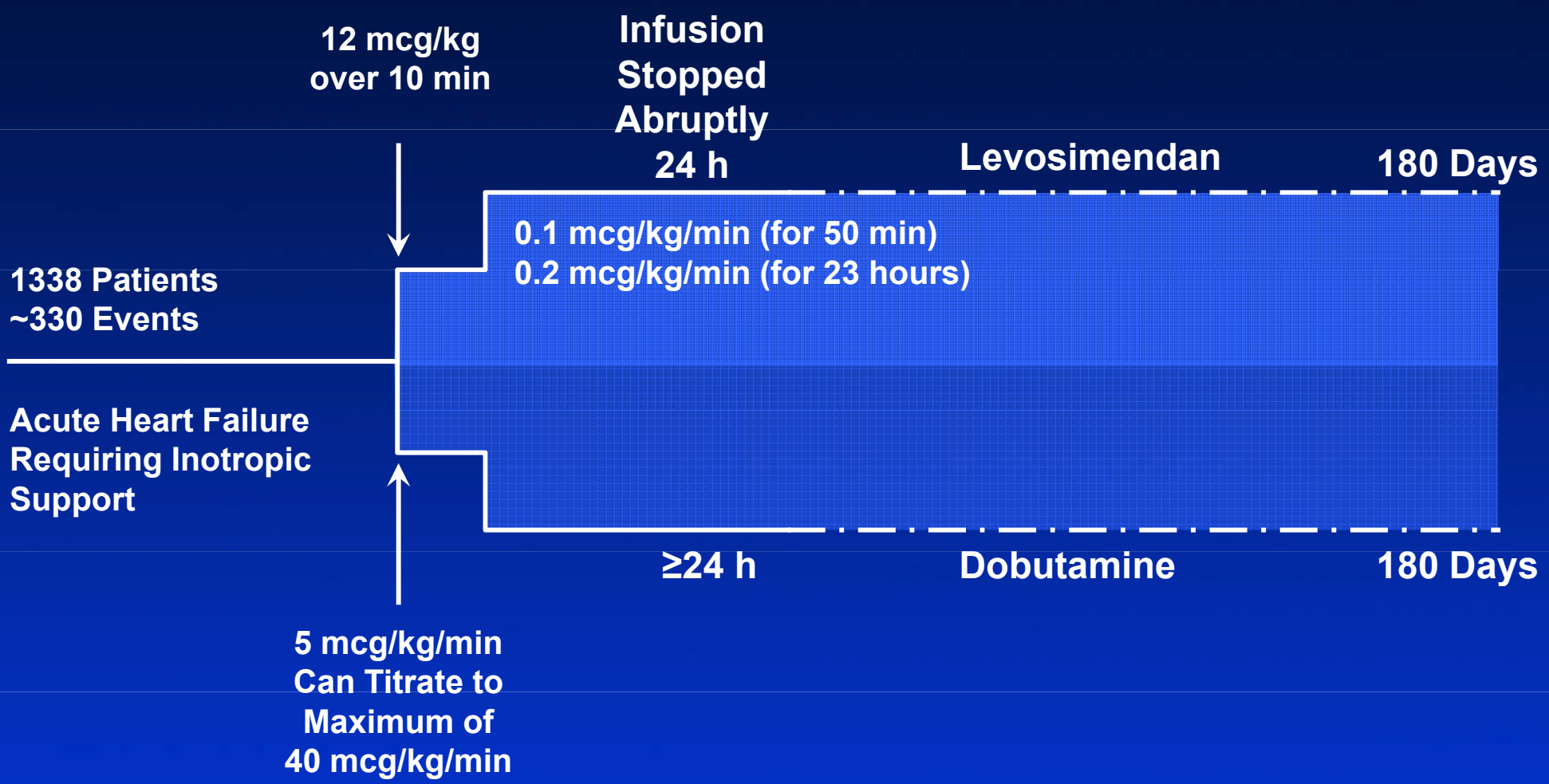
	Placebo	Levosimendan
Hypotension	107	147
Headache	44	88
Ventricular tachycardia	51	72
Cardiac failure	80	67
Atrial fibrillation	6	25
Ventricular extrasystoles	6	22

Table shows number of patients with an event

Effect of Levosimendan on Mortality

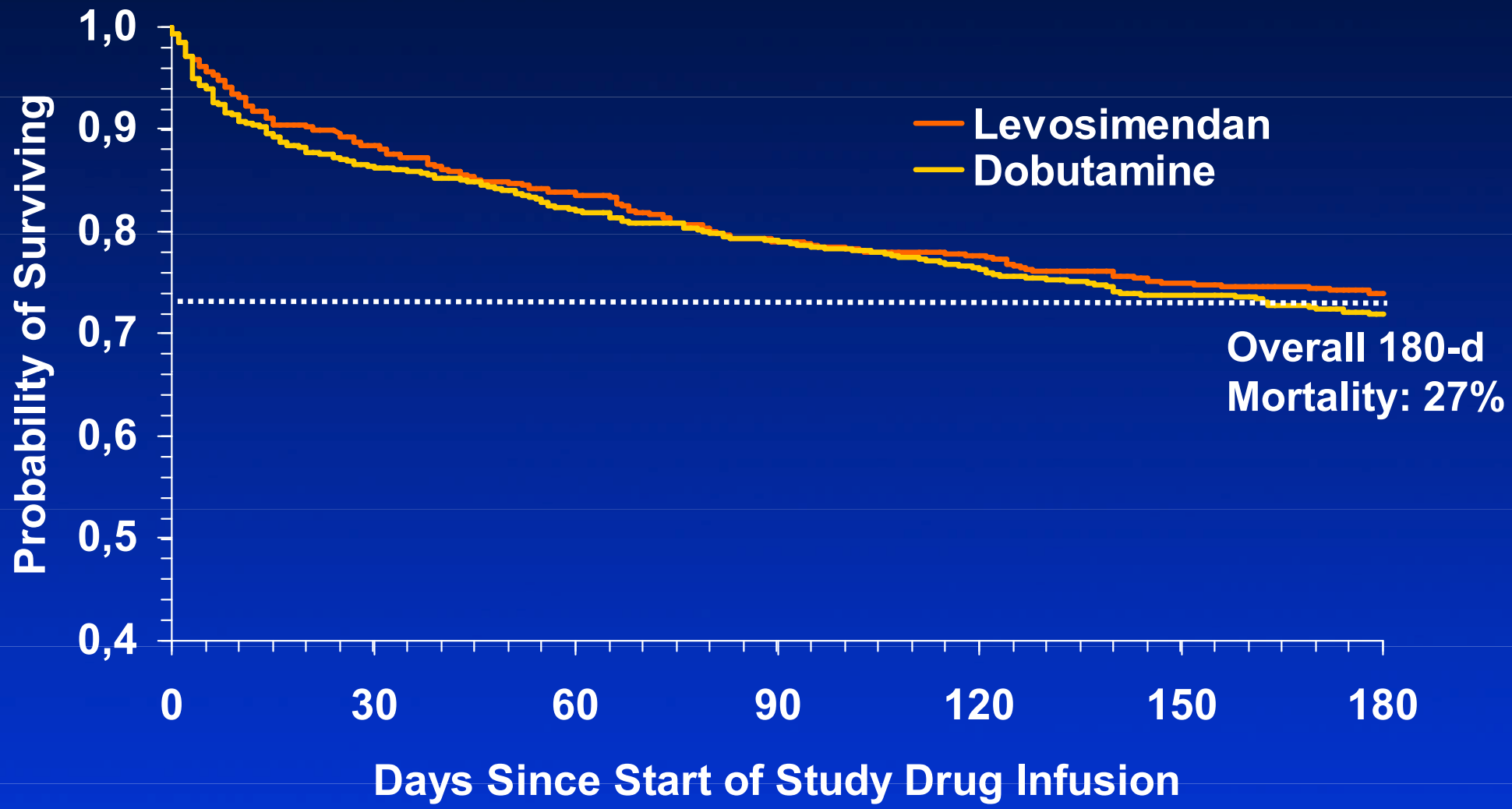
	Days Following Randomization			
	5	**14**	**31**	**90**
REVIVE II				
Placebo	1	5	12	35
Levosimendan	5	14	20	45
REVIVE I				
Placebo	0	1	4	5
Levosimendan	0	1	1	4
REVIVE I + II				
Placebo	1	6	16	40
Levosimendan	5	15	21	49

SURVIVE Study Design

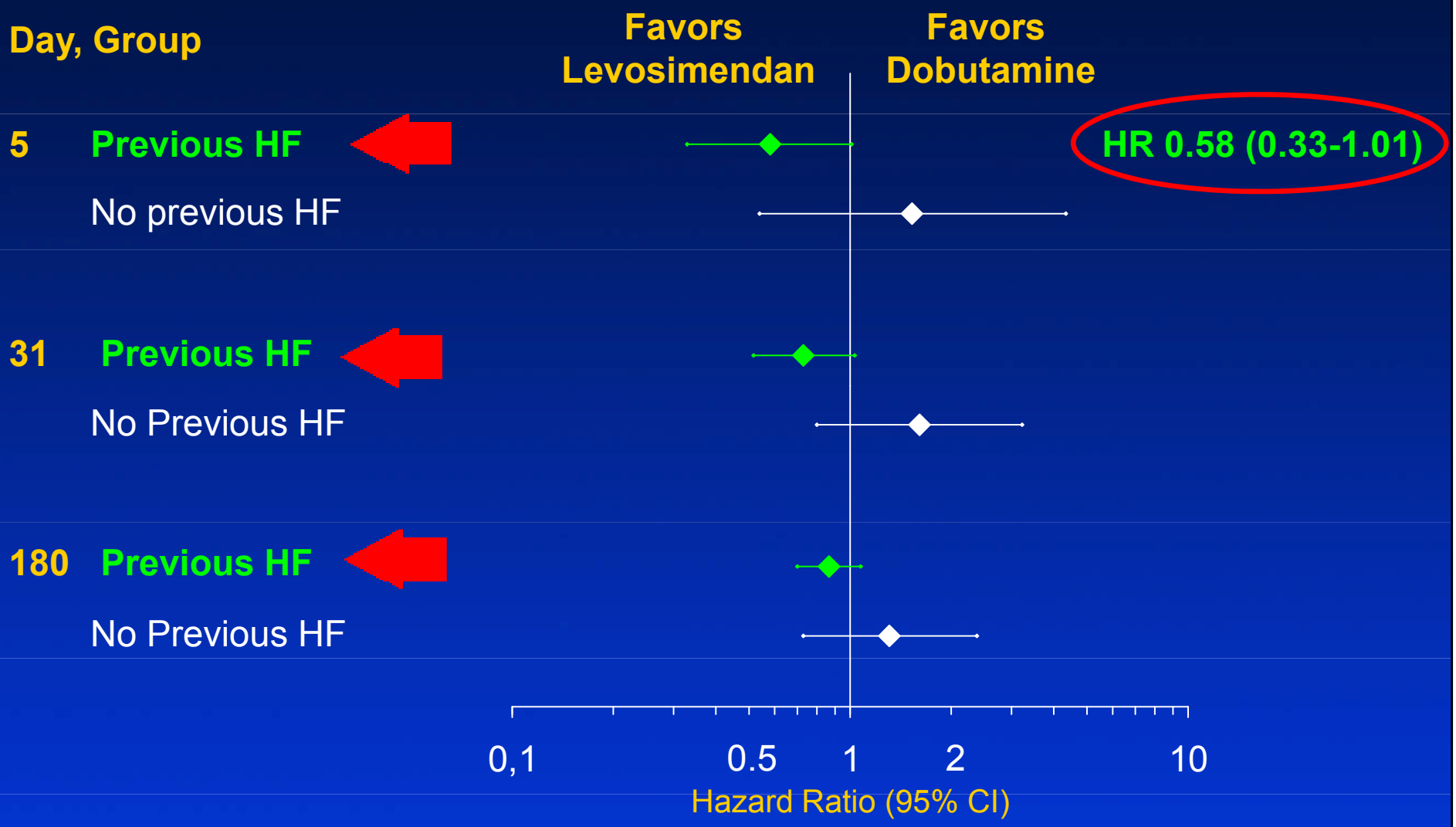


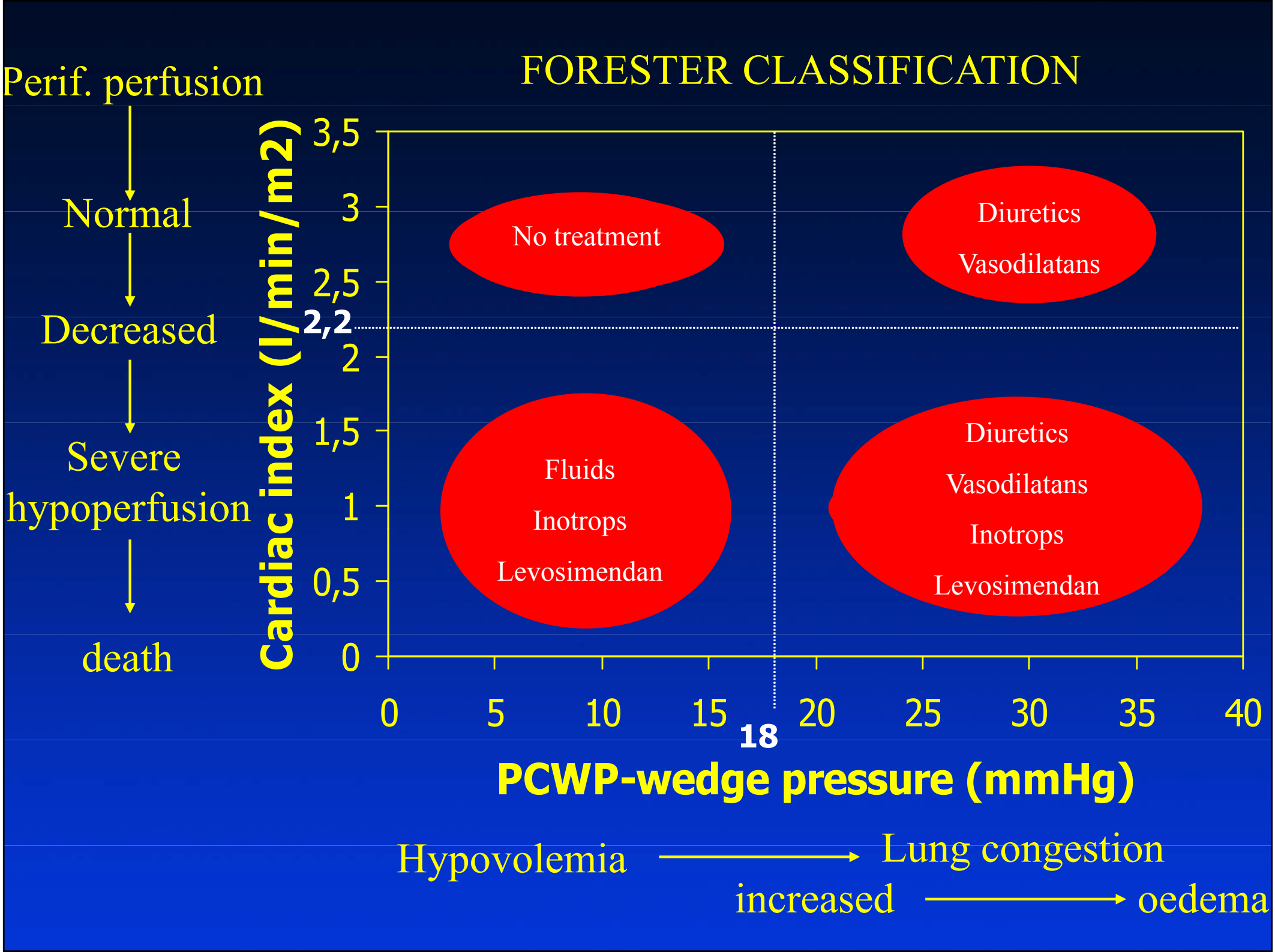
SURVIVE

180-Day All-Cause Mortality



All-Cause Mortality in Patients With / Without Previous HF




FORESTER CLASSIFICATION
Perif. perfusion
Normal
Decreased
Severe hypoperfusion
death
Cardiac index (l/min/m2)
3,5
3
2,5
2,2
2
1,5
1
0,5
0
No treatment
Diuretics
Vasodilatans
Fluids
Inotrops
Levosimendan
Diuretics
Vasodilatans
Inotrops
Levosimendan
0
5
10
15
18
20
25
30
35
40
PCWP-wedge pressure (mmHg)
Hypovolemia
Lung congestion
increased
oedema

THANK YOU FOR YOUR ATTENTION