Comment on RELAX-AHF

Frank Ruschitzka, MD, FESC, FRCP

Professor of Cardiology

Head, Heart Failure and Transplantation

University Hospital Zurich

Zürich, Switzerland

Conflict of interest: Bayer, Biomarin, Biotronik, Cardiorentis, Merck, Novartis, Pfizer

Interest in Conflict: none

Acute Heart Failure – Lessons Learned from ACS

	ACS	AHFS
Incidence	1 million/y	1 million/y
Mortality		
Prehospital	High	?
In-hospital	3%–4%	3%–4%
60–90 d	2%	10%
Targets of therapy	Clearly defined-thrombosis	Unclear
Clinical trial results	Beneficial	Minimal, no benefit, harmful
ACC/AHA Guidelines	Level A	Minimal level A/B, mostly C

Weintraub Circ 2010

Acute Heart Failure – Formerly known as the Bermuda Triangle of Cardiovascular Drugs

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The U.S. Navy and U.S. Coast Guard contend that there are no supernatural explanations for disasters at sea. Their experience suggests that the combined forces of nature and human fallibility outdo even the most incredulous science fiction. They add that no official maps exist that delineate the boundaries of the

Therapies for Acute Heart Failure

	Symptomatic Improvement	HR	Hypotension	LVFP	Cardiac Output	Arrhythmia	Coronary Perfusion	Effect on Viable But Dysfunctional Myocardium	Myocardial Injury (Tn)	Renal Function	Neurohormonal Activation	Effects on Mortality and/or Rehospitalization
Fluid removal												
Diuretics (IV)	Yes	Var	Poss	↓	Var	?	?	?	?	?↓	Yes	?
K-sparing diuretics	Poss	⇔	No	?	?	No	?	?	?	?	? No	↓*
Fluid removal—experimental												
Vasopressin antagonists (orally)	Yes	⇔	No	↓	⇔	No	?	?	?	⇔	?†	⇔
Adenosine antagonists (IV)	?↑	⇔	?	?	?	?	?	?	?	?↑	?	?↓
Vasodilators												
Nitroglycerin (IV)	Yes	Var	Poss	↓	No	No	?↑	?	?	?	?↑	?
Nitroprusside (IV)	Yes	Var	Yes	↓	Var	No	?↓	?	?	?	?	?
Nesiritide (BNP) (IV)	Yes	Var	Poss	↓	No	No	?	?	?	?↓	?	?↑
Enalaprilat (IV)	?	⇔	Poss	↓	No	No	?	?	?	?↓	↓	?
Vasodilators—experimental												
Ularitide (urodilatin)	Poss	⇔	Poss	↓	?↑	?	?	?	?	?⇔	?	?
Relaxin (IV)	?	?	Poss	↓	?	?	?	?	?	?	?	?
Inotropes												
Digoxin (IV)	?	↓	No	↓	↑	No‡	?	?	?	⇔	↓	↓
Dopamine (IV)	?	↑	No	Dose dependent	Dose dependent	Dose dependent	?	?	?	?	?	?
Dobutamine (IV)	? Yes	?↑	Poss	↓	↑	↑	?	?↓ (may cause injury)	Poss	?	?	?↑
Levosimendan (IV)	Yes	↑	Poss	↓	↑	↑	?	?	?	?	?	?↑
Enoximone	Poss	↑	Poss	↓	↑	↑	?	?	?	?	?	?
Milrinone (IV)	⇔	↑	Poss	↓	↑	↑	?	?	?	?	?	?↑ in CAD
Inotropes—experimental												
Cardiac myosin activators	?	?	?	?	↑	?	?	?	?	?	?	?
Istaroxime	?	↓	No	↓	↑	May	?	?	?	⇔	No	?
Endothelin antagonists												
Tezosentan	⇔	⇔	Yes	↓	↑	No	?	?	?	⇔	?	⇔

Gheorgiade JACC 2009

Therapies for Acute Heart Failure

	Symptomatic Improvement	HR	Hypotension	LVFP	Cardiac Output	Arrhythmia	Coronary Perfusion	Effect on Viable But Dysfunctional Myocardium	Myocardial Injury (Tn)	Renal Function	Neurohormonal Activation	Effects on Mortality and/or Rehospitalization
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Inotropes												
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Enoximone	Poss	↑	Poss	↓	↑	↑	?	?	?	?	?	?
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Endothelin antagonists												
Tezosentan	⇔	⇔	Yes	↓	↑	No	?	?	?	⇔	?	⇔

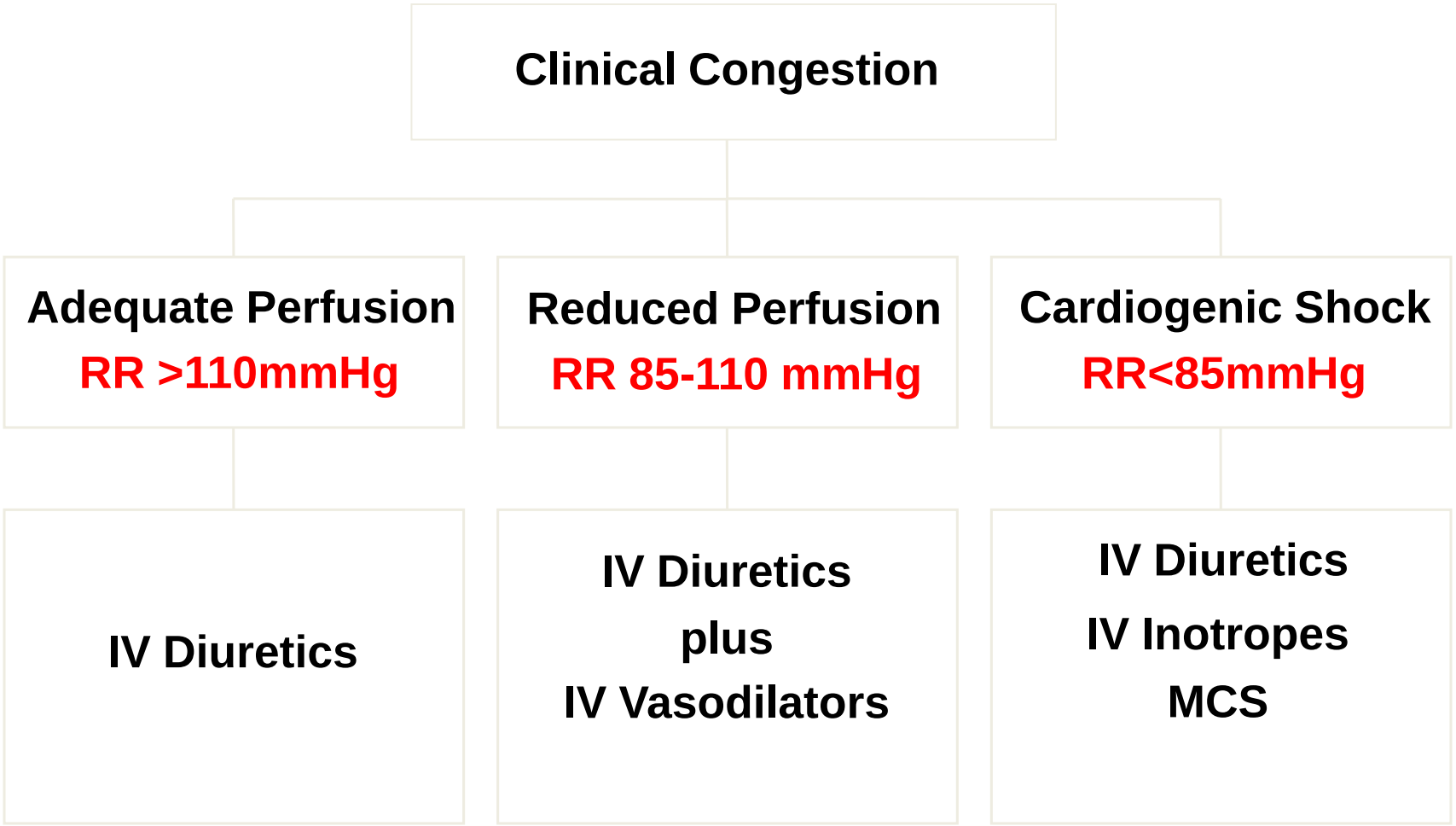
Gheorgiade JACC 2009

What Do Our ESC Heart Failure Guidelines say?

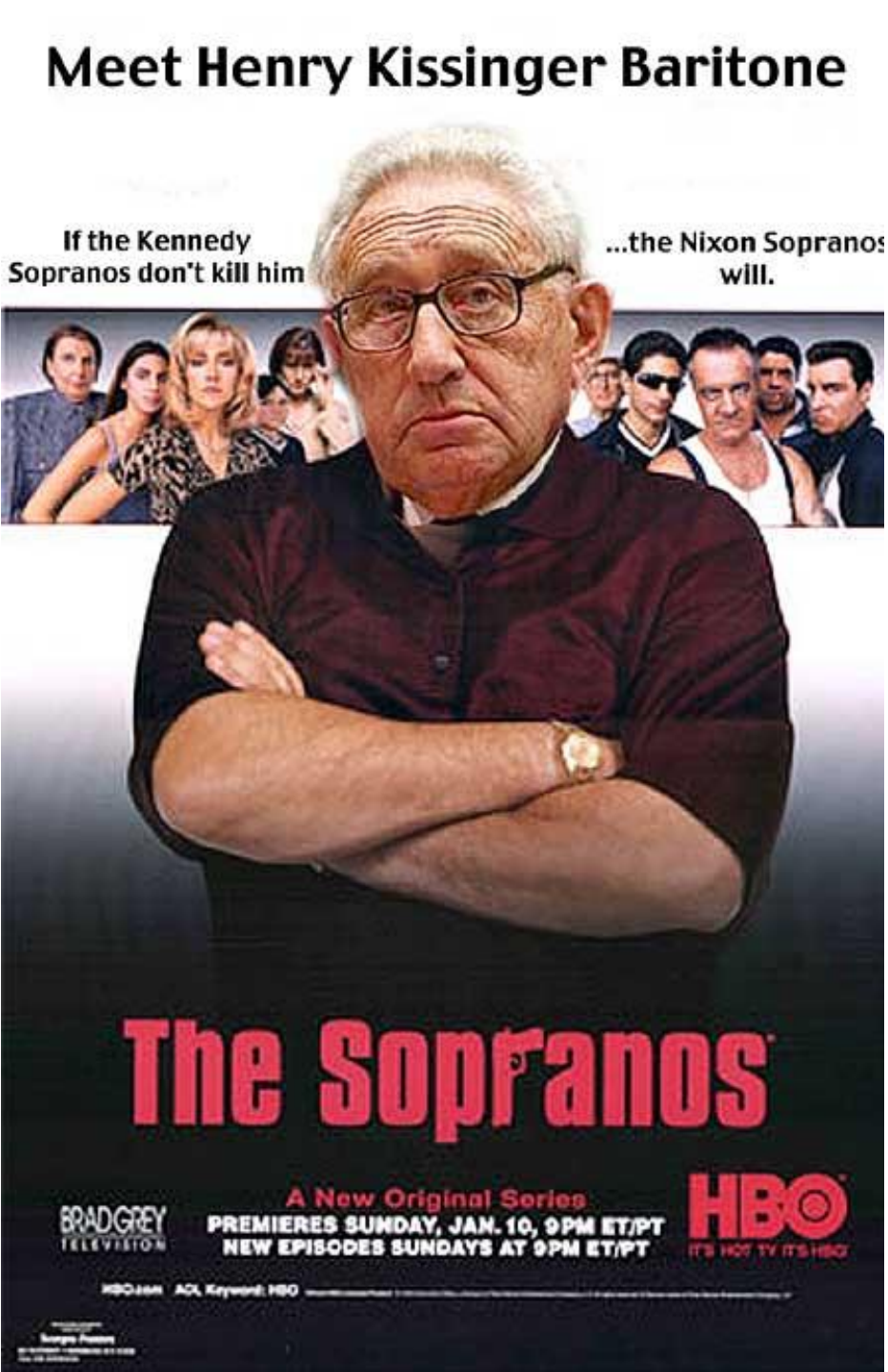
Recommendations	Class[a]	Level[b]	Ref[c]
Patients with pulmonary congestion/oedema without shock			
An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.	I	B	213
An i.v. infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.	IIa	B	218, 219
An i.v. infusion of sodium nitroprusside may be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Caution is recommended in patients with acute myocardial infarction. Nitroprusside may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitroprusside.	IIb	B	220
Inotropic agents are NOT recommended unless the patient is hypotensive (systolic blood pressure <85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischaemia, and death).	III	C	–

JJ McMurray EHJ 2012

Approach to Acute Therapy in Volume Overloaded Heart Failure Patients



mod. JJ McMurray EHJ 2012



The absence of alternatives clears the mind marvelously

Henry Kissinger (1923 -)

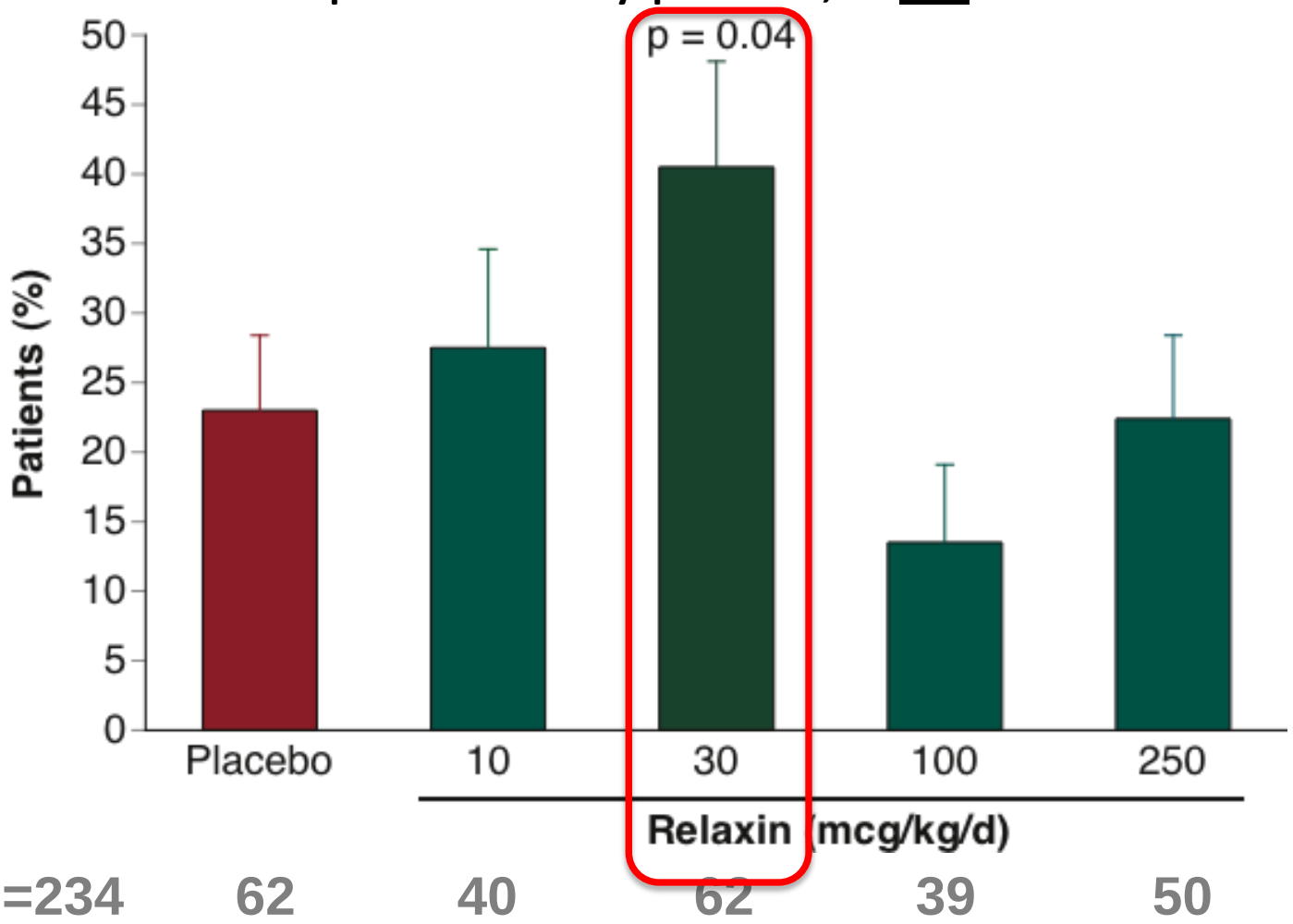
The Ideal Drug in Acute Heart Failure

1. Improve signs and symptoms (e.g. dyspnoea)
2. Improve haemodynamics without adversely effecting heart rate and blood pressure
3. Improve the neurohumoral profile
4. Do not cause myocardial and/or kidney damage
5. Be effective in the context of current evidence-based therapy such as ACE-I and beta-blockers
6. Demonstrate efficacy in both the acute and chronic setting
7. Be affordable
8. Reduce both in-hospital and post-discharge morbidity and mortality.

Pang EHJ 2010

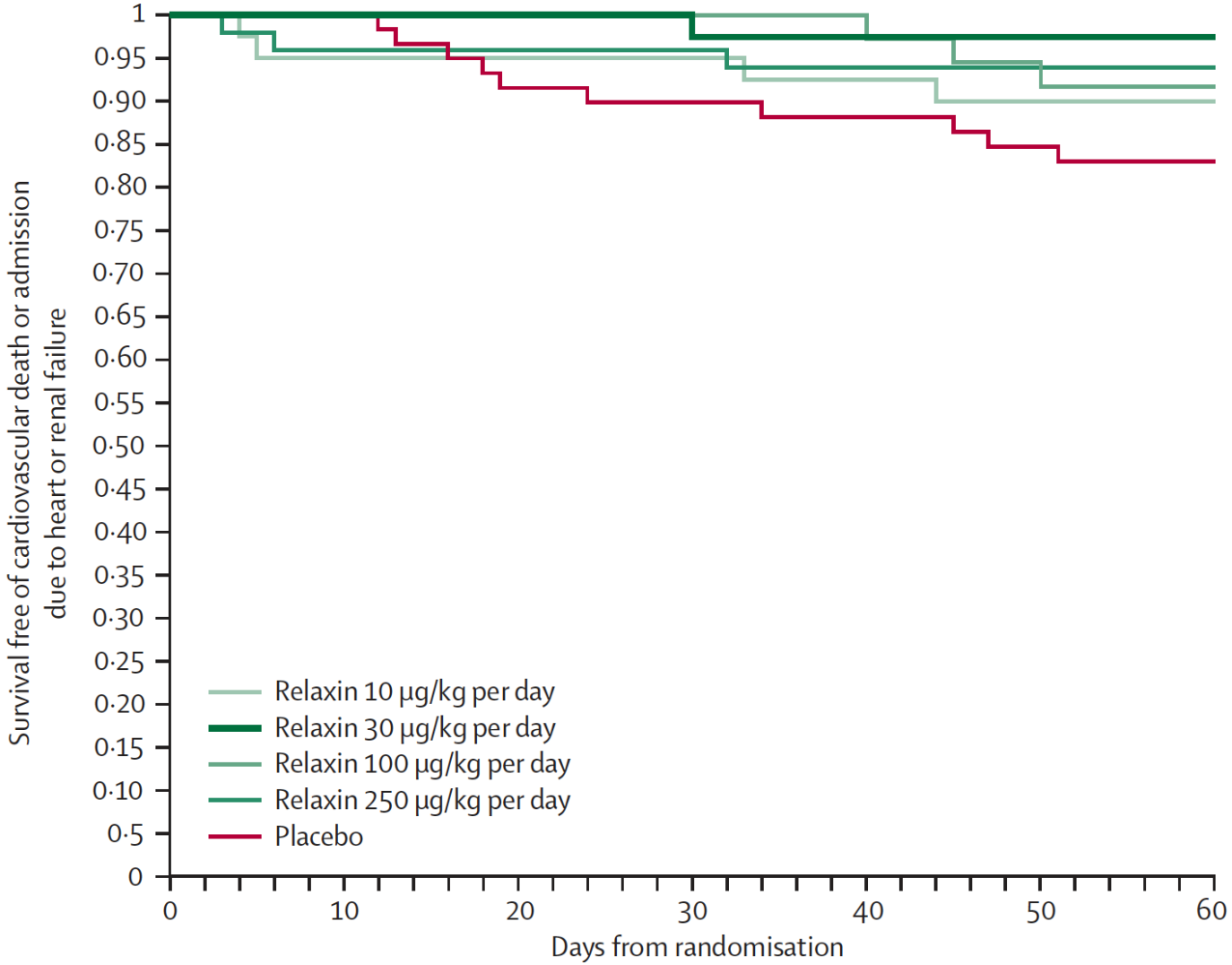
Pre-RELAX-AHF: Dyspnea Improvement through 24 hours (Likert Scale)

Proportion of Patients with Moderate/Marked Improvement in Dyspnea at 6, 12 and 24 hr



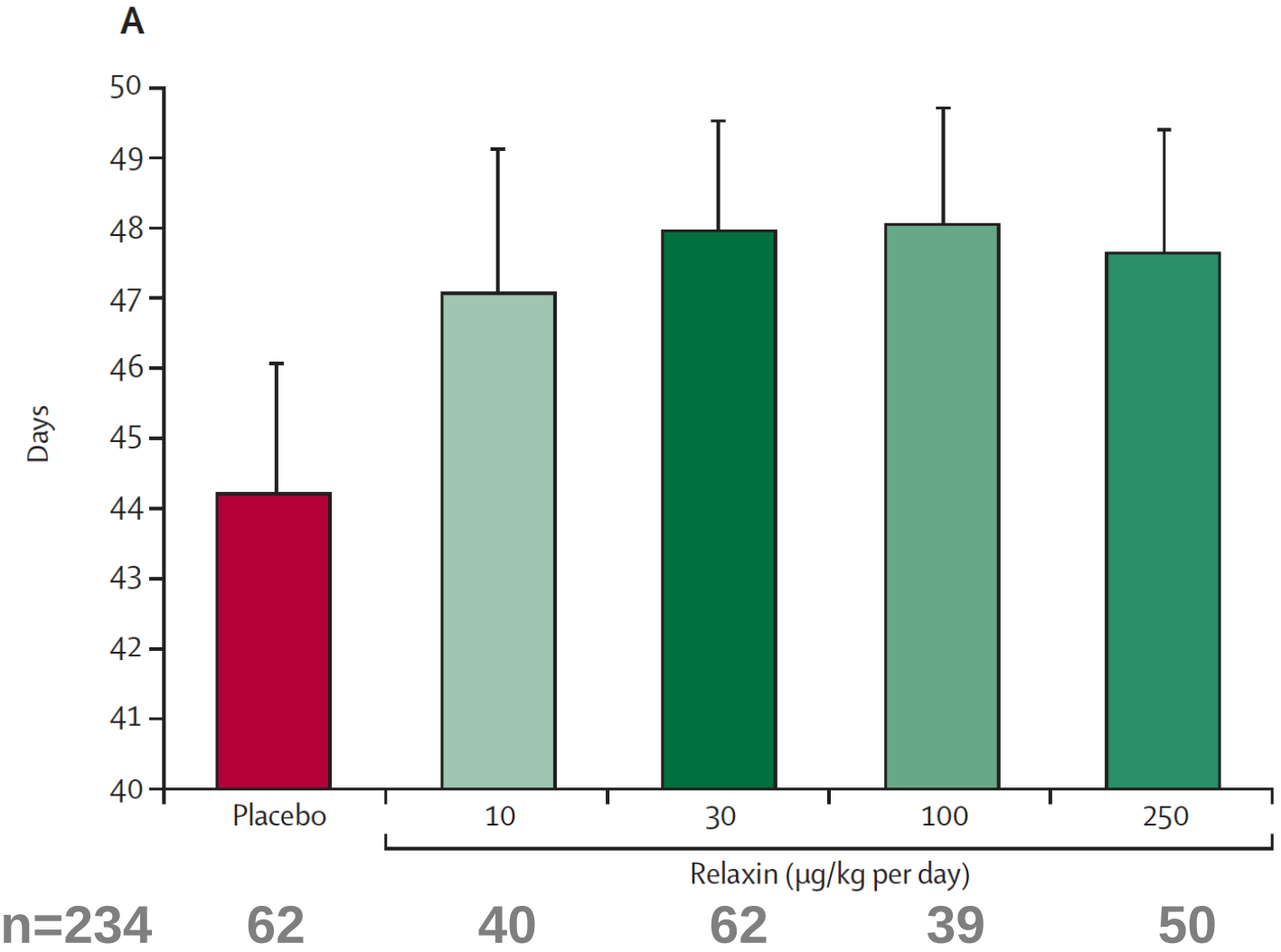
Teerlink Lancet 2009

Survival free of CV Death or Heart/Renal Failure Re-hospitalizations to Day 60



Teerlink Lancet 2009

Days alive and out of hospital from baseline to day 60



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RELAX-AHF: Primary and Secondary Endpoints

I. Primary efficacy endpoints:

(1) change in patient-reported dyspnoea from baseline to day 5 (VAS)

(2) moderately or markedly improved patient-reported dyspnoea relative to the start of study drug

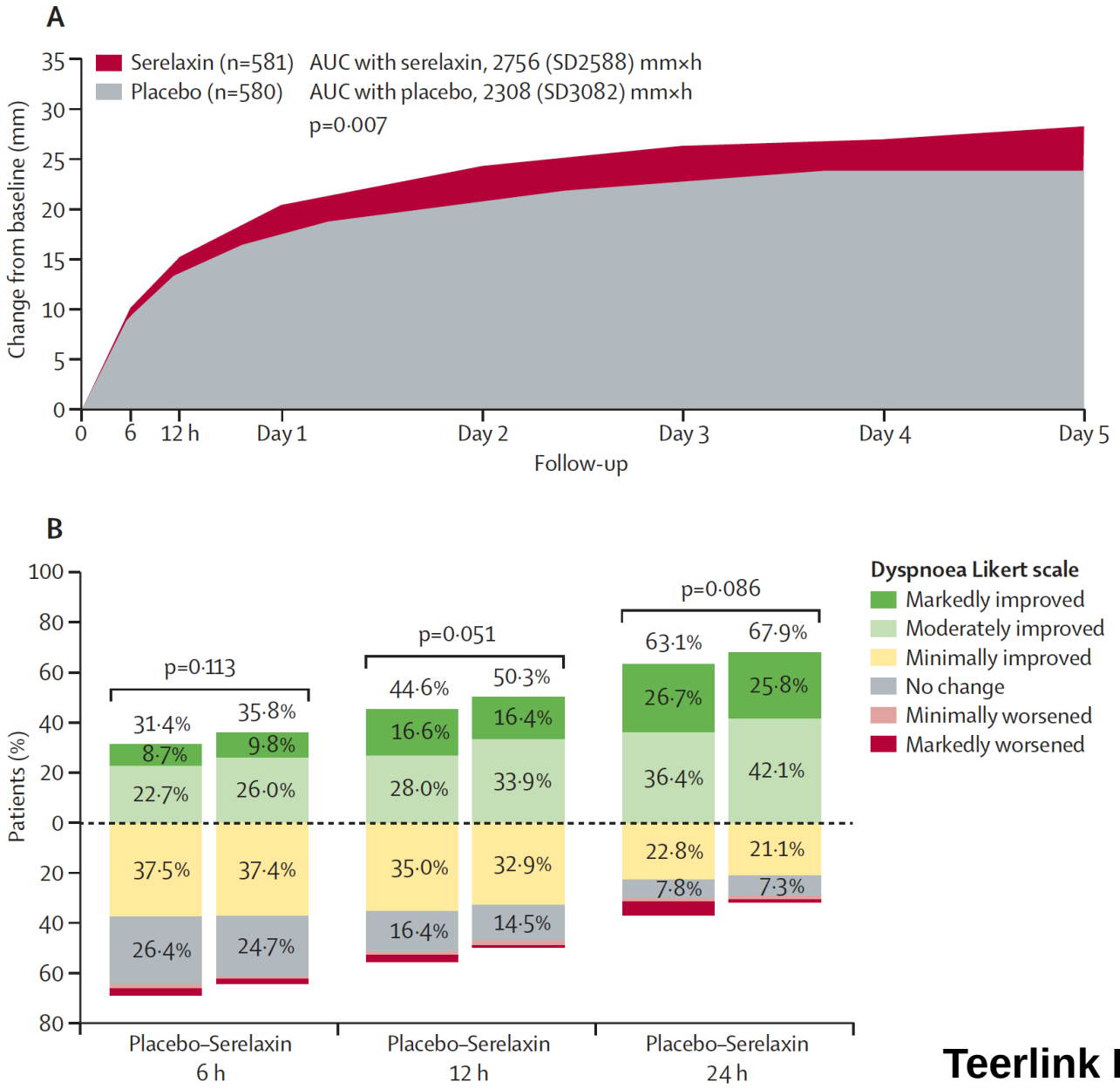
II. Secondary efficacy endpoints:

(1) days alive and out of the hospital to day 60 and

(2) cardiovascular death or readmission to hospital before day 60 (for heart failure or renal failure)

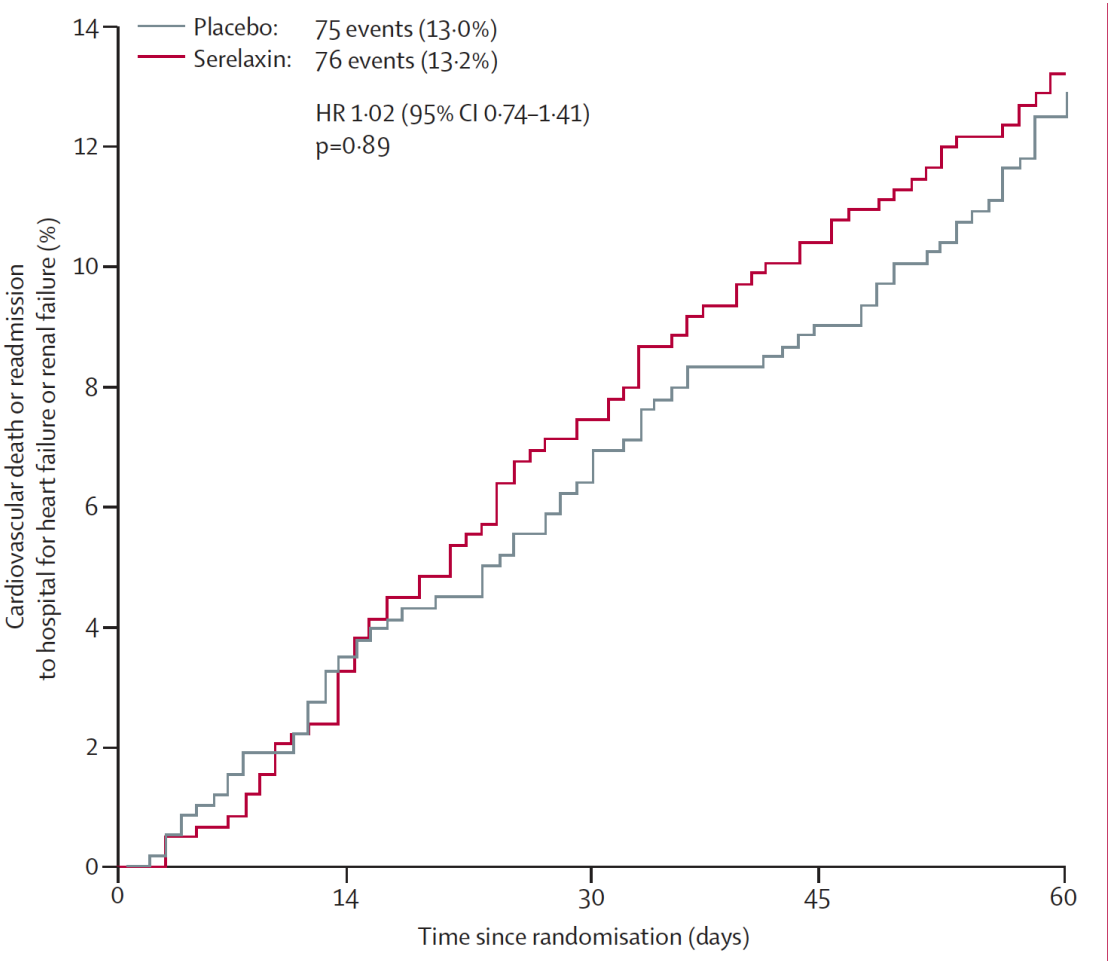
Teerlink Lancet 2012

RELAX-AHF: Patient reported Dyspnea



Teerlink Lancet 2012

RELAX-AHF: CV death or readmission to hospital for heart or renal failure during 60-day follow-up

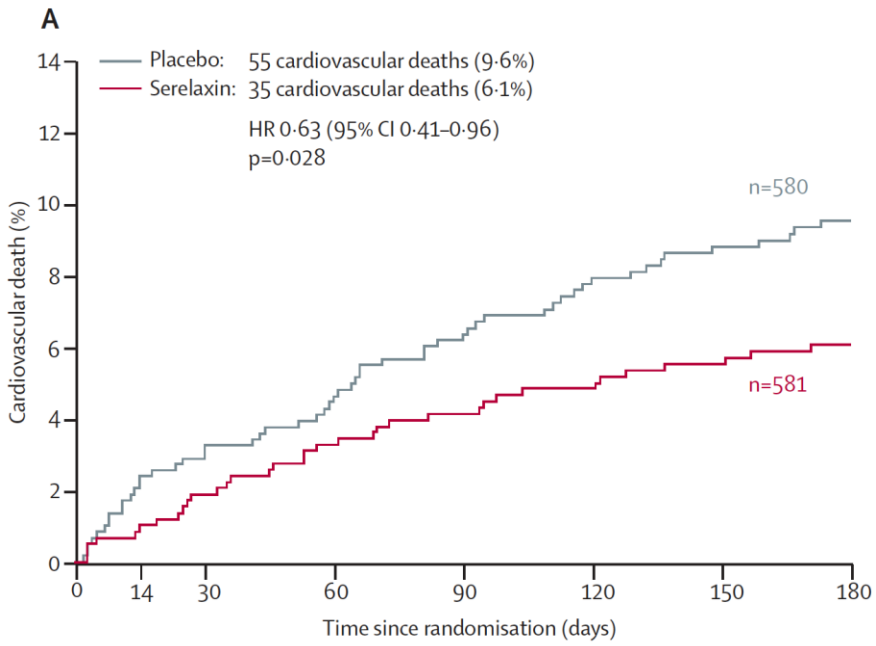


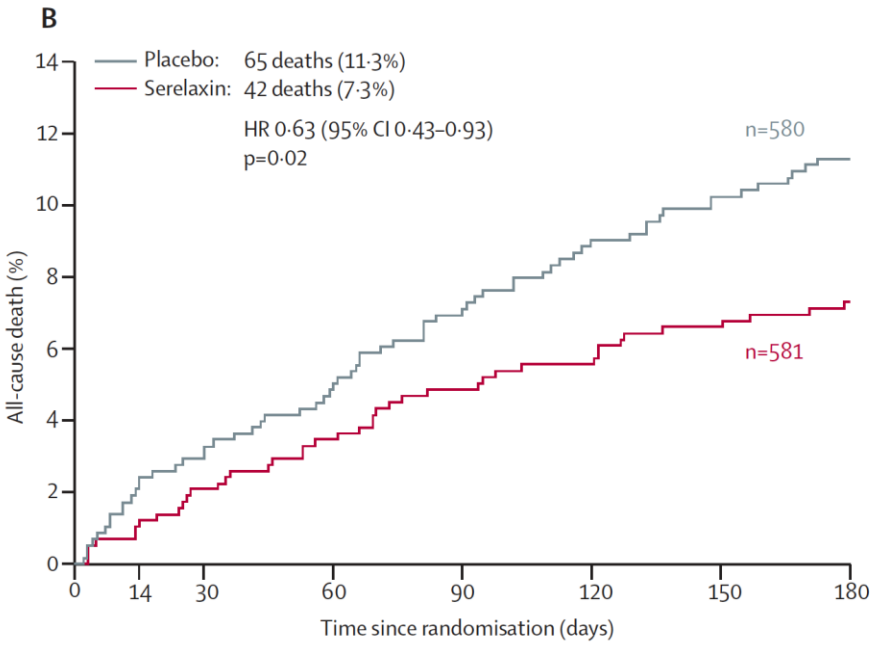
Number at risk

Placebo	580	559	539	522	501
Serelaxin	581	563	531	514	498

Teerlink Lancet 2012

RELAX-AHF: Cardiovascular and All-Cause Death





Number at risk

Placebo	580	567	559	547	535	523	514	444
Serelaxin	581	573	563	555	546	542	536	463

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Teerlink Lancet 2012

RELAX-AHF: Cardiovascular and All-Cause Death

	Placebo	Serelaxin	Treatment effect (95% CI)	p value
Study day of moderately or markedly improved dyspnoea before day 5**	1·9 (2·1)	1·5 (1·9)	−0·4 (−0·6, −0·2)*	0·002‖
Study day of worsening heart failure before day 5††	5·5 (1·4)	5·8 (0·9)	0·3 (0·1, 0·4)*	0·0009‖
Worsening heart failure before 14 days	91 (KM 15·7%)	66 (KM 11·4%)	0·70 (0·51, 0·96)‡‡	0·024§§
Total intravenous loop diuretic dose before day 5 (mg)¶¶	213 (358)	161 (265)	−52 (−88, −15)*	0·006†
Total oral loop diuretic dose before day 5 (mg)††	183 (189)	193 (195)	10 (−12, 32)*	0·382†
Change in bodyweight from baseline (kg)				
Day 1	−1·4 (1·9)	−1·5 (2·1)	−0·1 (−0·3, 0·2)*	0·540†
Day 2	−2·1 (2·3)	−2·0 (2·6)	0·1 (−0·2, 0·4)*	0·567†
Day 5	−3·0 (3·3)	−2·7 (3·4)	0·3 (−0·1, 0·7)*	0·167†
Day 14	−3·6 (4·4)	−3·0 (4·1)	0·6 (0·1, 1·1)*	0·023†
Length of initial hospital stay (days)	10·5 (9·6)	9·6 (9·1)	−0·9 (−1·9, 0·2)*	0·039‖
All-cause death or readmission to hospital for heart or renal failure before day 60	77 (KM 13·4%)	77 (KM 13·4%)	1·01 (0·74, 1·38)‡‡	0·959§§
Days alive out of hospital before day 30	20·4 (6·83)	20·9 (6·44)	0·5 (−0·3, 1·3)*	0·293‖
Cardiovascular death before day 180‖‖	55 (KM 9·6%)	35 (KM 6·1%)	0·63 (0·41, 0·96)‡‡	0·028§§
Days in intensive care unit or cardiac care unit	3·9 (7·0)	3·5 (7·1)	−0·3 (−1·1, 0·5)*	0·029‖

Teerlink Lancet 2012

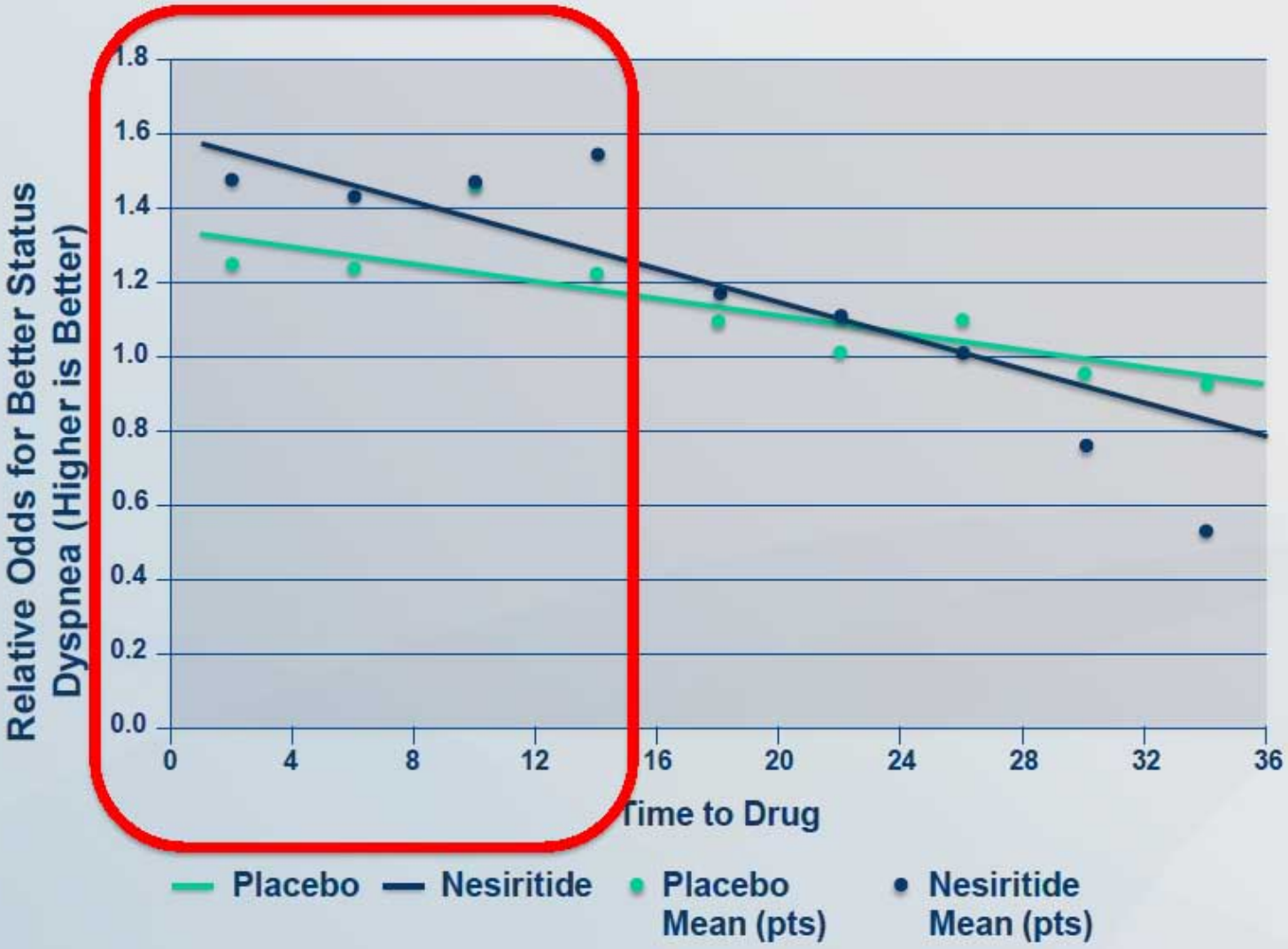
RELAX-AHF: Baseline Characteristics

	Placebo (n=580)	Serelaxin (n=581)
Intravenous loop diuretic	580 (100%)	578 (99%)
Time from presentation to randomisation (h)	7·9 (4·7)	7·8 (4·6)
Intravenous nitrates at randomisation	42 (7%)	39 (7%)
NT-proBNP (ng/L)	5003 (4633–5404)	5125 (4772–5506)
Troponin T (µg/L)	0·036 (0·034–0·039)	0·034 (0·032–0·037)
eGFR (mL/min per 1·73 m²)†	53·3 (12·9)	53·7 (13·1)

Teerlink Lancet 2012

Estimate of effect of nesiritide on 6 hour dyspnea relief based on time from presentation to study drug

ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure



Chi-square for treatment = 9.66 for 2 d.o.f., p = 0.0080

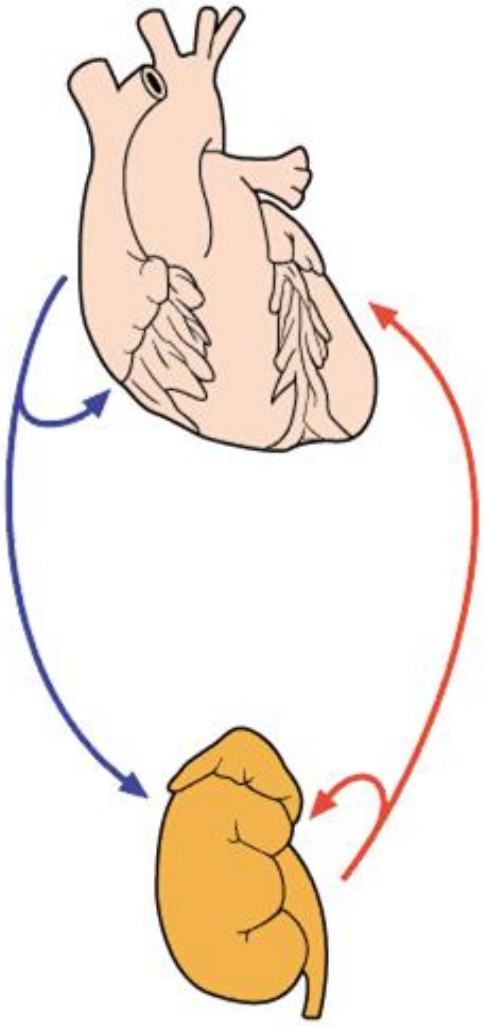
ASCEND: Symptoms and Clinical Outcomes by Time to Start Therapy

Post hoc ASCEND-HF analysis: Symptom and clinical outcomes by time to start of therapy

End point	Treatment started <15.5 h, n=3493	Treatment started >15.5 h, n=3514
% with marked improvement in		
Dyspnea at 6 h	16	12
Dyspnea at 24 h	32	25
"Well-being" at 6 h	15	10
"Well-being" at 24 h	28	24
Clinical events at 30 days (%)		
Death	3.5	4.2
Death/HF hospitalization	8.5	11.0
Death/all-cause hospitalization	13.4	17.0

Christopher M O'Connor, ESC-HFA Hotline 2011

Urodilatin



- Synthesized in distal tubular cells
- Binds downstream in IMC duct to NPR-A
- Increases Renal Plasma Flow (via cGMP)
- Increases GFR:
  - Dilates Vas afferens
  - Constricts Vas efferens
  - Relaxes mesangials cells
- Decreases sodium reabsorption in PCT and CD via cGMP dependent phosphorylation of ENaC
- Inhibits renin, aldosterone, and vasopressin secretion
- NOT degraded by NEP inhibition

mod. Forssmann Cardiovasc Res 2006

TRUE–AHF: TRial of Ularitide`s EFFICACY IN PATIENTS with ACUTE HEART FAILURE

STUDY DESIGN

Primary Efficacy: Global composite score (superiority)

Primary Safety: All-cause mortality and cardiovascular rehospitalisation and other significant cardiovascular events at 30 days / 3 months (non-inferiority)

Status: ***recruiting***

clinicaltrials.gov

Merci

Frank Ruschitzka, MD, FRCP, FESC

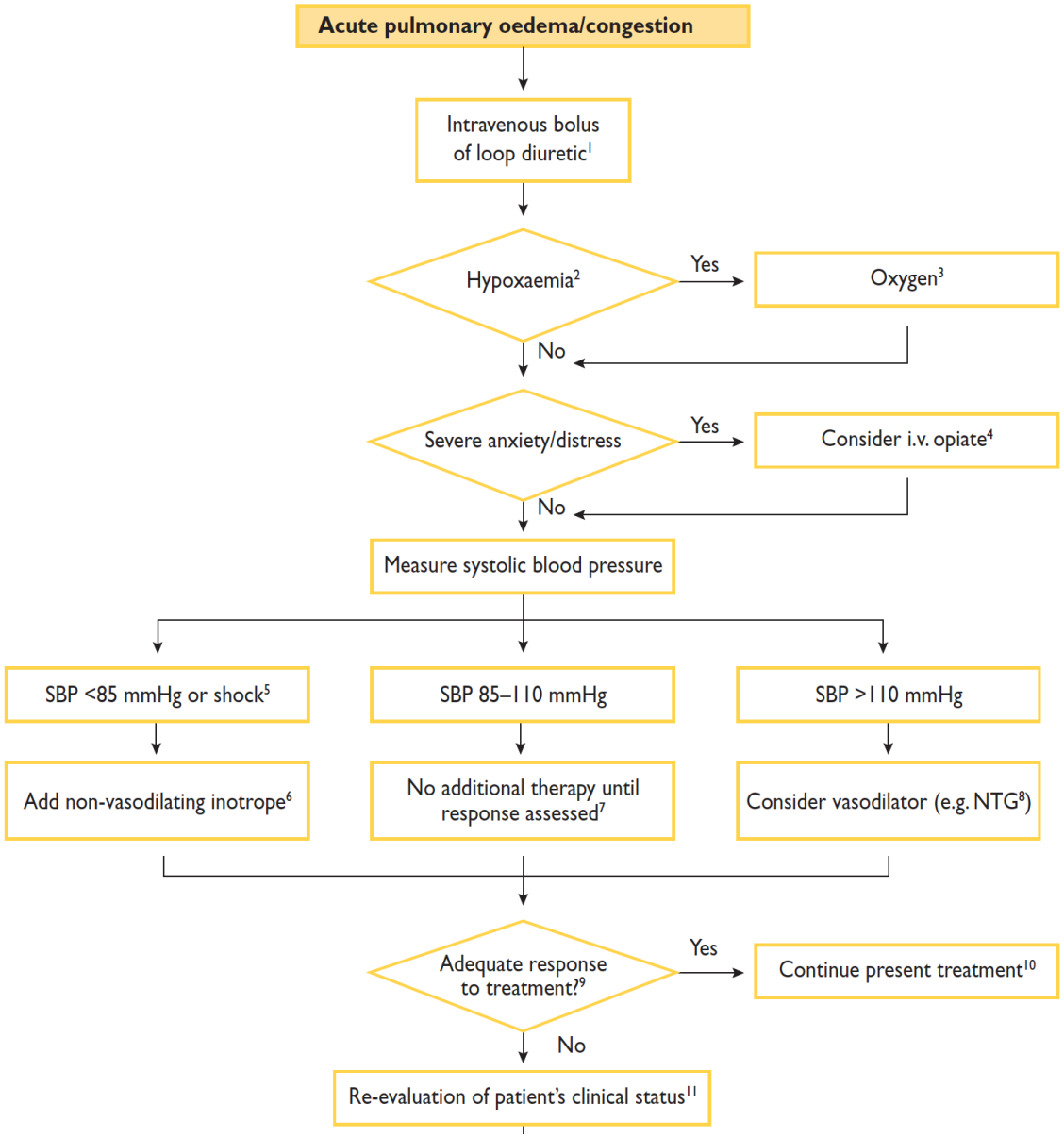
Professor of Cardiology

University Zürich

E-mail: frank.ruschitzka@usz.ch

University Hospital Zurich

Management of Acute Heart Failure



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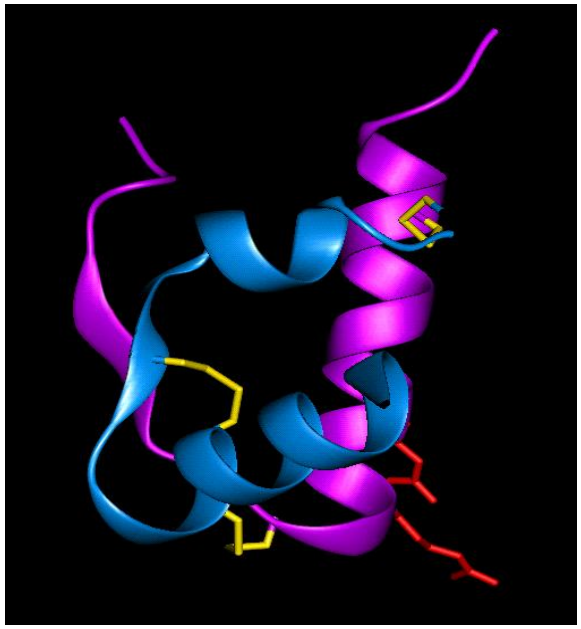
Relaxin

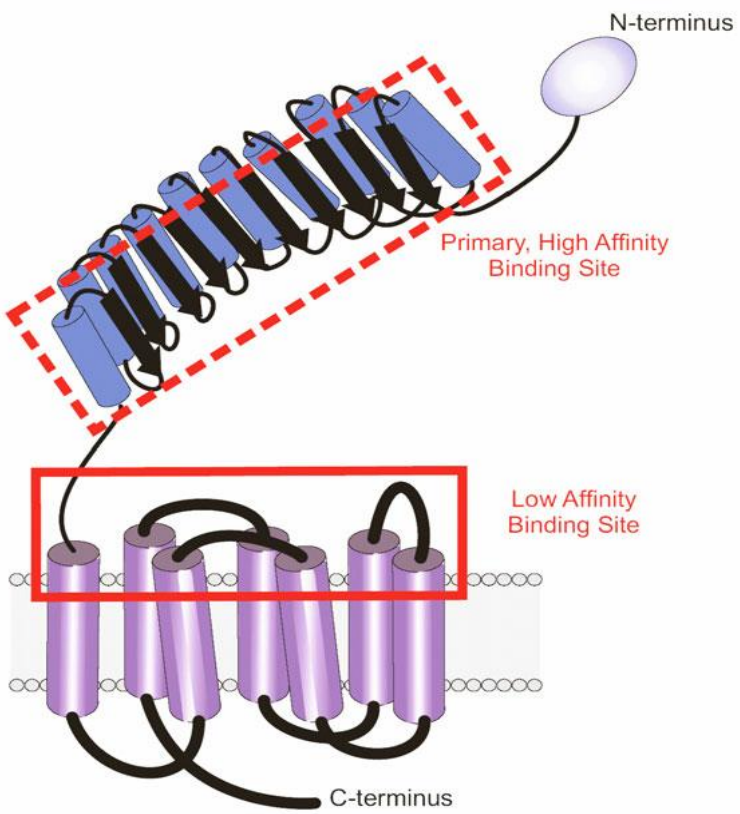


- Peptide hormone
- Similar in size and shape to insulin (MW 5963)
- Found in men and women
- Normal hormone of pregnancy
- Women “exposed” for 9 months to increased plasma concentrations: 0.8-1.6 ng/ml pregnancy*

Szlachter et al, *Obstet & Gynecol* 1982;59:167-70
Stewart et al, *J Clin Endocrinol Metab* 1990;70:1771-3.

Relaxin: Mechanisms of Action

Relaxin Receptor LGR7



- Vasodilation
  - NO, cGMP effectors
  - Induction of NOS II/III
  - Upregulation of ETB receptor
- Preferential dilation of constricted vessels
- Anti-inflammatory
- Anti-apoptotic
- Anti-fibrotic

Teichman, SL, et al. *Heart Fail Rev* 2009
Dschietzig, T, et al. *Pharmacol Therap* 2006

Relaxin

HEART FAILURE

RELAX-AHF: Positive results with new acute HF treatment

SEPTEMBER 24, 2012 Michael O'Riordan

Basel, Switzerland – A novel recombinant form of human relaxin 2 used in the treatment of acute heart failure (AHF) reduced shortness of breath as assessed by one of two dyspnea end points, the primary end points in the **RELAX-AHF** study, and also reduced all-cause mortality compared with placebo plus standard of care [1].

The early results of the study, which tested the compound **RLX030**, or **serelaxin**, were released by Novartis in advance of the **American Heart Association (AHA) 2012 Scientific Sessions** in Los Angeles, CA. The full results of RELAX-AHF will be presented November 6, 2012 during the late-breaking clinical-trials session at 3:45-5:35 pm.

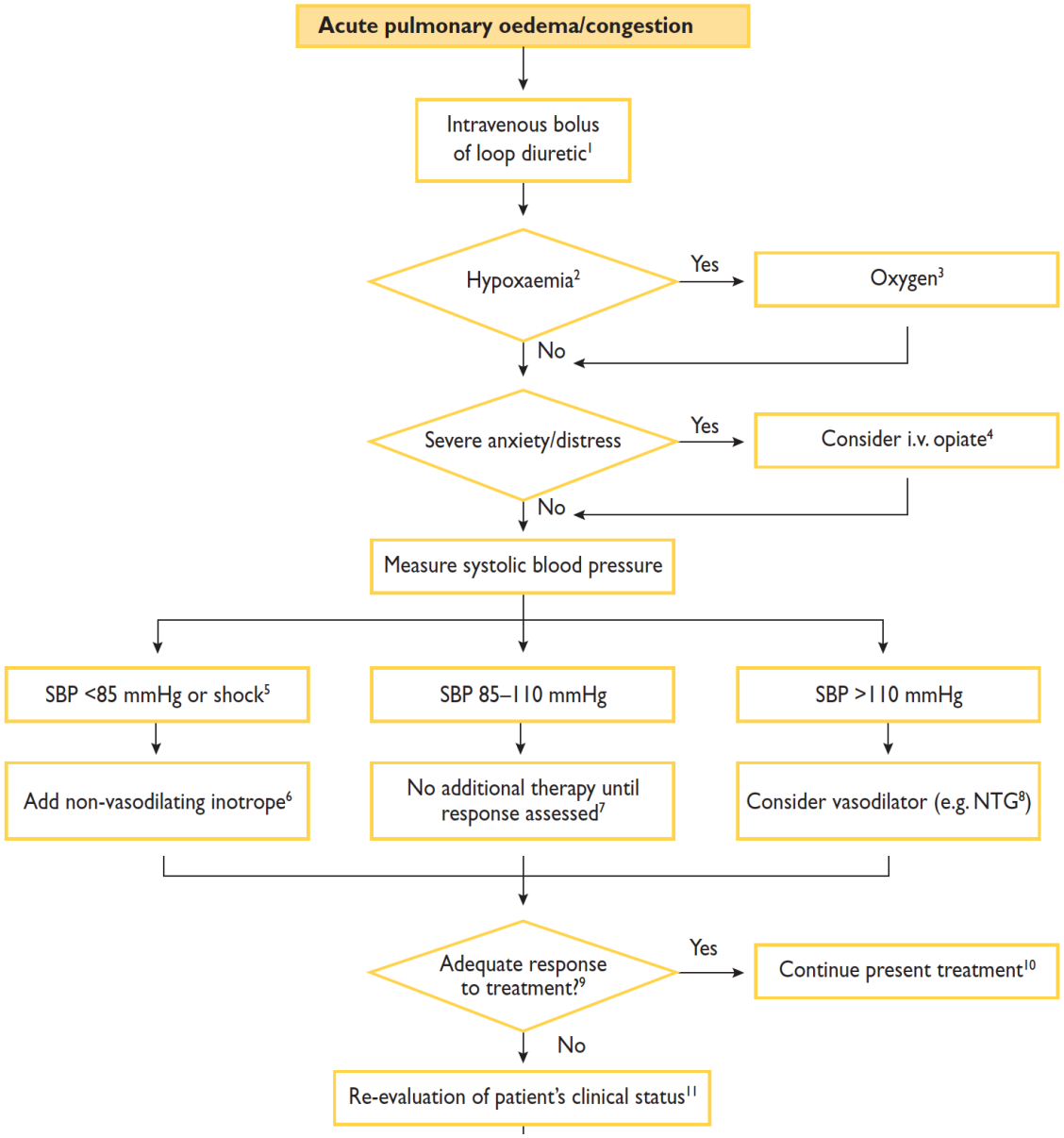
The study included 1160 patients with AHF and systolic blood pressure >125 mm Hg randomized to treatment with serelaxin via a 48-hour intravenous infusion within 16 hours of presentation or to placebo. The dose of serelaxin, 30 µg/kg per day, was selected based on a phase 2 dose-ranging study [1].

Serelaxin is a first-in-class recombinant form of human hormone relaxin 2. During pregnancy, the hormone modulates the cardiovascular responses by increasing vasodilation and renal function. Investigators also note that relaxin can modulate various important hemodynamic and neurohormonal effects, such as increases in cardiac output and decreases in systemic vascular resistance, pulmonary capillary wedge pressure, and N-terminal pro-brain natriuretic peptide (NT-proBNP) [2].

The top-line results of RELAX-AHF were released this week in advance of the AHA presentation in November —an increasingly common practice with study data that could materially affect stock prices.

Teerlink Lancet 2009

Management of Acute Heart Failure



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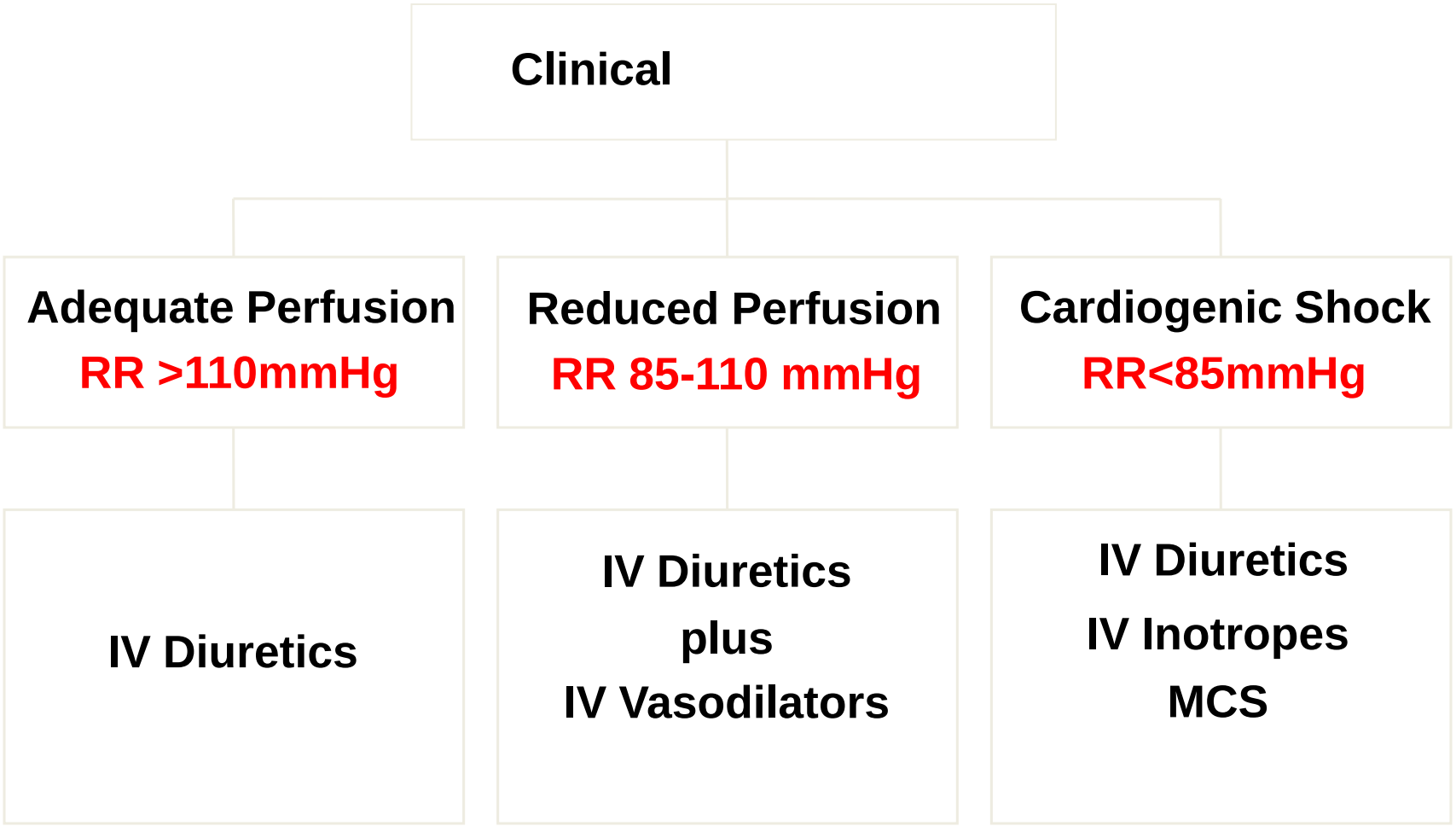
Approach to Acute Therapy in Volume Overloaded Heart Failure Patients



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Patients with Pulmonary Edema/without shock

Recommendations	Class[a]	Level[b]	Ref[c]
Patients with pulmonary congestion/oedema without shock			
An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.	I	B	213
High-flow oxygen is recommended in patients with a capillary oxygen saturation <90% or PaO_2 <60 mmHg (8.0 kPa) to correct hypoxaemia.	I	C	–
Thrombo-embolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.	I	A	214–216
Non-invasive ventilation (e.g. CPAP) should be considered in dyspnoeic patients with pulmonary oedema and a respiratory rate >20 breaths/min to improve breathlessness and reduce hypercapnia and acidosis. Non-invasive ventilation can reduce blood pressure and should not generally be used in patients with a systolic blood pressure <85 mmHg (and blood pressure should be monitored regularly when this treatment is used).	IIa	B	217
An i.v. opiate (along with an antiemetic) should be considered in particularly anxious, restless, or distressed patients to relieve these symptoms and improve breathlessness. Alertness and ventilatory effort should be monitored frequently after administration because opiates can depress respiration.	IIa	C	–
An i.v. infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.	IIa	B	218, 219
An i.v. infusion of sodium nitroprusside may be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Caution is recommended in patients with acute myocardial infarction. Nitroprusside may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitroprusside.	IIb	B	220
Inotropic agents are NOT recommended unless the patient is hypotensive (systolic blood pressure <85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischaemia, and death).	III	C	–

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Patients with pulmonary congestion/oedema without shock			
An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.	I	B	213
An i.v. infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.	IIa	B	218, 219
An i.v. infusion of sodium nitroprusside may be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Caution is recommended in patients with acute myocardial infarction. Nitroprusside may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitroprusside.	IIb	B	220
Inotropic agents are NOT recommended unless the patient is hypotensive (systolic blood pressure <85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischaemia, and death).	III	C	–

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Patients with Hypotension, Hypoperfusion or Shock

Patients with hypotension, hypoperfusion or shock		
Electrical cardioversion is recommended if an atrial or ventricular arrhythmia is thought to be contributing to the patient's haemodynamic compromise in order to restore sinus rhythm and improve the patient's clinical condition.	I	C
An i.v. infusion of an inotrope (e.g. dobutamine) should be considered in patients with hypotension (systolic blood pressure <85 mmHg) and/or hypoperfusion to increase cardiac output, increase blood pressure, and improve peripheral perfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia.	IIa	C
Short-term mechanical circulatory support should be considered (as a 'bridge to recovery') in patients remaining severely hypoperfused despite inotropic therapy and with a potentially reversible cause (e.g. viral myocarditis) or a potentially surgically correctable cause (e.g. acute interventricular septal rupture).	IIa	C
An i.v. infusion of levosimendan (or a phosphodiesterase inhibitor) may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypoperfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia, and, as these agents are also vasodilators, blood pressure should be monitored carefully.	IIb	C
A vasopressor (e.g. dopamine or norepinephrine) may be considered in patients who have cardiogenic shock, despite treatment with an inotrope, to increase blood pressure and vital organ perfusion. The ECG should be monitored as these agents can cause arrhythmias and/or myocardial ischaemia. Intra-arterial blood pressure measurement should be considered.	IIb	C
Short-term mechanical circulatory support may be considered (as a 'bridge to decision') in patients deteriorating rapidly before a full diagnostic and clinical evaluation can be made.	IIb	C

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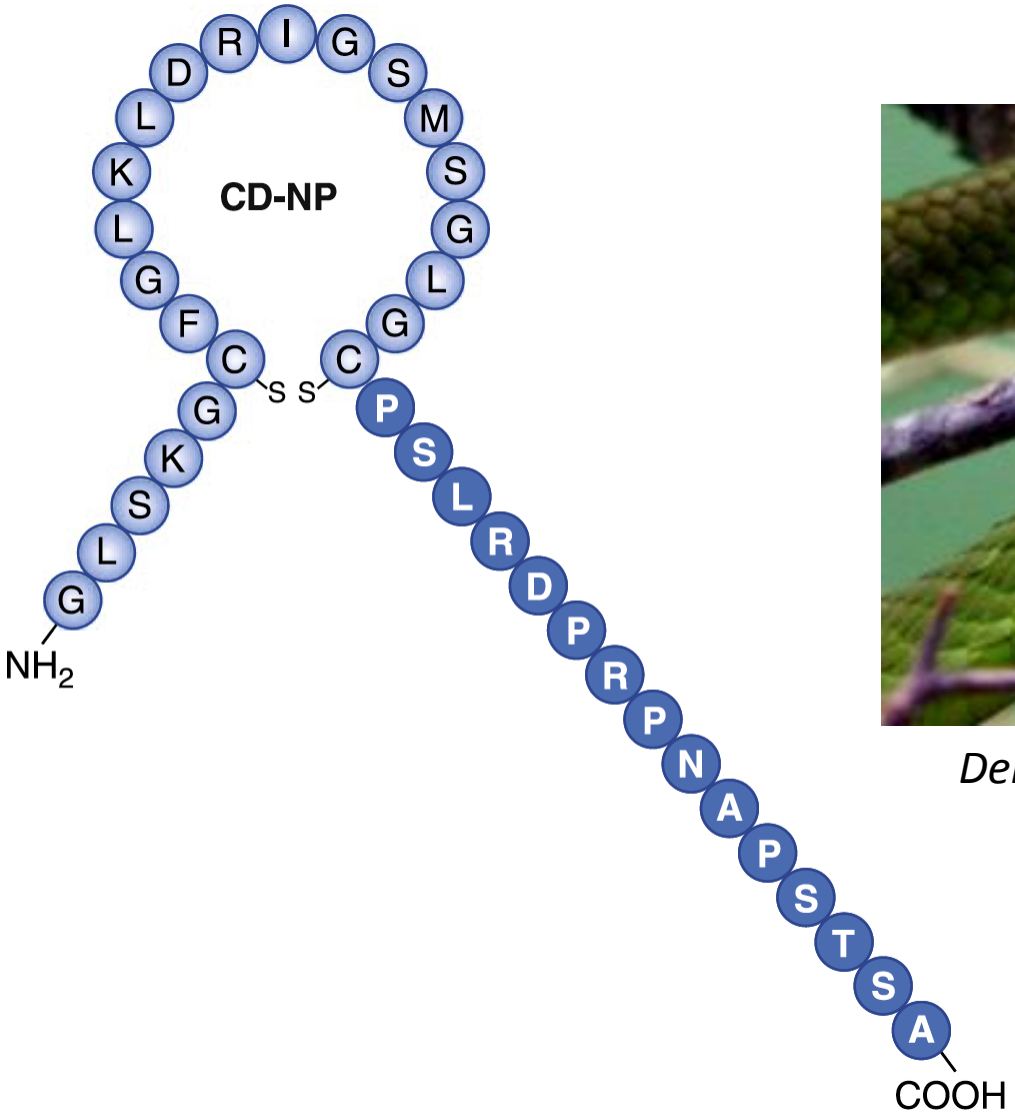
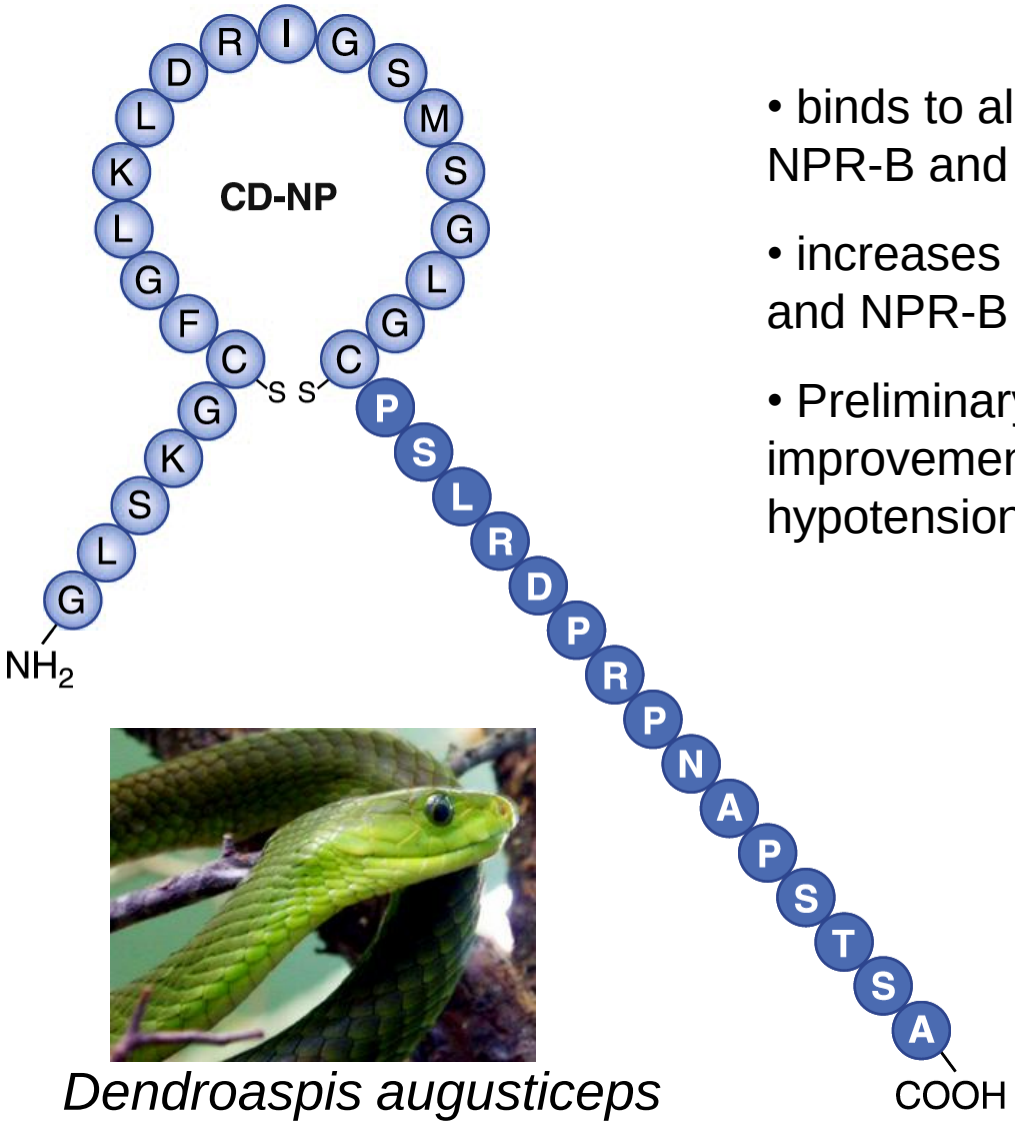
Amino Acid Sequence and Structure of CD-NP



Dendroaspis augusticeps

McKie, Burnett. Curr Heart Fail Rep 2009

CD-NP: A Chimeric Natriuretic Peptide

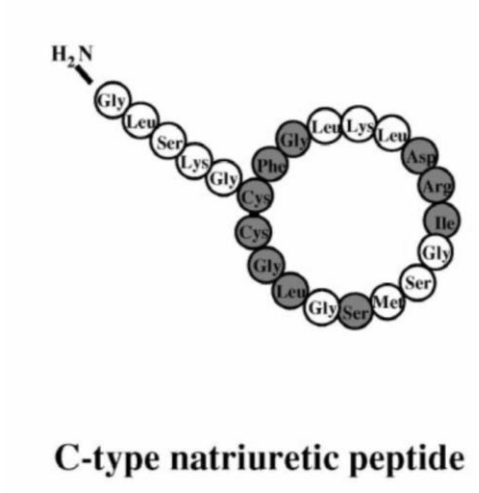


Dendroaspis augusticeps

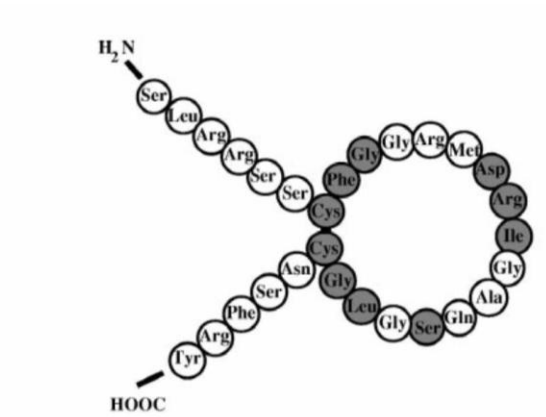
- binds to all three NP receptors (NPR-A, NPR-B and NPR-C)
- increases cGMP downstream of both NPR-A and NPR-B
- Preliminary data in HF pts suggests improvement of renal function without hypotension

McKie, Burnett. Curr Heart Fail Rep 2009

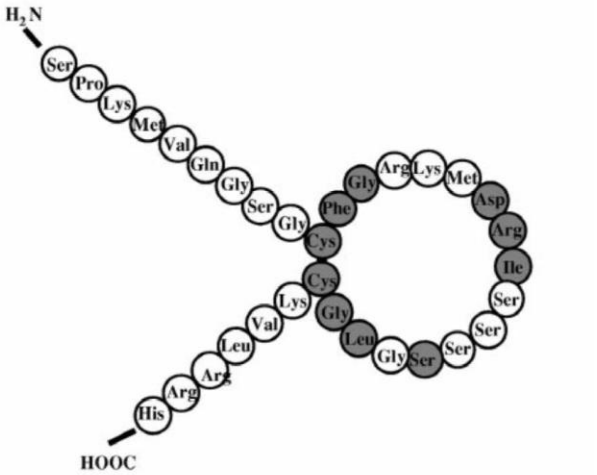
Rank Order of Hydrolysis by NEP is CNP>ANP>BNP>Urodilatin



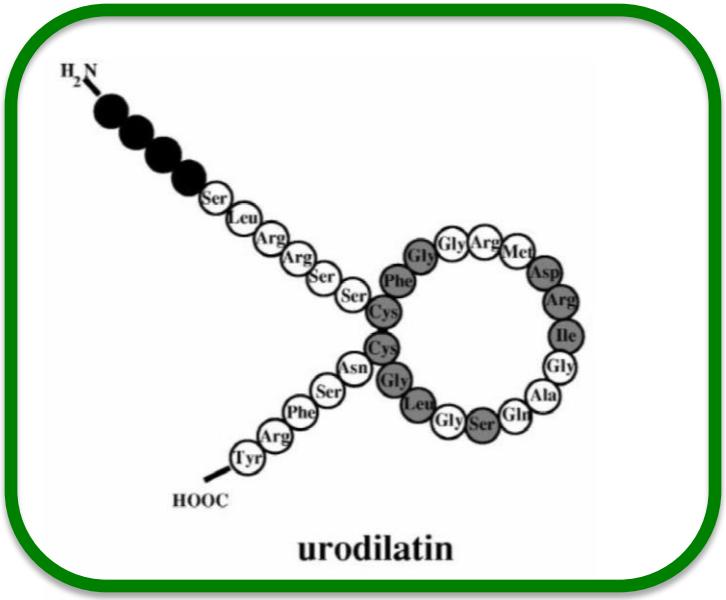
C-type natriuretic peptide



circulating CDD/ANP-99-126

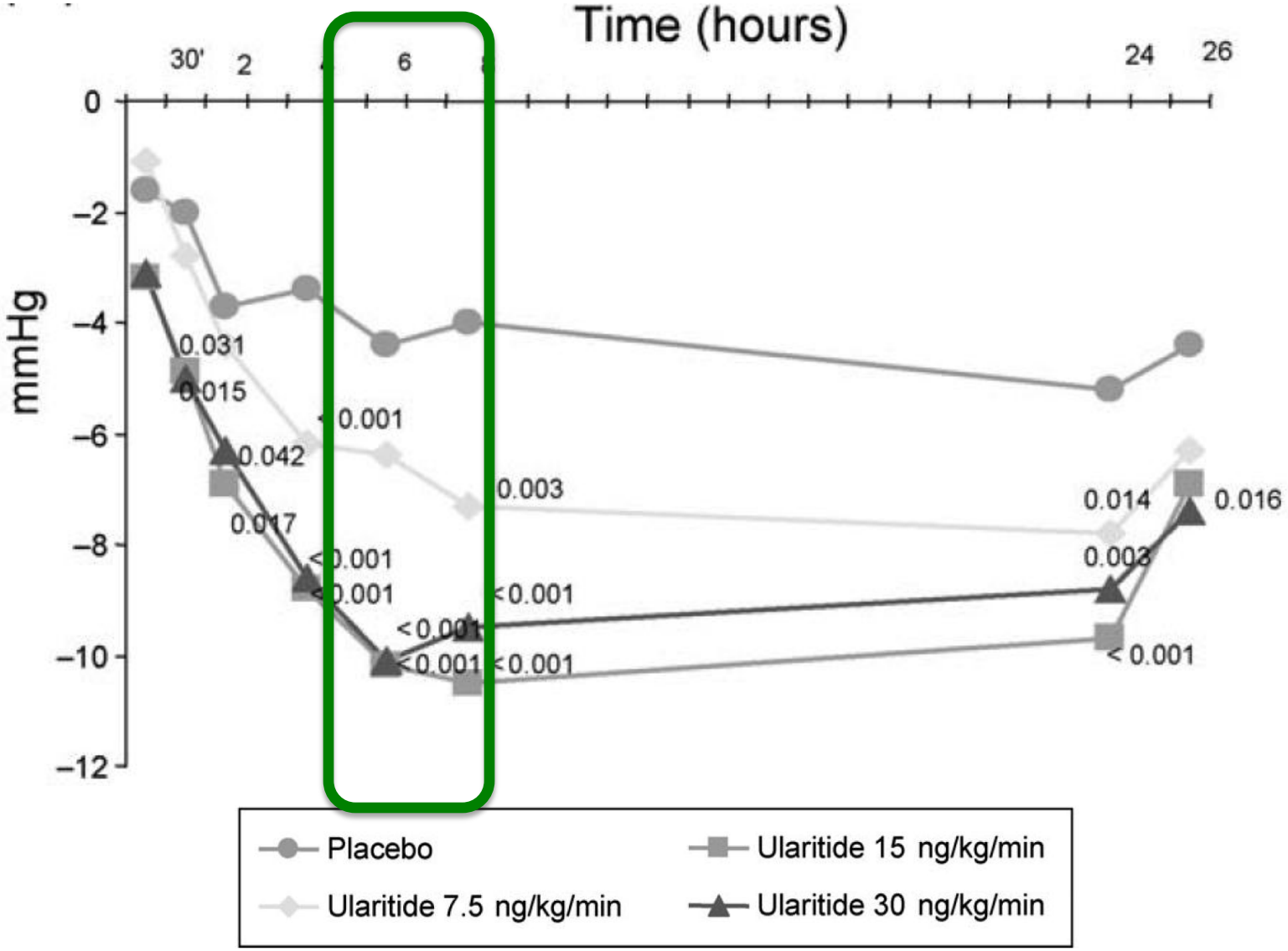


B-type natriuretic peptide



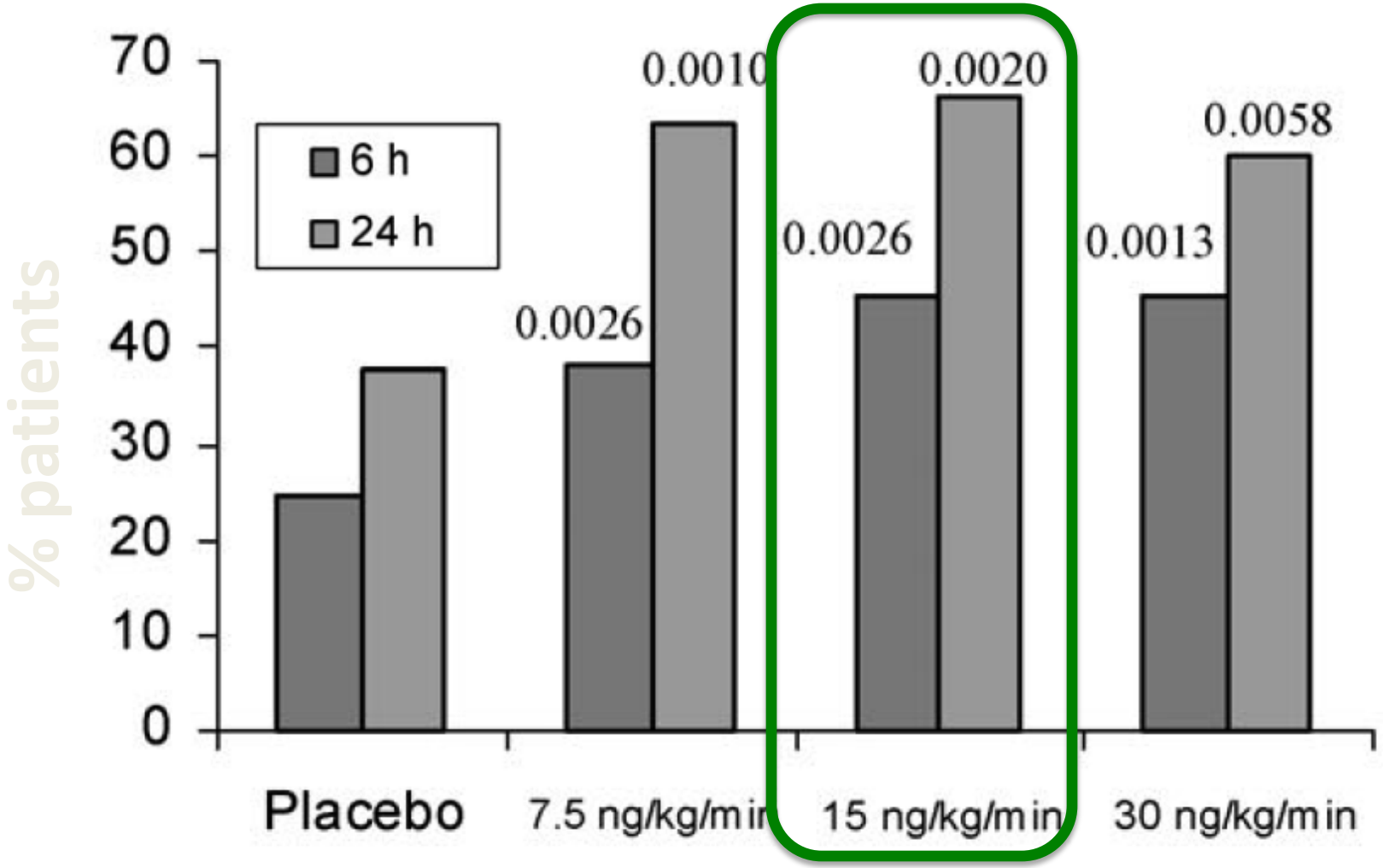
urodilatin

SIRIUS II: Wedge Pressure



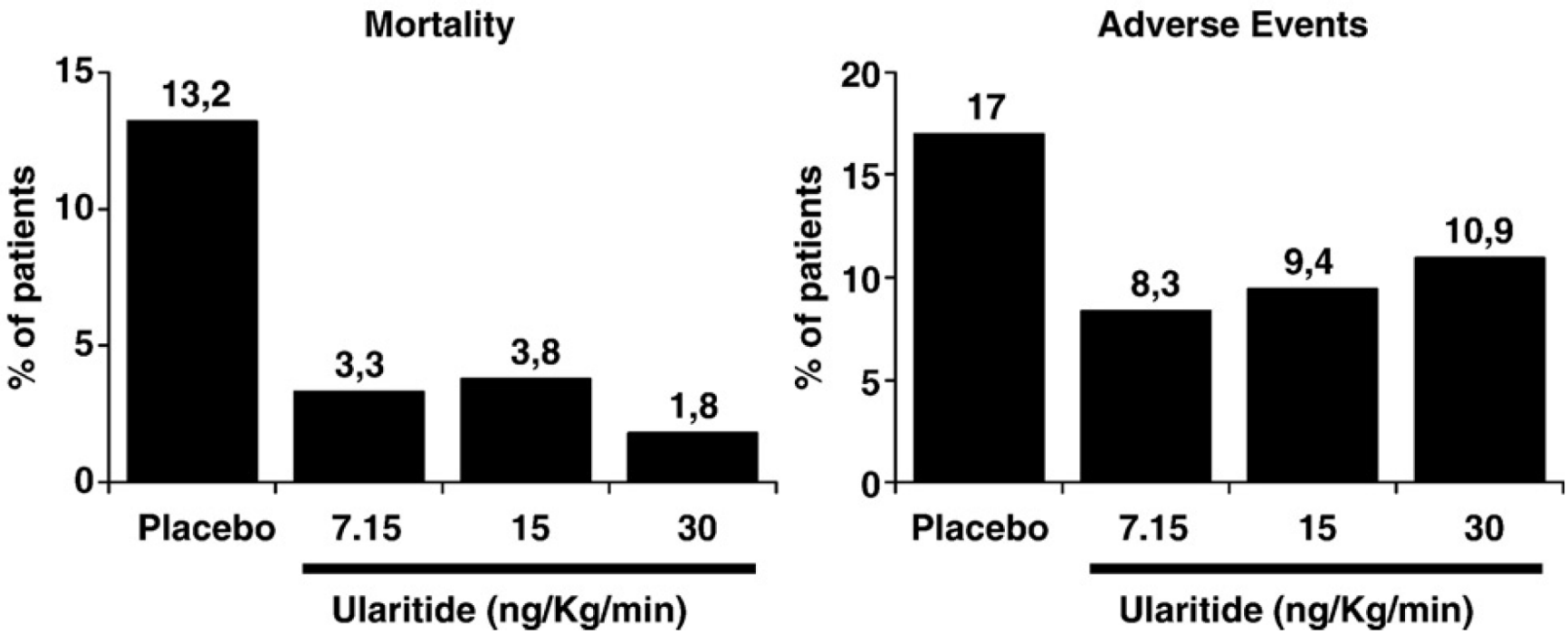
Mitrovic Eur Heart J 2006

SIRIUS II: Patient-assessed Dyspnea Moderately or Markedly Better



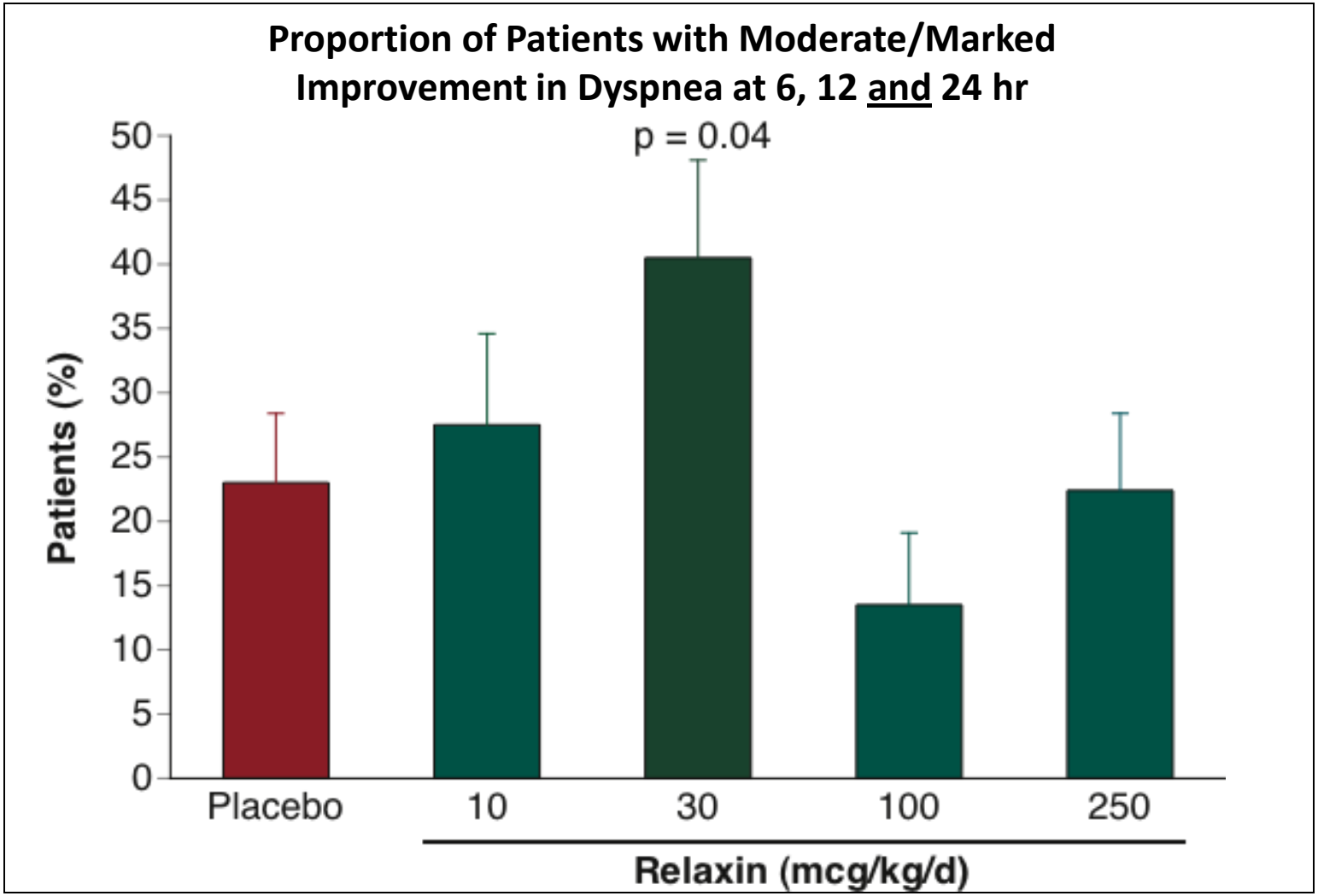
Mitrovic Eur Heart J 2006

Rates of total mortality and adverse events in the SIRIUS II trial



De Luca EJHF 2008

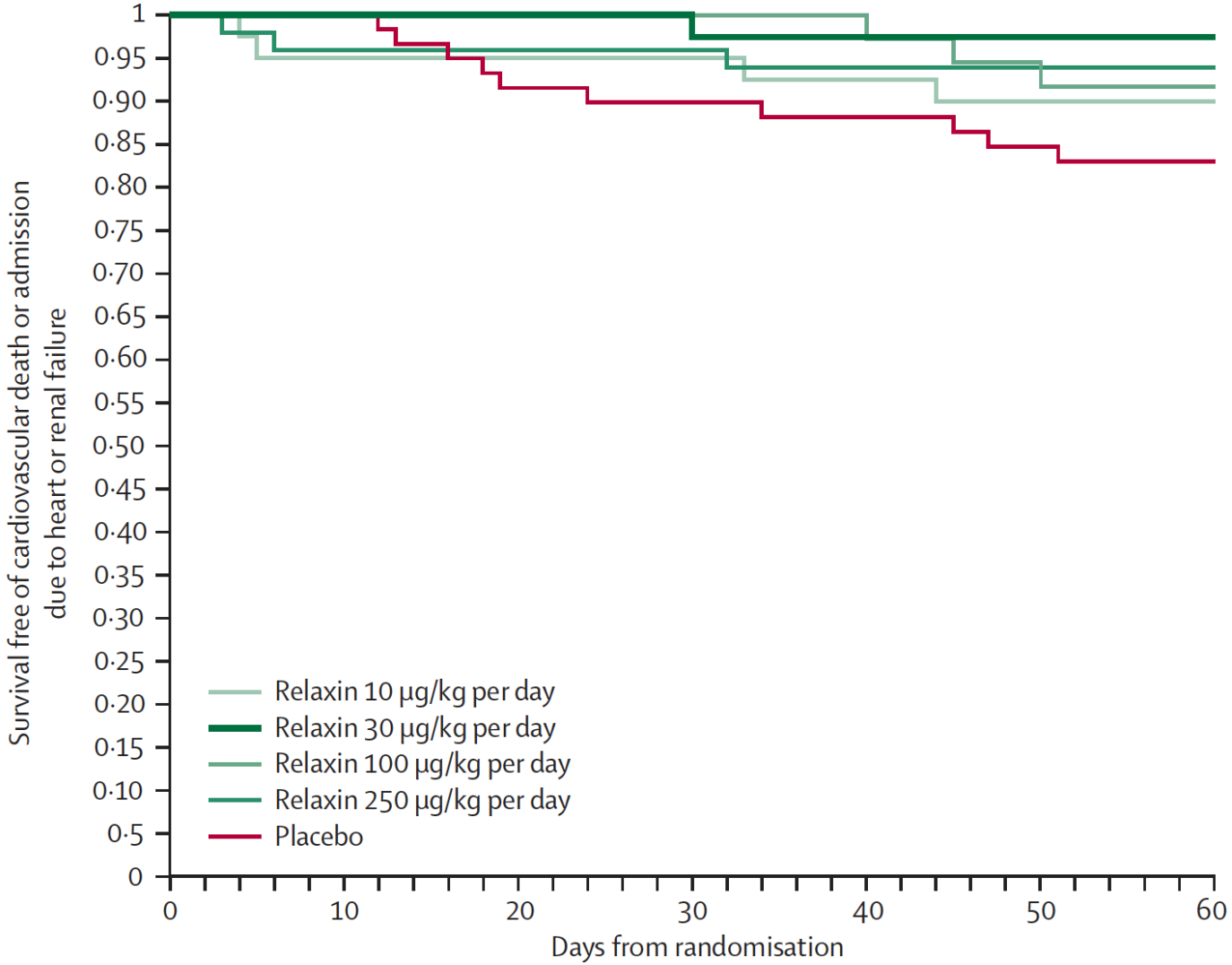
Pre-RELAX-AHF: Dyspnea Improvement through 24 hours (Likert Scale)



n=234 62 40 62 39 50

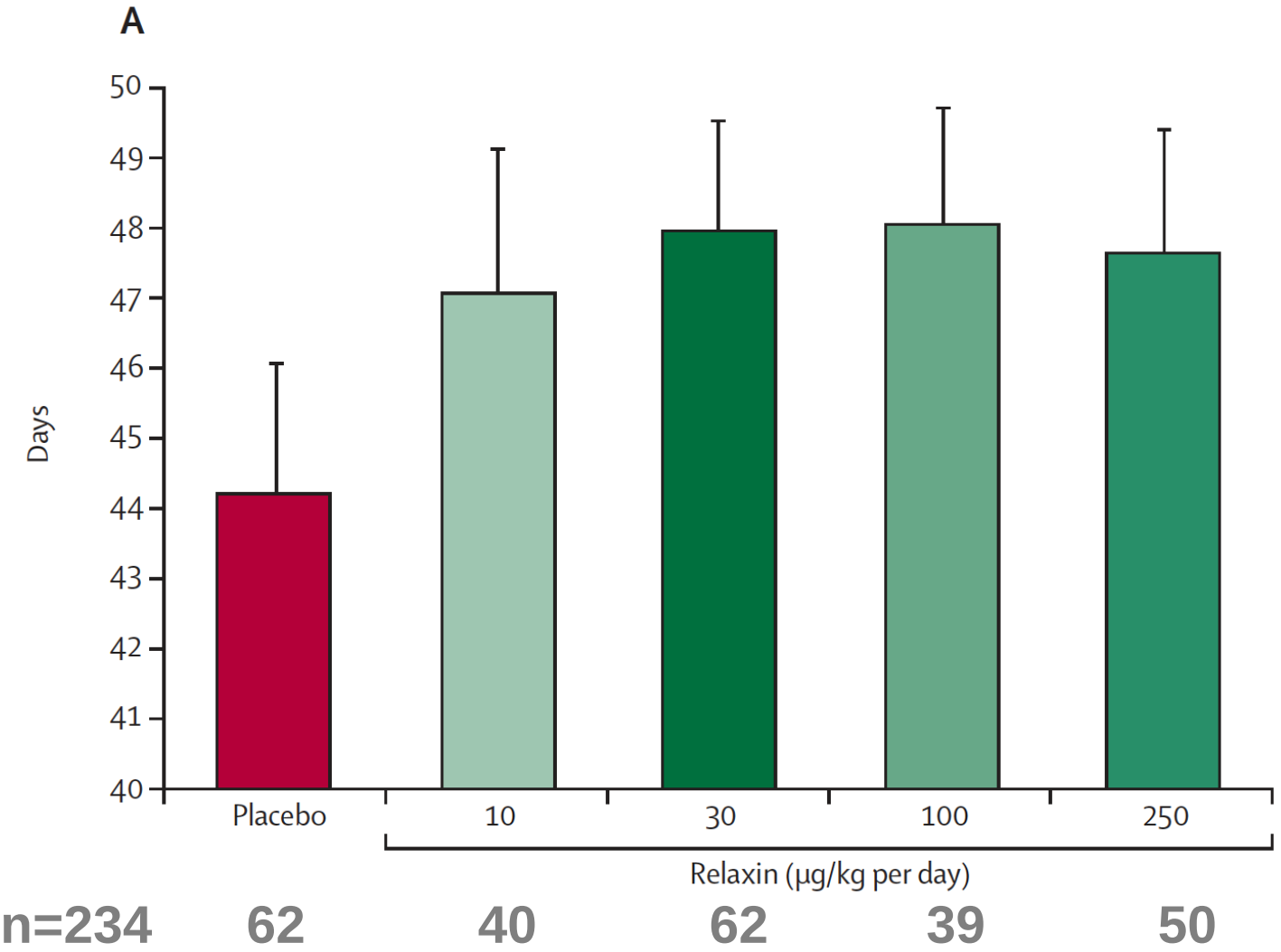
Teerlink Lancet 2009

Survival free of CV Death or Heart/Renal Failure Re-hospitalizations to Day 60



Teerlink Lancet 2009

Days alive and out of hospital from baseline to day 60



Teerlink Lancet 2009