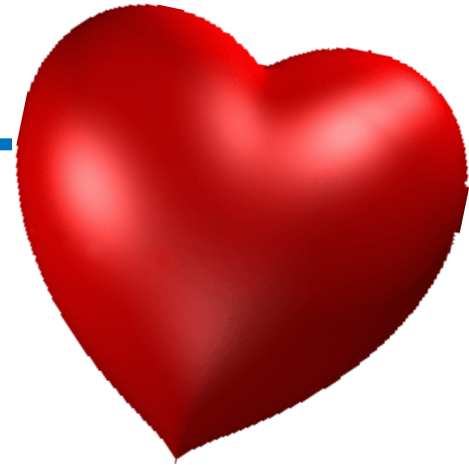


Ergebnisse der Vasodilatator - Therapie bei akut dekompensierter HI



1. Pathophysiologie
2. die Hypothesen
3. die Studien

Görlitz, 15. Oktober 2011

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ADHF = acute decompensated heart failure
(AHFS = acute heart failure syndrome)

Decompensated congestive heart failure (CHF) is the leading hospital discharge diagnosis in patients older than 65 years

1. Definitions, Causes
2. Pathophysiology
3. Principles of treatment

Possible Causes of Acutely Decompensated, Previously Stable CHF

- **Progression of the cardiac failure**
- **Stopping to take needed drugs (diuretics)**
- **Inadequately treated hypertension**
- **Arrhythmia (tachycardia)**
- **Additional infection (i.e. pneumonia/bronchitis)**
- **Pulmonary emboli**
- **Renal failure and fluid retention**
- **Myocarditis**
- **Vasculitis (LE etc.)**
- **Acute ischaemia**
- **Changes of viscosity**
- **Anaemia**
- **Additional treatment with NSAIDS, Ca-Blockers ...**

pathophysiology of cardiac decompensation

- Due to water and salt retention (RAAS)
- Preload rises
- The kidney retains Na in order to keep CO up
- Tachycardia ensues
- Increased intracardiac pressures augment wall stress
- O₂ consumption is augmented
- Decompensation goes into a vicious circle

Reduction of preload

- 1. Is possible through diuretics, nitrates, BNP-analogues, levosimendan etc.**
- 2. Patients either become resistant or the drug causes tolerance – or does not work**
- 3. A drug that has mild vasodilating effects and does not cause tachyphylaxis, might reduce pulmonary congestion (and resistance) and increase CO (slowly)**

Goals of Acute Heart Failure Therapy

1. Reduce extracellular fluid volume excess
2. Improve haemodynamics
 - a. decrease right and left ventricular filling pressures
 - b. increase cardiac output
3. Maintain perfusion to vital organs

Treatment of ADHF

- ACE-Inhibitors/ARBs
- Aldosterone antagonists
- Diuretics ([tolvaptan](#))
- Betablockers
- iv use of vasodilators ([nitroglycerine](#), [sodium nitroprusside](#))
- pos. inotropic agents ([dobutamine](#), dopamine, phosphodiesterase III inhibitors, [calcium sensitisers](#))
- Natriuretic peptides ([nesiritide](#))
- Endothelinantagonist ([tezosentane](#))
- Adenosin-A1-receptorantagonist ([rolofylline](#))
- [Cinaciguat](#)

Vasodilators

They act by activating soluble guanylate cyclase in the smooth muscle cells, leading to higher intracellular concentrations of cGMP and consequent vessel relaxation.

They may cause severe hypotension

According to the guidelines, intravenous nitroglycerin, sodium nitroprusside, or nesiritide may be added to diuretic treatment

Levosimendan

- **A calcium sensitiser**
- **A potassium channel opener**
- **Positive inotropic and vasodilatory effects**
- **Controlled studies have shown an improvement of well being, decrease of BNP, no mortality benefit but:**
- **Hypotension (50 vs 34 %)**
- **VT (25 vs 17 %), AF (9 vs 2 %)**

HFSA 2006 Heart Failure Practice Guidelines

Evaluation and Management of Patients with Acute Decompensated Heart Failure

HEART FAILURE SOCIETY OF AMERICA
St. Paul, Minnesota

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Treatment considerations in ADHF

“Relief of congestion and volume overload generally is accomplished with sodium and fluid restriction and the use of diuretics. Intravenous vasodilators may be added. Agents to consider for the improvement of hemodynamic parameters include intravenous nitroglycerin, sodium nitroprusside, and nesiritide. The use of inotropes should be severely limited.”

Therapeutic recommendations

Parameter	Strength of recommendation	Strength of evidence
IV diuretics	Is recommended	B
	Is recommended	C
IV vasodilators	May be considered	B

“In the absence [of] symptomatic hypotension, intravenous nitroglycerin, nitroprusside, or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients admitted with ADHF. Frequent blood pressure monitoring is recommended with these agents.”



The VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) Trial

Patients presenting to the hospital with dyspnea at rest or with minimal activity (such as talking, eating, or bathing) due to acutely decompensated CHF that was severe enough to require hospitalization.

- These decompensated CHF patients included patients with acute decompensation of chronic heart failure, gradual worsening of chronic heart failure, or with new onset of acutely decompensated CHF

Objective: To compare the hemodynamic and clinical effects of nesiritide to nitroglycerin or placebo, when added to standard therapy

Primary Endpoints

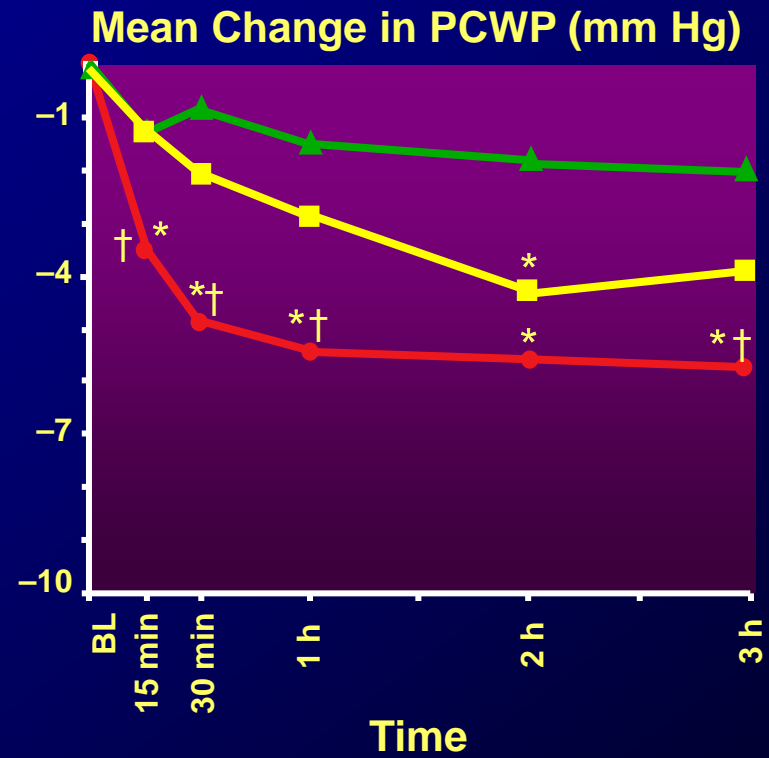
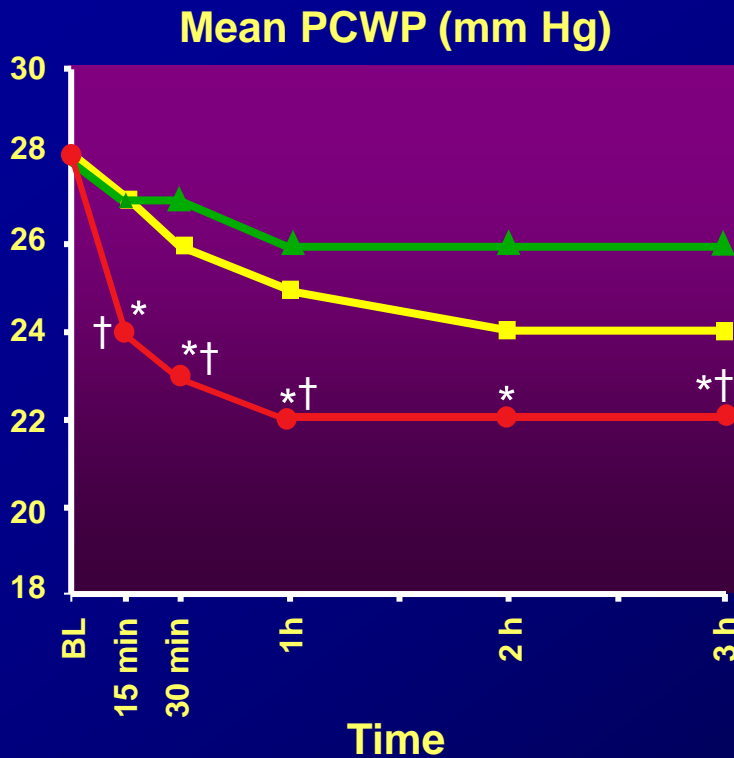
- 3 hour dyspnea assessment by subject (all subjects)
- 3 hour PCWP (catheterized subjects only)

Standard therapy could include:

[JAMA, 2002;287:1531-1540](#)

- IV / oral diuretics, dobutamine, dopamine
- Long-term cardiac or non-cardiac therapies

VMAC: PCWP Through 3 Hours



* $P < 0.05$ vs placebo.

† $P < 0.05$ vs nitroglycerin.

▲ Placebo ■ Nitroglycerin ● Nesiritide

Added to standard therapy.

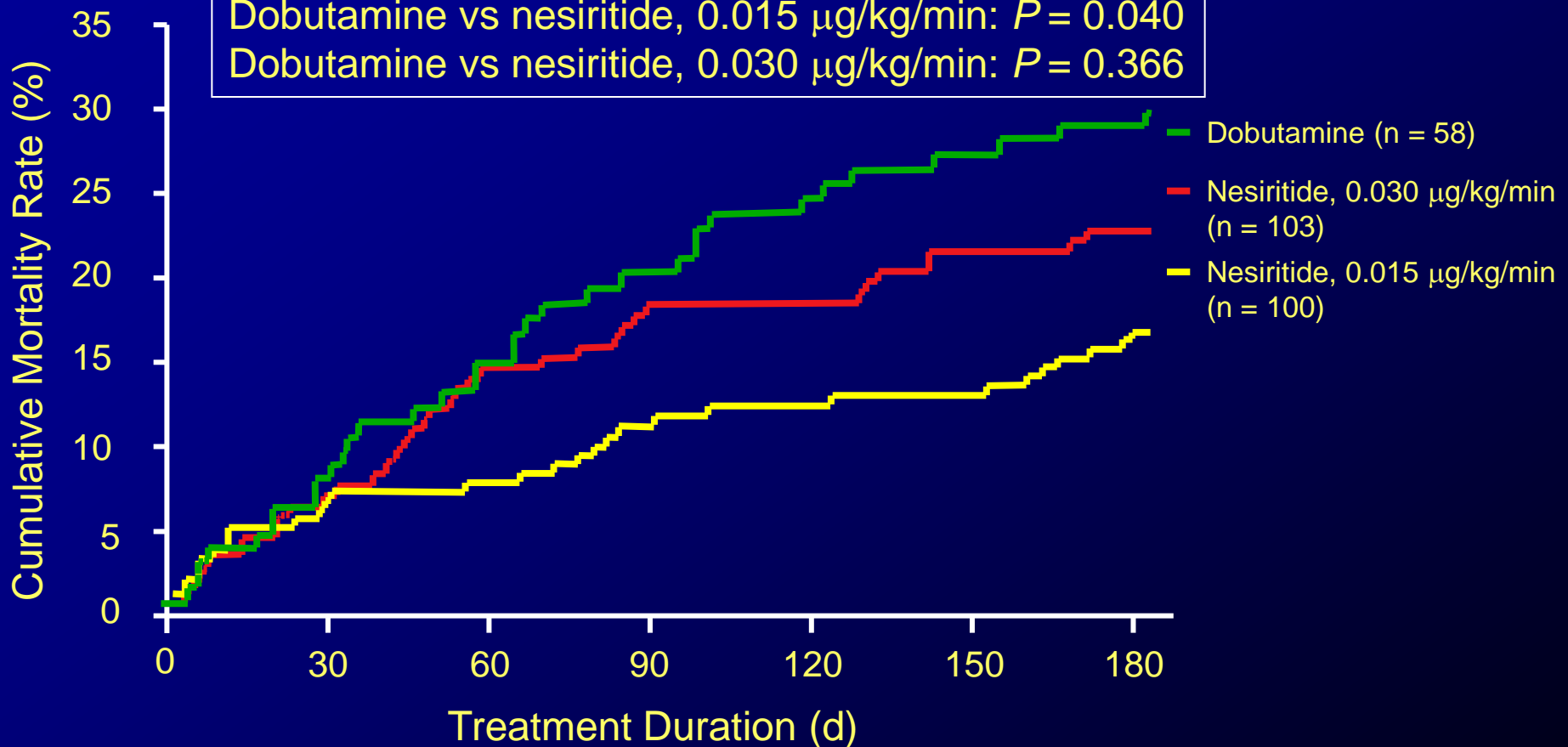
(n = 498)

VMAC Investigators. JAMA. 2002;187:1531-1540.



Effect of Short-Term Nesiritide vs Dobutamine on 6-Month Survival

Log-rank test:
 Dobutamine vs nesiritide, 0.015 $\mu\text{g}/\text{kg}/\text{min}$: $P = 0.040$
 Dobutamine vs nesiritide, 0.030 $\mu\text{g}/\text{kg}/\text{min}$: $P = 0.366$



However, there is controversy

Circulation 2005;111:1487-1491

Heart Failure

Risk of Worsening Renal Function With Nesiritide in Patients With Acutely Decompensated Heart Failure

Jonathan D. Sackner-Bernstein, MD; Hal A. Skopicki, MD, PhD; Keith D. Aaronson, MD, MS

JAMA. 2005;293:1900-1905.

Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure A Pooled Analysis of Randomized Controlled Trials

Jonathan D. Sackner-Bernstein, MD

Marcin Kowalski, MD

Marshal Fox, MD

Keith Aaronson, MD, MS

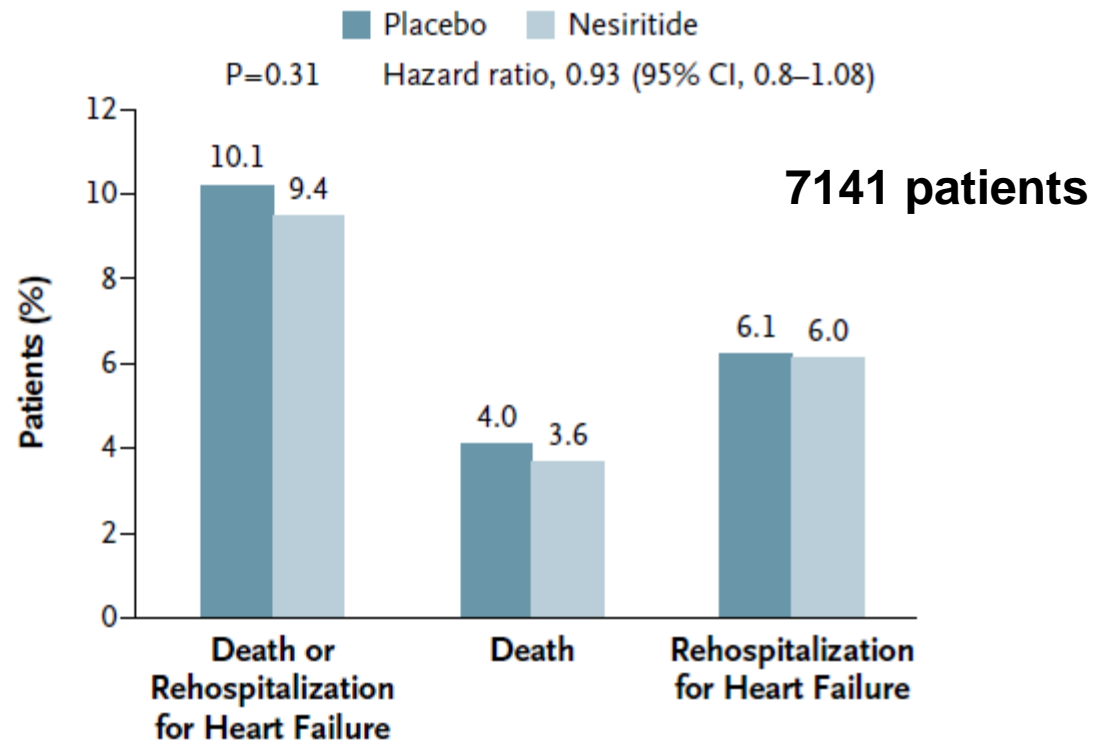
Context Nesiritide improves symptoms in patients with acutely decompensated heart failure compared with placebo and appears to be safer than dobutamine. Its short-term safety relative to standard diuretic and vasodilator therapies is less clear.

Objective To investigate the safety of nesiritide relative to noninotrope-based control therapies, primarily consisting of diuretics or vasodilators.

ORIGINAL ARTICLE

Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

Death from Any Cause or Rehospitalization for Heart Failure at 30 Days



Percentage Point Difference (95% CI)

-0.7 (-2.1 to 0.7) -0.4 (-1.3 to 0.5) -0.1 (-1.2 to 1.0)

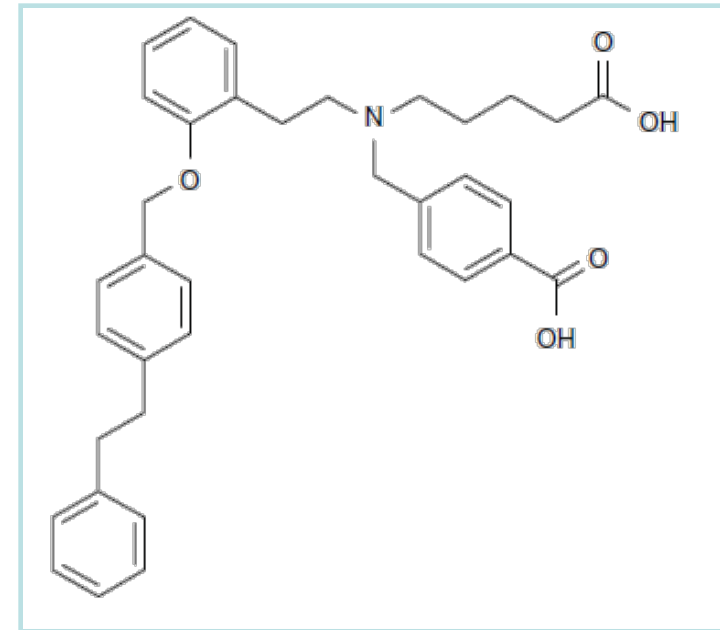
N Engl J Med 2011;365:32

Negative Studien mit Vasodilatorien bei ADHF

1. **EVEREST 4133 Tolvaptan Vasopressin Antagonist**
(Gheorghide et al., JAMA 2004; 291: 1963)
2. **PROTECT 2033 Rolofyllin Adenosin A1-Rezeptor Antagonist**
(Massie et al., N Engl J Med 2010;363:1419)
3. **VERITAS 1448 Tezosentan Endothelin Antagonist**
(McMurray et al., JAMA. 2007;298:2009)
4. **SURVIVE 1327 Levosimendan Calcium Sensitizer**
(Mebazaa et al., JAMA 2007;297:1883)
5. **OPTIME-HF 951 Milrinon Phosphodiesterase Inhibitor**
(Cuffe et al., JAMA 2002;287:1541)

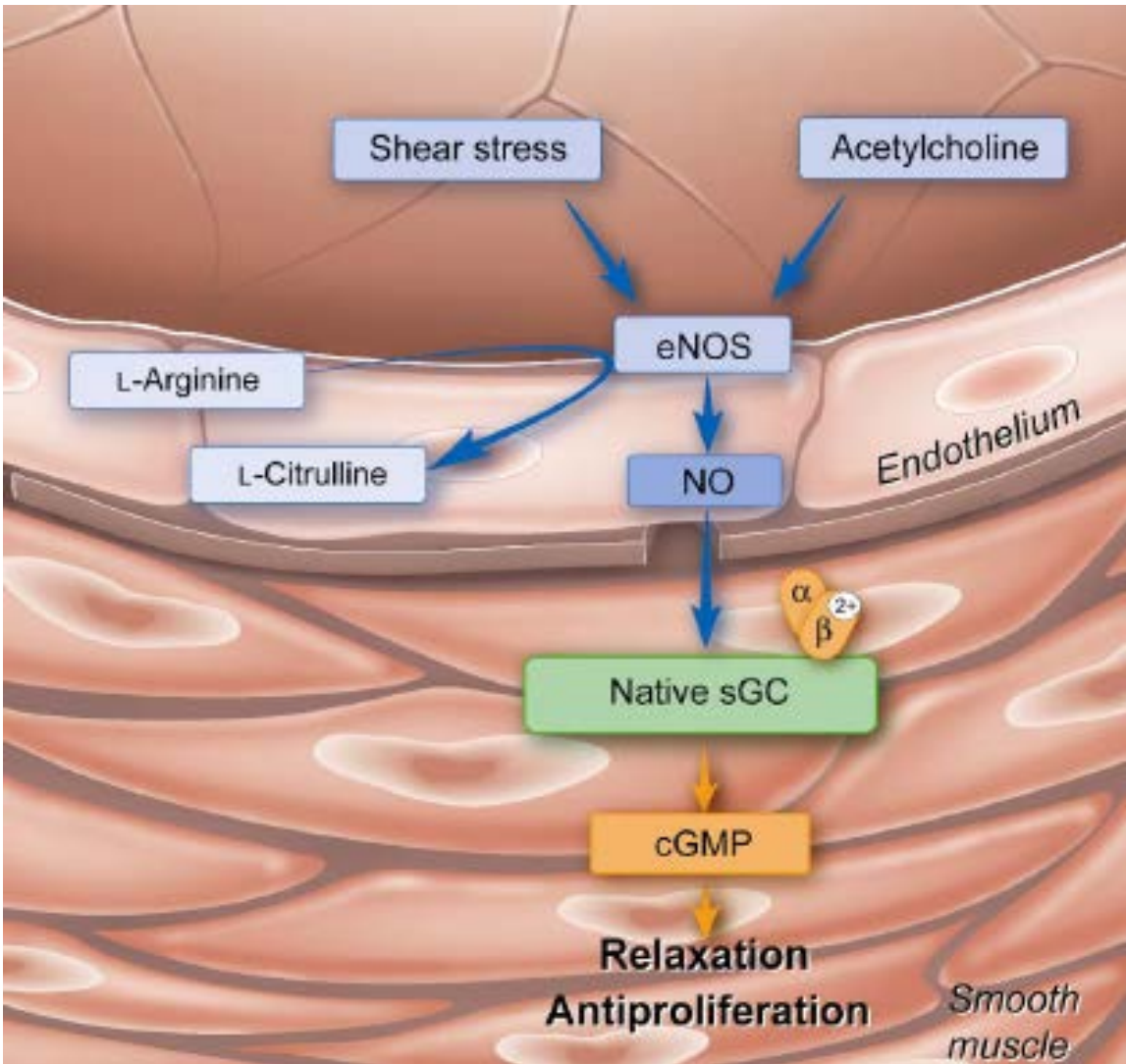
Cinaciguat (BAY 58-2667)

- Cinaciguat is a nitric oxide- and haem-independent activator of soluble guanylate cyclase (sGC)
- Cinaciguat selectively targets a modified sGC that is prevalent under disease conditions
- Cinaciguat preferentially activates sGC in its oxidized or haem-free state, when the enzyme is insensitive to its endogenous ligand nitric oxide and exogenous nitro vasodilators
- In animal models of cardiovascular disease, an organ protective effect was observed



Cinaciguat induces cyclic guanosine monophosphate (cGMP) generation and vasodilation preferentially in diseased vessels

Endotheliale Funktion der sGuanylat Cyclase



Flow and humoral factors stimulate eNOS to produce NO

NO binds to its receptor sGC in vascular smooth muscle cells and increases synthesis of cGMP

cGMP promotes vasorelaxation and inhibits cell proliferation

Cinaciguat

- cinaciguat exerted potent vasodilation while preserving the glomerular filtration rate, and had antihypertrophic and antifibrotic effects
- cinaciguat caused venous as well as arterial vasodilation

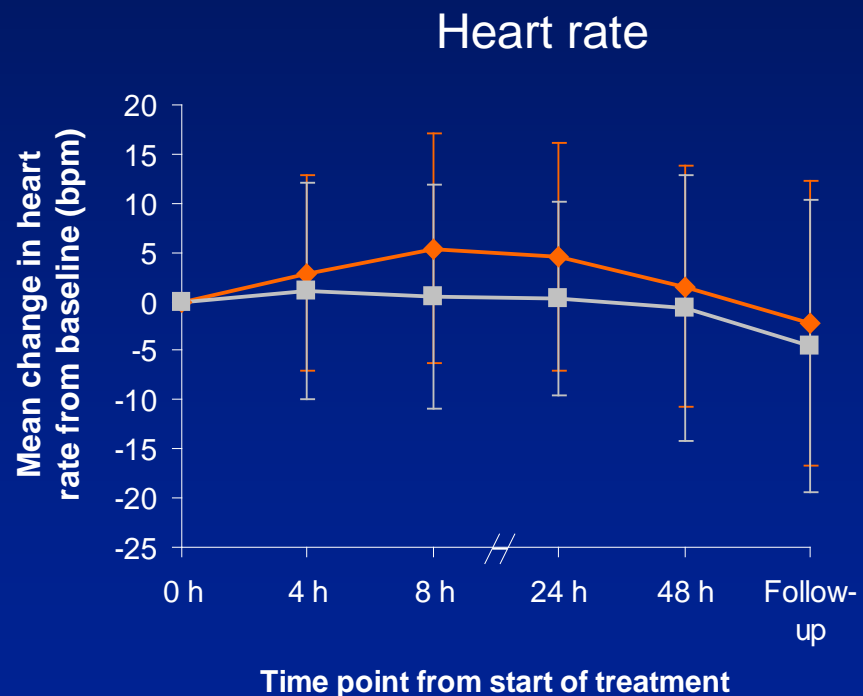
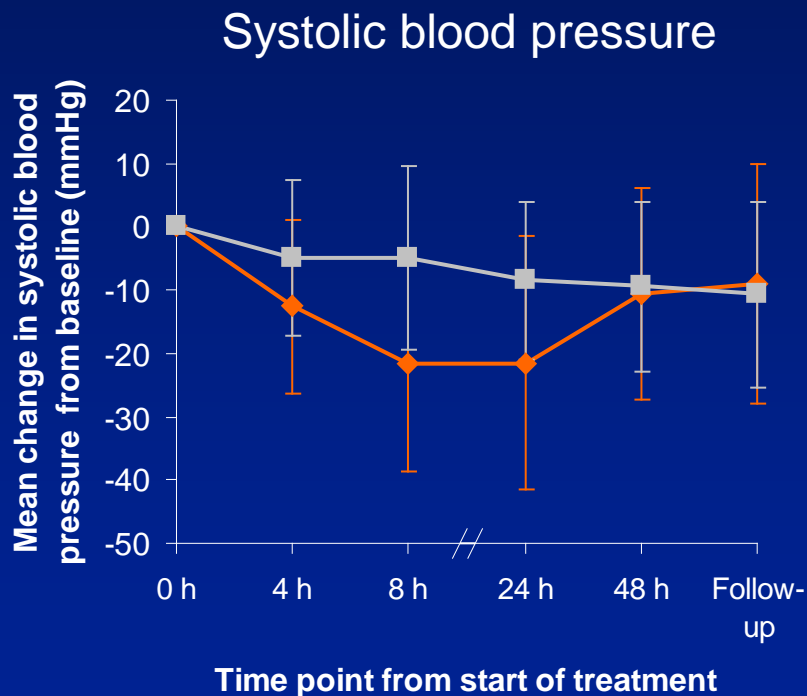
Study design

- Placebo-controlled, randomized, double-blind, multicentre, international dose-finding phase IIb study
- Inclusion criteria
 - Patients admitted with acute decompensated heart failure (ADHF), monitored via **pulmonary artery catheterization**
 - New York Heart Association (NYHA) functional class III and IV
 - Pulmonary capillary wedge pressure [PCWP] ≥ 18 mmHg
- Objectives
 - To investigate the safety and efficacy of intravenous cinaciguat as an add-on to conventional therapy and find the maximum tolerated dose
 - **Primary endpoint:** change in PCWP after 8 h compared with placebo
 - Secondary endpoints: haemodynamic and safety parameters, and **30-day mortality**



Cinaciguat caused vasorelaxation without a clinically relevant change in heart rate

- Reduction in systolic blood pressure
- No clinically significant change in heart rate



◆ Conventional therapy + cinaciguat
■ Conventional therapy + placebo



List of adverse events

Primary system organ class / preferred term	Cinaciguat* (N = 97)		Placebo* (N = 51)	
	n	(%)	n	(%)
Any adverse event ¹	75	(77.3)	30	(58.8)
Any treatment-emergent event ²	69	(71.1)	23	(45.1)
– Hypotension	49	(50.5)	6	(11.8)
– Ventricular tachycardia	6	(6.2)	0	(0.0)
– Headache	6	(6.2)	0	(0.0)
Any drug-related treatment-emergent event	58	(59.8)	9	(17.6)
Any serious adverse event ³	22	(22.7)	6	(11.8)
Any serious treatment-emergent event	9	(9.3)	1	(2.0)

*In addition to conventional therapy.

¹Adverse event as defined individually by the investigator.

²Adverse event starting after first application of double-blind study drug up to 2 days after stop of double-blind study drug.

³Adverse event that is life threatening, leads to death, leads to or prolongs hospitalization (duration of stay \geq 12 h), results in persistent or significant disability or incapacity, or is an important medical event.

Background – Cinaciguat in Acute Heart Failure Syndromes (AHFS)



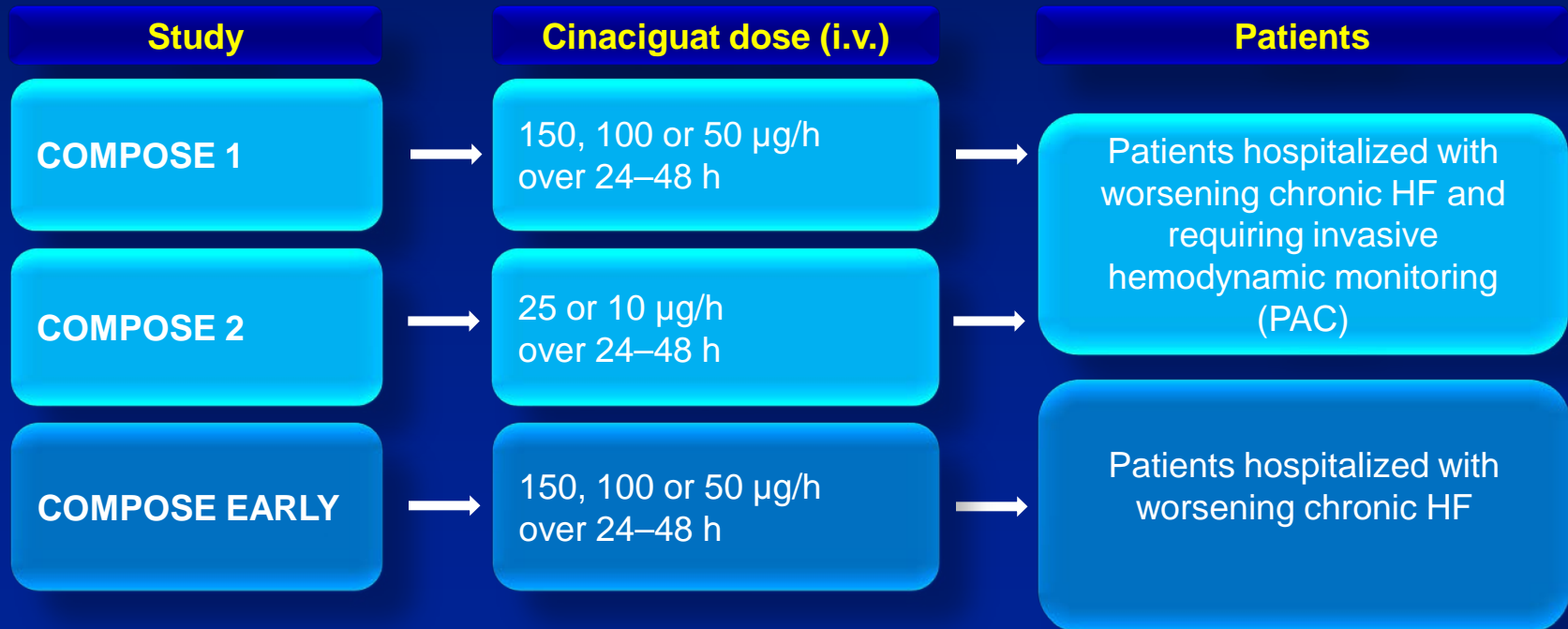
- In AHFS, we are still searching for an agent to improve symptoms and hemodynamics without causing myocyte damage, arrhythmias, hypotension or renal dysfunction given the negative results of the recent trials
- In heart failure, there is endothelial dysfunction associated with **impaired** soluble guanylate cyclase (sGC) and cGMP (cyclic guanosine monophosphate)
- Cinaciguat preferentially activates sGC in its oxidized or heme-free state, which is prevalent in heart failure (**improves endothelial function**)
- Pre-clinical studies of cinaciguat, a soluble guanylate cyclase (sGC) activator has shown to have cardio and renal protective effects, in addition of being a powerful vasodilator
- Maximally tolerated doses of cinaciguat ($\geq 200 \mu\text{g/h}$) resulted in significant improvement in central hemodynamics at the expense of a major decrease in systemic pressure¹

¹Erdmann E et al. *J Am Coll Cardiol* 2010;55:A10.E147.



COMPOSE Program Study Design

- Previous studies used cinaciguat doses titrated up to 600 $\mu\text{g}/\text{h}$
- The **COMPOSE** program (a set of **three** randomized, double-blind, placebo-controlled, multinational studies) was initiated to assess fixed doses of cinaciguat ($< 200 \mu\text{g}/\text{h}$) in patients with AHFS requiring parenteral pharmacotherapy





Patient Disposition at Study Termination

COMPOSE 1
Total screened
n = 14 (7 centers)

Screen failure
n = 2

Safety population
n = 12

ITT population
n = 12 (6 centers)

COMPOSE 2
Total screened
n = 7 (2 centers)

Screen failure
n = 2*

Safety population
n = 4

ITT population
n = 4 (2 centers)

COMPOSE EARLY
Total screened
n = 73 (24 centers)

Screen failure
n = 10*

Safety population
n = 62

ITT population
n = 62 (20 centers)

Treatment arm	n
Placebo	3
Cinaciguat 50 µg/h	4
Cinaciguat 100 µg/h	2
Cinaciguat 150 µg/h	3

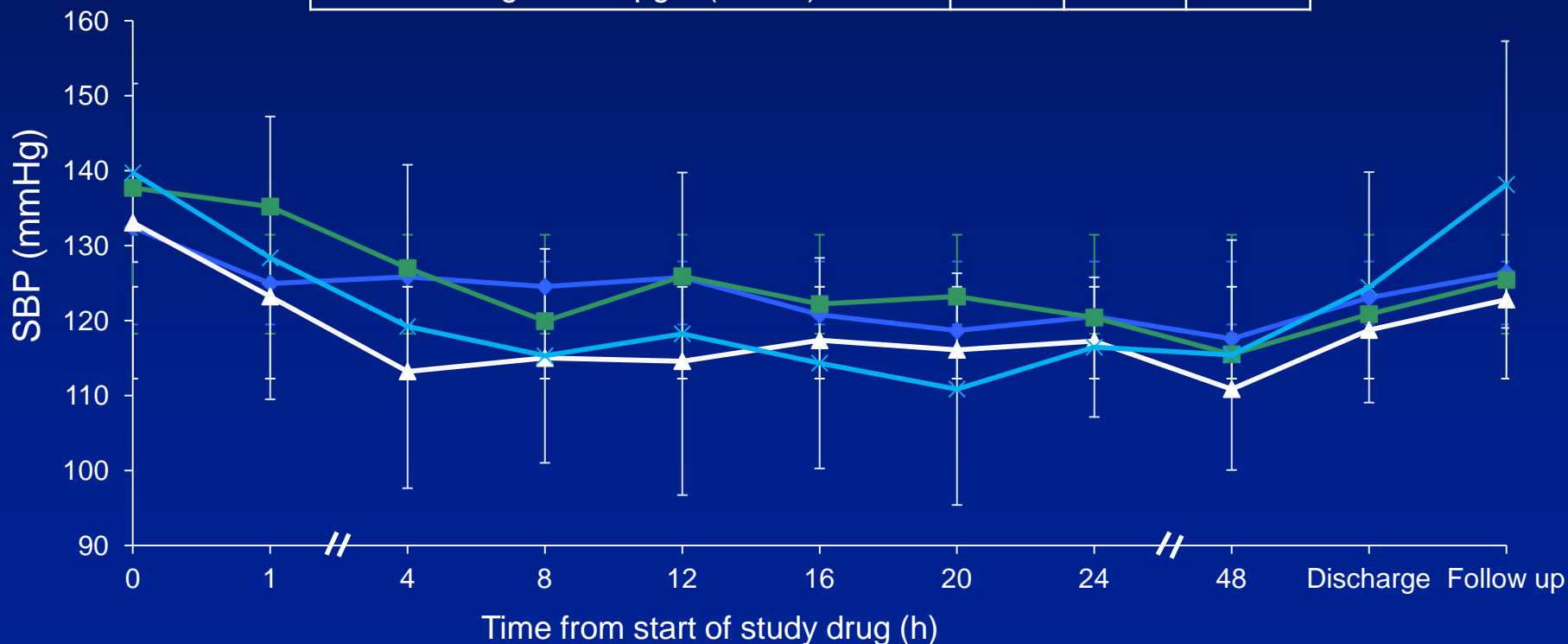
Treatment arm	n	n
Placebo	1	
Cinaciguat 10 µg/h	2	
Cinaciguat 25 µg/h	1	

Treatment arm	n
Placebo	19
Cinaciguat 50 µg/h	14
Cinaciguat 100 µg/h	15
Cinaciguat 150 µg/h	14

*One patient in COMPOSE 2 and one patient in COMPOSE EARLY were randomized but did not receive treatment

SBP by Cinaciguat Dose in COMPOSE EARLY

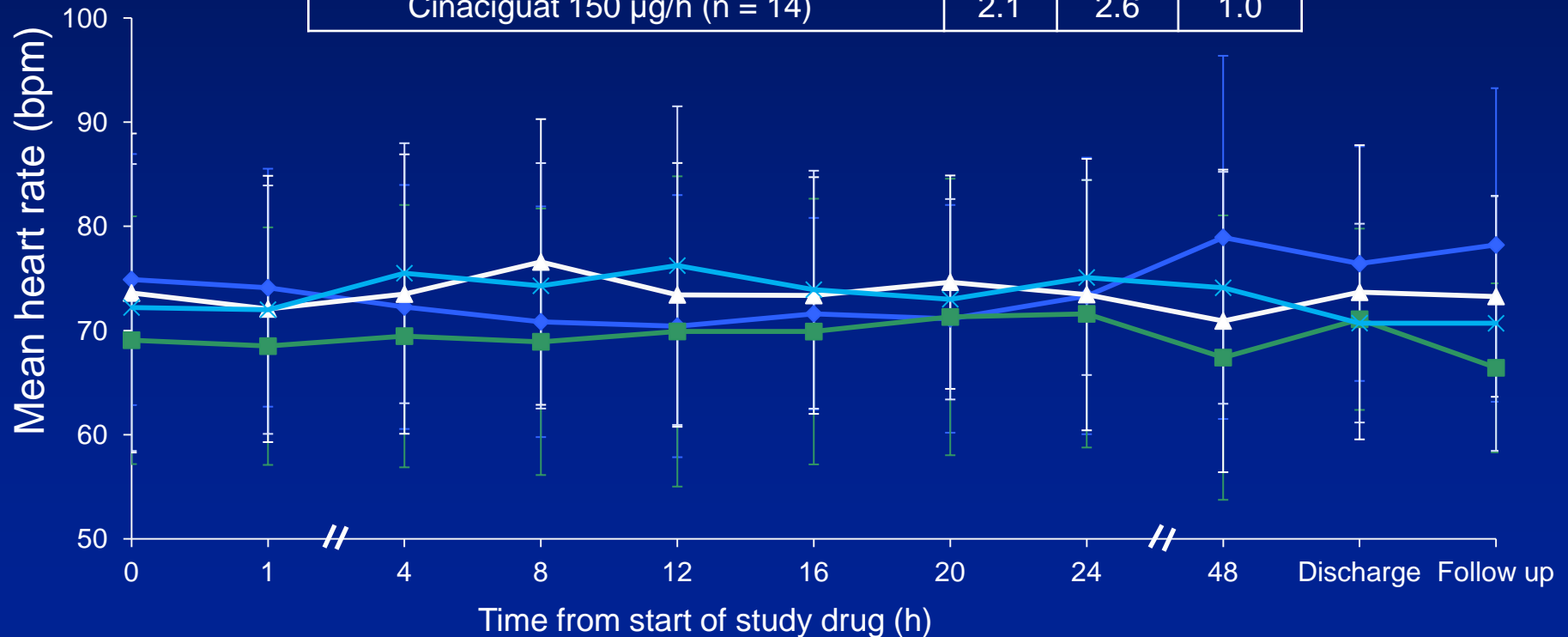
Mean change from baseline (mmHg)	8 h	24 h	48 h
◆ Placebo (n = 19)	-7.9	-11.9	-15.0
■ Cinaciguat 50 µg/h (n = 14)	-17.8	-17.2	-22.9
▲ Cinaciguat 100 µg/h (n = 15)	-15.1	-11.7	-20.3
✕ Cinaciguat 150 µg/h (n = 14)	-24.4	-22.5	-25.0



COMPOSE EARLY, ITT population

Heart Rate by Cinaciguat Dose in COMPOSE EARLY

Mean change from baseline (beats/min)	8 h	24 h	48 h
Placebo (n = 19)	-4.1	-1.6	2.2
Cinaciguat 50 µg/h (n = 14)	-0.5	1.0	-4.9
Cinaciguat 100 µg/h (n = 15)	4.9	2.6	-0.6
Cinaciguat 150 µg/h (n = 14)	2.1	2.6	1.0



COMPOSE EARLY, ITT population

Safety Summary

Number (%)	COMPOSE 1		COMPOSE EARLY	
	Placebo (n = 3)	Cinaciguat (n = 9)	Placebo (n = 19)	Cinaciguat (n = 43)
Patients with any AE	3 (100)	7 (78)	11 (58)	26 (60)
Patients with a treatment-emergent AE	2 (67)	5 (56)	9 (47)	22 (51)
Hypotension	0 (0)	2 (22)	1 (5)	12 (28)
Patients with a treatment-emergent SAE[†]	1 (33)	4 (44)	2 (11)	7 (16)
Ventricular extrasystoles	0 (0)	0 (0)	1 (5)	2 (5)
Ventricular tachycardia	1 (33)	2 (22)	1 (5)	2 (5)
Hypotension	0 (0)	1 (11)	0 (0)	2 (5)
Patients with AEs leading to study withdrawal	0 (0)	3 (33)	0 (0)	12 (28)
Deaths up to 35 days after last dose	0 (0)	1 (11)	0 (0)	1* (2)
Patients rehospitalized up to 35 days after last dose	0 (0)	0 (0)	2 (11)	5 (12)

[†]Serious adverse events occurring in ≥ 2 patients in any treatment group

*One patient died after the 30–35 days follow-up visit

Hypotension is a common adverse event in clinical studies of vasodilators in ADHF.

- Nesiritide (Ascend-HF Trial)
- Cinaciguat
- Levosimendane (Survive Trial)
- Milrinone (OPTIME-HF)
- Tezosentan (Veritas Trial)

At present, vasodilation cannot be recommended in ADHF

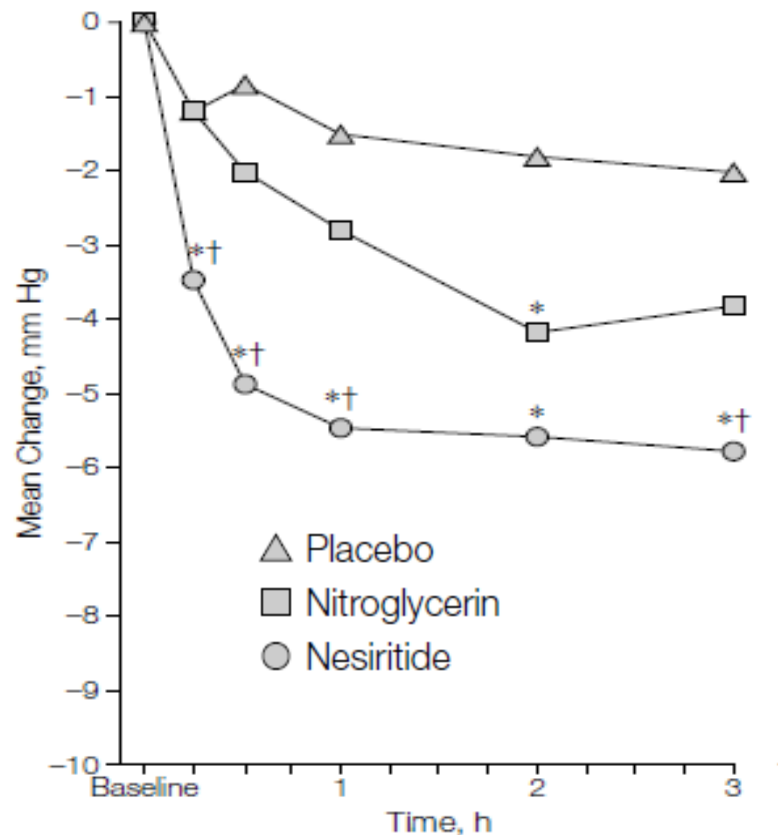
What About Nitrates ?

- A prevalent venodilatory effect
- Rapid decline of pulmonary venous and LV filling pressure
- Some improvement of pulmonary congestion
- Reduction of dyspnoea
- Decrease of oxygen consumption
- Vasodilation of epicardial vessels
- Increased myocardial blood flow
- Higher doses lead to arterial hypotension

Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure

A Randomized Controlled Trial

The VMAC Trial



asymptomatic and symptomatic hypotension was similar

	Baseline	0.5 h	1 h	2 h	3 h	
No. of Patients						
Nitroglycerin	60	58	58	58	56	59
Nesiritide	124	121	122	121	118	121
Placebo	62	62	62	62	61	62

Ergebnisse der Vasodilatator - Therapie bei akut dekompensierter HI

- a. Die positiv inotrope Therapie führt zu erhöhter Mortalität**
- b. Alle Vasodilantien verursachen Hypotension**
- c. nur wenige kontrollierte Outcome Studien**
- d. Nitrate sind am ehesten vertretbar**