

Neurohormonal players in heart failure

- Vasoconstrictor systems

- ✓ sympathetic
- ✓ renin-angiotensin
- ✓ aldosterone
- ✓ endothelin
- ✓ vasopressin

- Vasodilator systems

- ✓ bradykinin
- ✓ nitric oxide
- ✓ prostacyclin
- ✓ *natriuretic peptides*

Powerful neurohormonal vasoconstrictor forces *dominate*

Clinical uses of BNP

- diagnosis
- rule out symptomatic LV dysfunction
- staging
- risk stratification
- monitor/titrate therapy
- admission/discharge decisions

- therapy

Conventional Treatments of Acute Heart Failure

Diuretics

**Reduce
fluid
volume**

Vasodilators

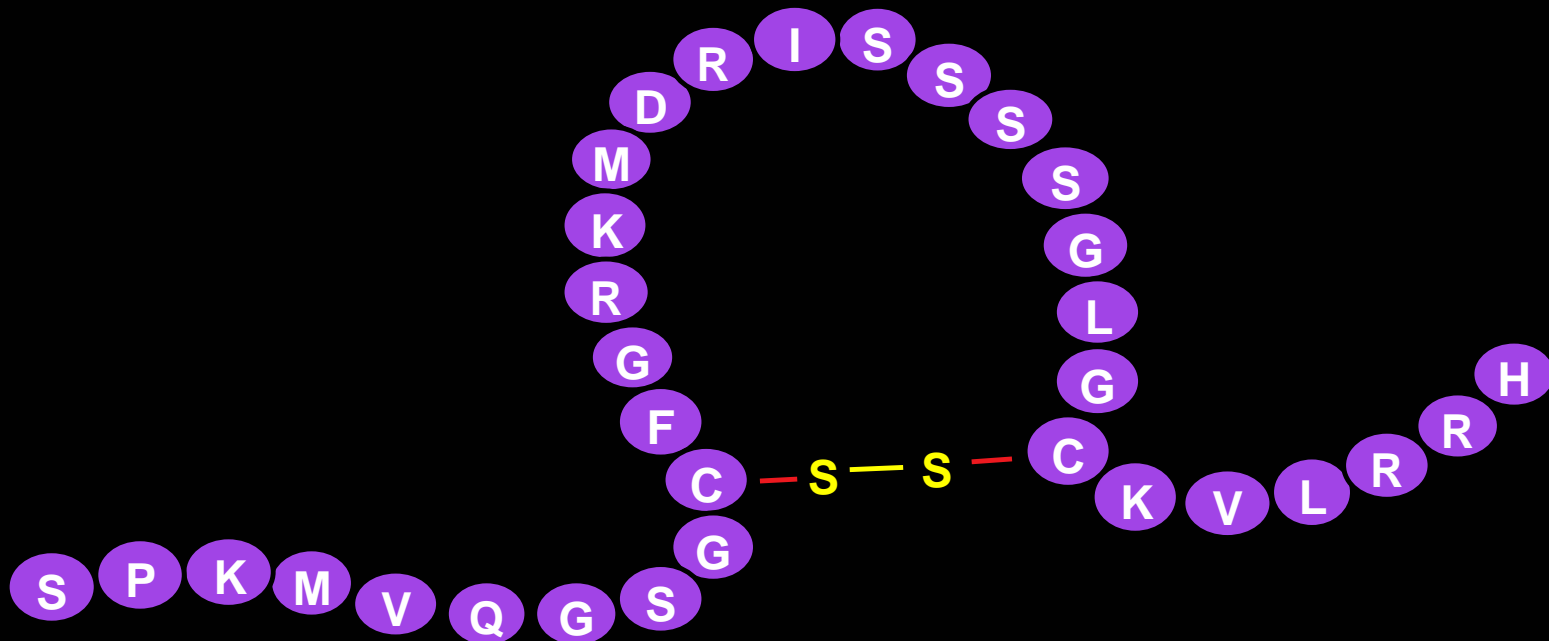
**Decrease
preload
and/or
afterload**

Inotropes

**Augment
contrac-
tility**

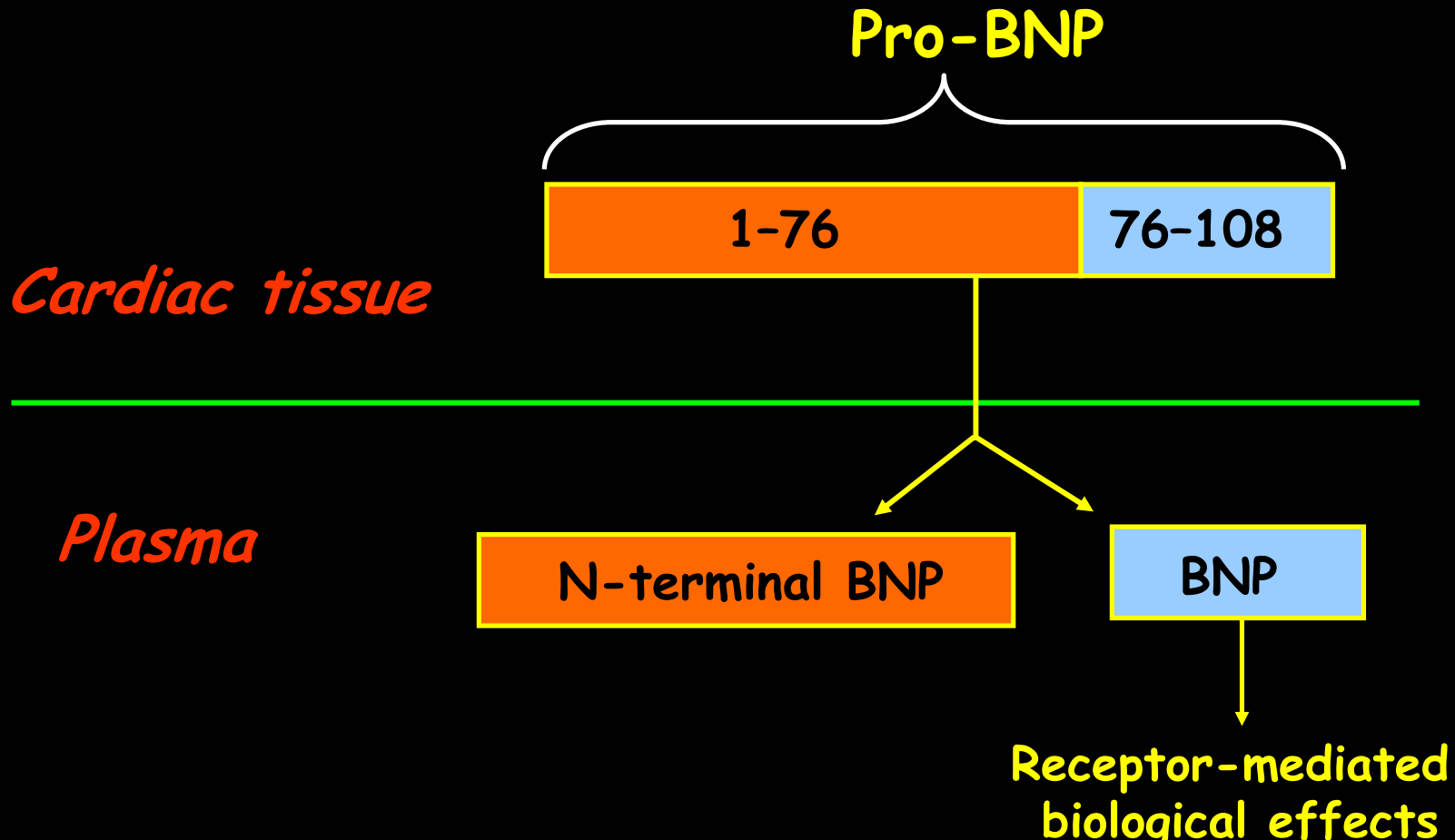
Nesiritide:

present and future
roles in HF management



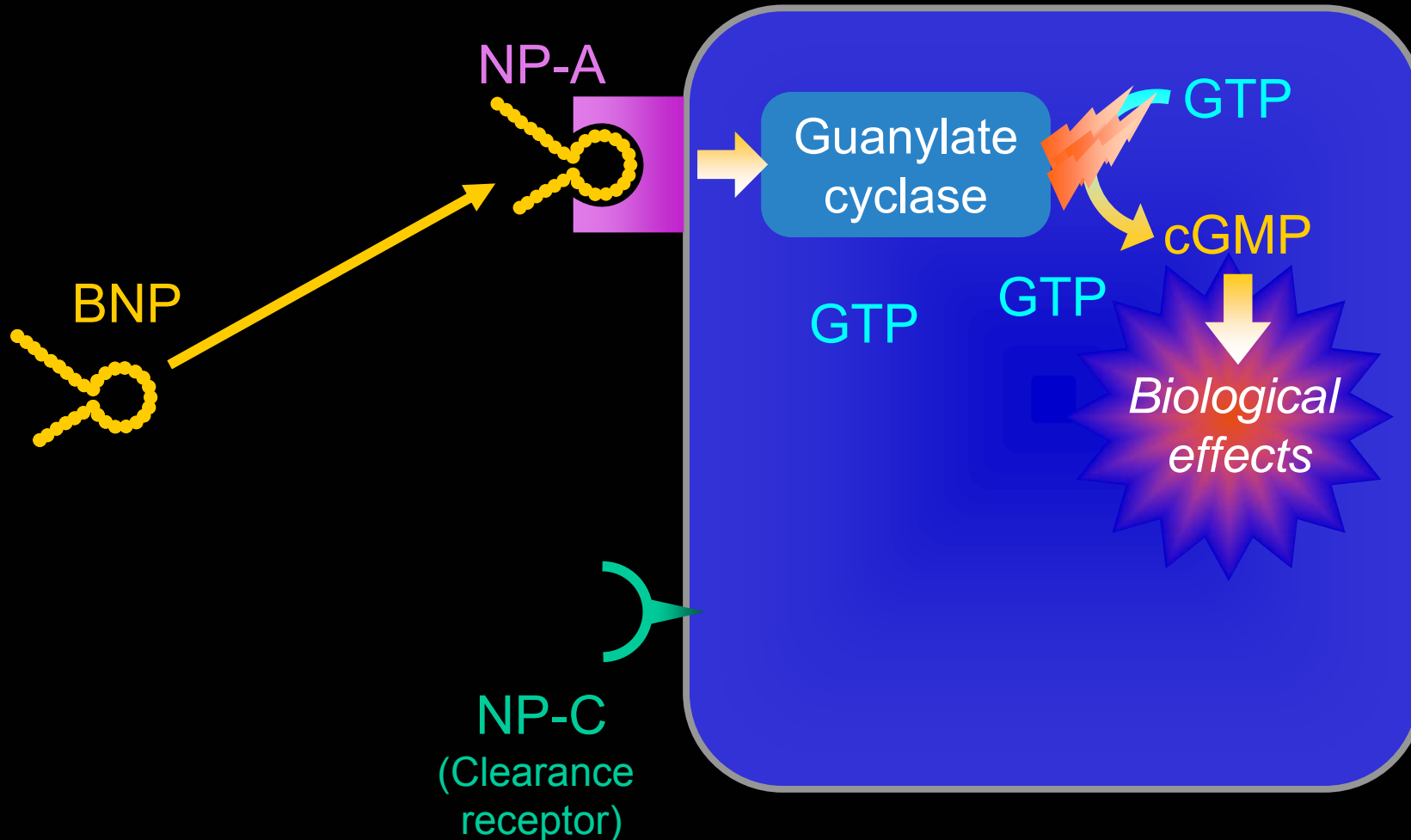
BNP storage and secretion

response to sustained increases in ventricular wall stretch, volume and pressure overload



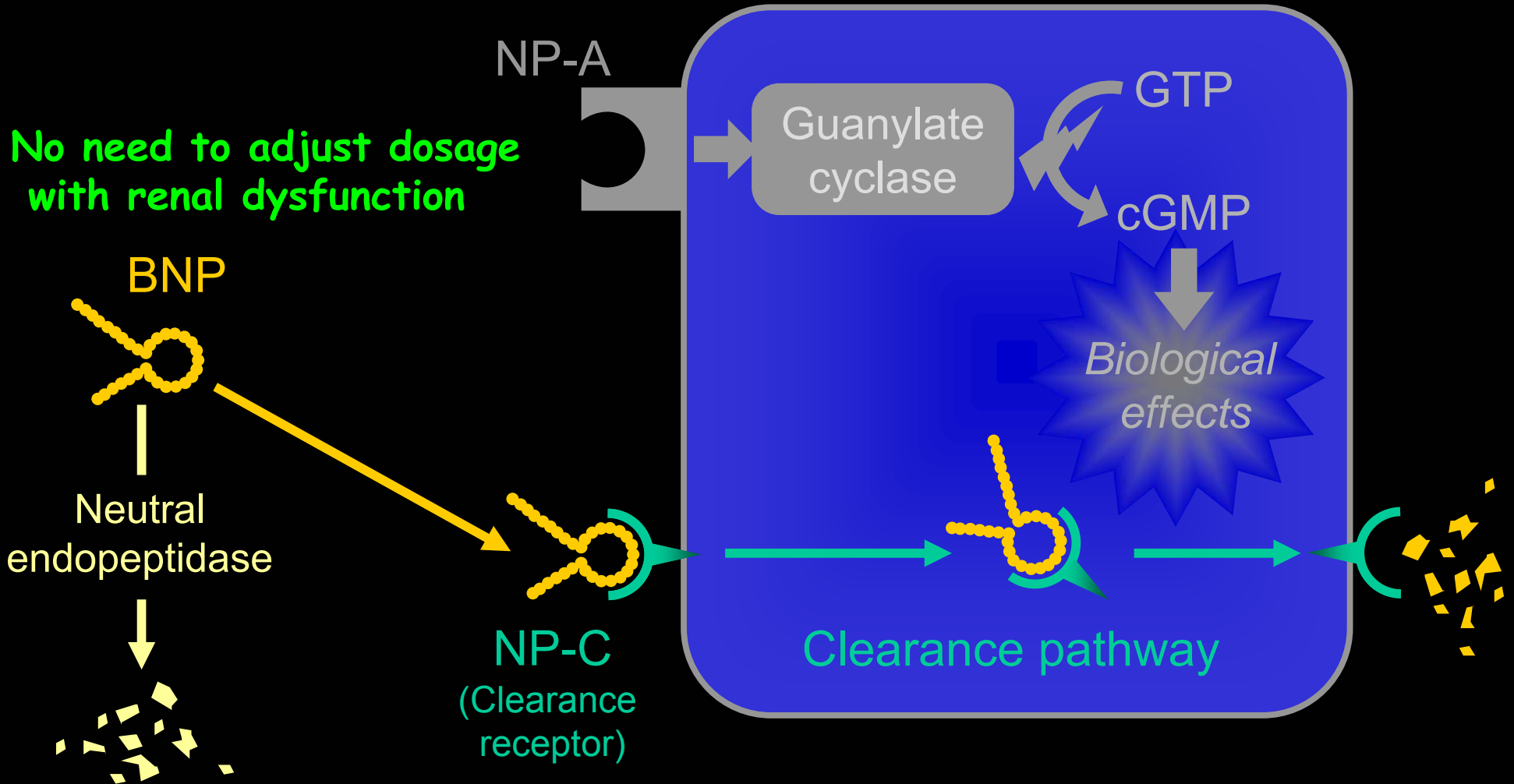
BNP mechanism of action

Vascular smooth muscle cell



BNP clearance

Vascular smooth muscle cell



BNP

- endogenous BNP is an adaptive response to pressure and volume overload
- ✓ vasodilation
- ✓ diuresis
- ✓ natriuresis
- ✓ neurohumoral inhibition
- ✓ coronary vasodilation
- *relief of dyspnoea and oedema*

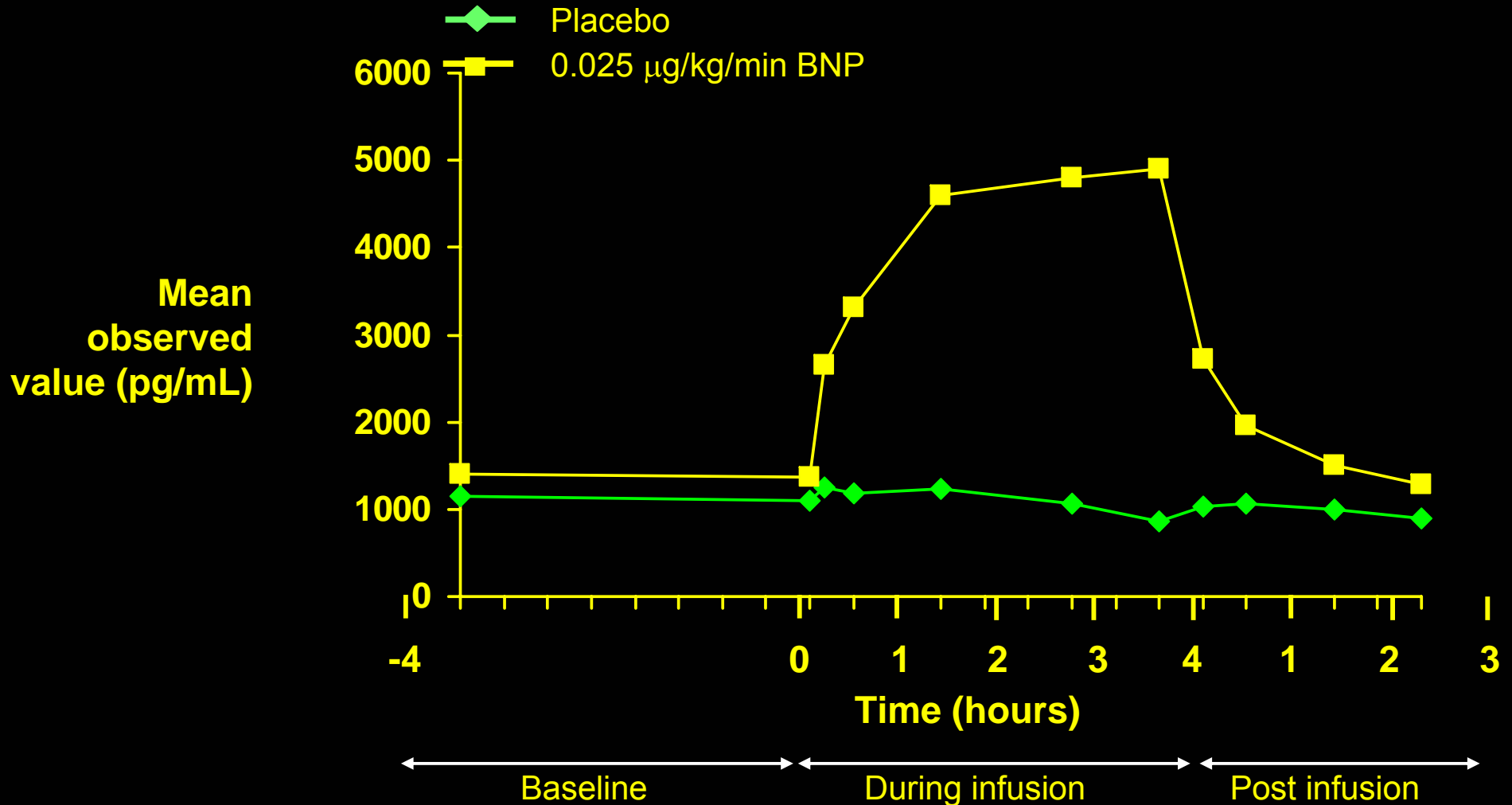
Why isn't endogenous BNP enough?

- Downregulated NP receptors
- Increase in clearance receptors
- Augmented NEP system
- Cleavage failure
- Decreased delivery of sodium to glomerulus and tubules

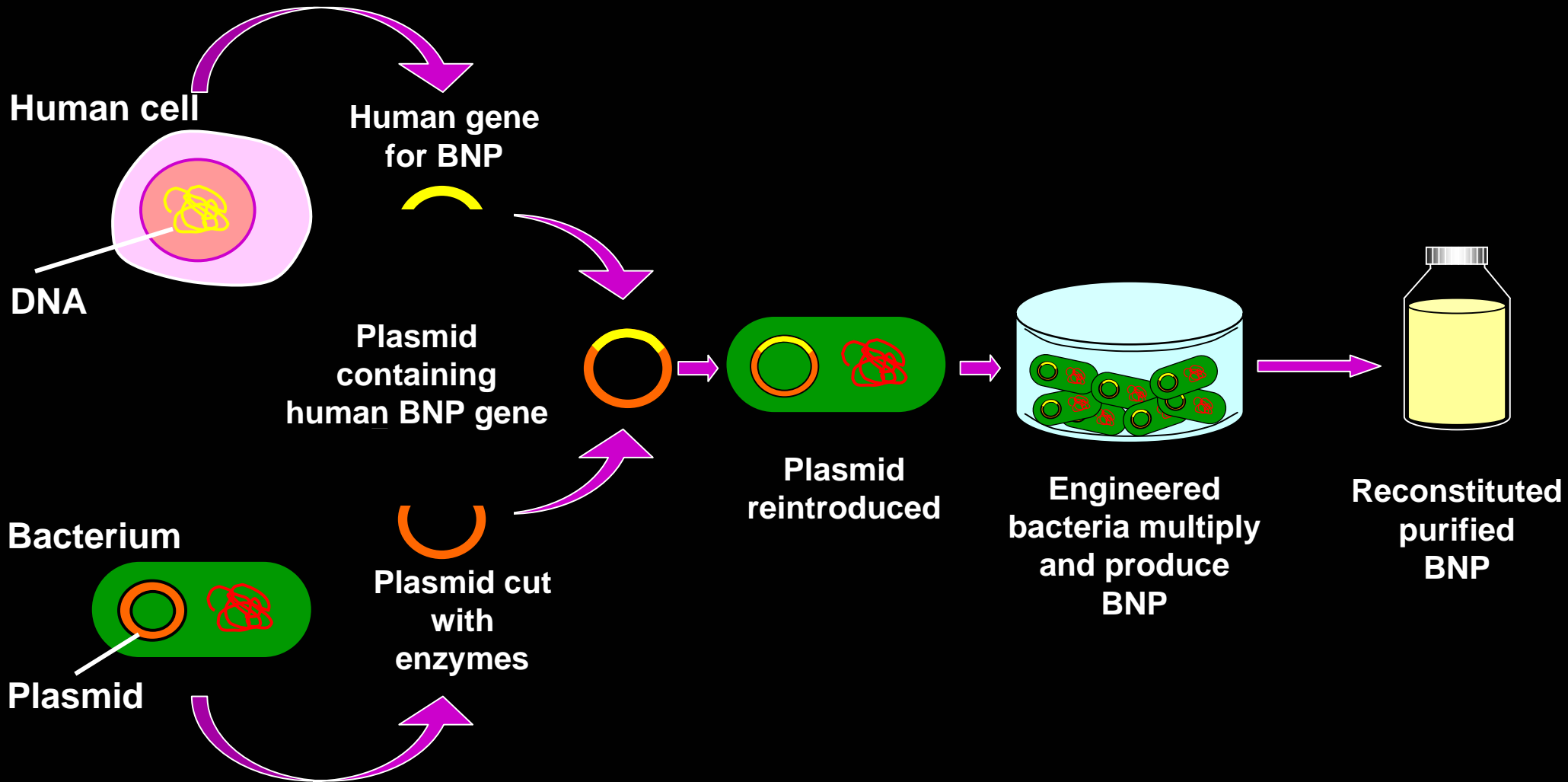
Therapeutic strategy

- ✓ Pharmacological not
physiological doses
of BNP

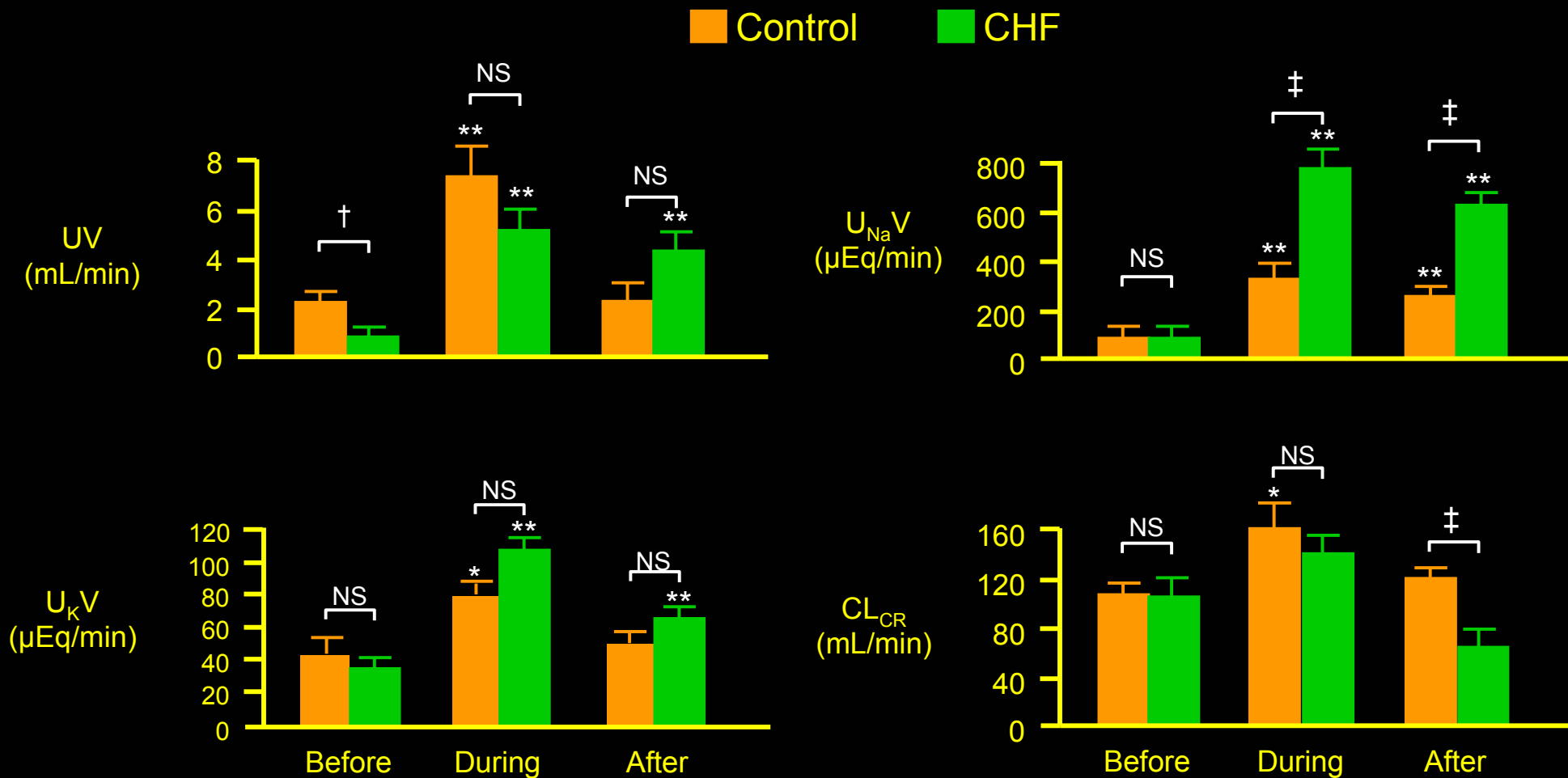
BNP plasma concentrations



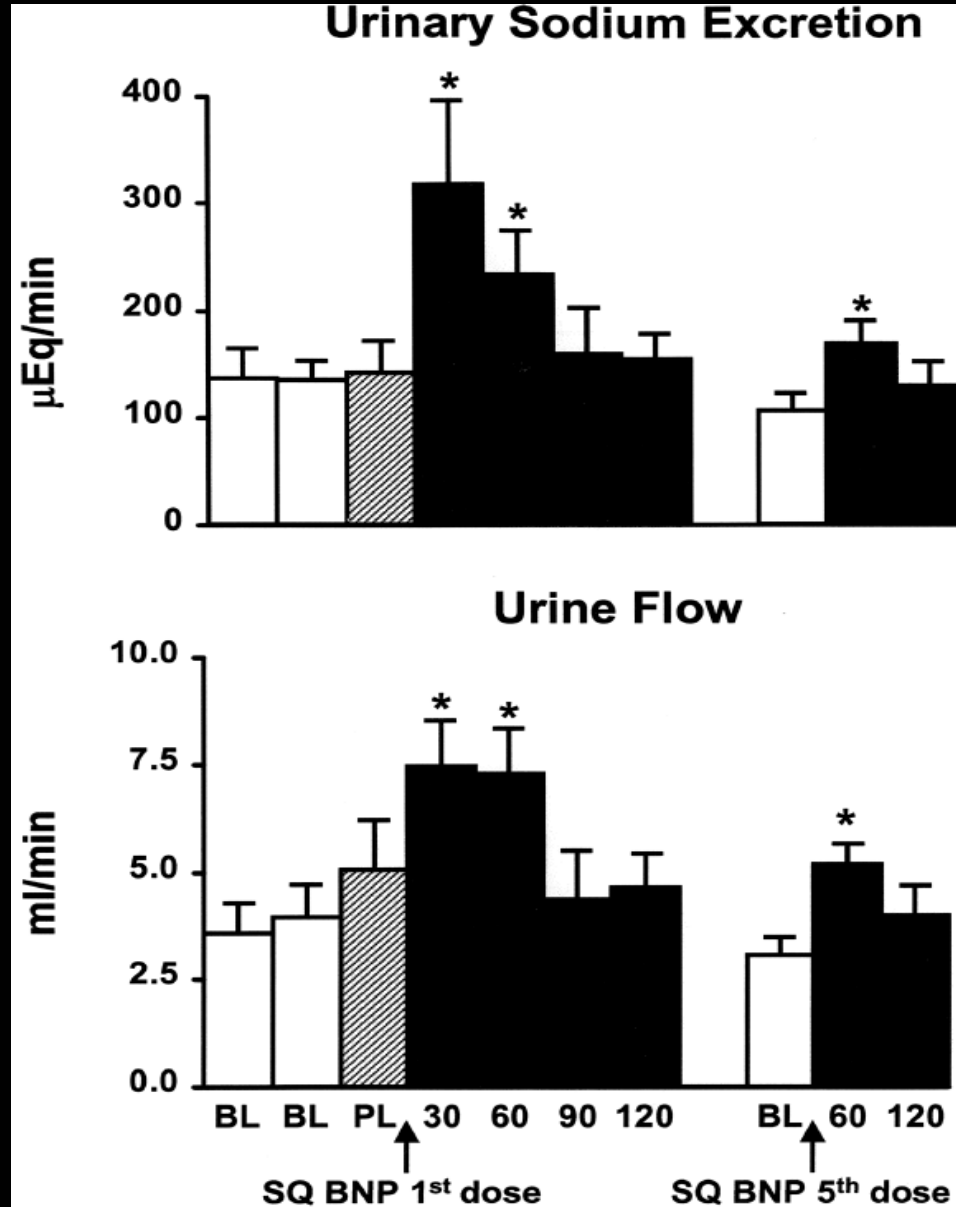
Nesiritide: recombinant DNA process



Renal responses to BNP infusion (0.1 $\mu\text{g}/\text{kg}/\text{min}$) in patients with CHF



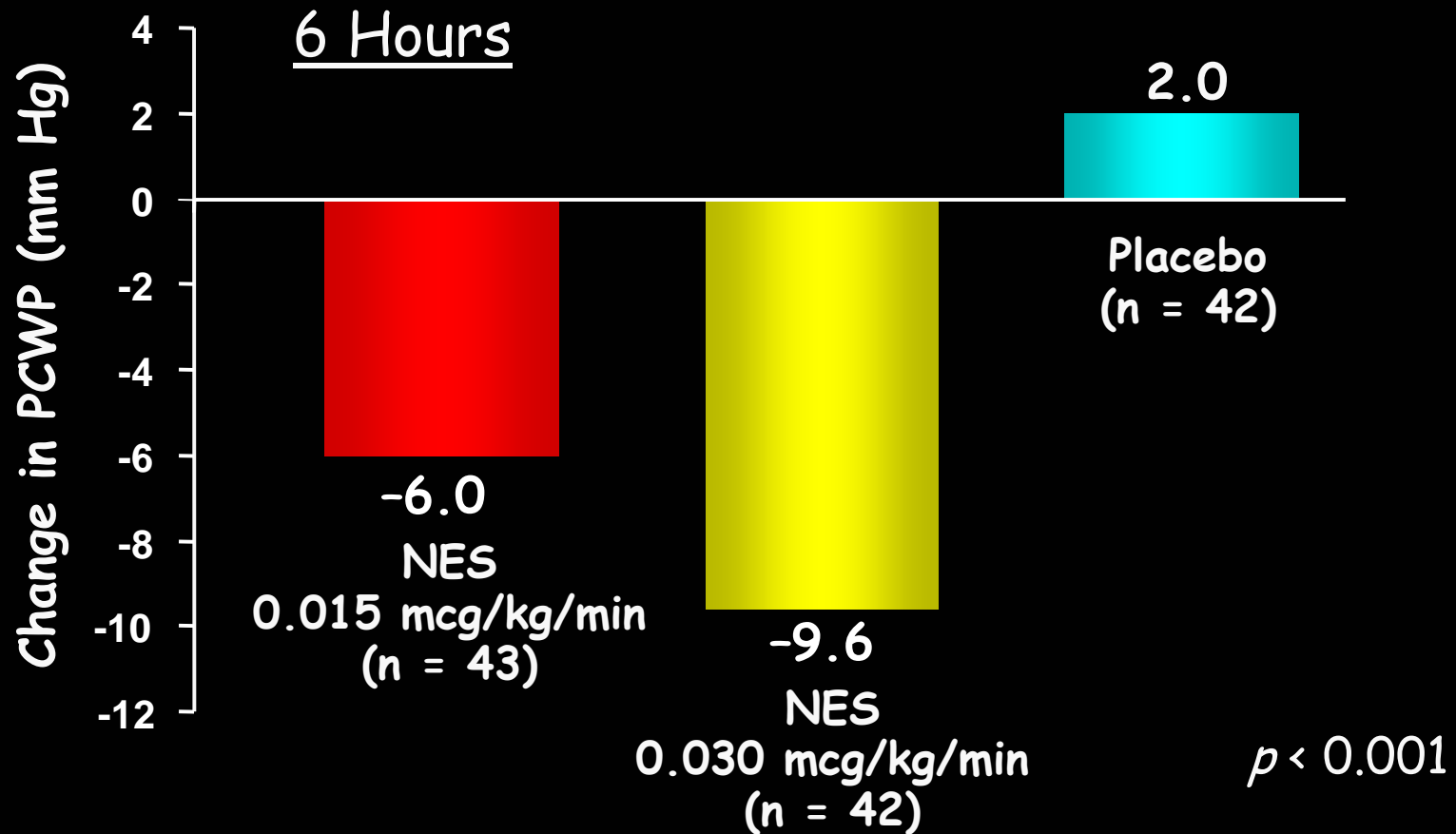
SC ADMINISTRATION OF BNP IN HEART FAILURE



Nesiritide - Clinical Studies

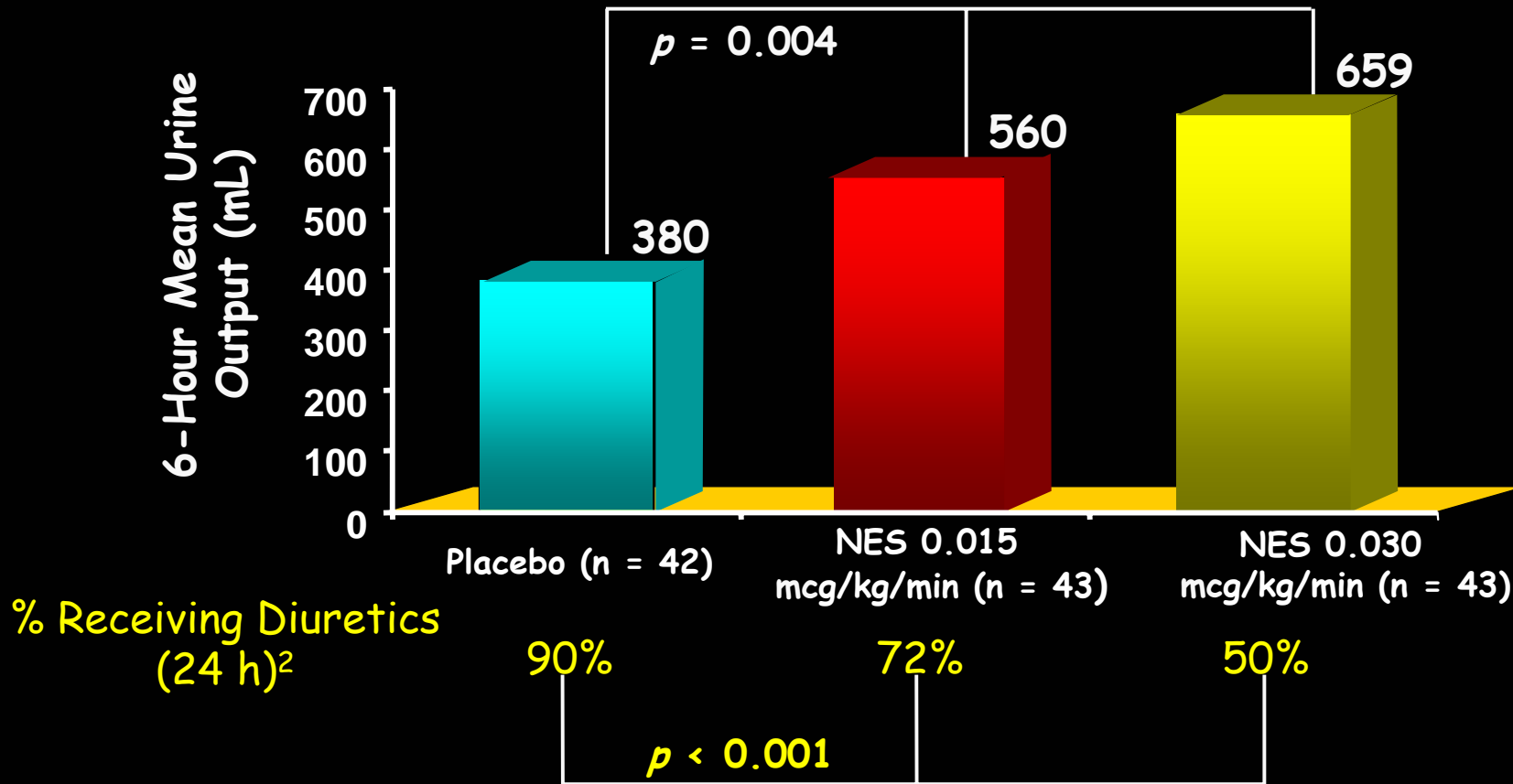
- nesiritide has been studied in 10 clinical pre-FDA approved studies
 - ✓ 941 Acute Decompensated Heart Failure patients requiring hospitalisation
 - ✓ NYHA class: II-III (61%), class IV (36%)
 - ✓ Mean age: 60 years

Nesiritide Efficacy Trial: Effect of Nesiritide on PCWP



300% of recommended dose

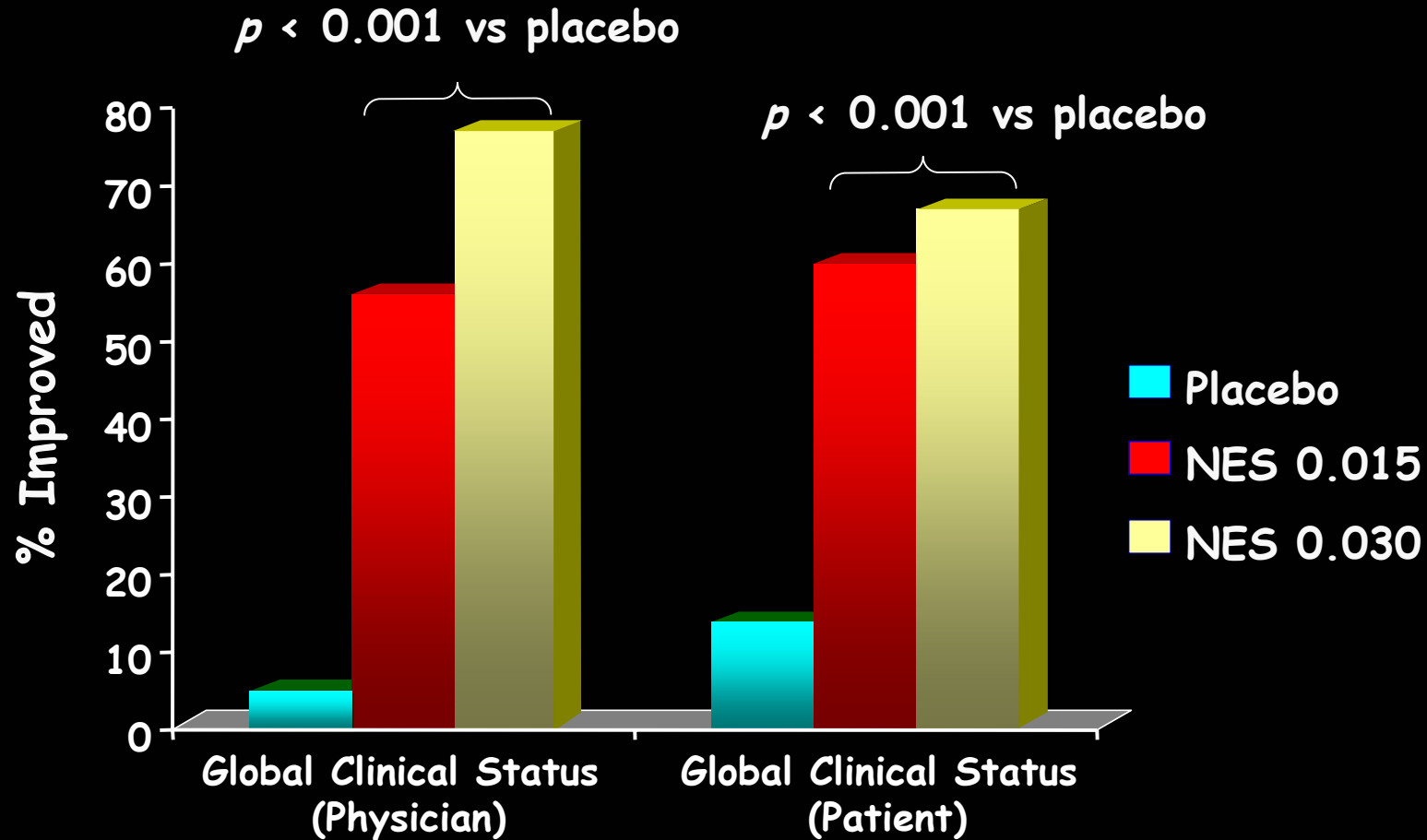
Nesiritide Efficacy Trial: Effects of Nesiritide on Urine Output¹ and Diuretic Use²



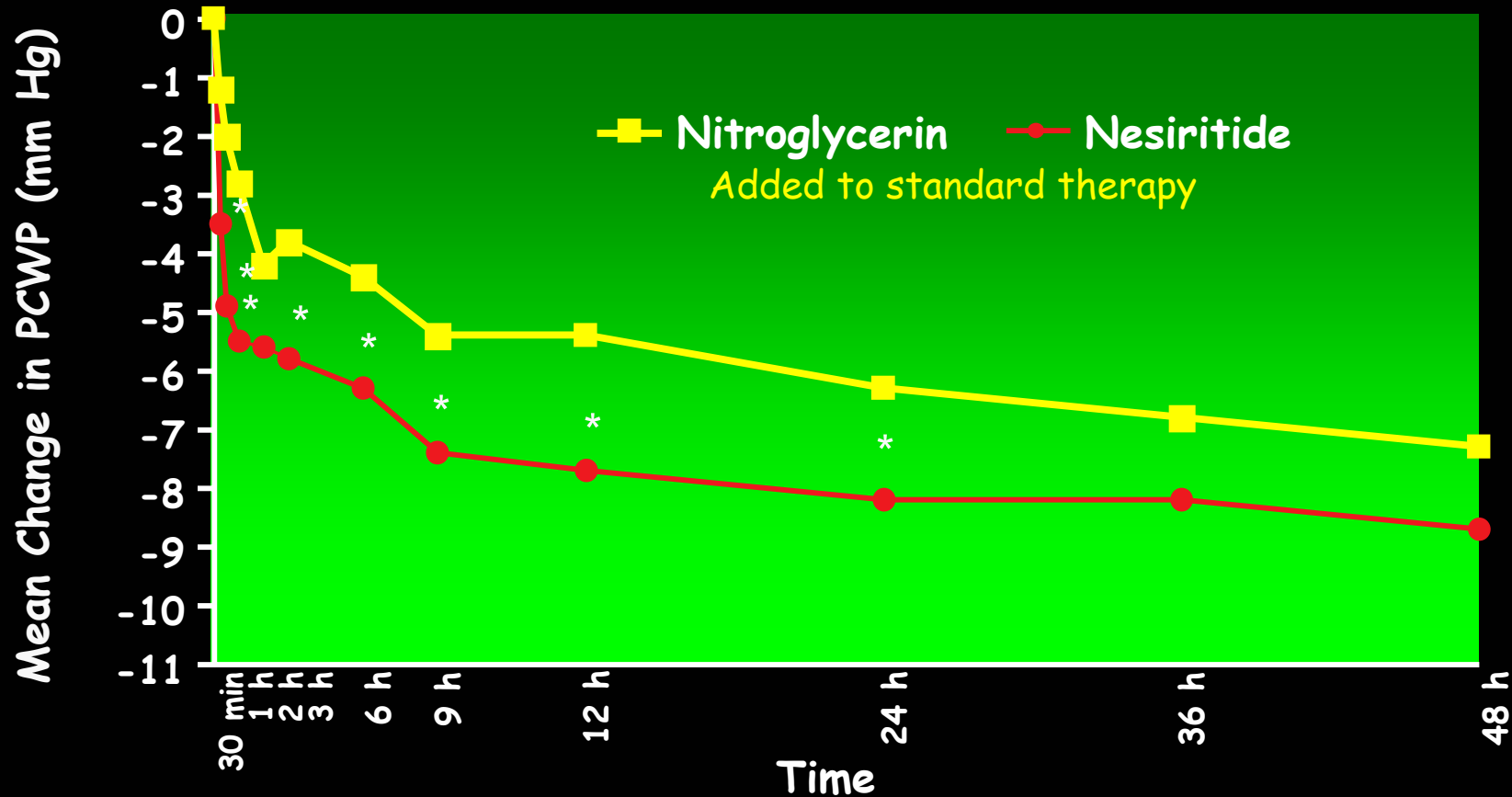
1. N Engl J Med 2000;343:246-253

2. Data on file, Scios Inc

Nesiritide Efficacy Trial: Clinical Outcomes



VMAC: PCWP Through 48 Hours



* $p < 0.05$ nesiritide vs nitroglycerin

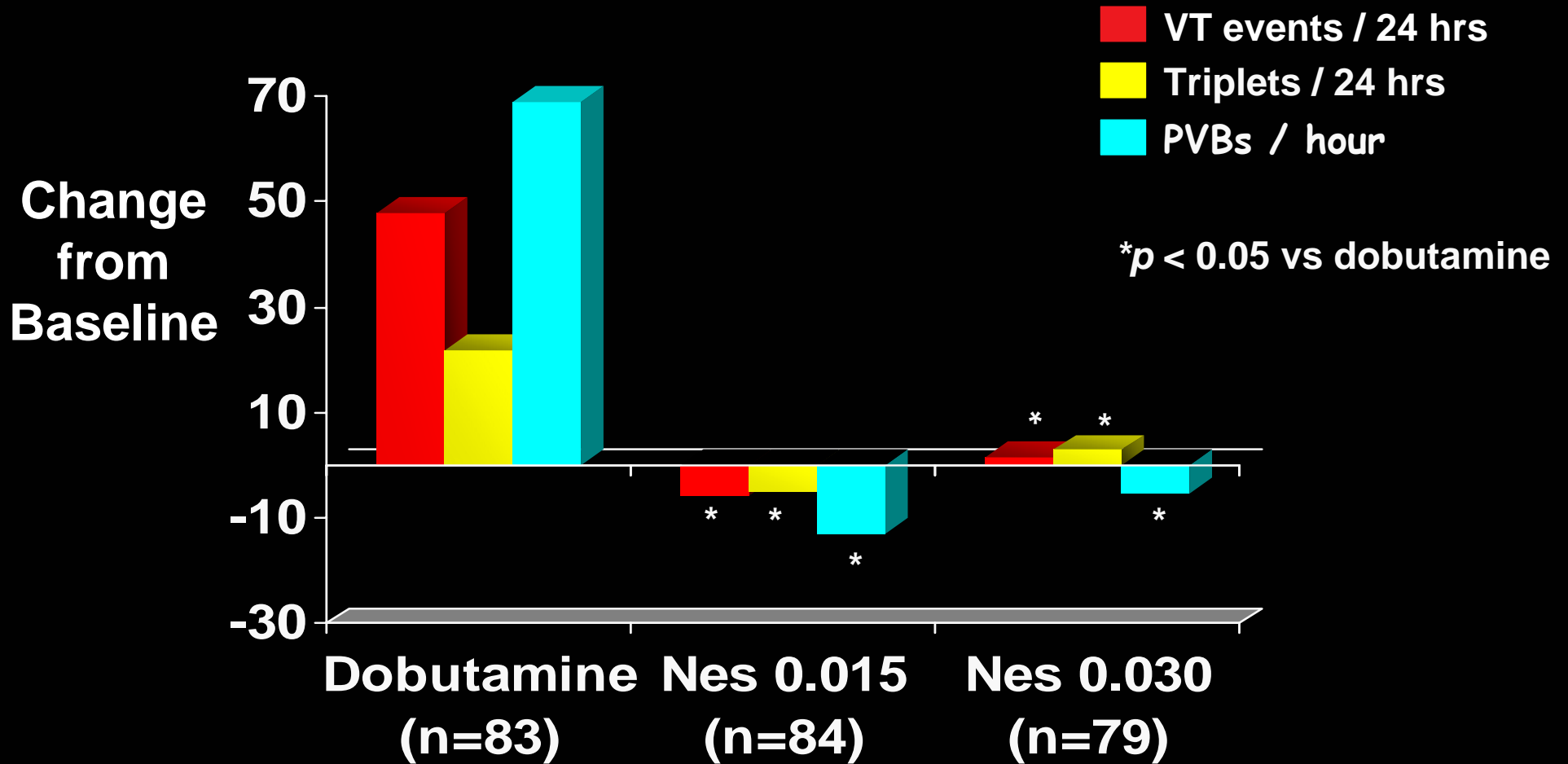
Primary endpoints

Adverse Events During Treatment Standard Care Plus Nesiritide or IV Nitroglycerin

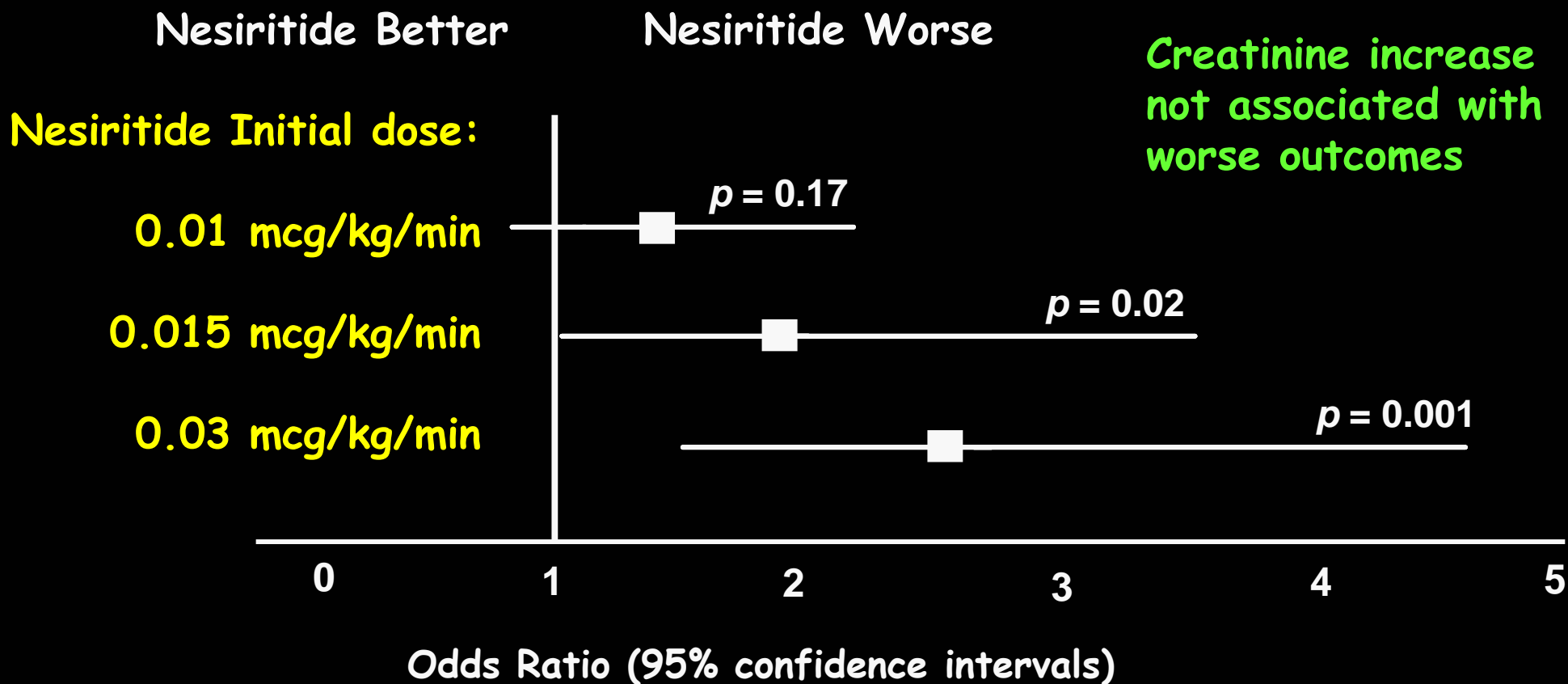
Most Common Adverse Events through 24 Hours (VMAC trial)	Nesiritide (n = 273)	Nitroglycerin (n = 216)
Symptomatic hypotension	4%	5%
Asymptomatic hypotension	8%	8%
Ventricular tachycardia (VT)	3%	5%
Nonsustained ventricular tachycardia	3%	5%
Headache	8%*	20%
Abdominal pain	1%*	5%
Nausea	4%	6%

* $p < 0.05$, compared to nitroglycerin

PRECEDENT: Nesiritide vs. Dobutamine



Odds Ratios Of SCr increase >0.5 mg/dL by Nesiritide Initiation Dose

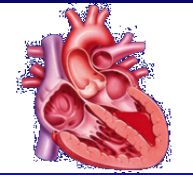


Includes data from 5 studies: Mills et al., Efficacy, Comparative, PRECEDENT, and VMAC (n = 1,222)

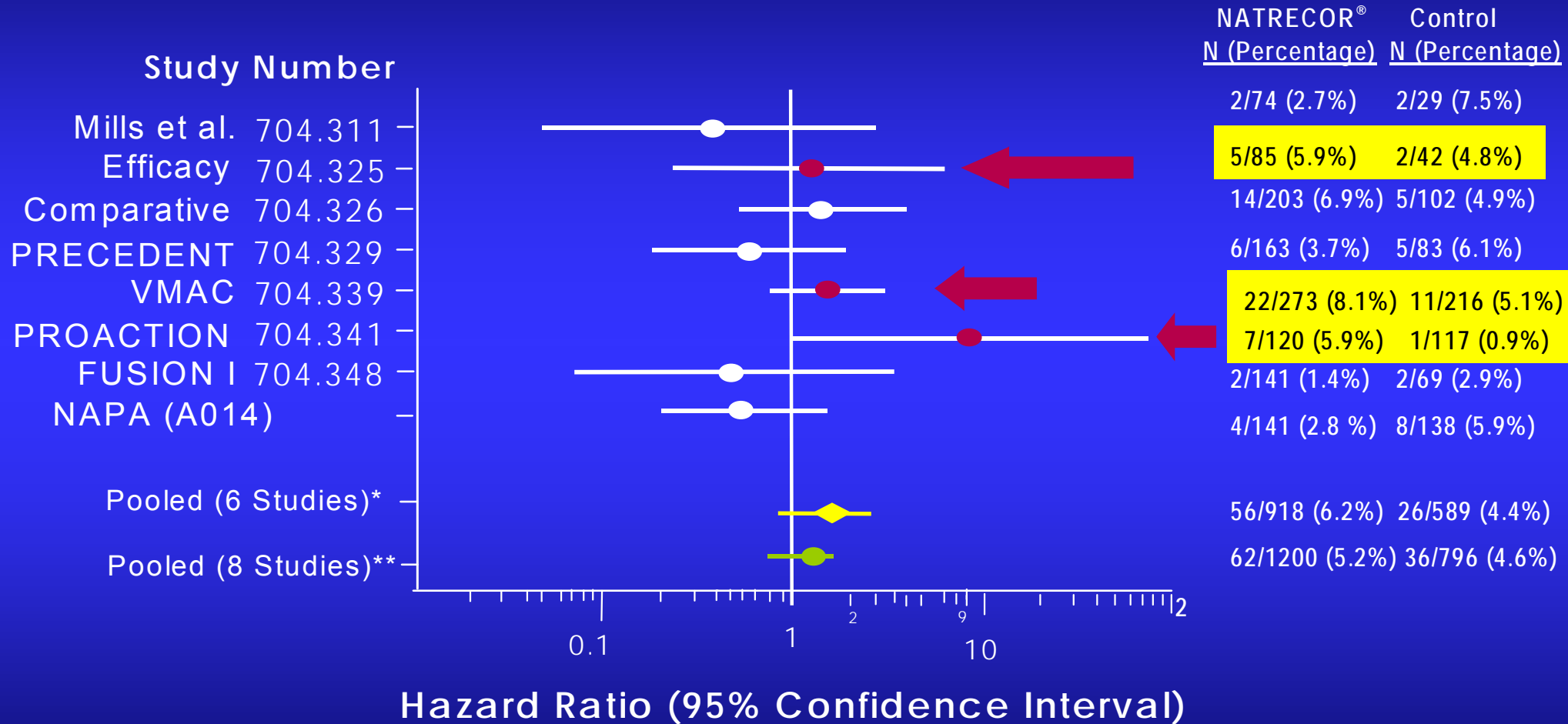
Unadjusted 30-day mortality by treatment in 3 randomized trials

Randomized trial	Nesiritide (%)	Control (%)	RR (95% CI)
Nesiritide Study Group Efficacy Trial (NSGET) (n=127)	7.1	4.8	1.48 (0.31-7.03)
Vasodilatation in the Management of Acute Congestive Heart Failure (VMAC) (n=498)	8.6	5.5	1.56 (0.80-3.04)
Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor (PROACTION) (n=237)	4.2	0.9	4.88 (0.58-41.1)
Combined	7.2*	4.0	1.74 (0.97-3.12)*

* p=0.059



30-Day Mortality Hazard Ratios



Note: Arrows depict studies included in JAMA publication

30-Day Mortality

All nesiritide controlled trials with 30-day mortality data

	Nesiritide	Control
Mills et al. (311)	2.7% (2/74)	7.5% (2/29)
Efficacy (325)	5.9% (5/85)	4.8% (2/42)
Comparative (326)	6.9% (14/203)	4.9% (5/102)
PRECEDENT (329)	3.7% (6/163)	6.1% (5/83)
VMAC (339)	8.1% (22/273)	5.1% (11/216)
PROACTION (341)	4.2% (5/120)	0.9% (1/117)
FUSION I (348)	1.4% (2/141)	2.9% (2/69)
Pooled (6 studies)	5.9% (54/918)	4.4% (26/589)
Pooled (7 studies)	5.3% (56/1059)	4.3% (28/658)

180-Day Mortality:

All nesiritide controlled trials with 180-day mortality data

	Nesiritide	Control
Efficacy (325)	23.1% (19/85)	19.3% (8/42)
Comparative (326)	20.8% (42/203)	23.5% (24/102)
PRECEDENT (329)	16.3% (26/163)	22.2% (18/83)
VMAC (339)	25.1% (67/273)	20.8% (44/216)
Pooled (4 studies)	21.7% (56/1059)	21.5% (28/658)

Expert Panel Report

Chaired by Professor Eugene Braunwald on June 8, 2005

- Effect of Nesiritide on Renal Function:

- The mechanism and clinical significance of nesiritide's renal effects are unclear
- There is no evidence that nesiritide improves renal function

- Effect of Nesiritide on Mortality:

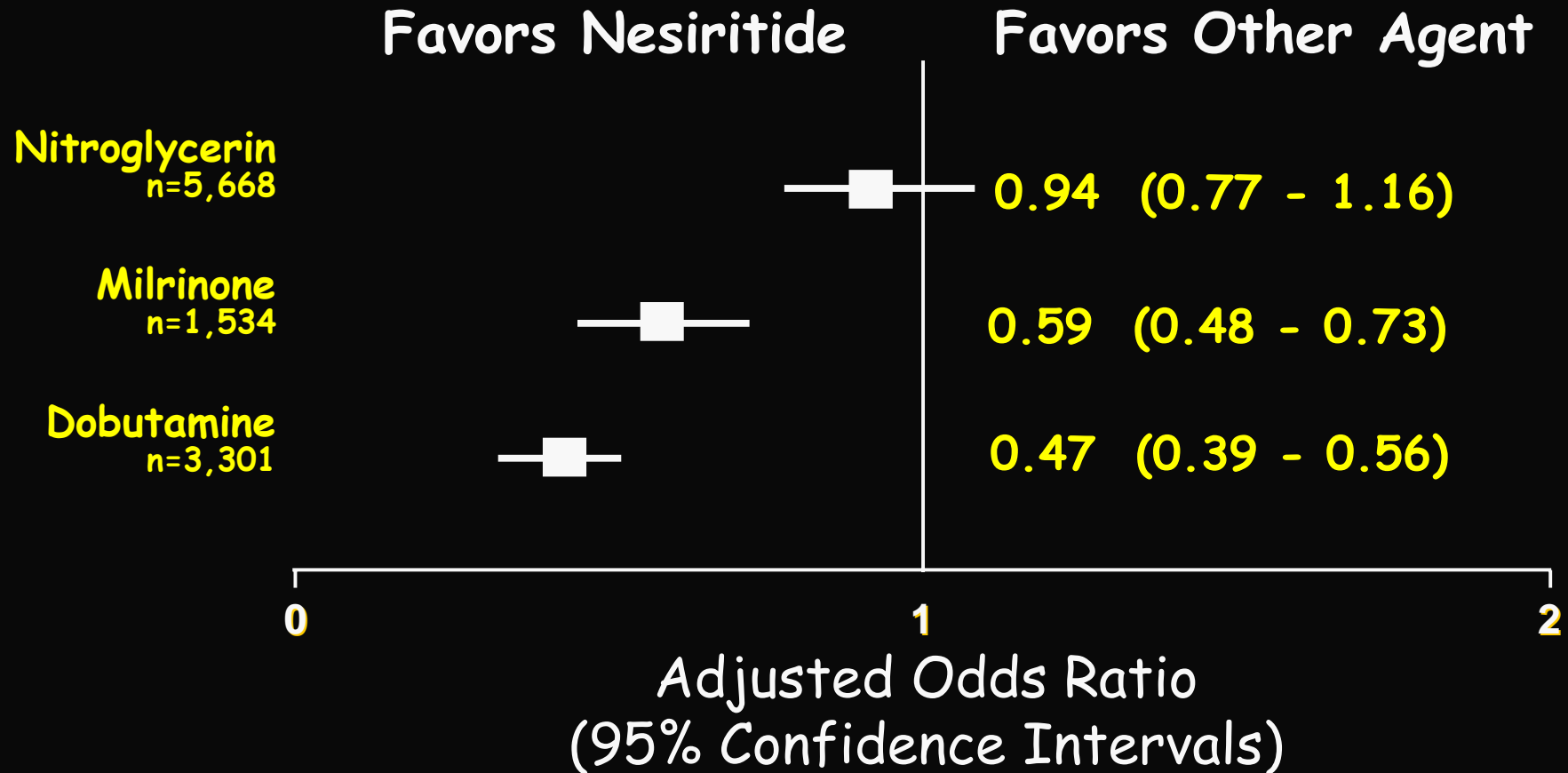
- Completed trials show a trend toward increased mortality at 30 days
- There are potentially important imbalances in baseline characteristics and in other treatments received concomitantly and the trials differ with respect to the treatments with which nesiritide was compared
- No increased hazard is observed at 180 days

- Regarding Nesiritide Clinical Trials:

- The panel strongly recommends continued enrollment in ongoing clinical trials
- The panel endorses Scios' plan to conduct a large outcomes trial

ADHERE

In-Hospital Mortality and Use of IV Vasoactive Medications **180,000** hospital admissions



Identifying the Appropriate Patient

- Nesiritide is appropriate for IV treatment of patients with acutely decompensated congestive heart failure severe enough to require hospitalization

Contraindications

- Nesiritide should not be used as primary therapy for patients with cardiogenic shock or in patients with a systolic blood pressure < 90 mm Hg

Warnings

- Should be avoided in patients suspected of having low cardiac filling pressures
- may cause hypotension and blood pressure should be monitored closely
- associated with a dose dependent increase in serum creatinine

GUIDELINES for the EARLY STABILIZATION and TREATMENT of ACUTE or DECOMPENSATED HEART FAILURE in the EMERGENCY DEPARTMENT

Stat HF Consensus Panel

Emergency Department Patient with Suspected Acute or Decompensated Heart Failure

Imminent Respiratory Failure Anticipated

Yes

Options:

- BiPAP/CPAP Trial
- Endotracheal intubation
- If BP elevated consider rapid vasodilation with nitroglycerin or nitroprusside
- ICU admission

No

Cardiogenic Shock or Symptomatic Hypotension?

Yes

Options:

- Inotropes
- Consider hemodynamic monitoring
- ICU admission

No

Perform History & Physical Exam

Hypoperfusion (cool extremities) or Altered Mental Status?

Yes

Perform Work-Up

- BNP
- ECG
- CXR
- O₂SAT
- Cardiac markers
- CBC
- Electrolytes

Decompensated Heart Failure Likely?

No

Consider Other Diagnosis & Treatment

Unsure

If diagnosis is clear initiate work-up simultaneously with treatment

Critical Severity
(~10% of all HF patients)

- Oxygen
- Loop diuretic
- Nesiritide, nitroglycerin, or nitroprusside

Moderate Severity
(~80% of all HF patients)

- Oxygen
- Loop diuretic
- Nesiritide
- Nitropaste or SL nitroglycerin PRN
- Patient Education

Low Severity
(~10% of all HF patients)

- Oxygen
- Nitropaste, or SL nitroglycerin
- Loop diuretic trial
- Patient education

Disposition

ICU

Telemetry or Observation Unit

Observation Unit or Medical Floor

Discharge Home

The Estimate of Severity is Increased by:

- Abnormal vital signs or oximetry
- History of multiple HF admits
- Chronic renal insufficiency
- Weight above normal dry weight
- ECG with LVH, elevated BP
- ↑ BUN to BUN >45mg/dL, creatinine >2.7mg/dL
- Known low ejection fraction
- Poor response to therapy

Concurrent with Work-up

Initiate early ED therapy based on clinical estimate of severity

The Cleveland Clinic
Center for Continuing
Education

Ongoing Clinical Trials with Nesiritide

Trial	Intent	Size (n)
FUSION II	<u>F</u> ollow- <u>U</u> p <u>S</u> erial <u>I</u> nfusions of <u>N</u> esiritide in patients with chronic decompensated HF	920
TMAC	<u>T</u> ransplant-eligible HF Patients with Continuous <u>I</u> nfusion of Nesiritide or Placebo (28 days)	120

Planned Clinical Trial with Nesiritide

FPI

Q1 2007

Trial	Intent	Size (n)
Outcomes Trial	Efficacy and Safety of Nesiritide vs. Placebo in the Management of Patients with Acute Decompensated Heart Failure	<u>7000</u>

Ideal Agent for Acute Heart Failure

- Vasodilation
- Rapidly decreases ventricular filling pressures
- Rapidly decreases symptoms of congestion
- Does not increase HR or myocardial oxygen demand
- Not proarrhythmic
- No tachyphylaxis
- Provides neurohormonal suppression
- Promotes diuresis/natriuresis
- Conveniently dosed
- Well tolerated

Summary:

Nesiritide Mortality Data

- Studies were not designed or powered to address mortality
- Total number of events is small
- Confidence intervals for hazard ratios are wide
- Baseline imbalances in risk factors influence mortality rates
 - Data confounded by presence of co-existing multiple risk factors

We know a lot more about managing acute MI than decompensated heart failure

	Decompensated heart failure	Acute myocardial infarction
Hospitalisations (1997 US)	957,000	800,000
Mortality	High	High
Readmission rate	High	Low
Consensus definition	No	Yes
Guidelines for therapy	Yes	Yes
Guidelines for risk stratification	No	Yes
Large randomized trials	No	Yes
MEDLINE citation (1997-2001)	180	5080
	Update 2006??????	

VMAC Baseline Imbalances

	Nesiritid e (n = 273)	Control (n = 216)	p value
Sex, male	73%	64%	.04
Any ACS in prior 7 days	10%	16%	.05
History of angina	14%	7%	.04
History of arrhythmia	42%	34%	.08
History of AICD/PM, sudden death, or ventricular fibrillation	31%	24%	.09
History of ventricular tachycardia	31%	22%	.03
Dobutamine/dopamine use at baseline	21%	10%	.001
Inotrope use prior to study drug	24%	14%	.01

NAPA Trial

Nesiritide Administered Peri-Anesthesia
in Patients Undergoing Cardiac Surgery

Objective

Explore the impact of nesiritide on postoperative renal function, hemodynamics, clinical outcomes, and safety in patients undergoing CABG surgery utilizing CPB

Patient

N = 279 with advanced HF, EF < 40%

Population

- NYHA Class IV, or Class III & CrCl < 60
- 2 hospitalizations within past year

FUSION II Trial

Follow-Up Serial Infusions Of Nesiritide

Objective

To evaluate the efficacy and safety of nesiritide administered as serial outpatient infusions

Patient

N = 900 with advanced HF, EF < 40%

Population

- NYHA Class IV, or Class III & CrCl < 60**
- 2 hospitalizations within past year**

TMAC Trial

Transplant-eligible Management of Congestive Heart Failure

Objective

Assess the safety and efficacy of nesiritide administered as a 28-day continuous infusion in cardiac transplant candidates receiving dobutamine or milrinone

N = 120

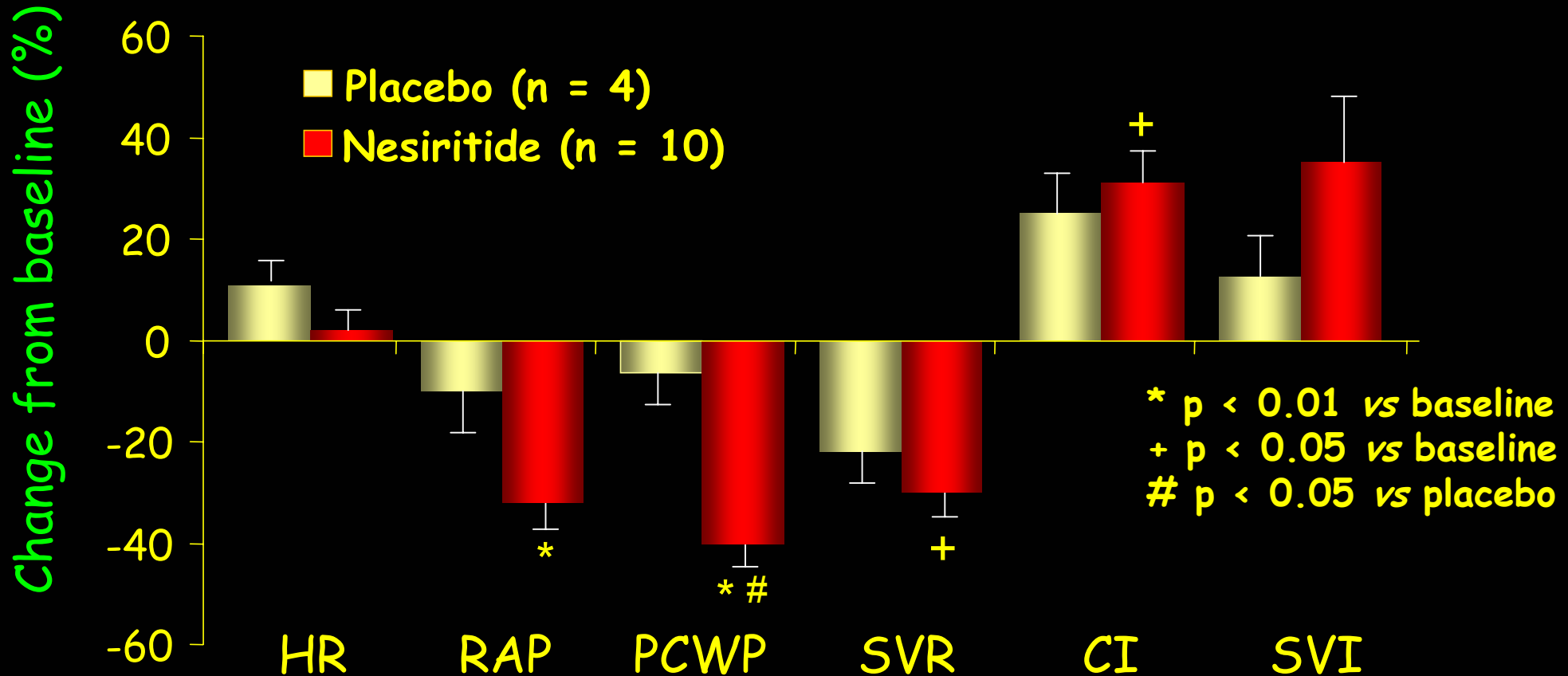
Patient

Patients with UNOS Status 1B criteria

Population

Hemodynamic Effects of Nesiritide in Heart Failure Patients

A Randomized, Double-Blind, Placebo-Controlled Trial



Rate of SCr Increases > 0.5mg/dL in Nesiritide Clinical Trials

	Control	Nesiritide
Mills et al. (311)	10% (3/29)	11% (8/74)
Efficacy (325)	2% (1/41)	14% (12/85)
Comparative (326)	5% (5/99)	15% (30/197)
PRECEDENT (329)	11% (9/81)	17% (28/162)
VMAC (339)	21% (45/212)	27% (73/268)
NAPA (A014)	23% (31/134)	7% (10/137)
All 6 studies pooled	16% (94/596)	17% (161/923)

Unadjusted and Adjusted Mortality Hazard Ratios

30-Day (7 trials)*

n = 1717 Unadjusted

1.27 (0.81 – 2.01) $p = 0.30$

Adjusted

1.12 (0.71 – 1.78) $p = 0.63$

30-Day (6 trials)*

n = 1507 Unadjusted

1.34 (0.84 – 2.15) $p = 0.22$

Adjusted

1.18 (0.74 – 1.90) $p = 0.49$

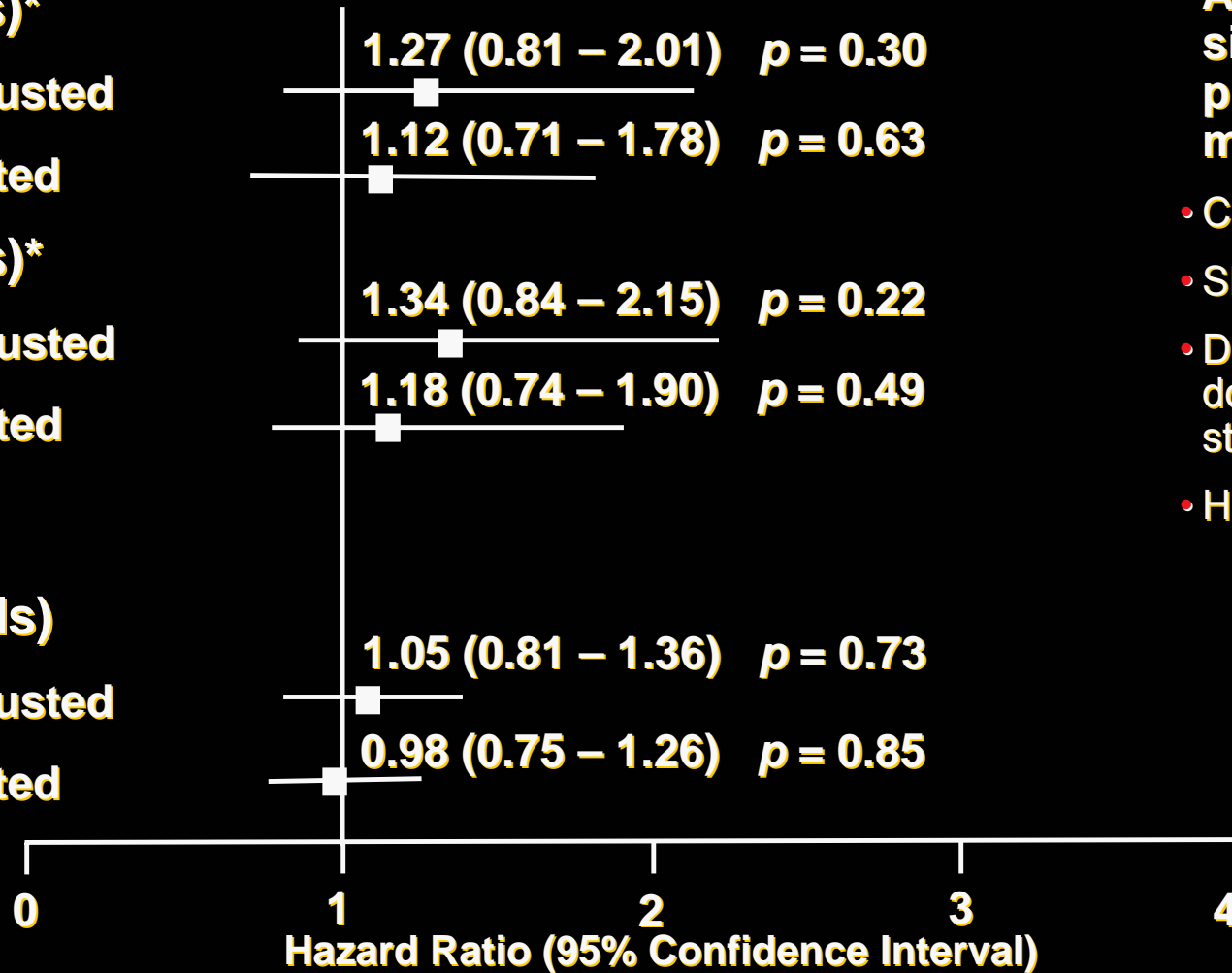
6-Month (4 trials)

n = 1167 Unadjusted

1.05 (0.81 – 1.36) $p = 0.73$

Adjusted

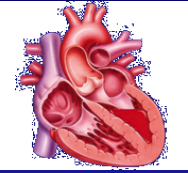
0.98 (0.75 – 1.26) $p = 0.85$



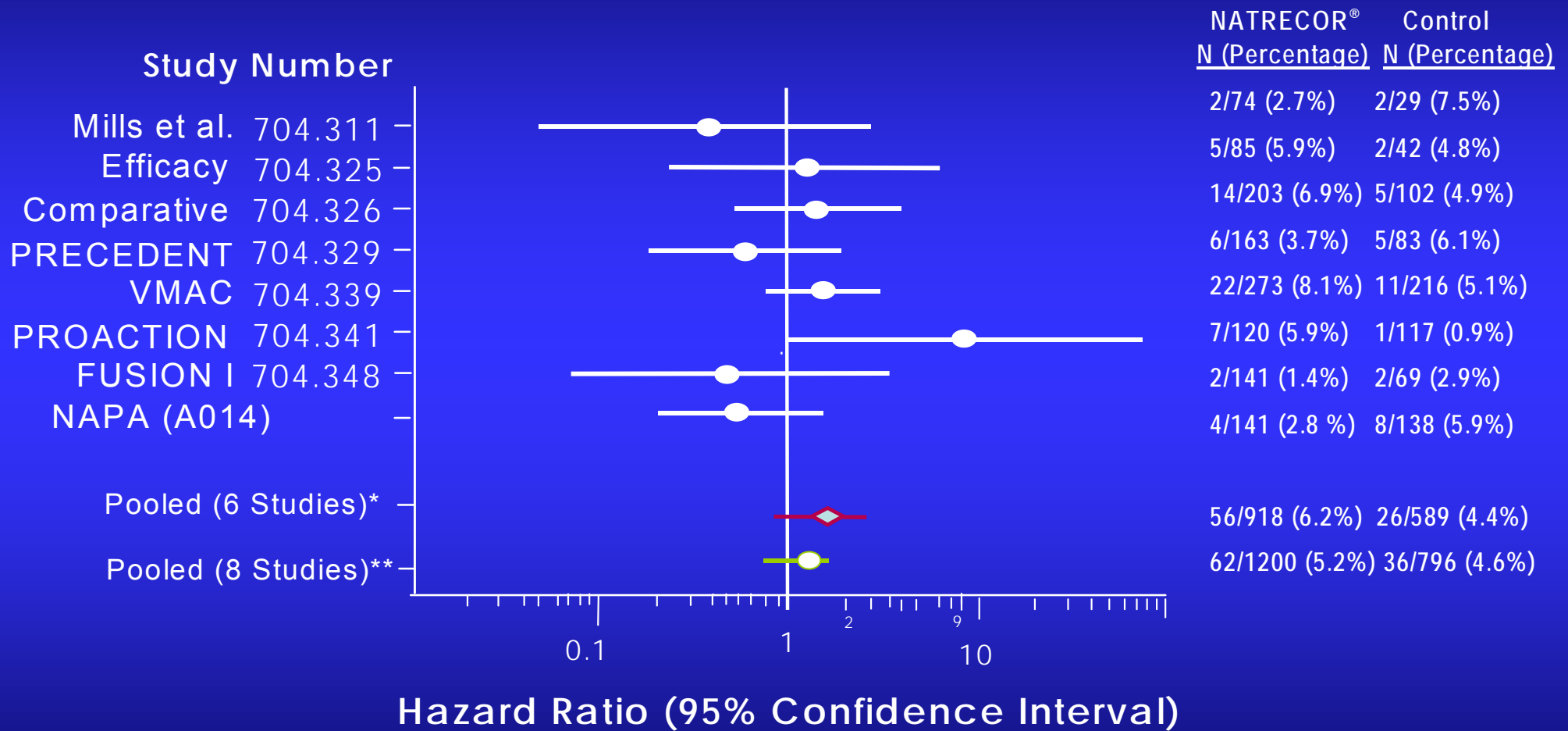
Adjusted for significant predictors of mortality:

- CrCl ≤ 60 mL/min
- SBP ≤ 100 mm Hg
- Dopamine or dobutamine prior to study drug
- History of V.Tach

* Analyses do not include 2 additional 30-day deaths identified after completion of the PROACTION studies



30-Day Mortality Hazard Ratios



*Studies 704.311, 704.325, 704.326, 704.329, 704.339, and 704.341

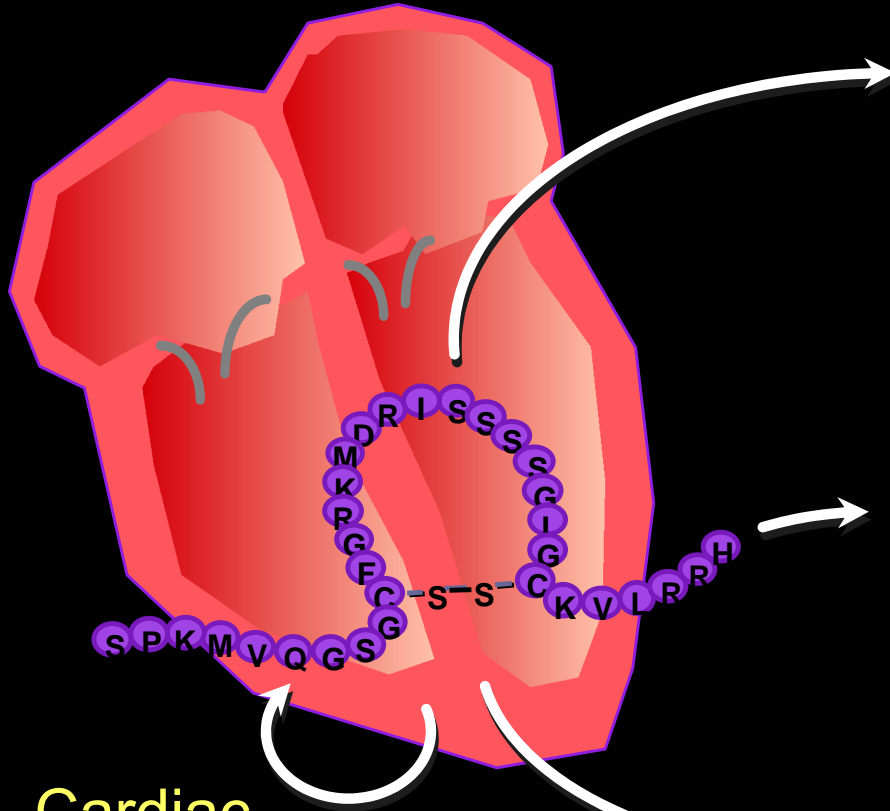
** Studies 704.311, 704.325, 704.326, 704.329, 704.339, 704.341, 704.348, and A014

Reference: NATRECOR® Full Prescribing Information.

Outcomes Trial

- 7000 patients with adHF
- Global study
- Symptom – relief (dyspnea, well-being), rehospitalisation, mortality renal effects, quality of life, pharma-economics
- Independent ARO
- Enrollment to start Q1 2007

Pharmacological actions of human BNP



Haemodynamic

- veins
- arteries
- coronary arteries

Neurohormonal

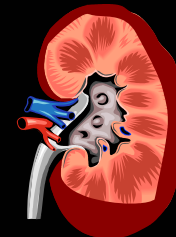
- ↓ aldosterone
- ↓ endothelin-1
- ↓ noradrenaline

Cardiac

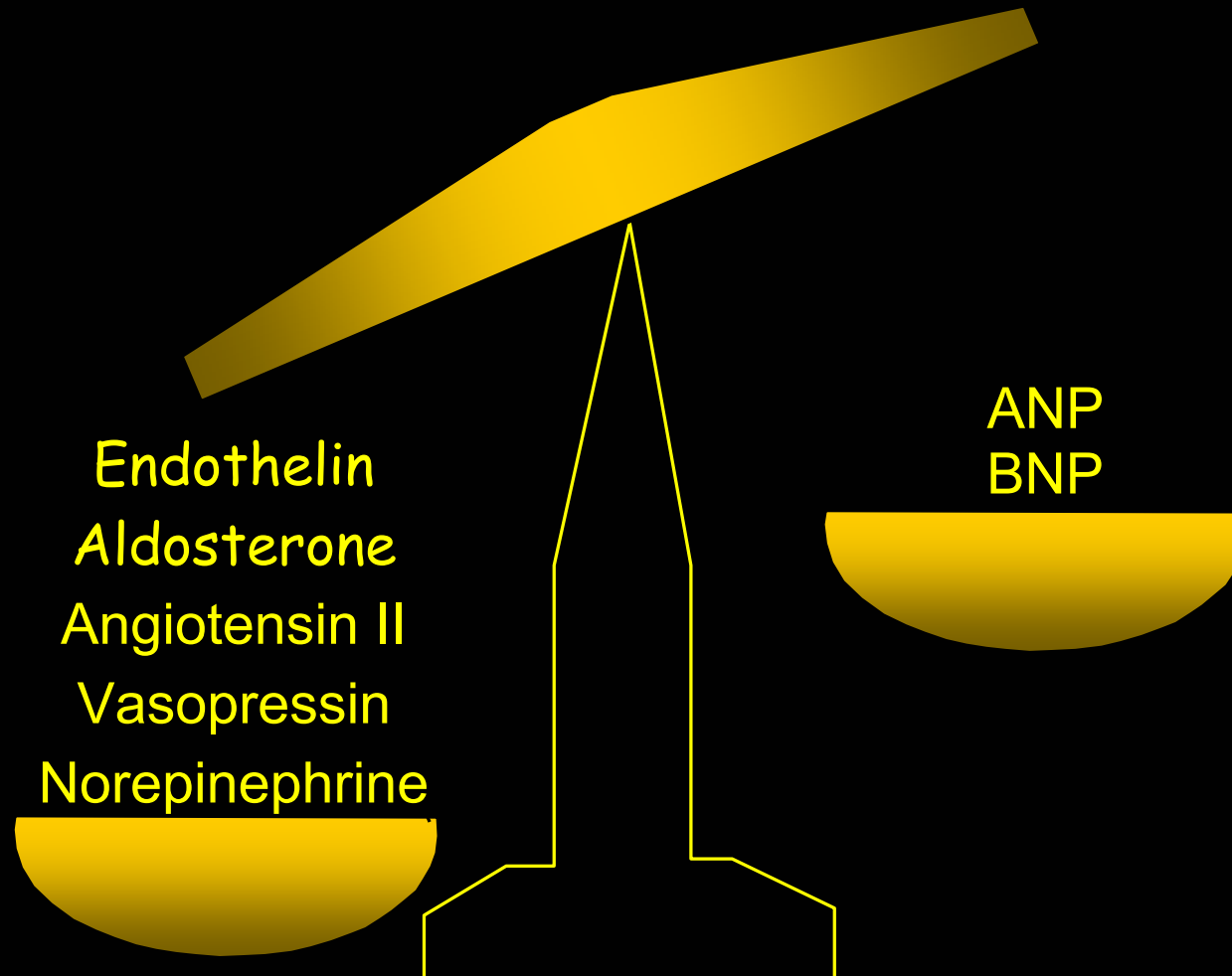
- lusitropic
- anti-fibrotic
- anti-remodeling

Renal

- ↑ diuresis
- ↑ natriuresis



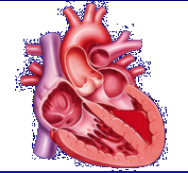
Powerful neurohormonal vasoconstrictor forces *dominate*



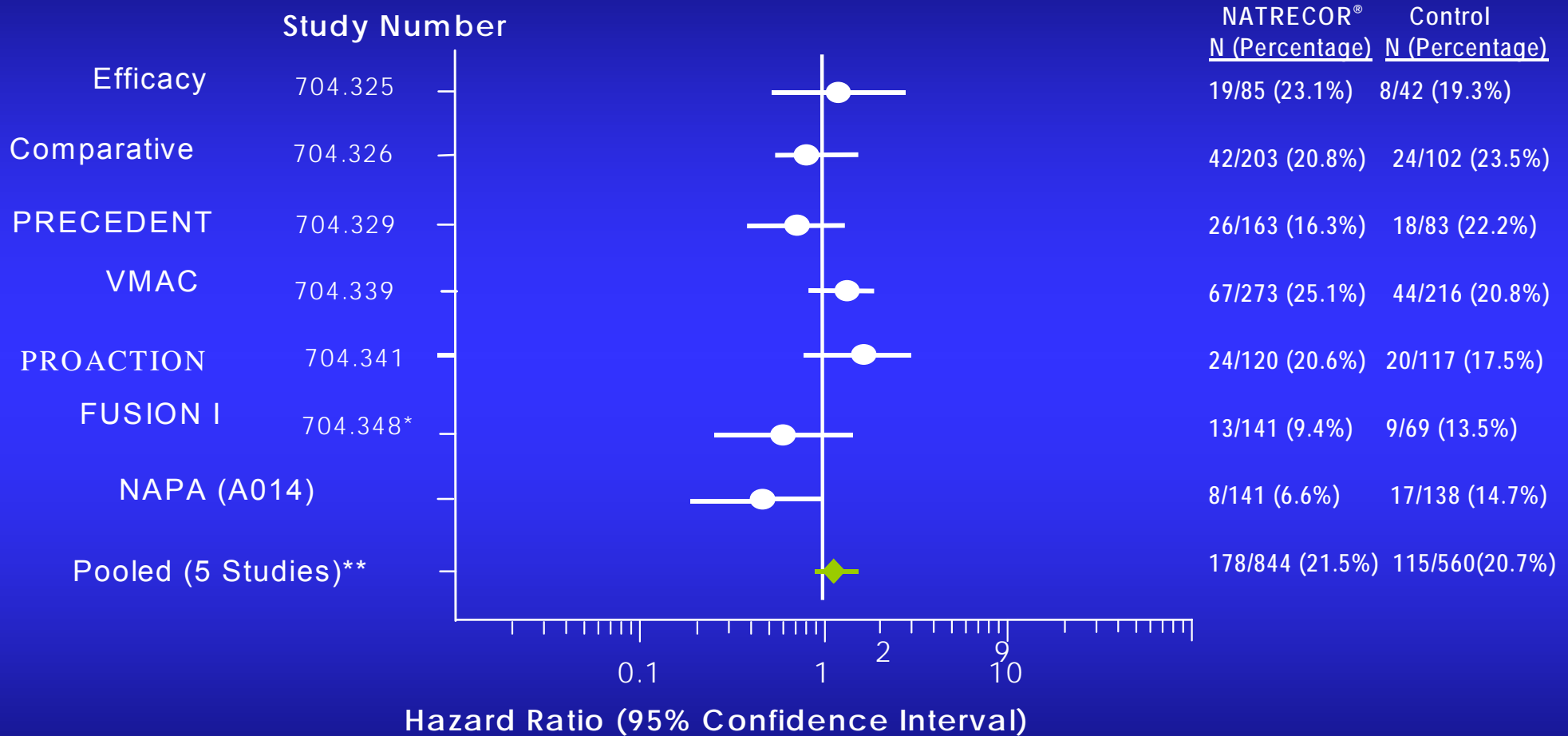
NATRECOR® (nesiritide)

Important Safety Information

- Nesiritide may cause hypotension and blood pressure should be monitored closely
- If symptomatic hypotension occurs, infusion rate should be immediately decreased or discontinued
- At the recommended dose of nesiritide the incidence of symptomatic hypotension (4%) was similar to that of IV nitroglycerin (5%)
- Nesiritide is associated with a dose dependent increase in serum creatinine



180-Day Mortality Hazard Ratios



*Data collected through week 16

**Studies 704.325, 704.326, 704.329, 704.339, 704.341, 704.348, and A014

Low-dose BNP infusions in normal subjects

