# Novel Treatments in the Management of ADHF

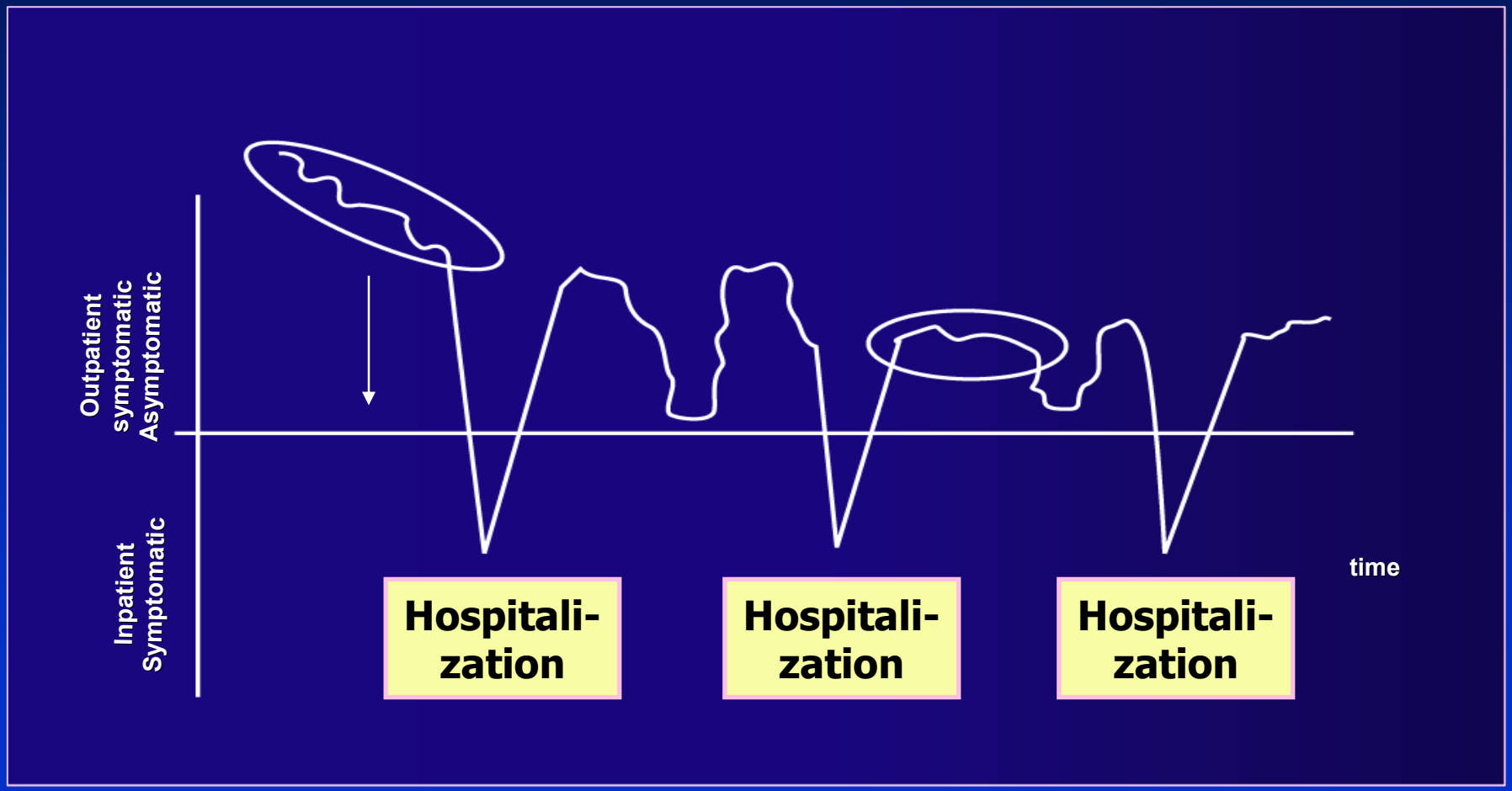
*Henry Krum MBBS PhD FRACP*

**NHMRC Centre of Clinical Research Excellence in Therapeutics, Monash University/Alfred Hospital;**

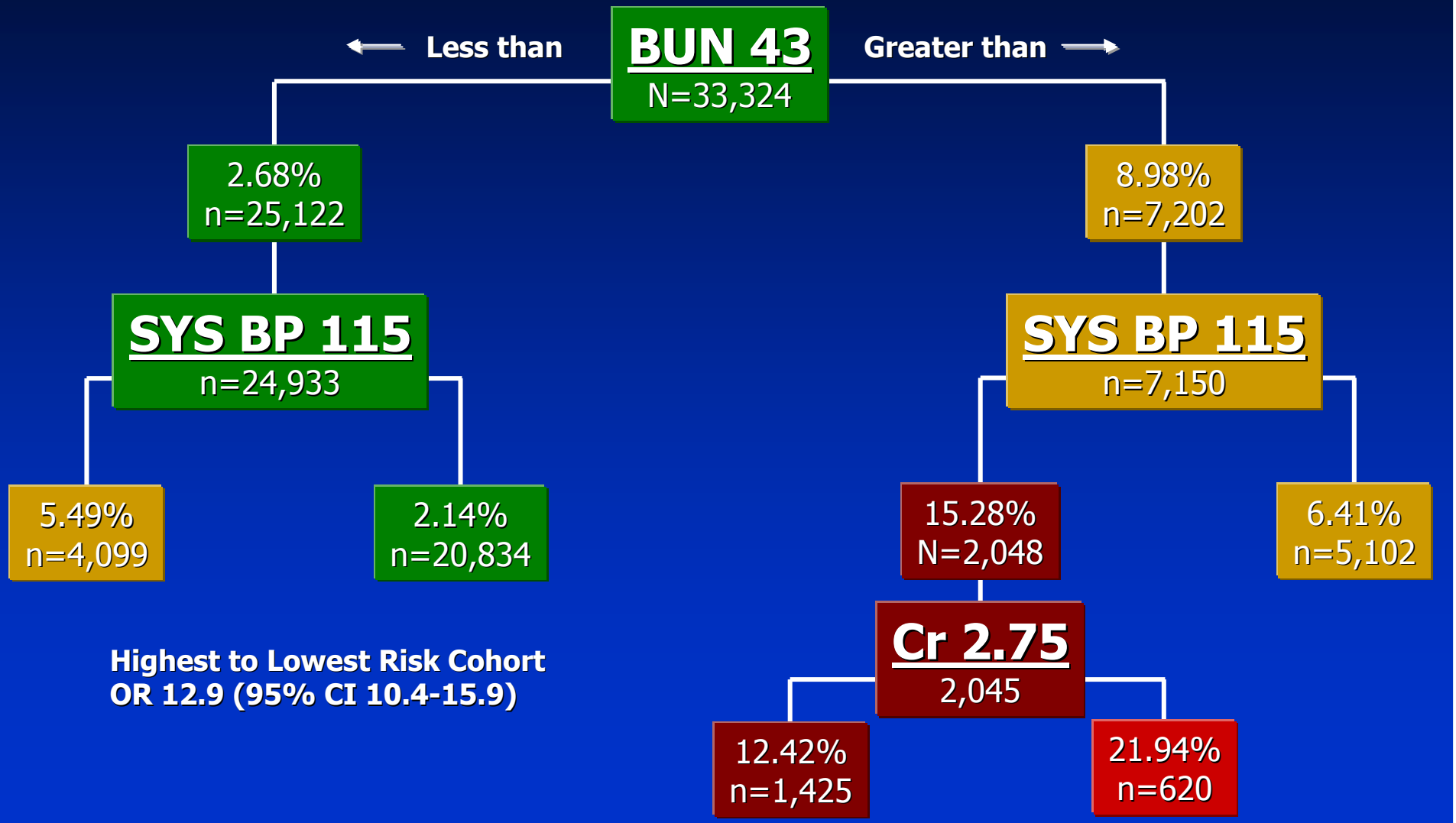
**Alfred Heart Centre, The Alfred Hospital, Melbourne**

CCRE THERAPEUTICS

# Clinical Course of Heart Failure in Individual Patient



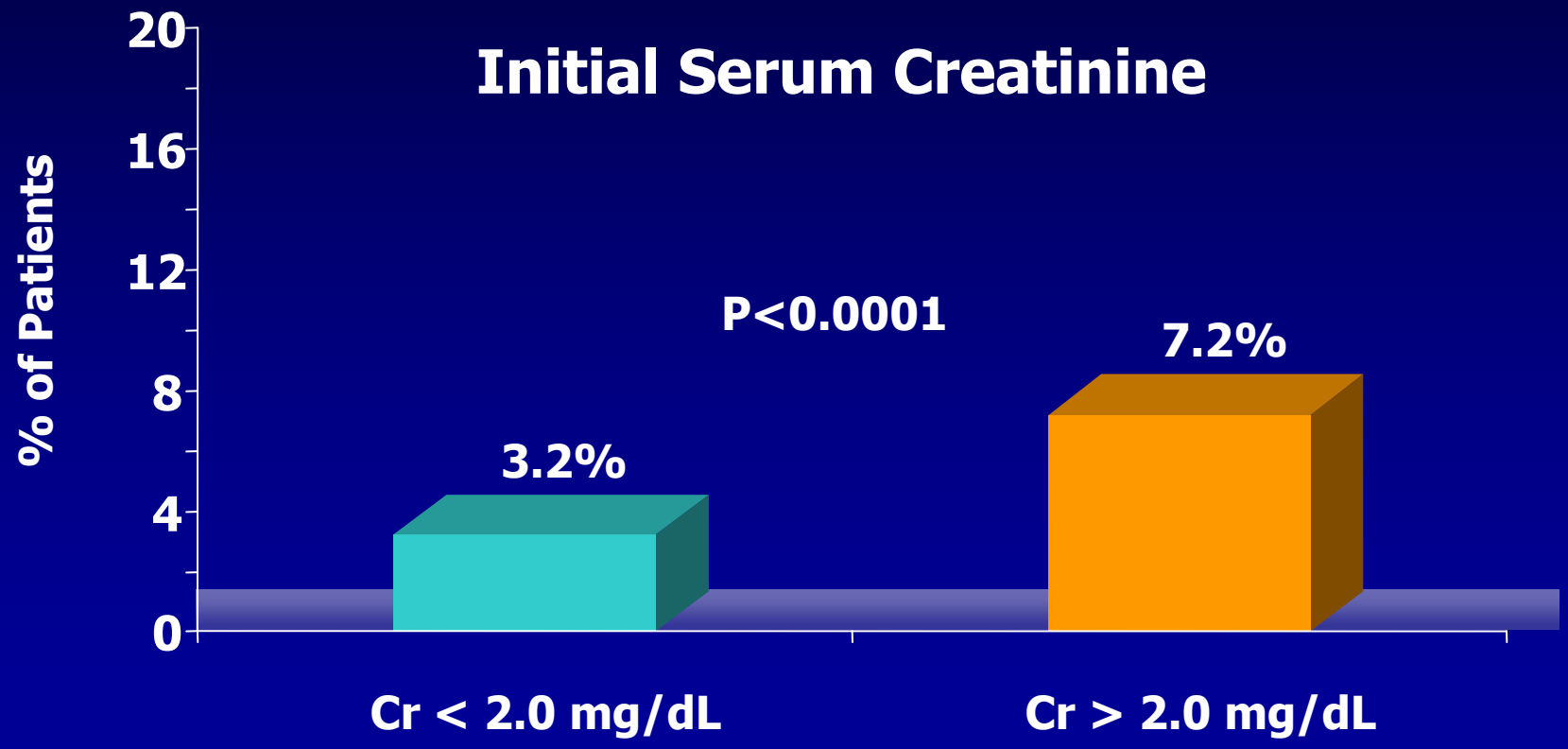
# ADHERE: Predictors of Mortality




**Highest to Lowest Risk Cohort**
**OR 12.9 (95% CI 10.4-15.9)**

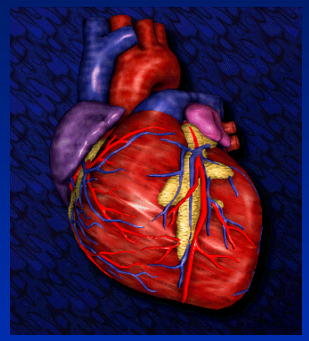
*Fonarow G et al. JAMA 2005*

# In-Hospital Mortality in Patients with ADHF




45,740/46,599 patients 98.2% with Cr value ADHERE April 2003 transfer

# Heart-Kidney Interactions in Heart Failure



Increased morbidity and mortality

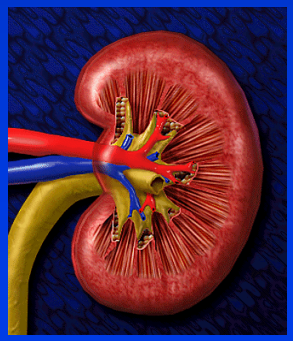
Pathologic remodeling

Congestion

Neurohormonal activation

Diuretic resistance

Impaired renal function



Decreased renal perfusion

Diminished blood flow

Vasoconstriction

Neurohormonal activation

Diuretic therapy

# Cardiorenal Syndrome

## *Definition*

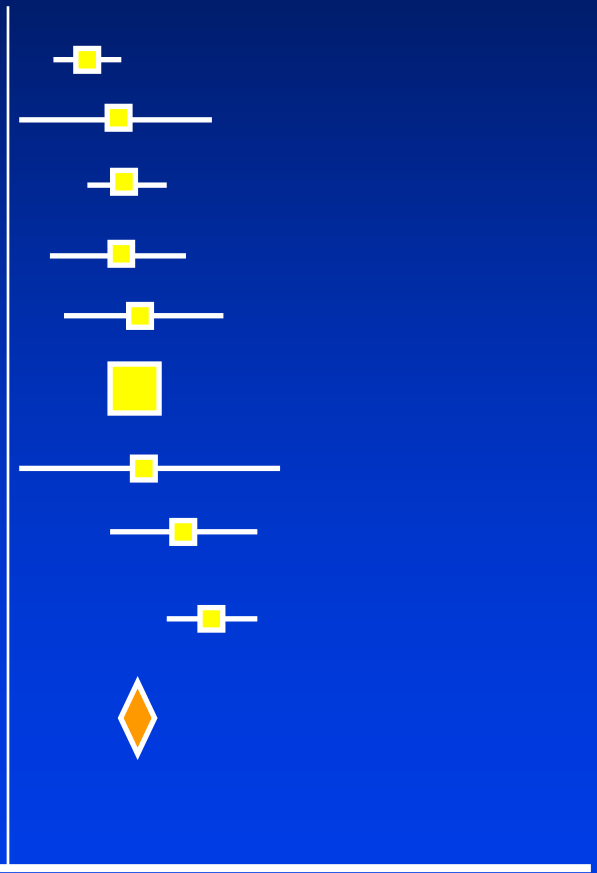
- '….. A syndrome in which the heart or kidney fails to compensate for the functional impairment of the respective other organ…'

- '….worsening renal function in patients hospitalised for heart failure…'

***Boerrigter G et al Curr Cardiol Reports 2004***

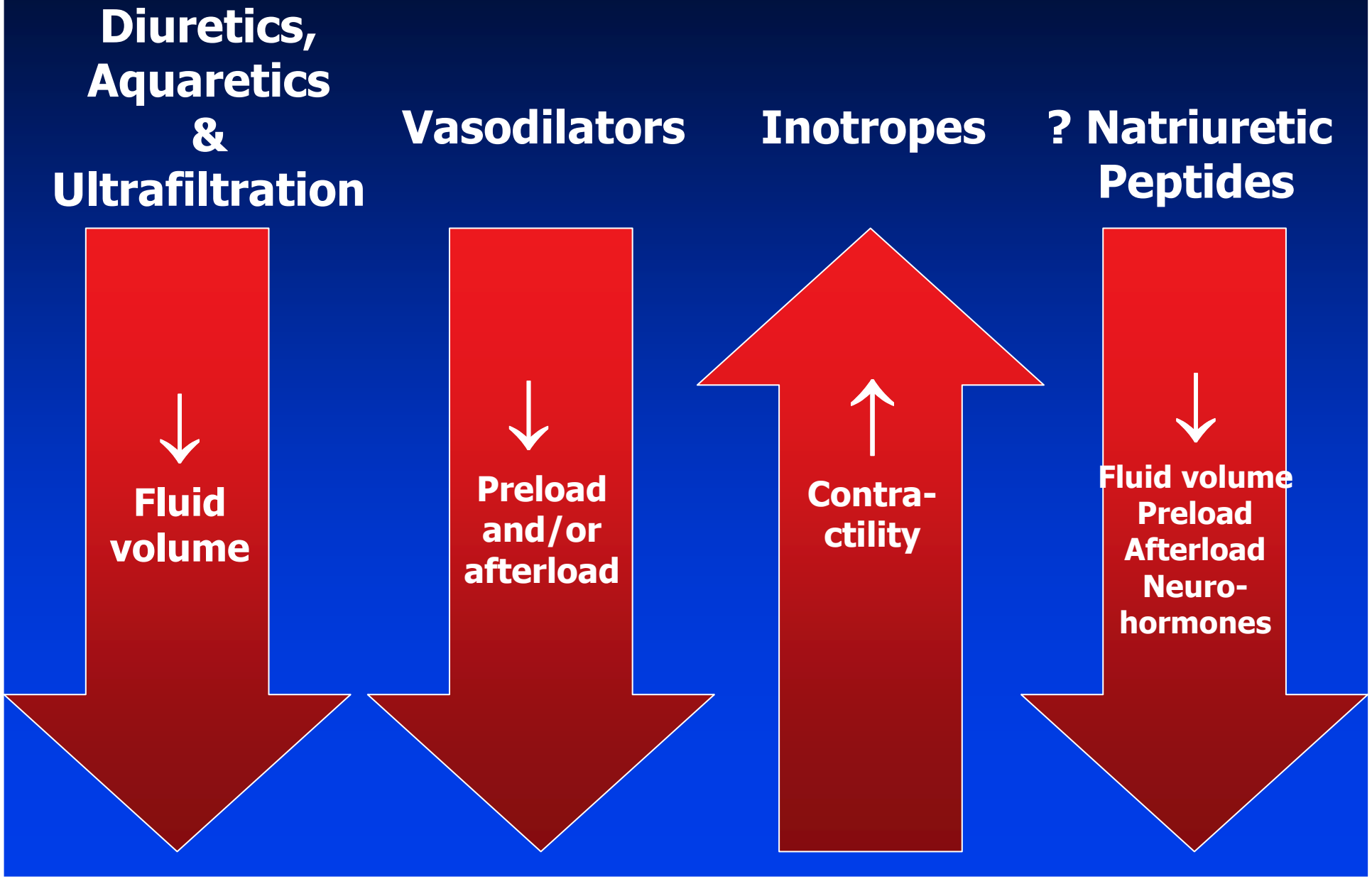
# Renal Dysfunction and Mortality Risk in Heart Failure Patients

| Study | N* | HR |
|---|---|---|
| McClellan | 665 | 1.26 |
| Shlipak | 279 | 1.38 |
| Dries | 2,161 | 1.41 |
| Dries | 3,673 | 1.41 |
| Mahon | 585 | 1.55 |
| Smith | 53,640 | 1.57 |
| Shlipak | 6,800 | 1.64 |
| Bibbins-Domingo | 702 | 1.84 |
| Hilege | 1,906 | 2.10 |
| **Total** | | |
| Heterogeneity $X^2$ | P<0.001 | 1.56 |
| Overall Z | P<0.001 | |

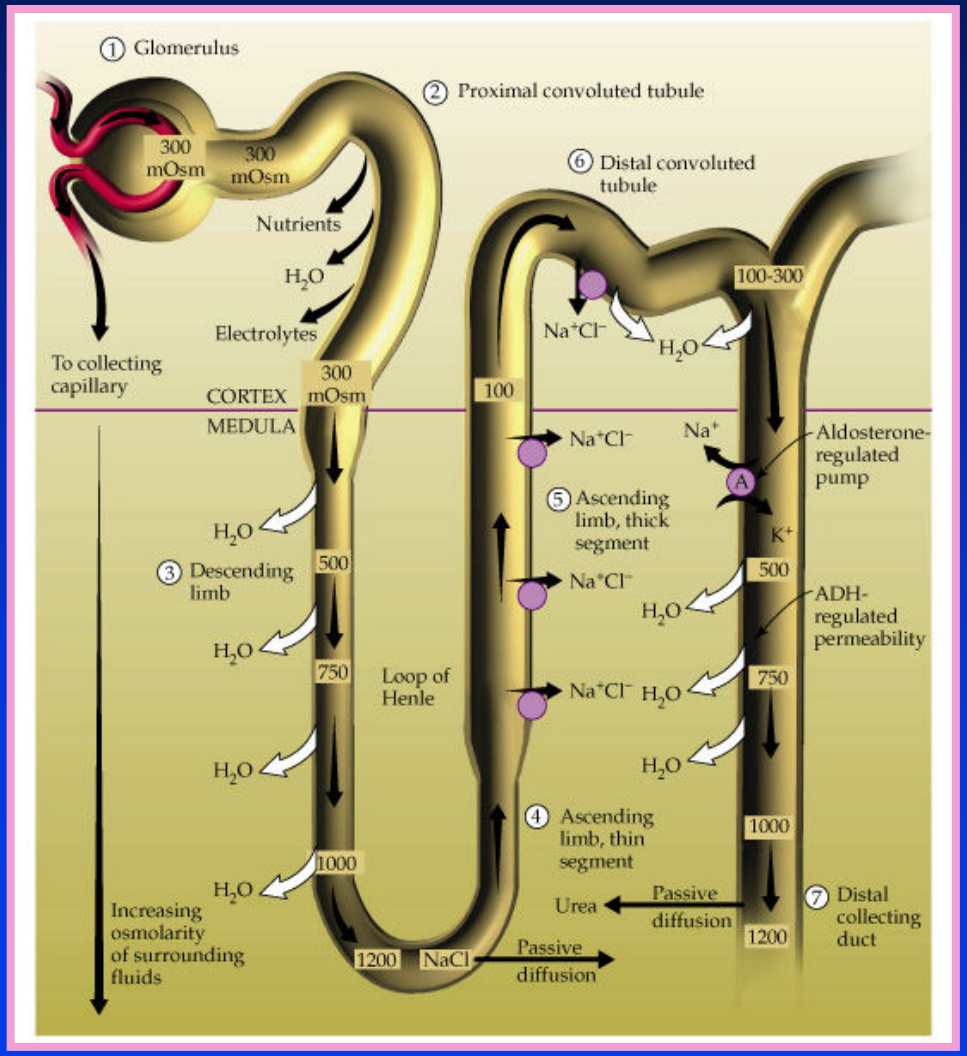



*Smith GL et al JACC 2006*

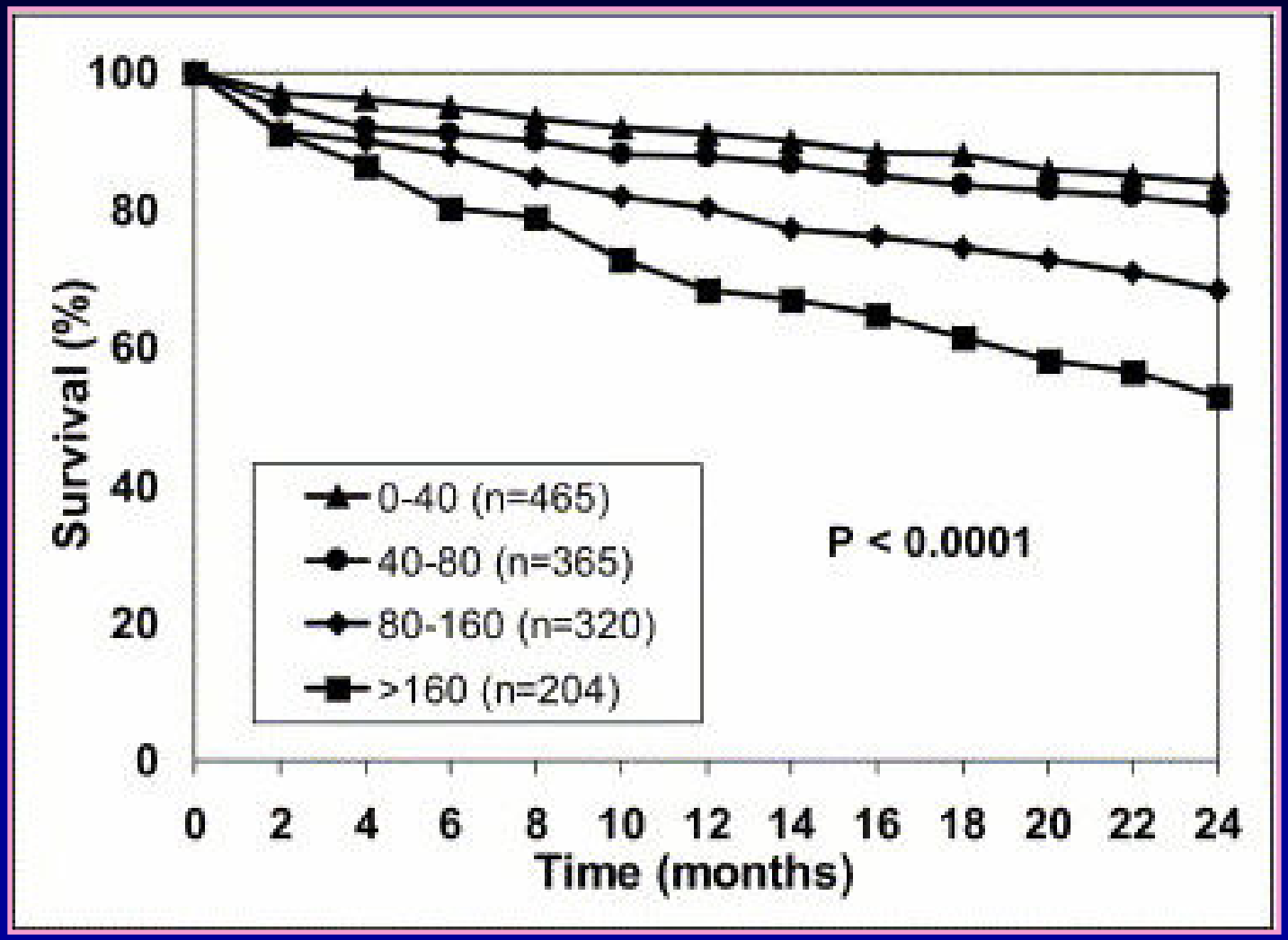
# Current Treatments for ADHF



# Sites of Action of Diuretic Therapy

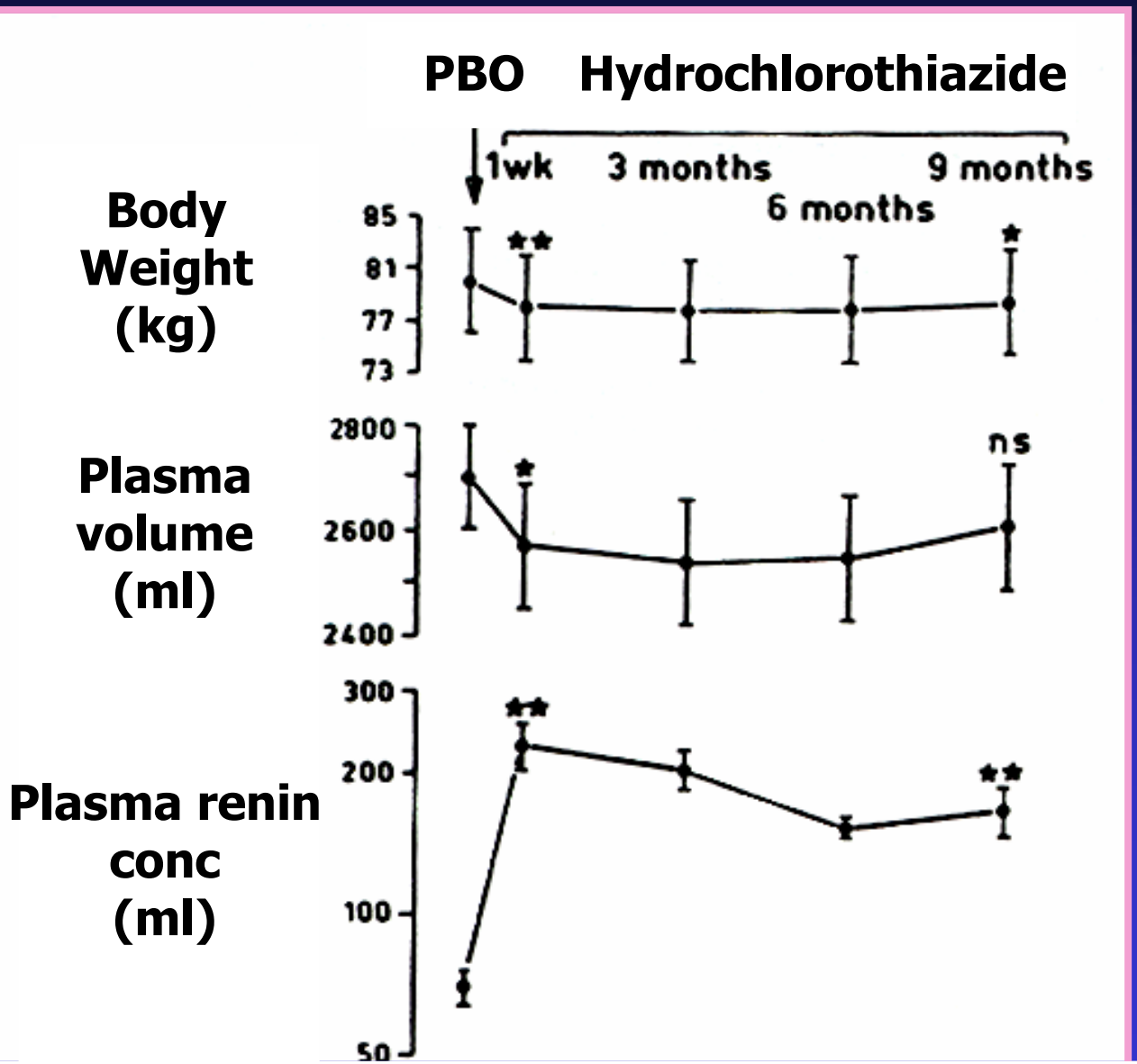


# Diuretic Dose & Mortality in Advanced Heart Failure




*Eshagian S et al Am J Cardiol 2007*

# RAAS Activation with Diuretics




*Birkenhäger, WH J Hypertens et al 1990*

# Disadvantages of Conventional Diuretic Therapy in CHF

- Has potential to activate neurohormonal vasoconstrictor systems
- Can cause electrolyte abnormalities
- Has been associated with increased risk of morbidity and mortality
- Can lead to development of pre-renal azotemia
- May result in diuretic resistance

# Diuretic Resistance

- Inadequate response to diuretic therapy
- Represents an extension of cardiorenal syndrome
- Failure to respond to IV loop diuretics
- Decreased efficacy of diuretics with prolonged treatment

***Boerrigter G et al Curr Cardiol Reports 2004***

# Mechanisms Contributing to Diuretic Resistance

- Compensatory mechanisms (RAAS, SNS activation)
- Failure of diuretic to reach tubular site of action:
  - Decreased G.I. absorption
  - Decreased secretion into tubular lumen
  - Decreased availability in tubular lumen
- Interference by other drugs (e.g. NSAID's)
- Tubular adaptation (chronic loop diuretic use)

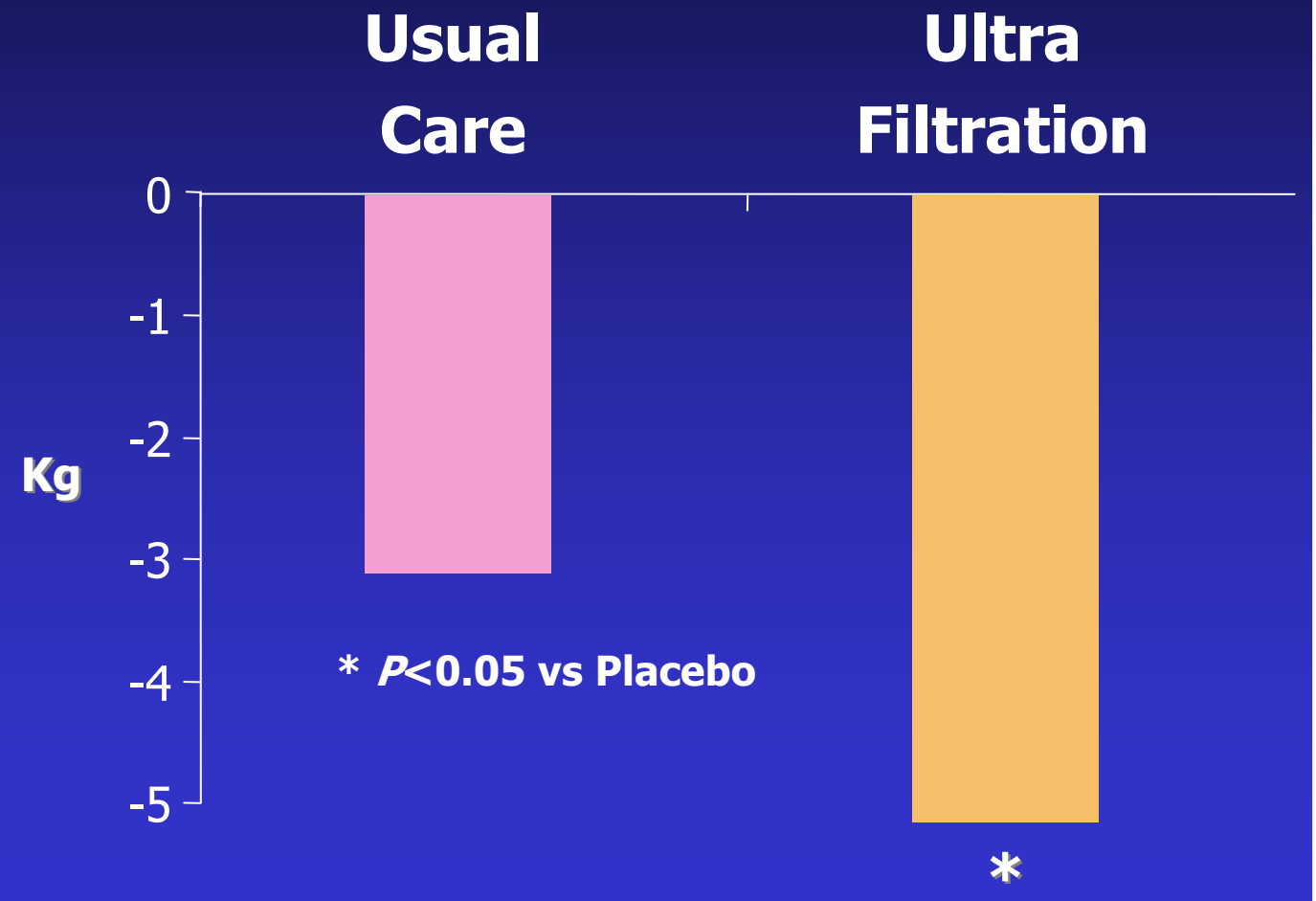
# Management of Diuretic Resistance

- Fluid, sodium restriction
- Avoid over-aggressive vasodilation
- Avoid NSAID's
- More frequent/continuous administration of diuretiic
- Combination of diuretic classes (sequential nephron blockade)
- Adequate neurohormonal blockade

# Ultrafiltration

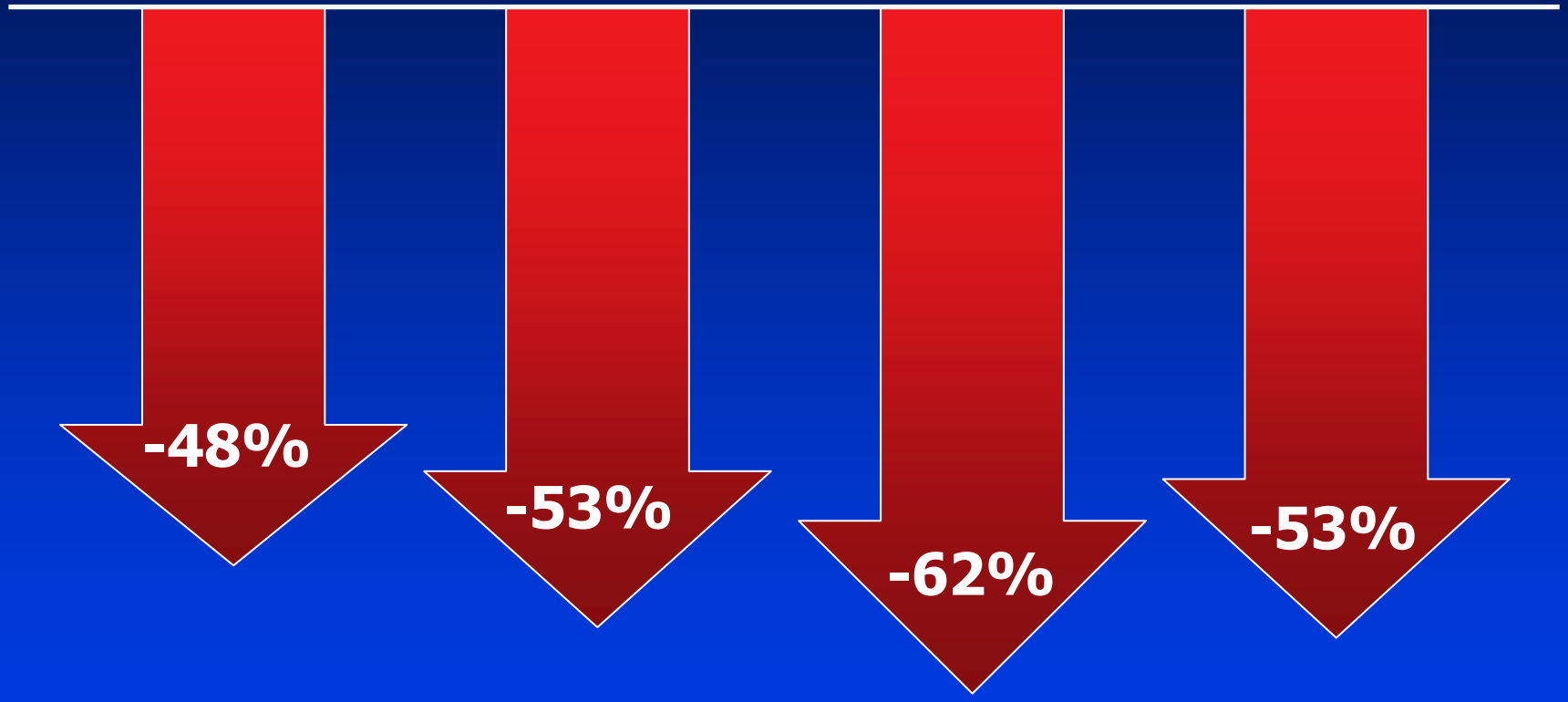
# Ultrafiltration

## *UNLOAD: Wt Loss at 48 Hrs*

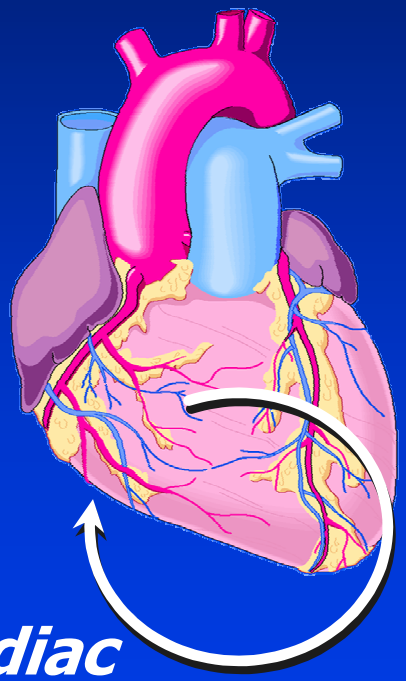


# Ultrafiltration

## *UNLOAD: Secondary Endpoints*



# Putative Pharmacological Effects of Natriuretic Peptides



BNP

***Hemodynamic***

**Vasodilation:**

- **Veins**
- **Arteries**
- **Coronary arteries**

***Neurohormonal***

- **↓ Aldosterone**
- **↓ Endothelin-1**
- **↓ Noradrenaline**

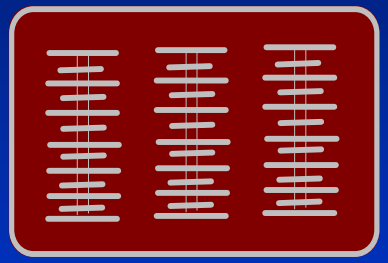
***Renal***

- **Diuresis**
- **Natriuresis**

***Cardiac***

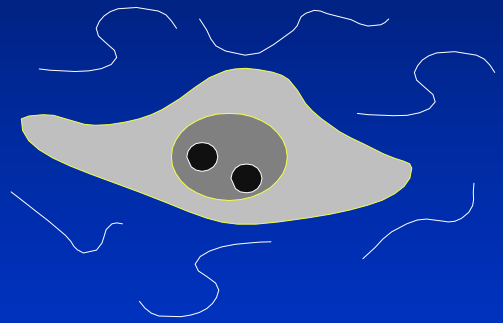
- **Lusitropic**
- **Anti-remodeling**
- **Anti-fibrotic**

# Putative CV Effects of B-Type Natriuretic Peptide



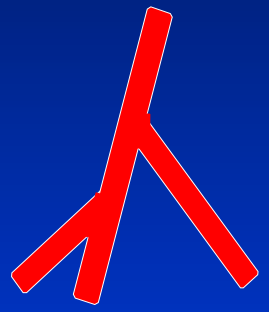
**Cardiac Myocyte**

- ↓ Hypertrophy
- Decreased wall stress
- Decreased $O_2$ consumption
- Improved relaxation



**Fibroblast**

- ↓ Hyperplasia
- ↓ Collagen synthesis
- Anti-fibrotic



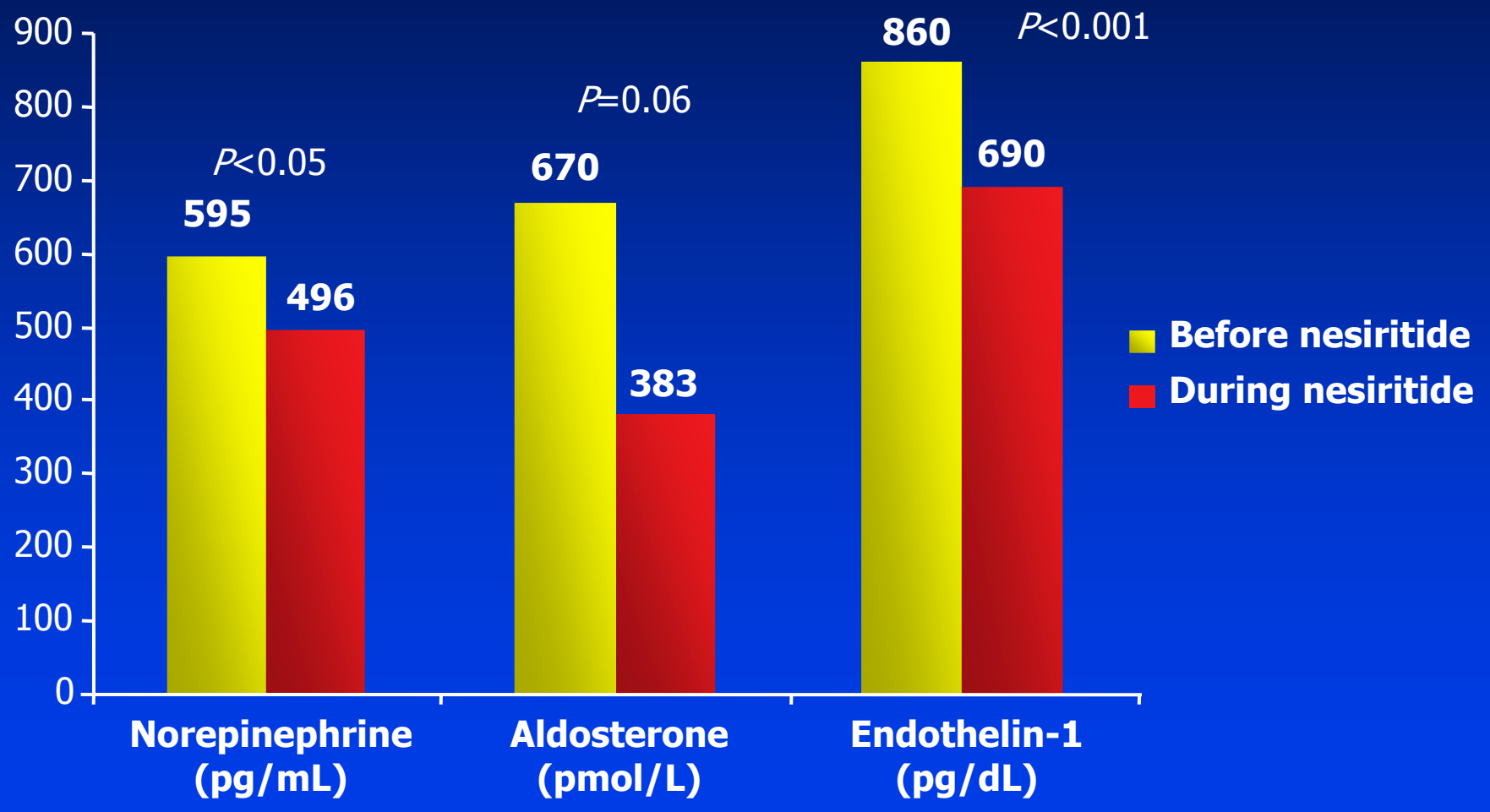
**Peripheral Artery**

- Vasodilation
- ↑ Endothelial function
- ↓ Hypertrophy
- Improved compliance

**Coronary Artery**

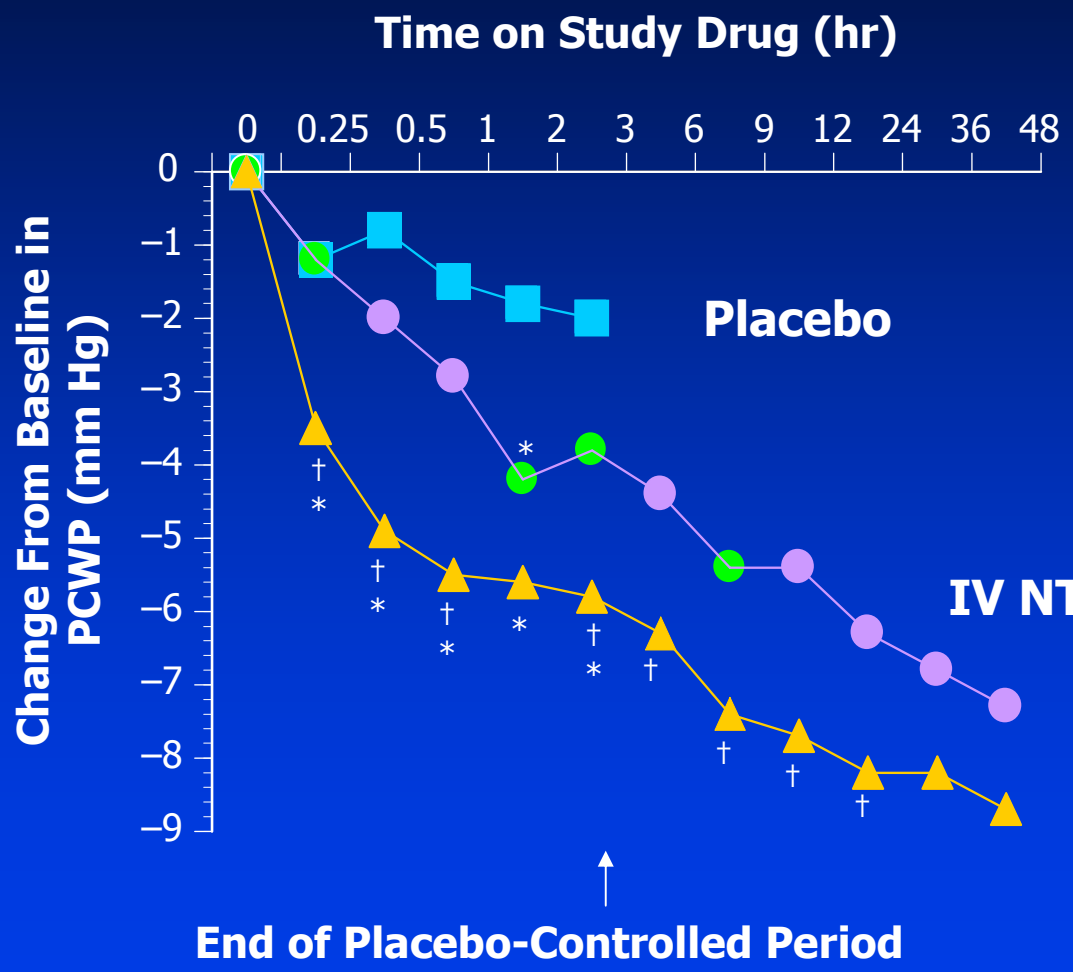
- Vasodilation
- ↑ Endothelial function

# Effect of Nesiritide on Plasma Neurohormones




*Abraham WT et al. J Card Fail. 1998: Aronson D et al. J Am Coll Cardiol. 2001*

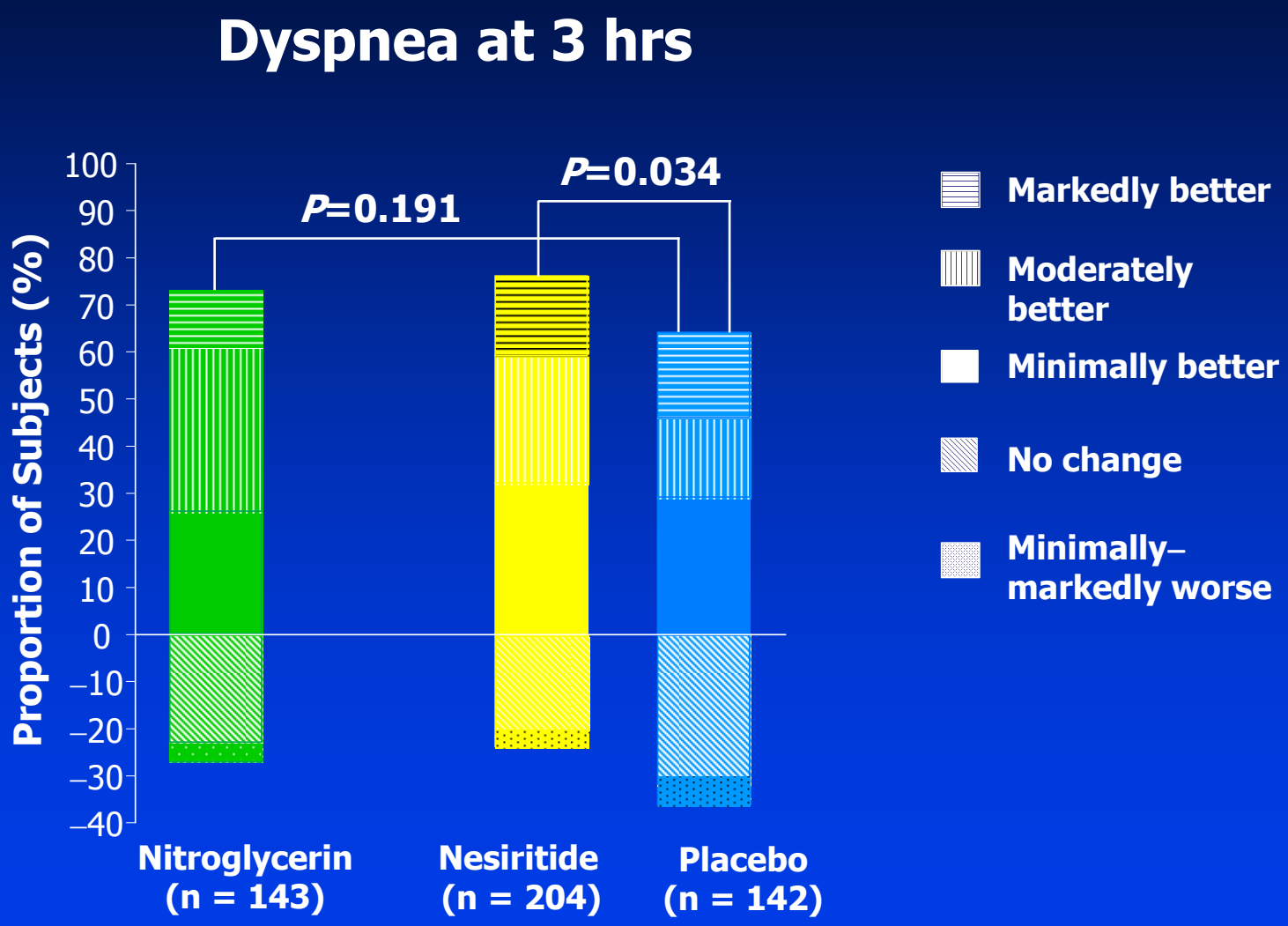
# Effect of Nesiritide on PCWP




* $P \leq 0.05$ vs placebo
† $P \leq 0.05$ vs IV NTG

*VMAC Investigators. JAMA 2002*

# Effect of Nesiritide on Dyspnoea




*VMAC Investigators. JAMA. 2002*

# Nesiritide & Increased Mortality

## Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure

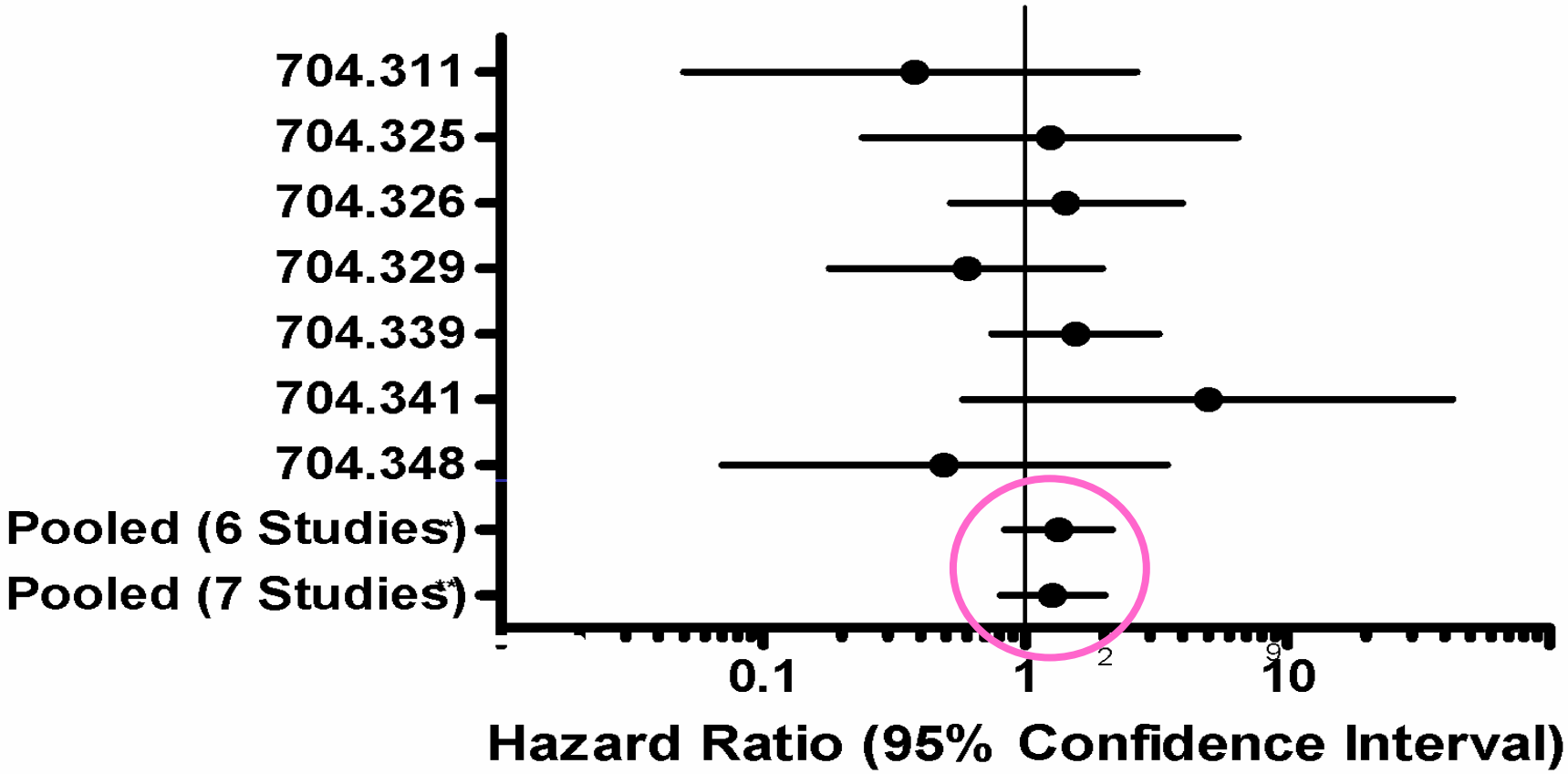
### A Pooled Analysis of Randomized Controlled Trials

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.

# Nesiritide & Increased Mortality




**Sackner-Bernstein HR =1.86**

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

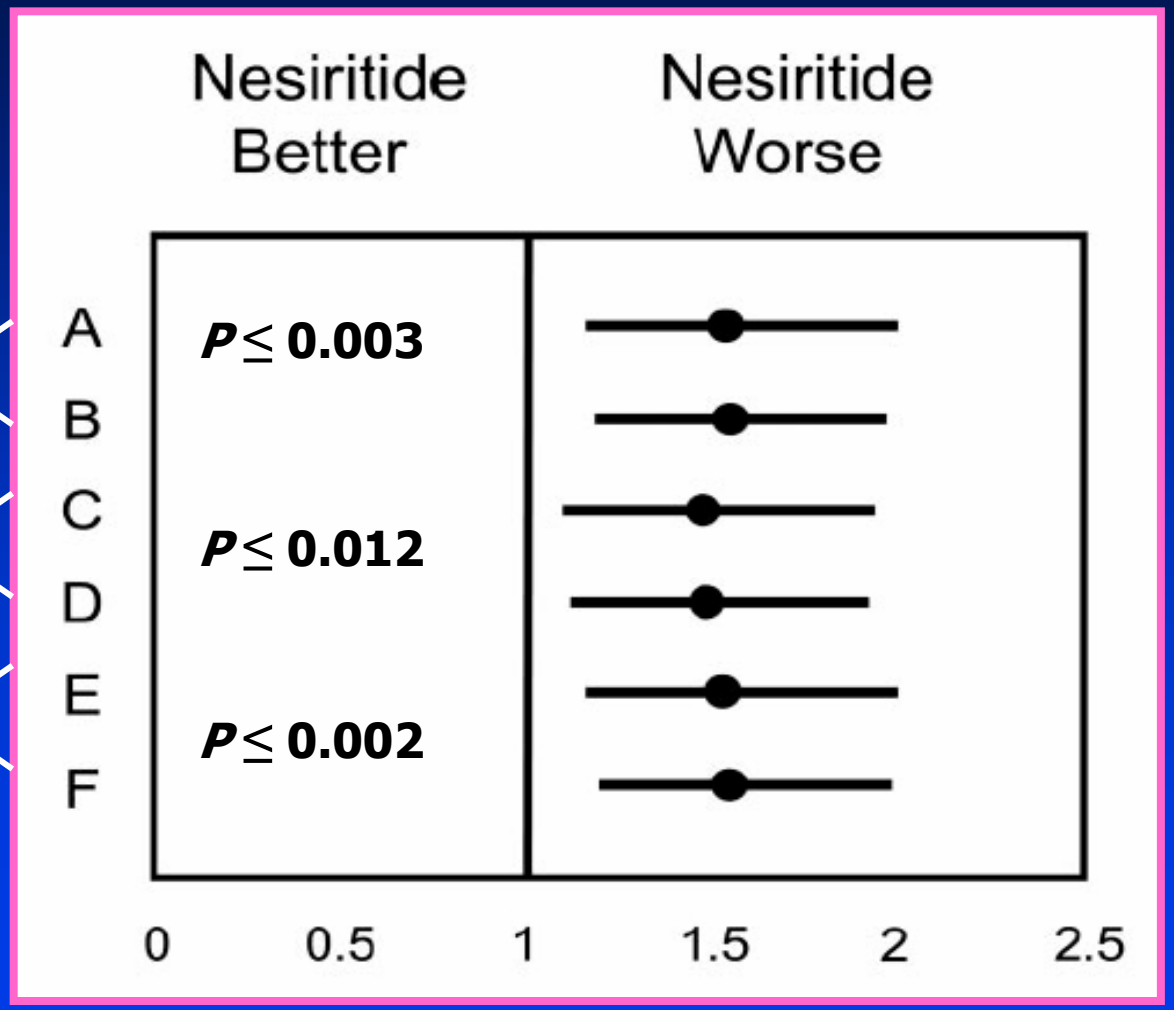
** Studies 704.311, 704.325, 704.326, 704.329, 704.339, 704.341, and 704.348

# Nesiritide & Renal Function

≤ 0.03 mcg/kg/min

≤ 0.015 mcg/kg/min

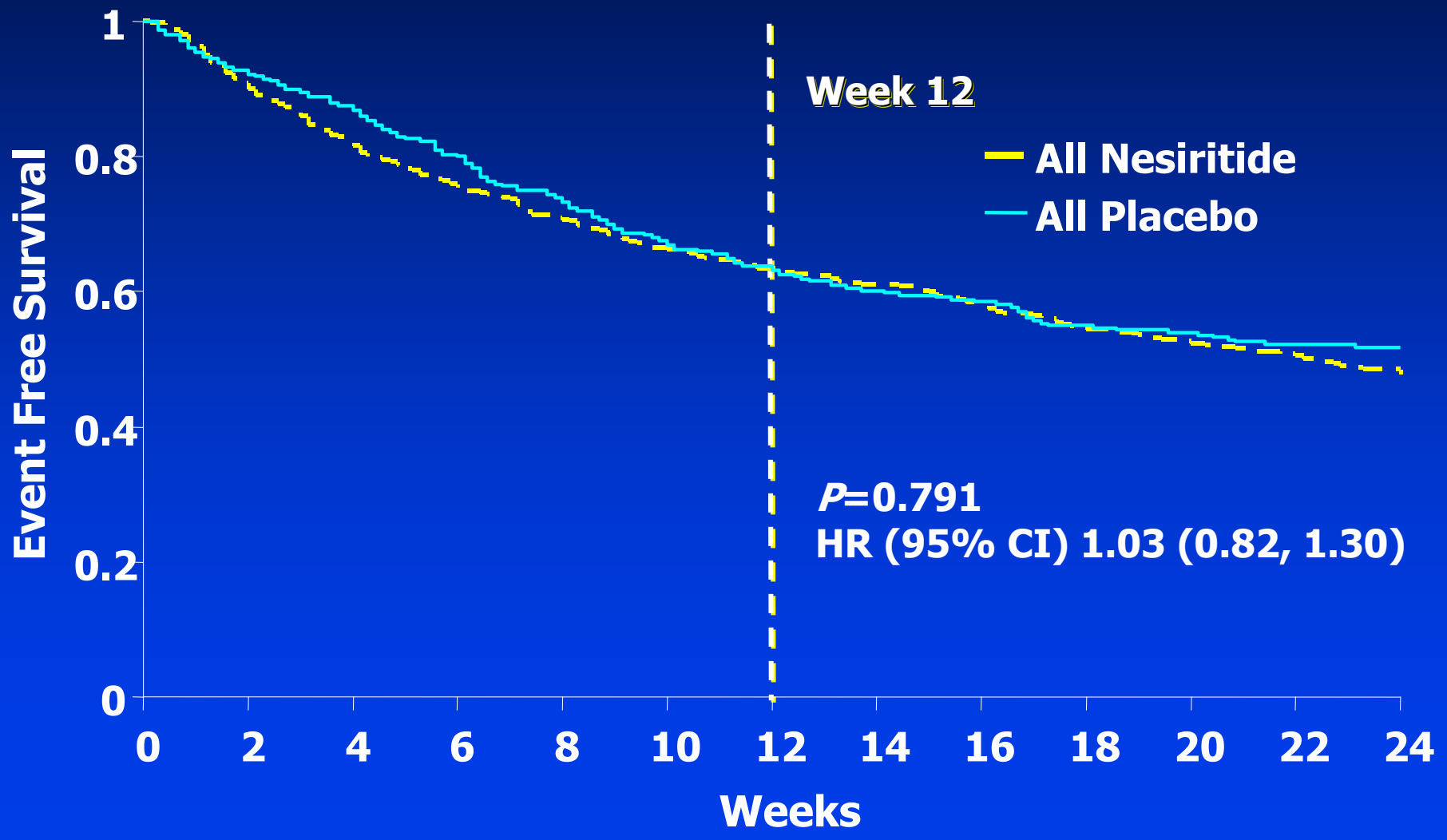
≤ 0.06 mcg/kg/min




*Sackner-Bernstein JD et al. Circulation 2005*

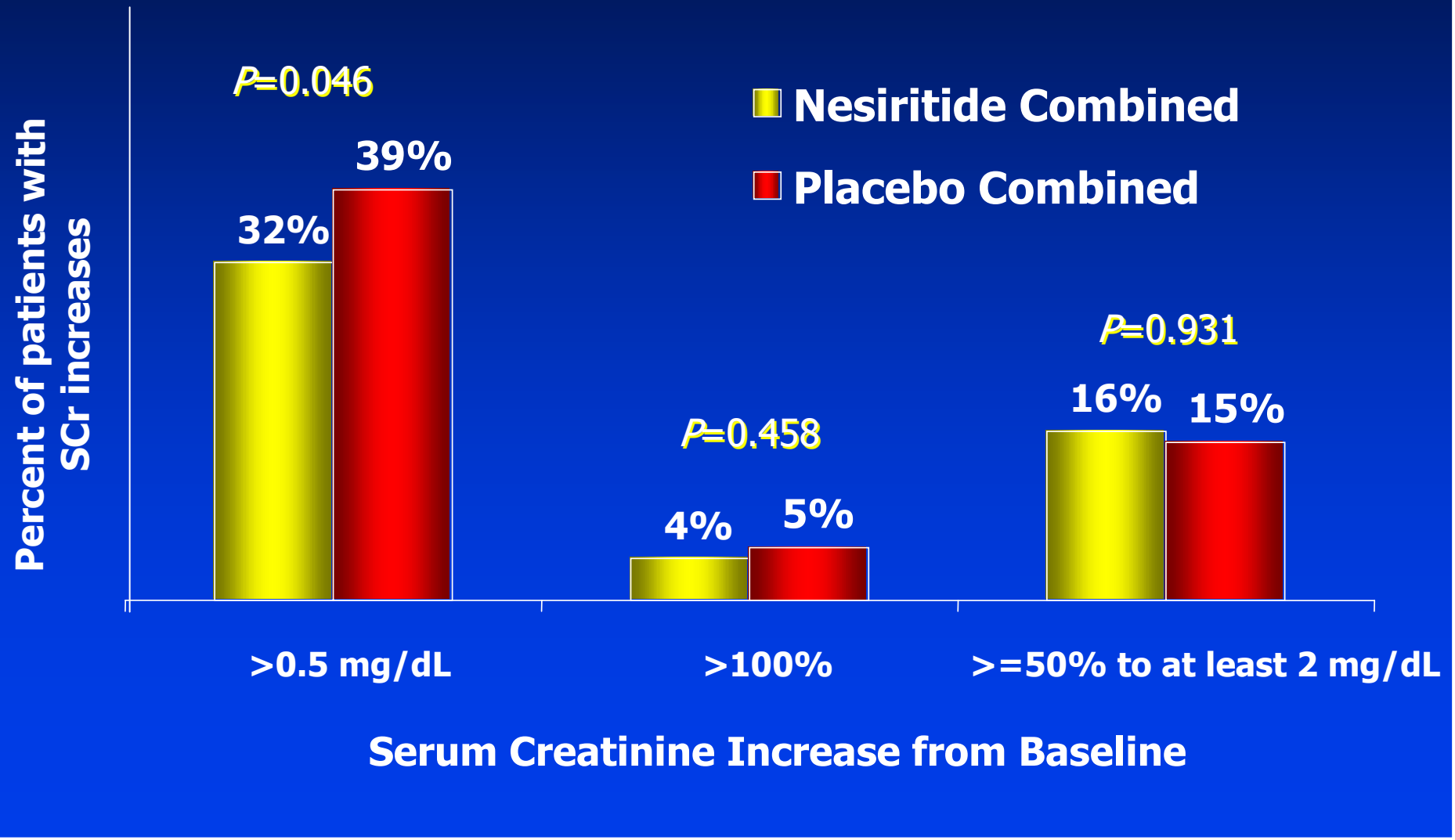
# FUSION II

## *Primary Endpoint*

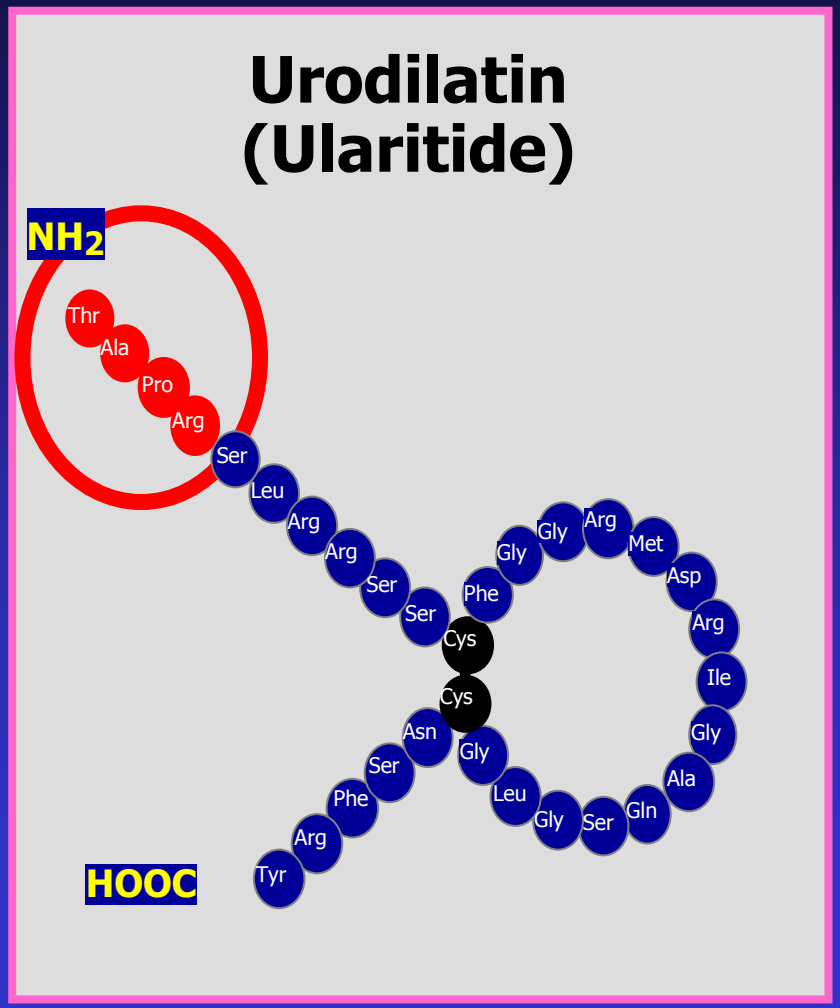


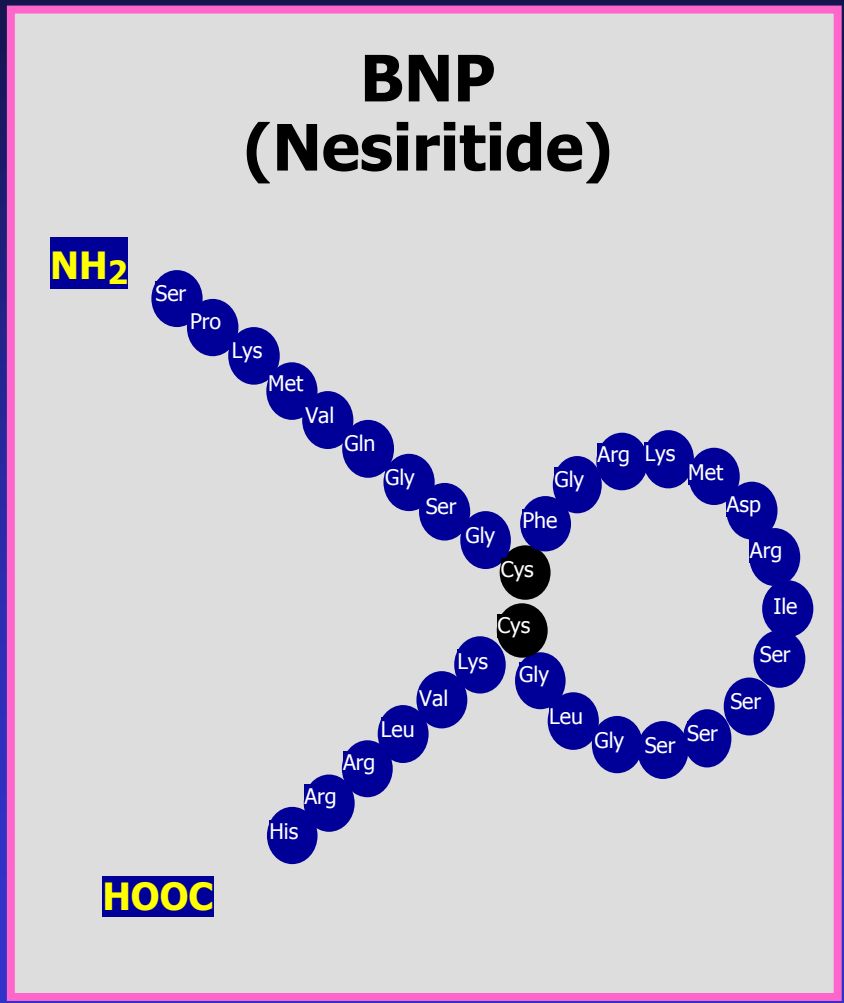
# FUSION II

## *Renal Function*

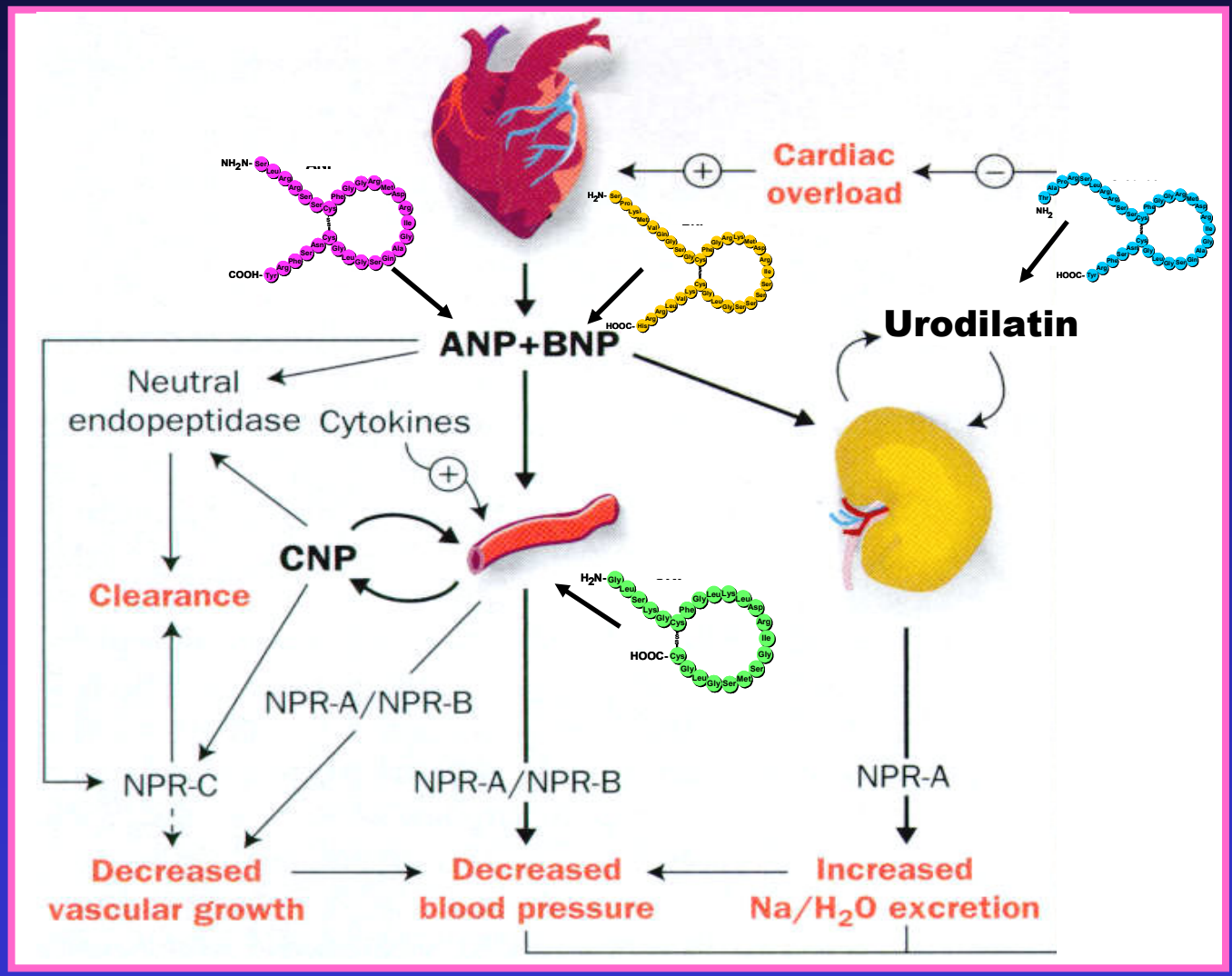


# Urodilatin vs Nesiritide



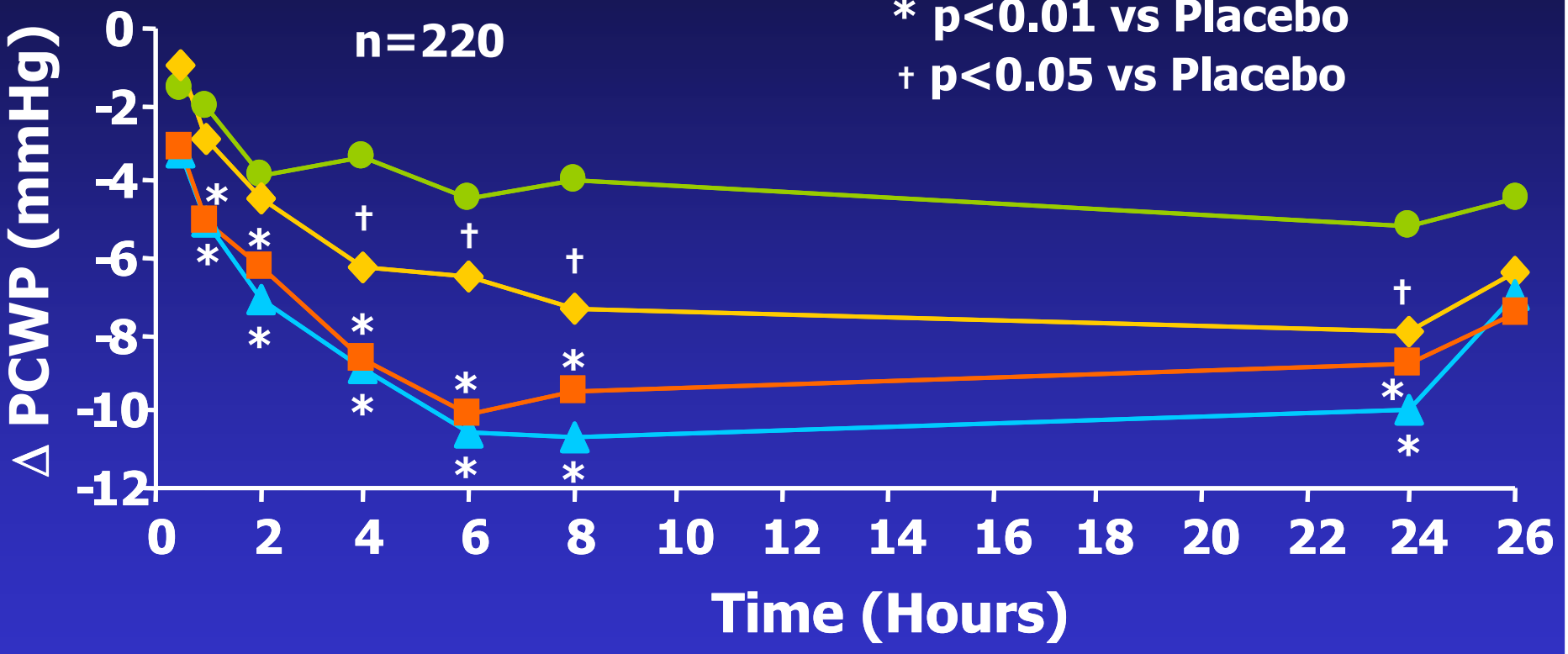



# Urodilatin Mechanism of Action

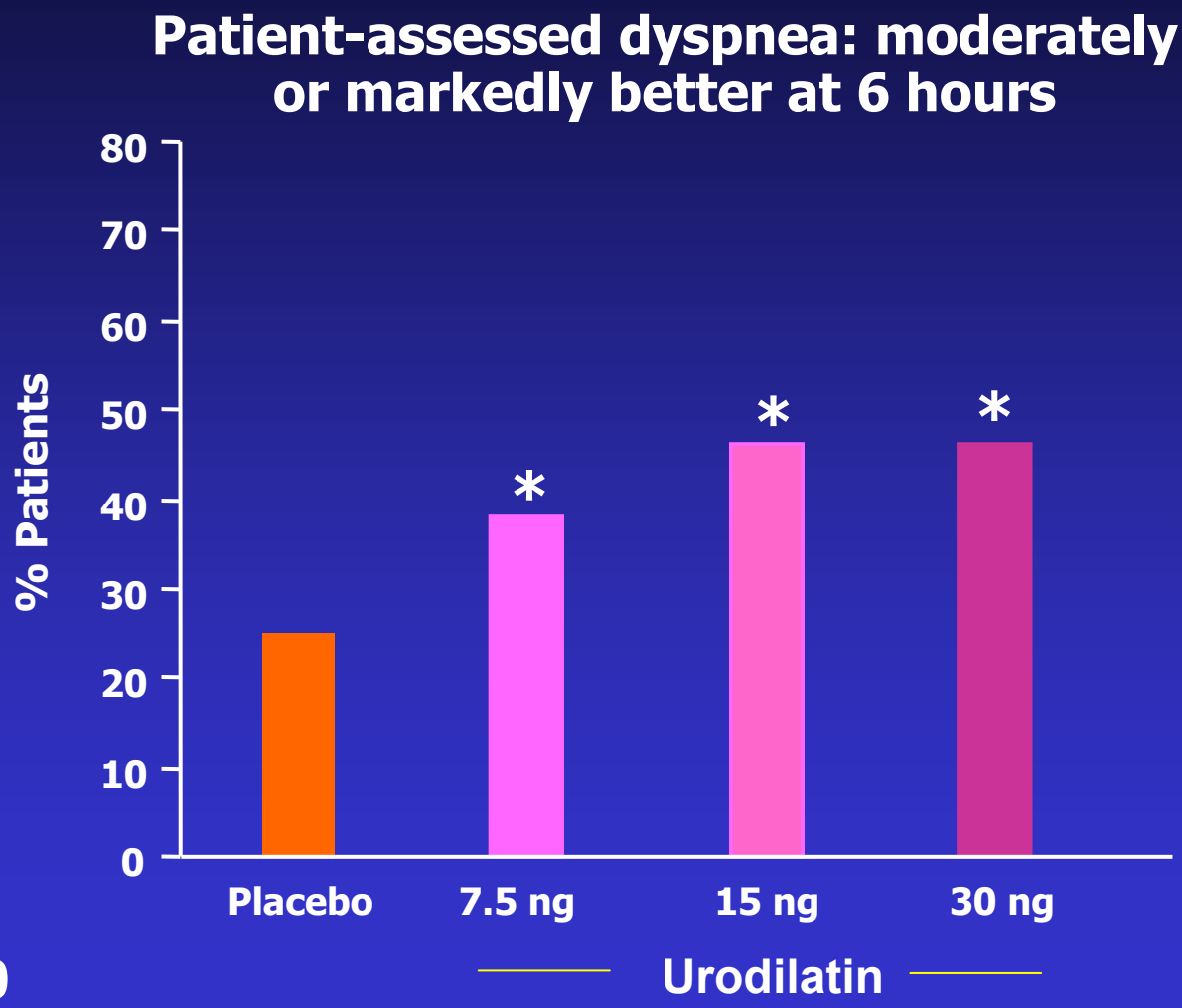



*Wilkins M et al, Lancet 1997*

# Effect of Urodilatin on ΔPCWP



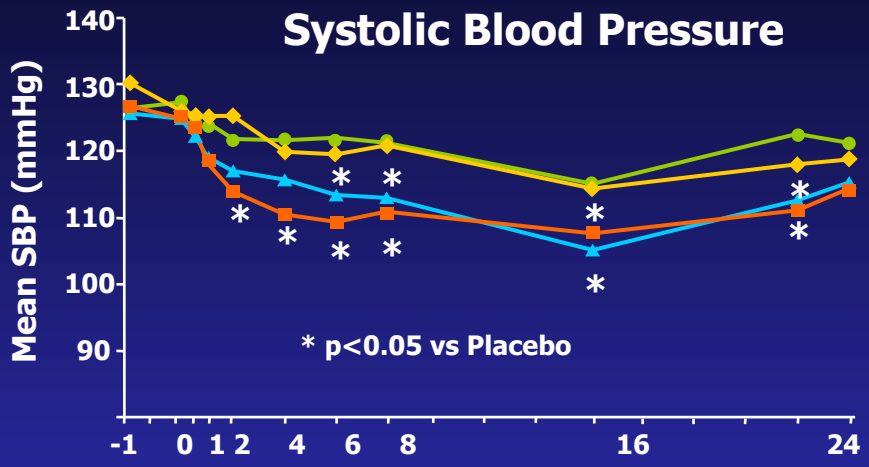
# Effect of Urodilatin on Dyspnea

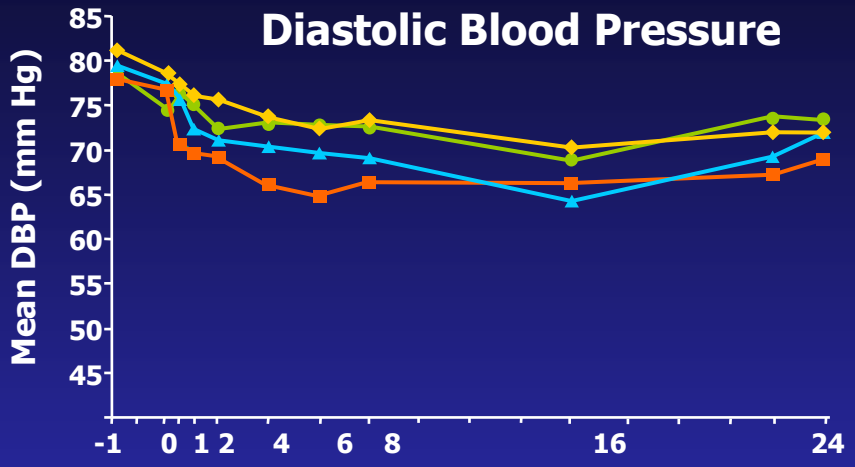



n=220

* p<0.05 vs Placebo

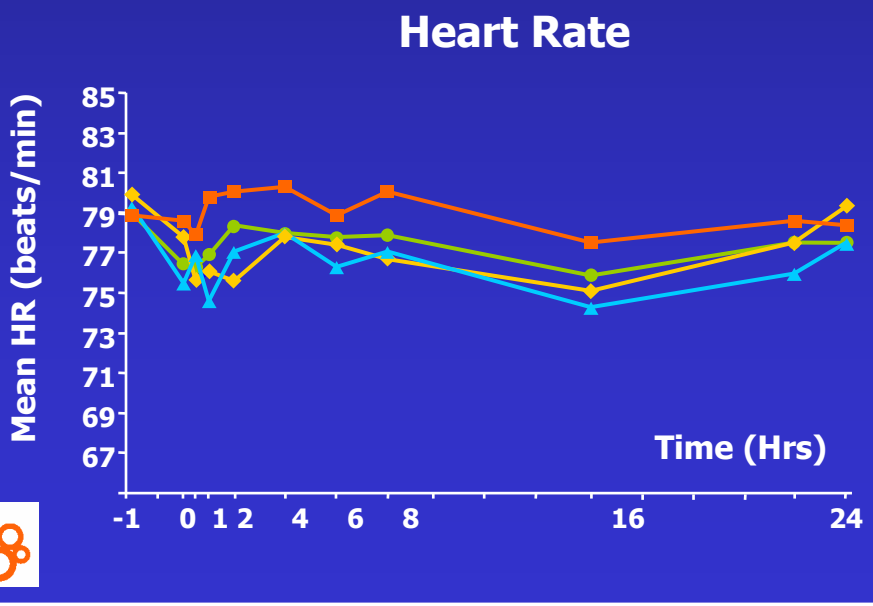
# Hemodynamic Effects of Urodilatin

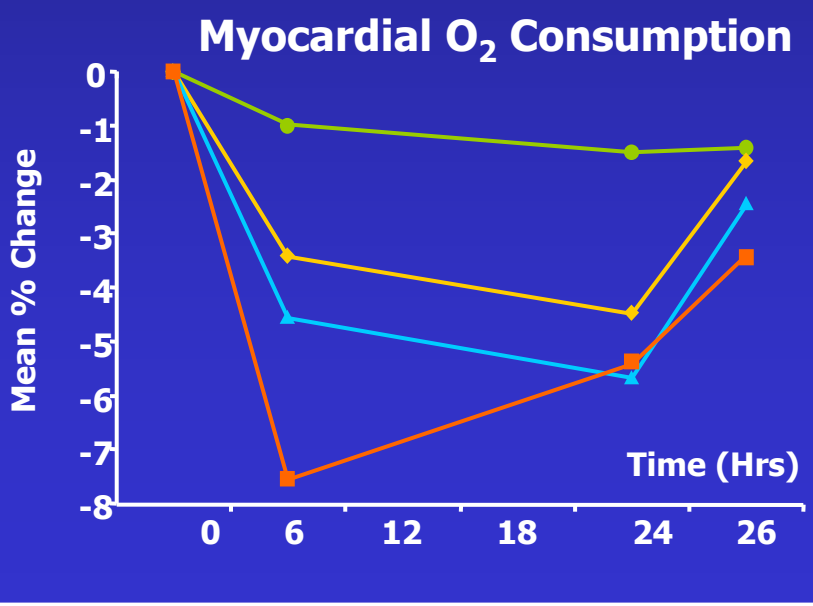


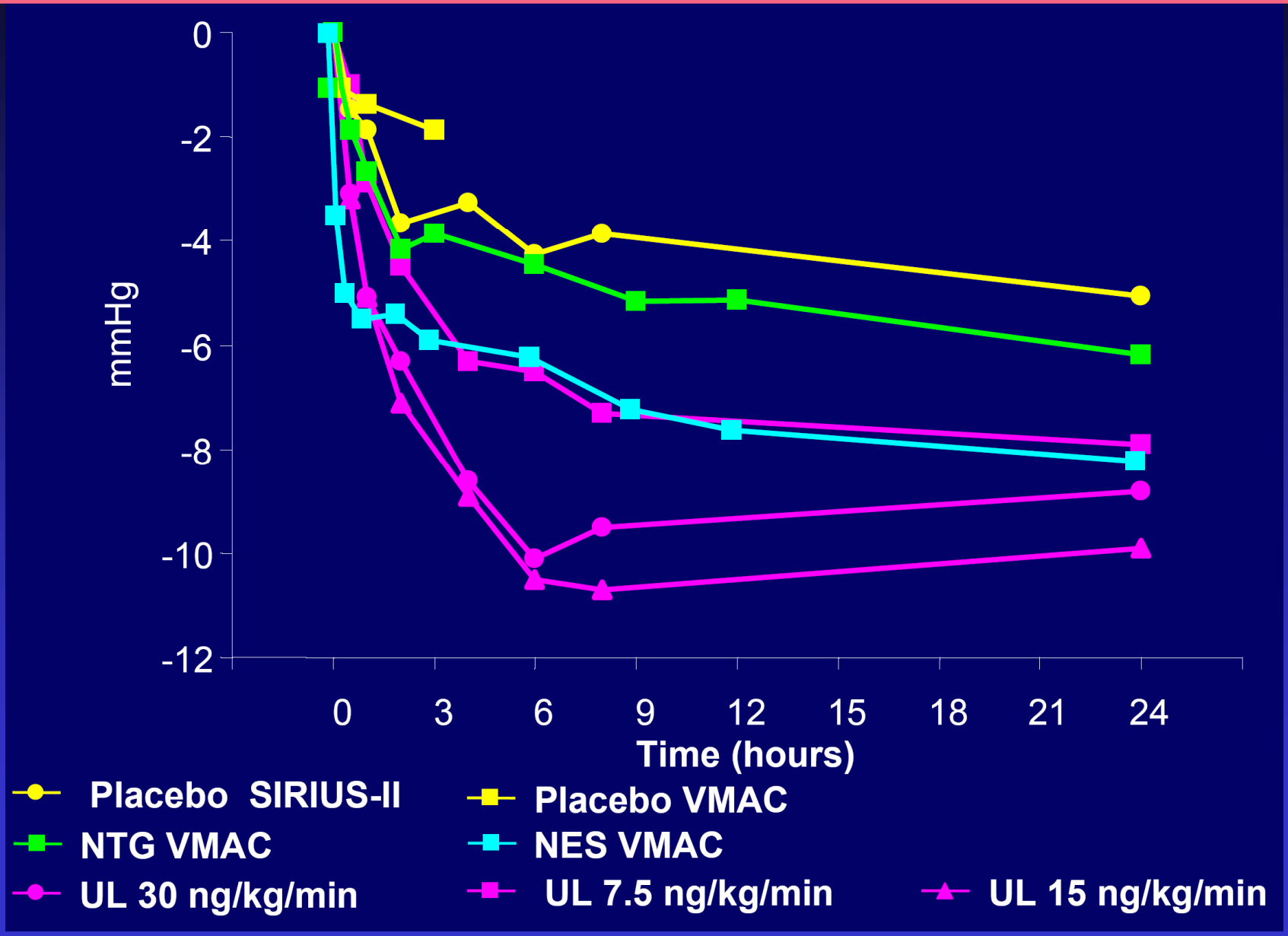

n=220

Placebo | 7.5 ng/kg/min | 15 ng/kg/min | 30 ng/kg/min



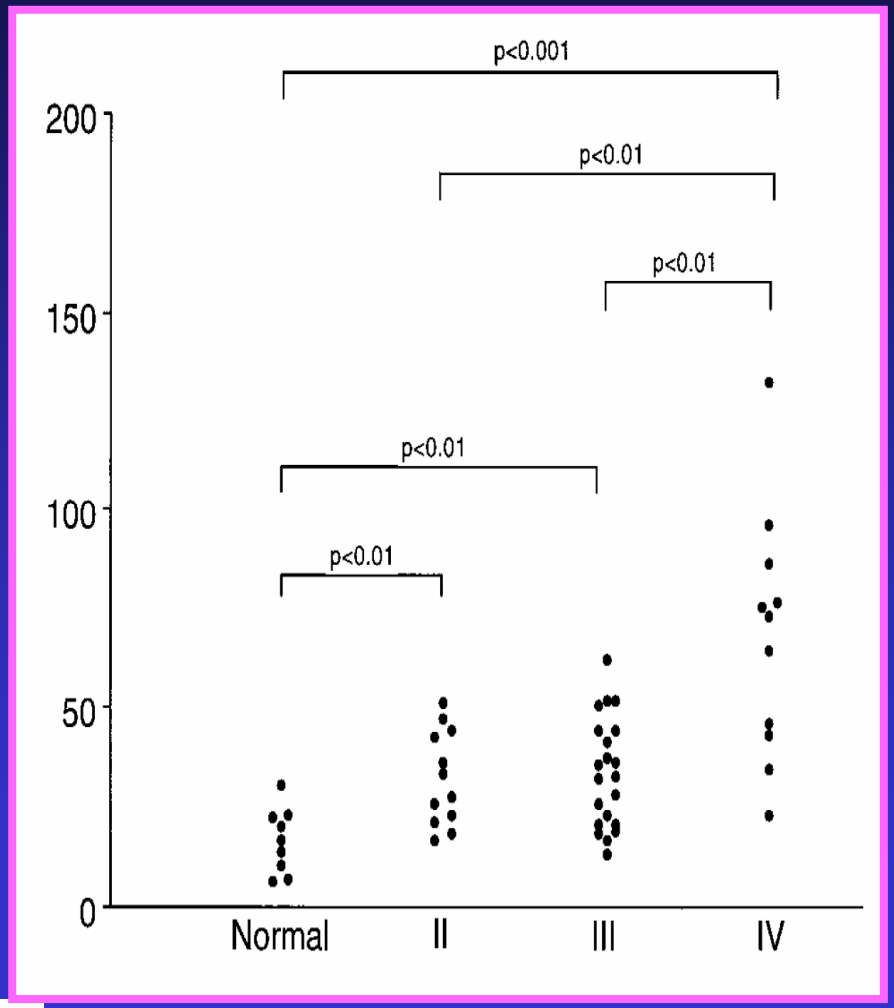



# Urodilatin vs Nesiritide on PCWP

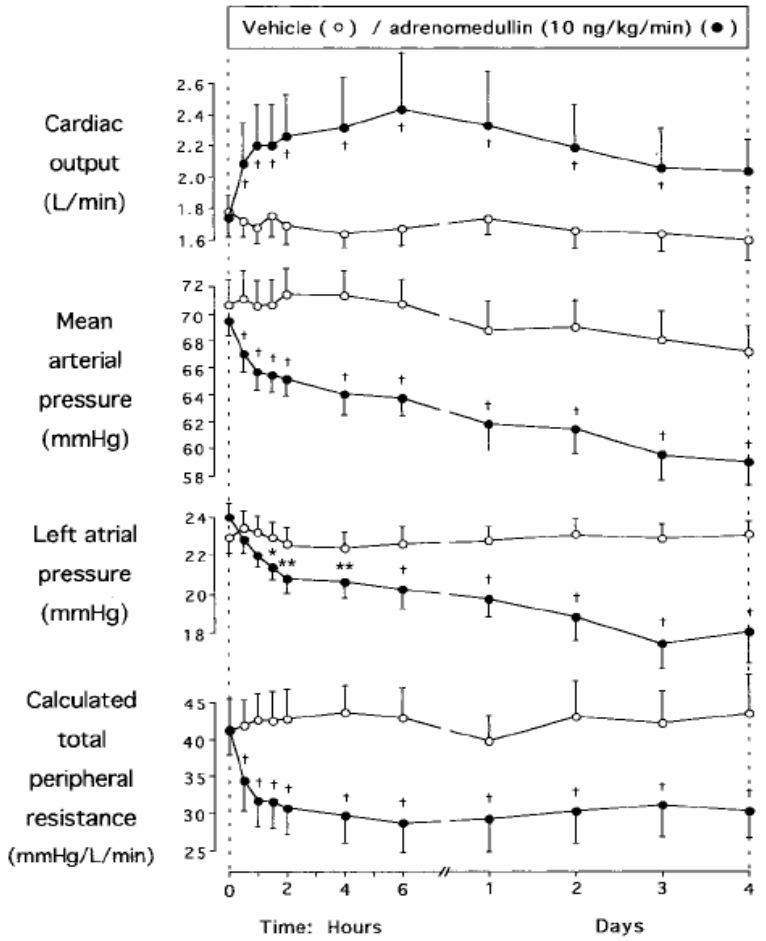


# Role of Adrenomedullin in CHF

## Plasma Levels in CHF

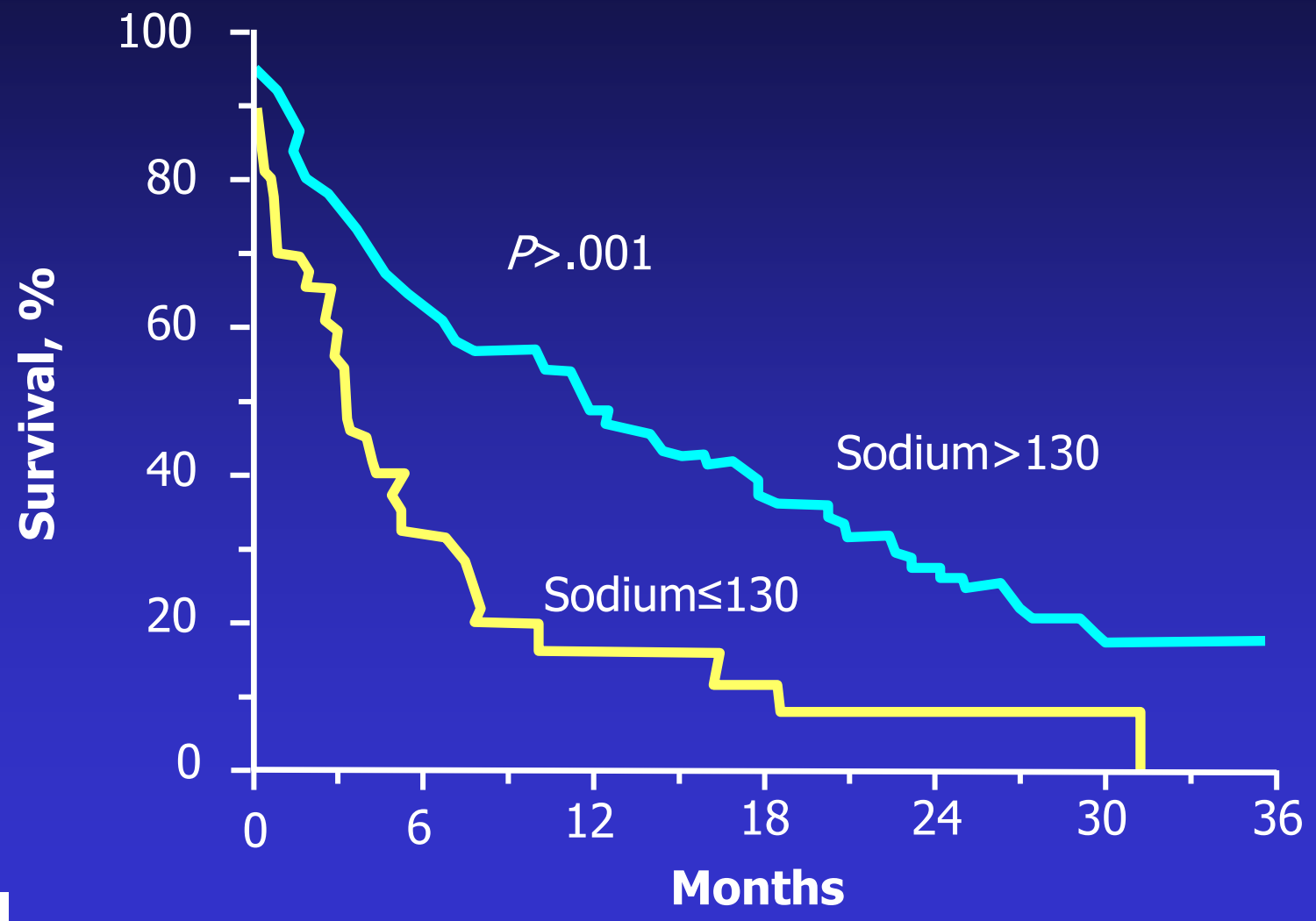



## Effects of IV Infusion



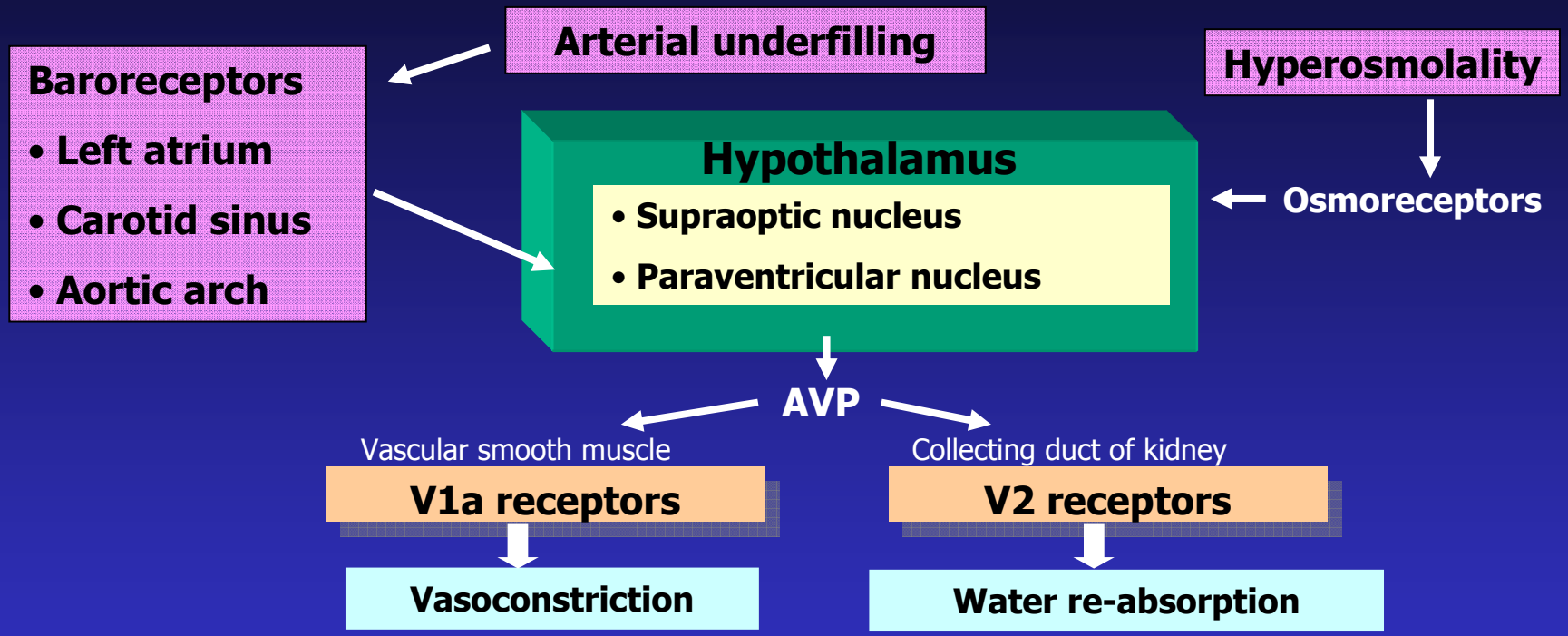

*Jougasaki M, et al. JCI 1996, Rademaker M, Circulation 2003*

# Hyponatraemia & Prognosis in Chronic Heart Failure Patients



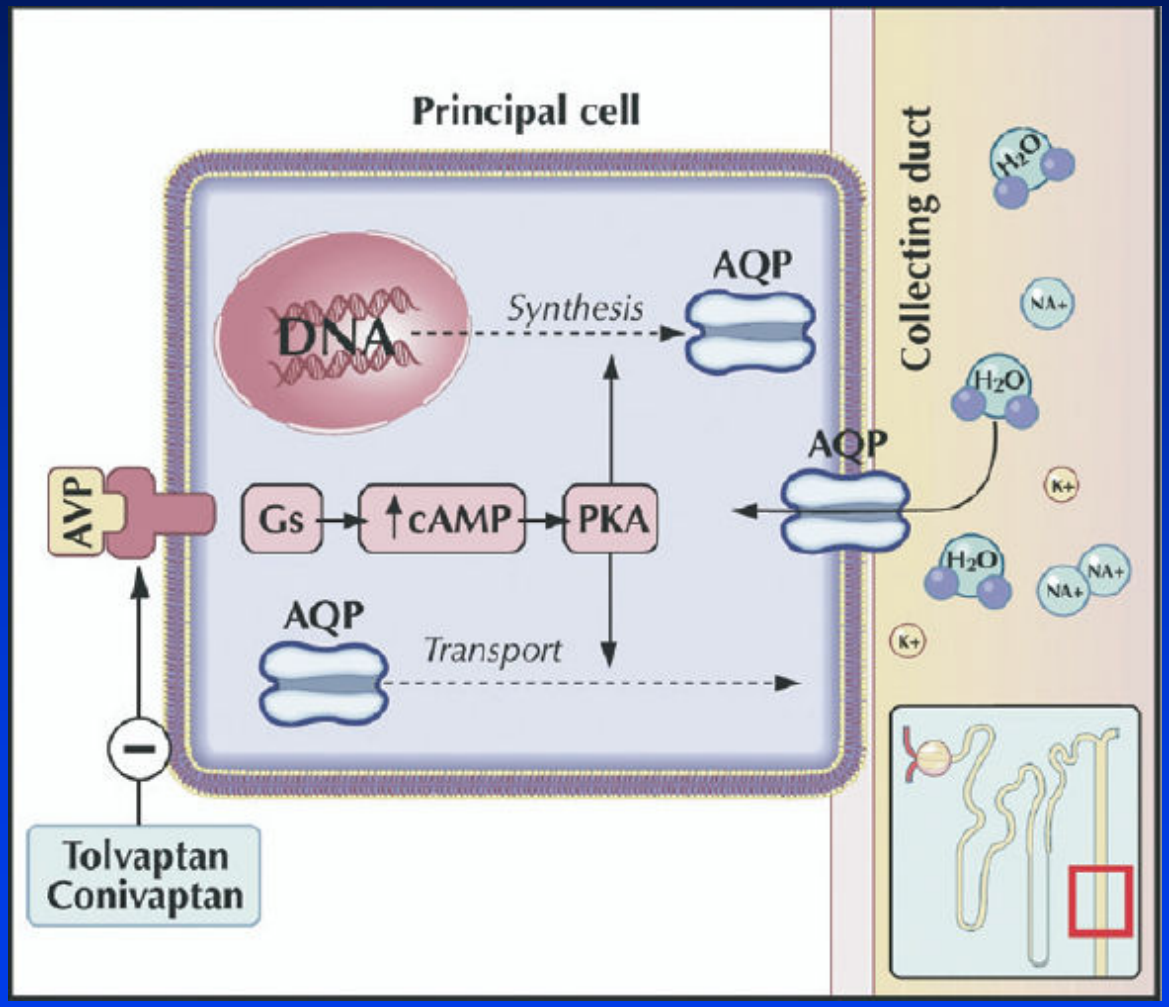

*Packer M et al Circulation 1986*

# Vasopressin System



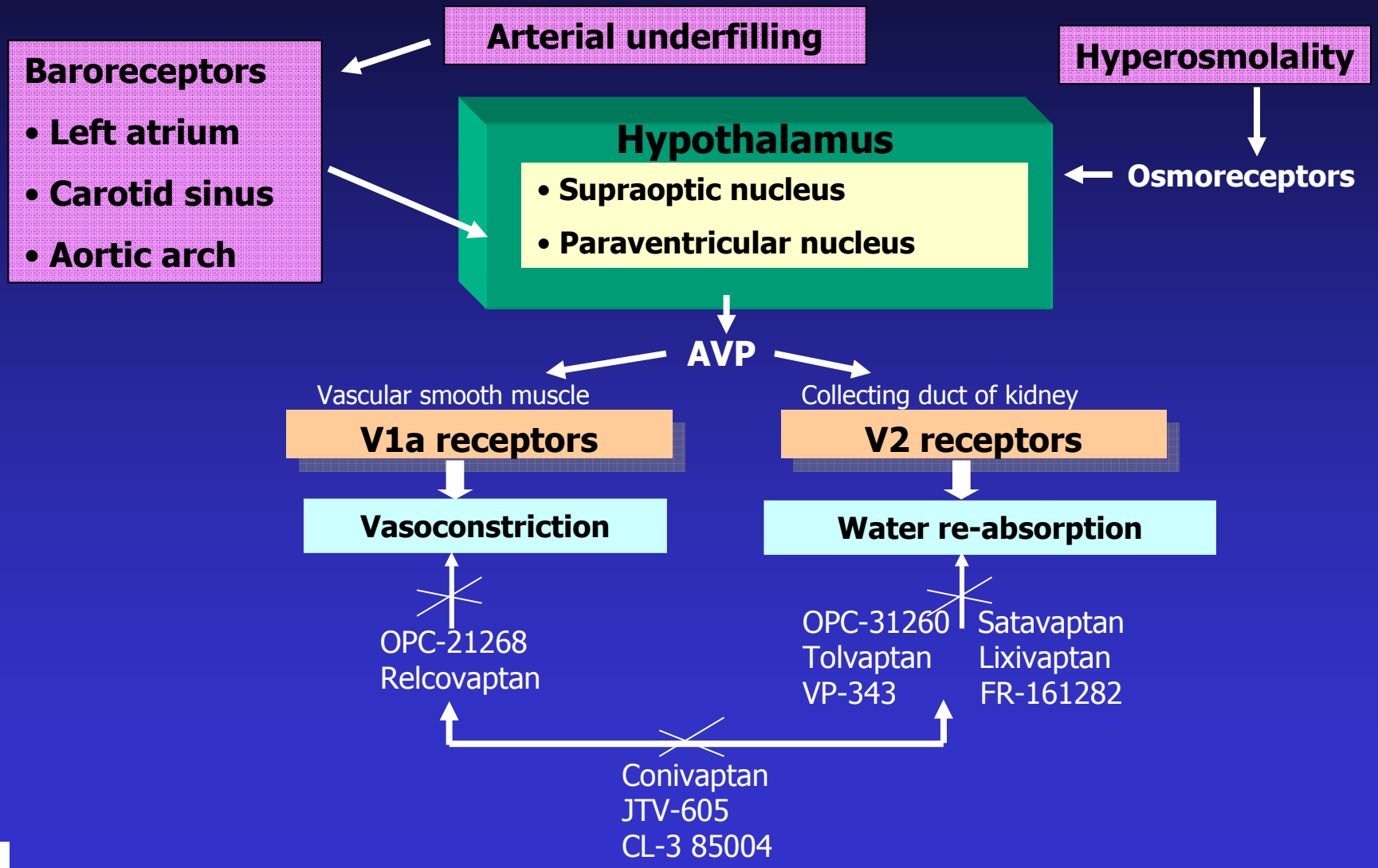

Adapted from Sanghi et al *Eur Heart J* 2005

# Mechanism of Action of Vasopressin Antagonists




*deGoma, et al. JACC, 2006.*

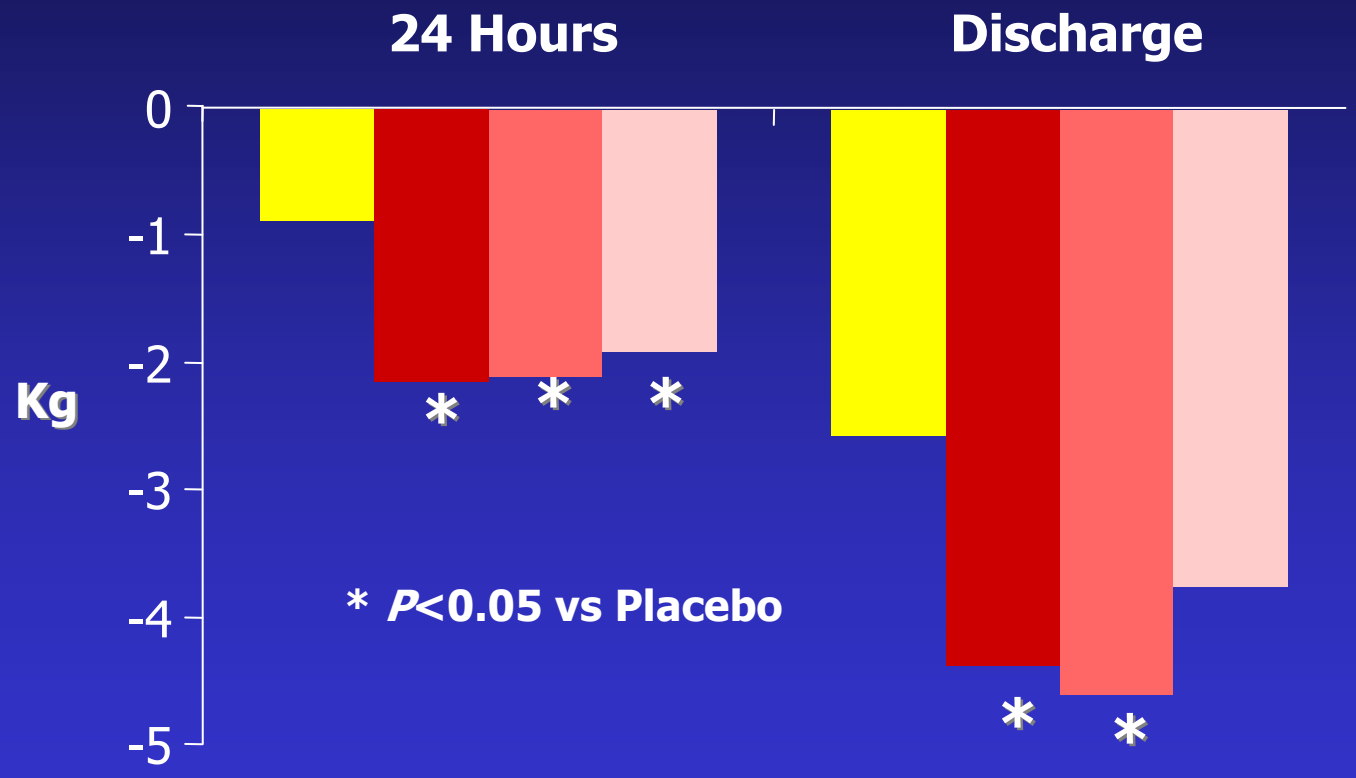
# Vasopressin System




Adapted from Sanghi et al *Eur Heart J* 2005

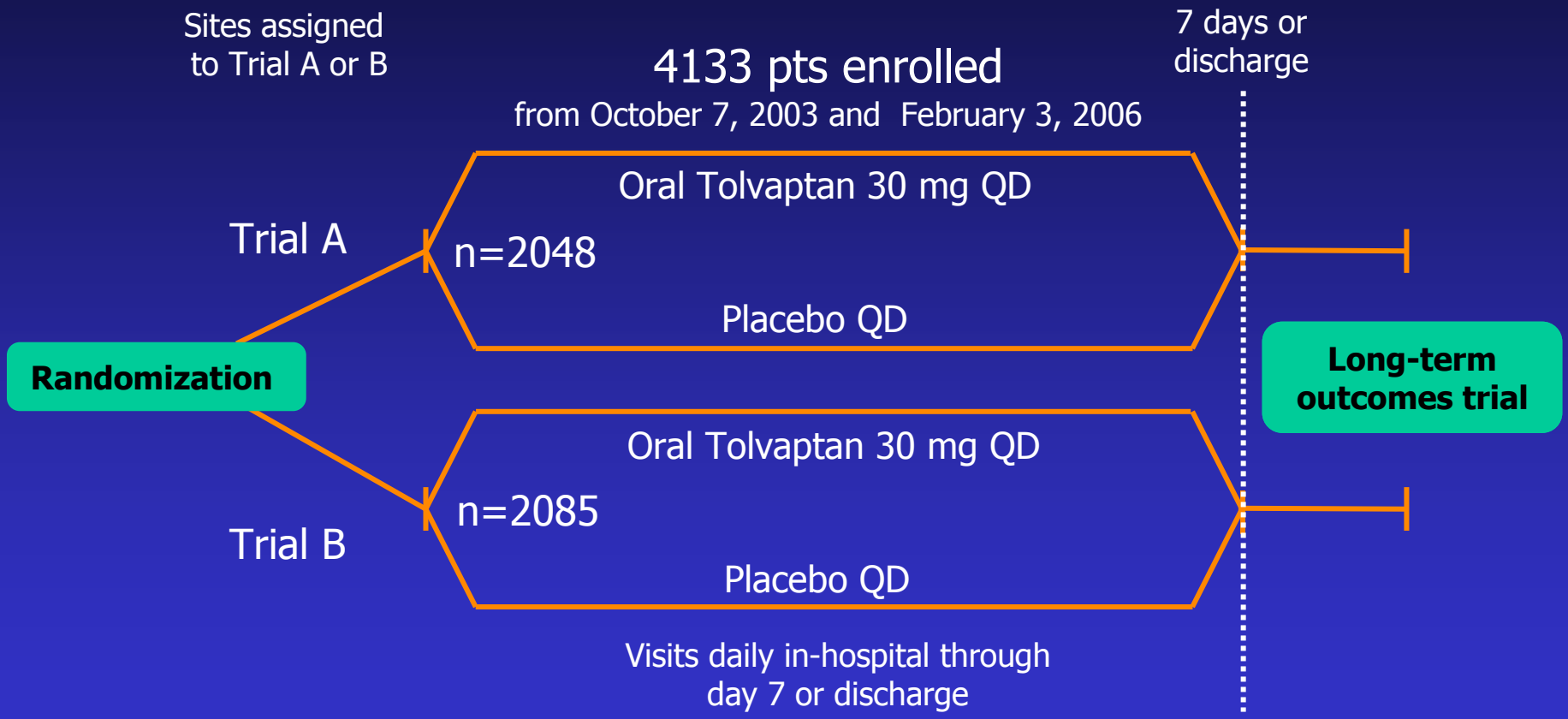
# ACTIV-CHF

## Mean Body Weight Changes During Hospitalization




*Giorghiade M et al. JAMA 2004*

# EVEREST Short-Term Study

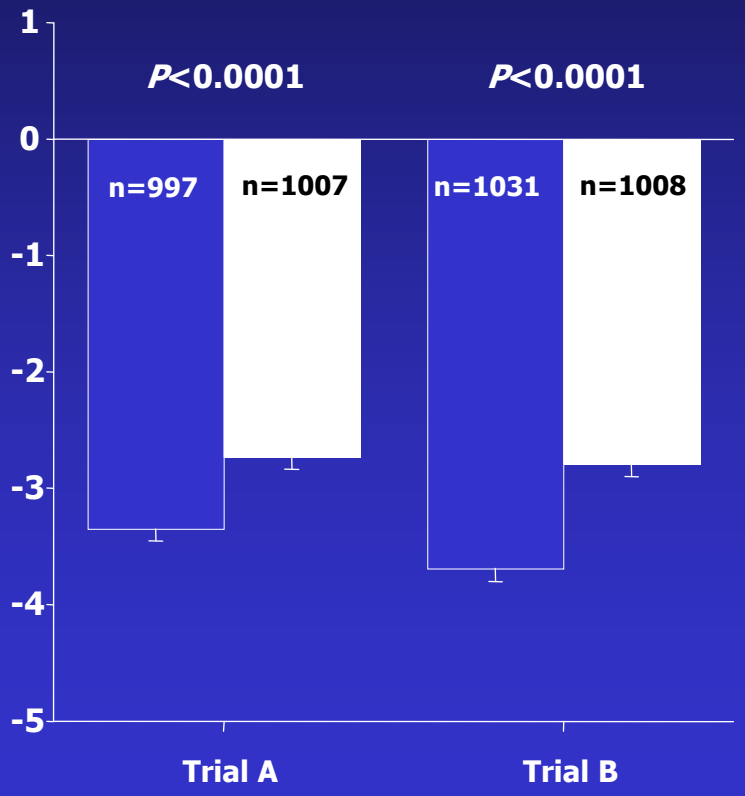



**Primary Endpoint: Composite of change in body weight and improvement in patient-assessed global status**

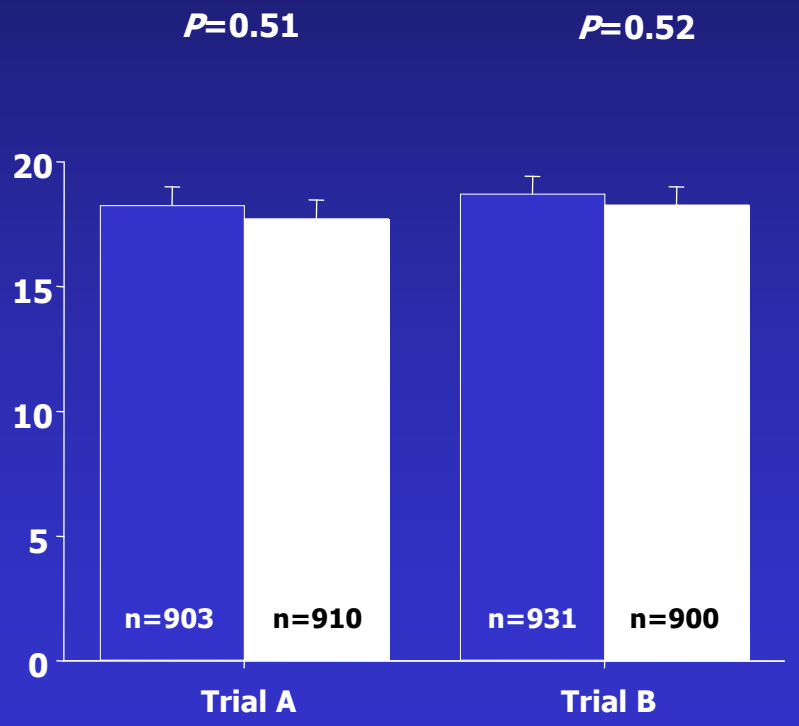
# EVEREST Short-Term Study

## *Primary Endpoint*

### Change in Body Weight (kg)




### Change in Global Clinical Status

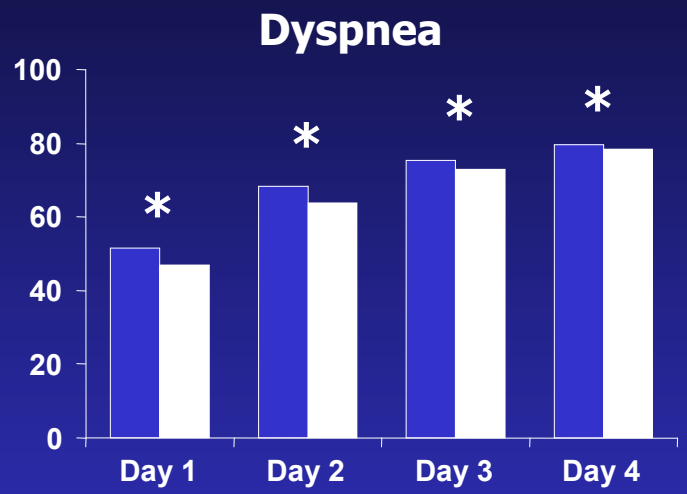


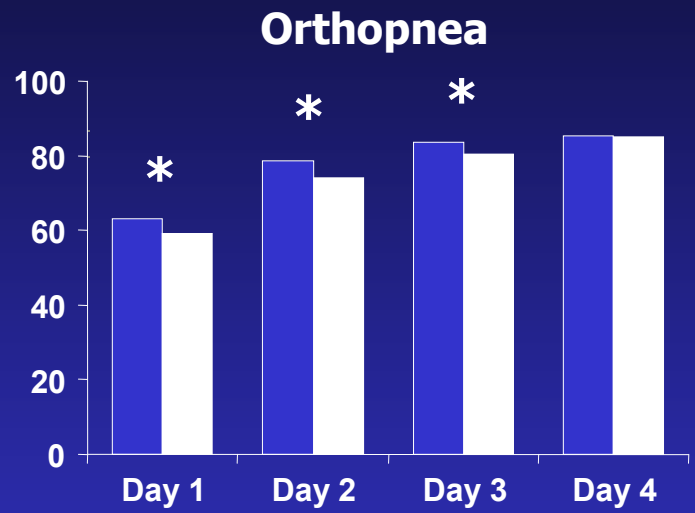

Tolvaptan  Placebo

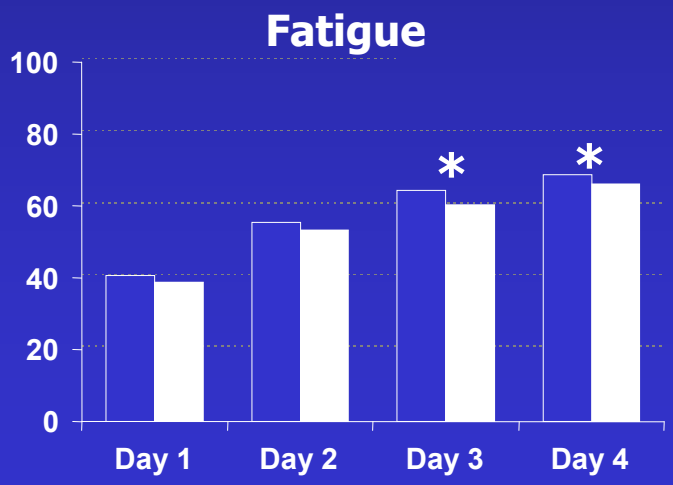
*Giorghiade M et al. JAMA 2007*

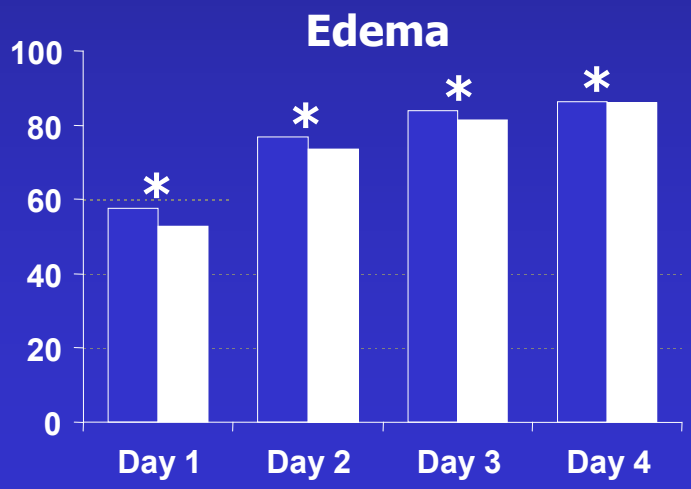
# EVEREST Short-Term Study

## *Secondary Endpoints*




* *P*<0.05

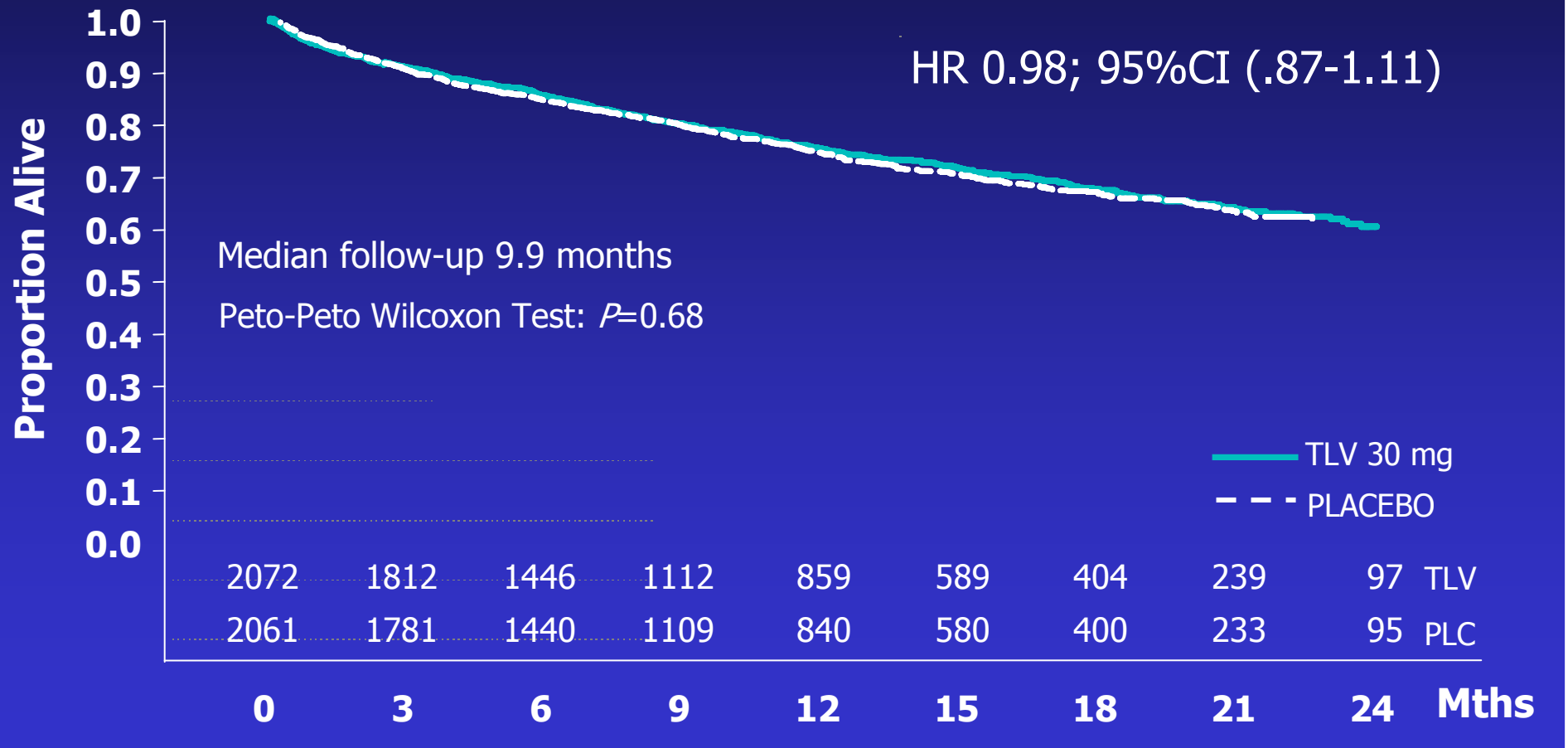
Tolvaptan

Placebo

*Giorghiade M et al. JAMA 2007*

# EVEREST Long-Term Study

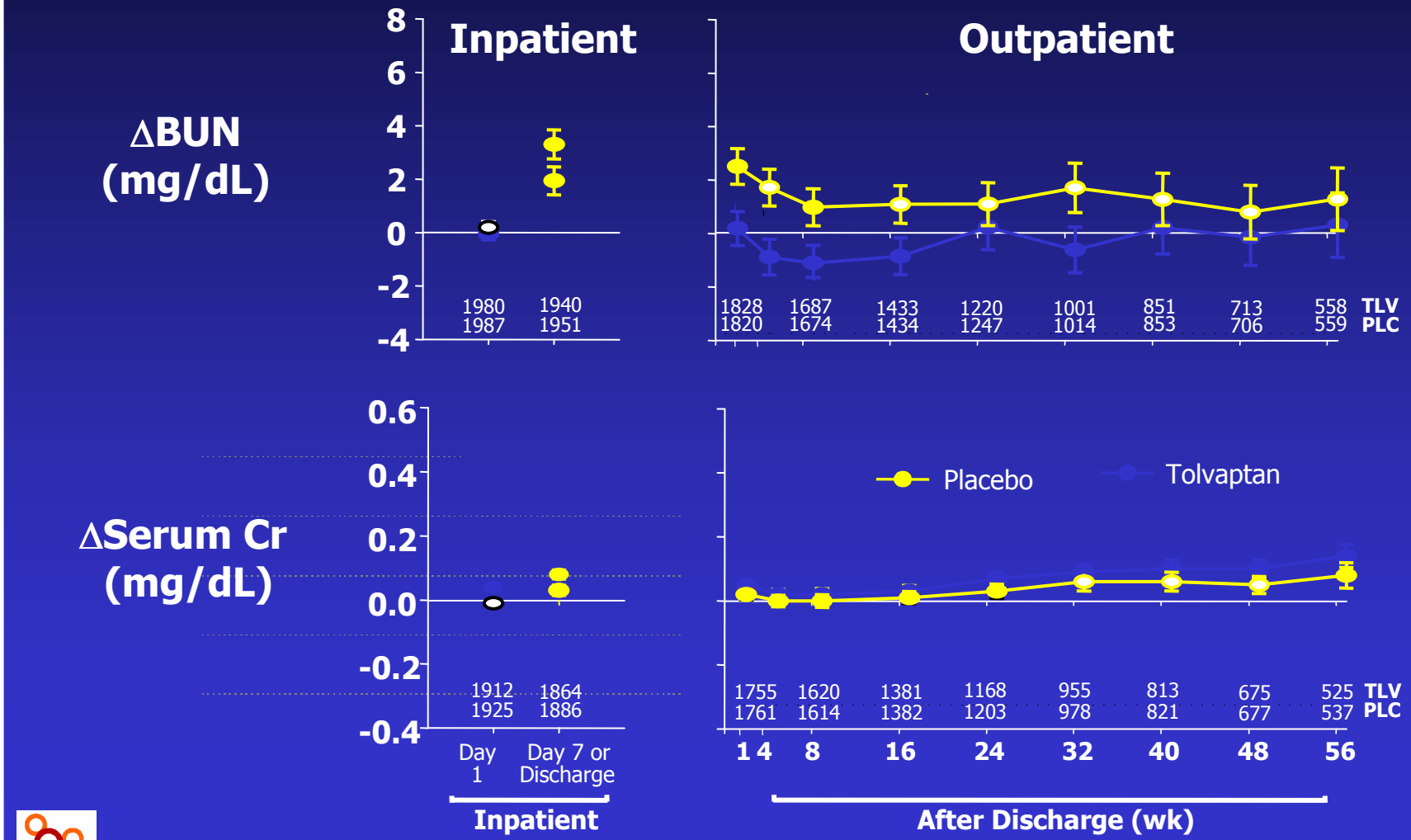
## *All-Cause Mortality*




*Konstam M et al. JAMA 2007*

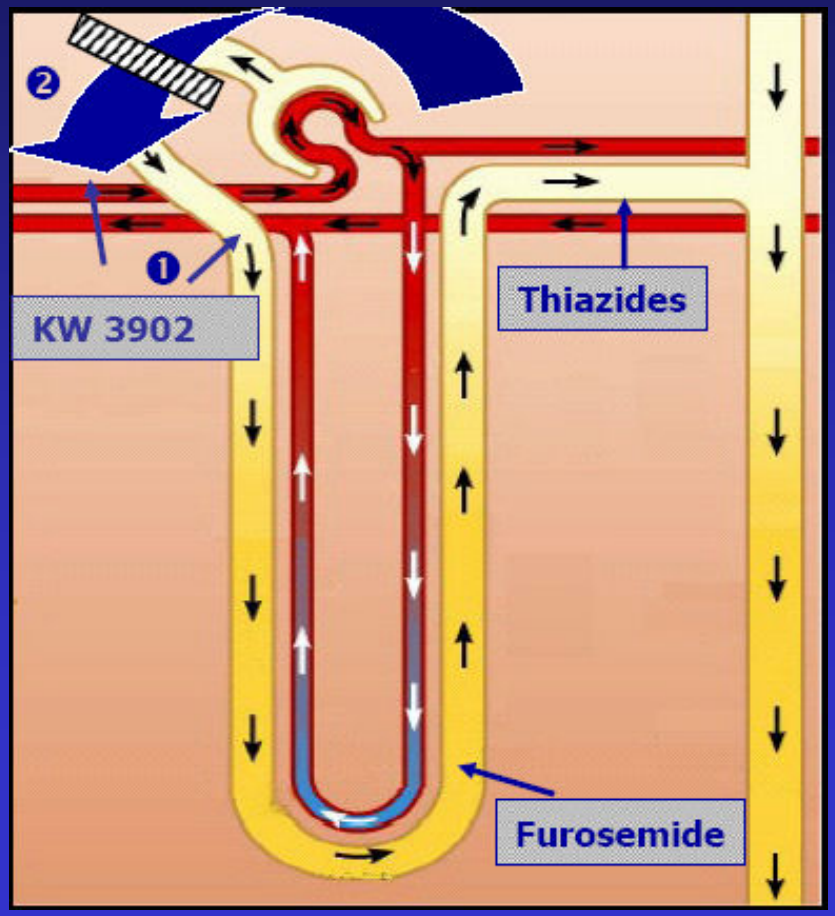
# EVEREST

## Δ Renal Function




*Konstam M et al. JAMA 2007*

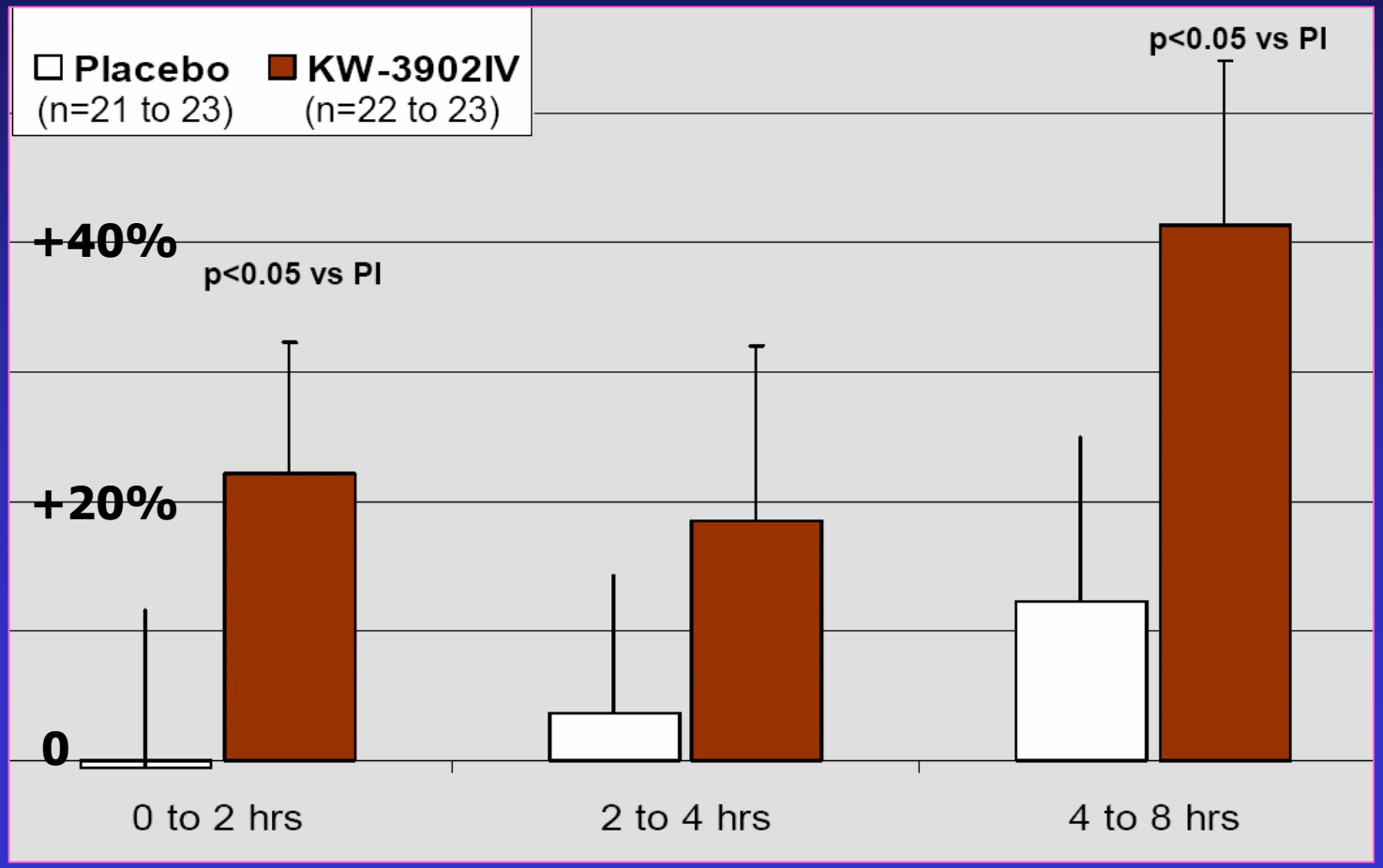
# Adenosine A1 Receptor Antagonists: Mode of Action



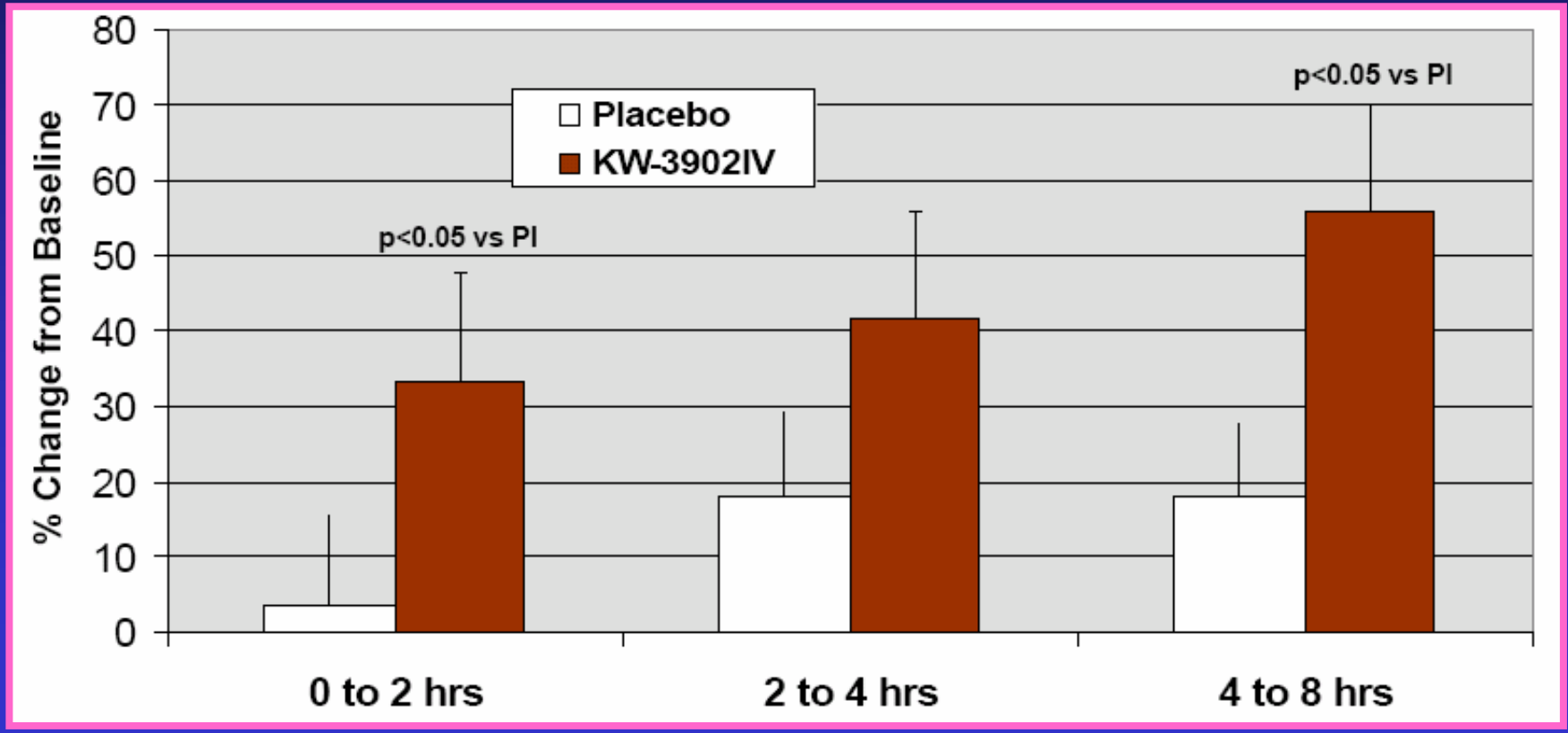

1. Inhibits proximal tubular sodium reabsorption → Enhanced diuresis

2. Blocks adenosine-mediated vasoconstriction of afferent arteriole → Maintains GFR

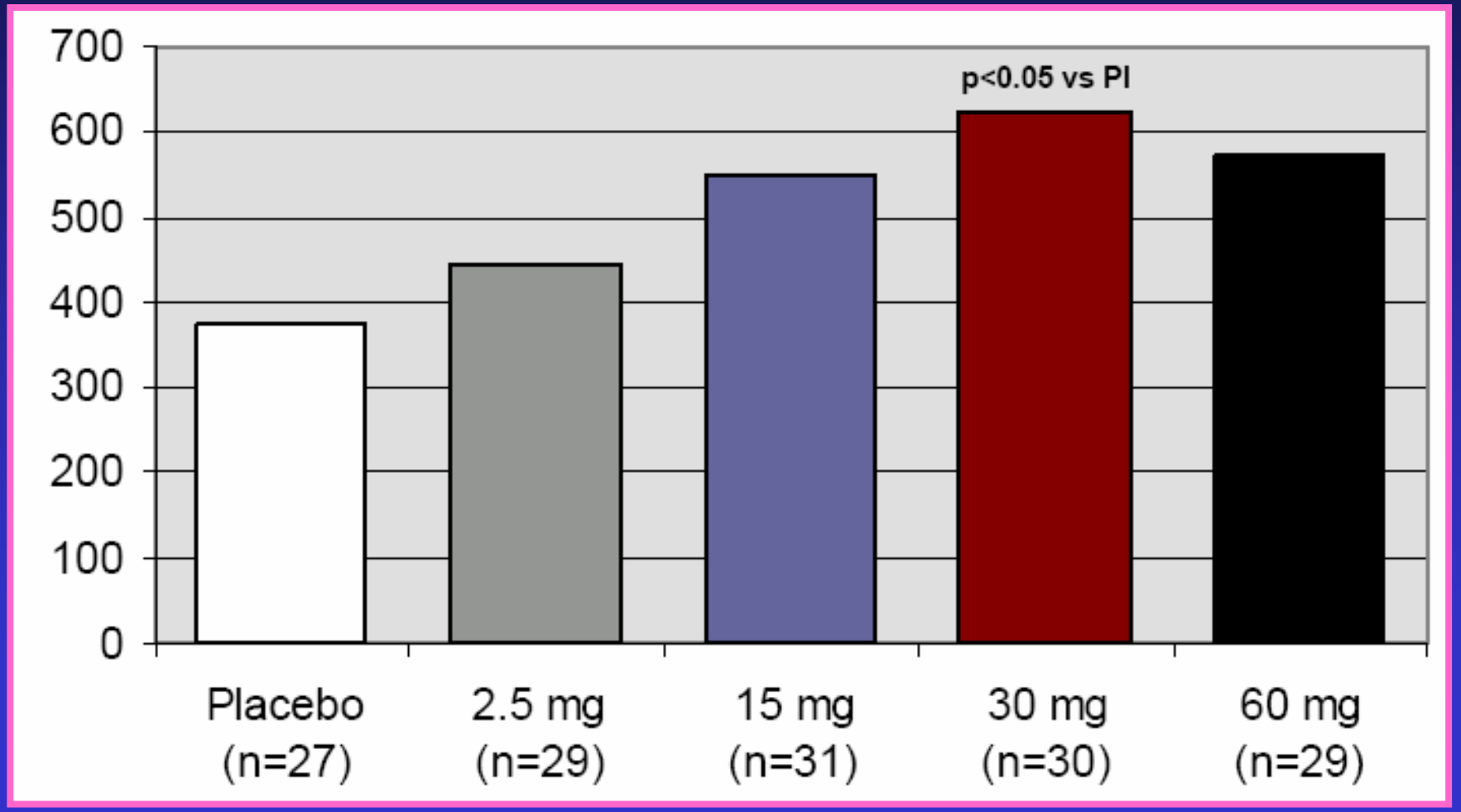
# Adenosine A1 Receptor Antagonists: Effect on GFR



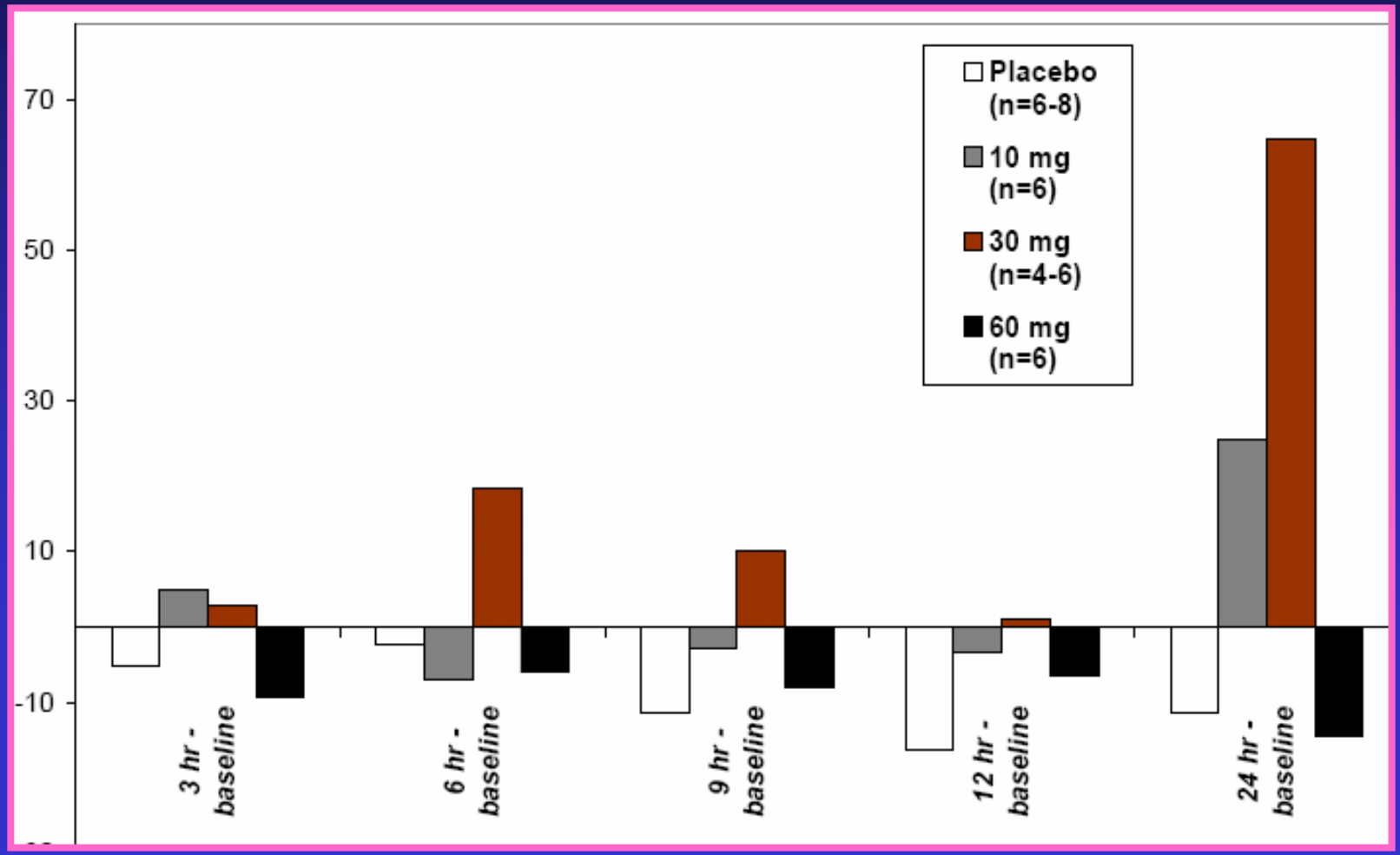
# Adenosine A1 Receptor Antagonists: Effect on RBF



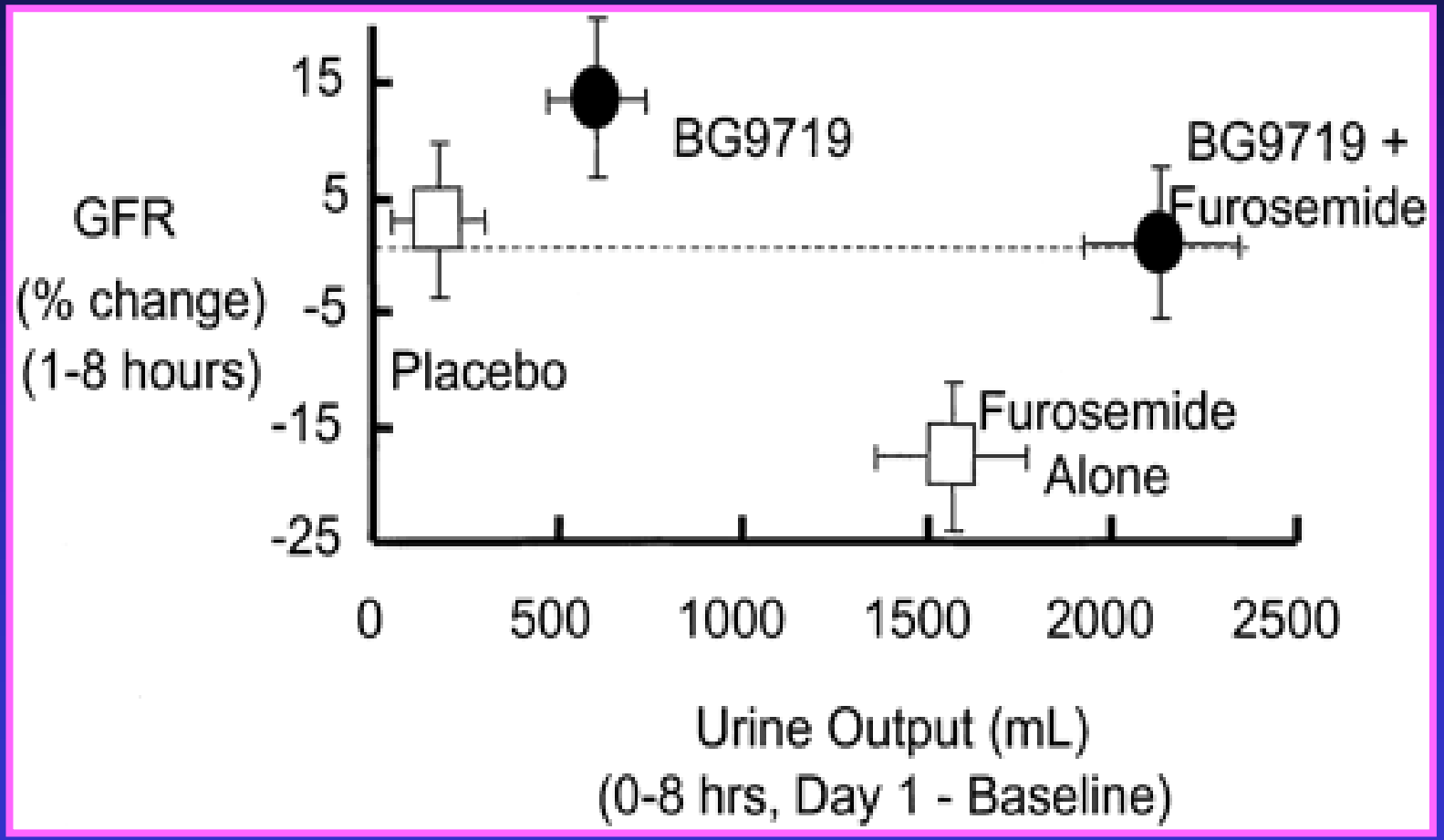
# Adenosine A1 Receptor Antagonists: Effect on Urine Vol.



# Adenosine A1 Receptor Antagonists: Effect on eGFR

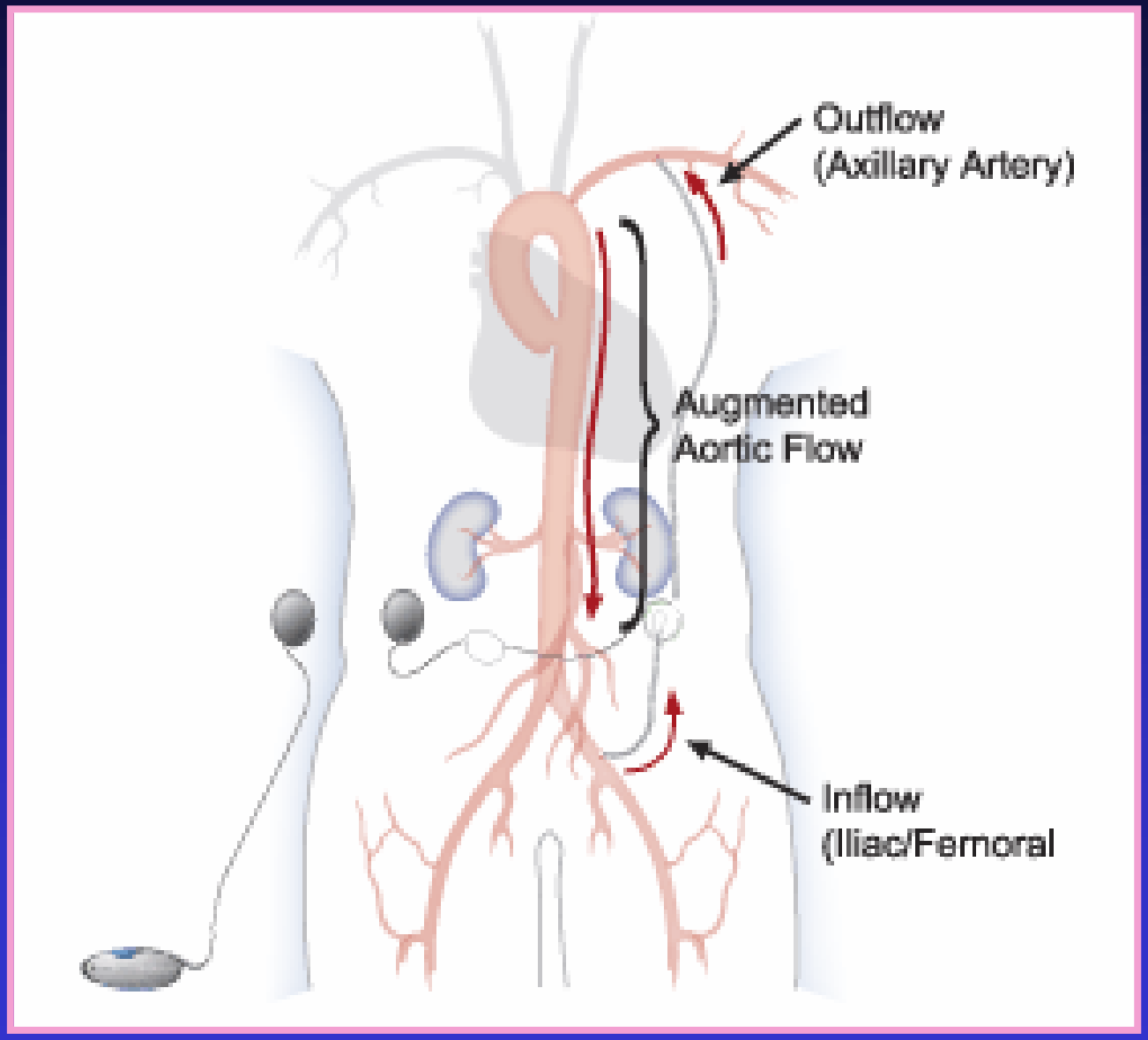


# Effect of Adenosine Antagonist on GFR in Patients with CHF

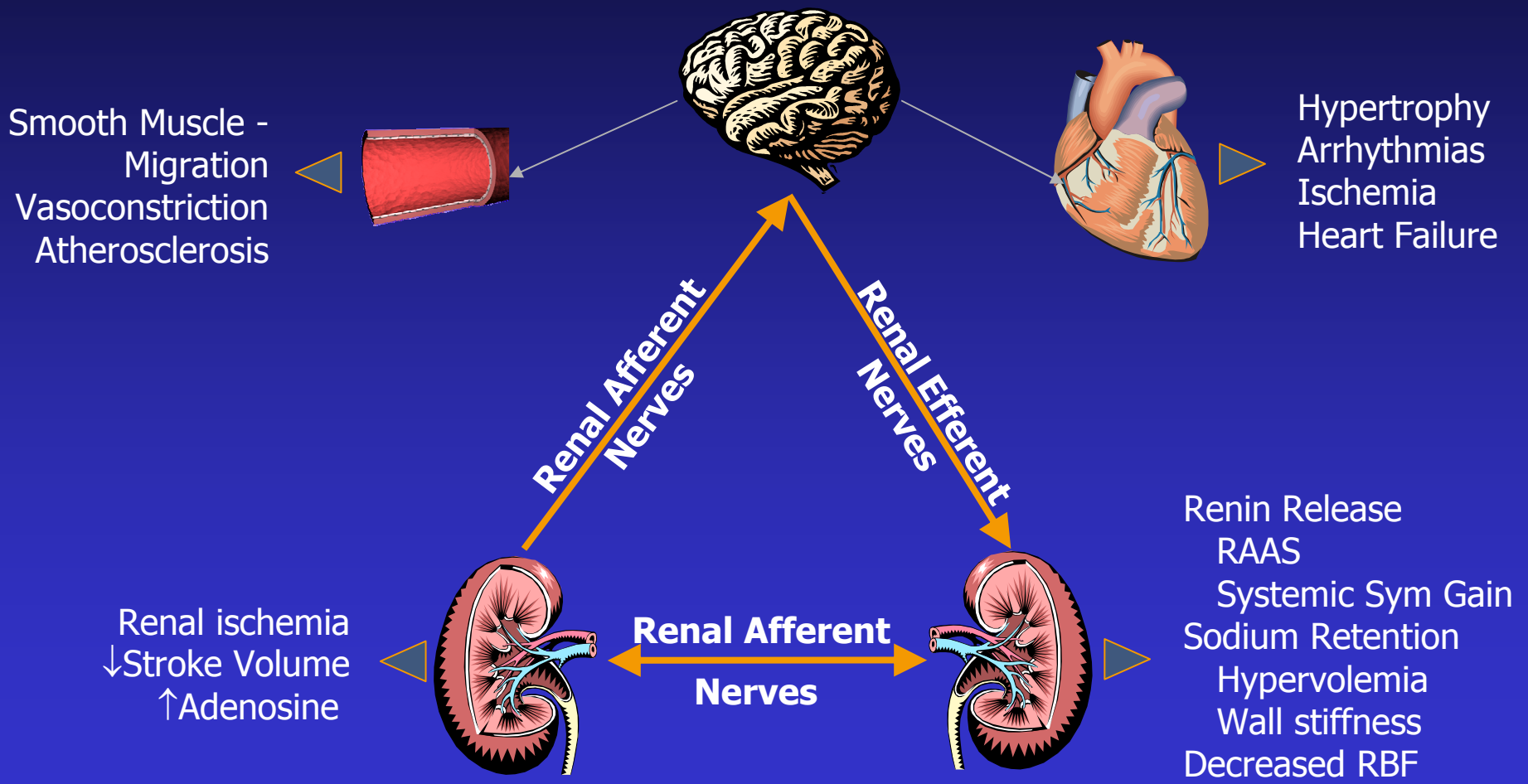



*Gottlieb S et al. Circulation 2002*

# Orqis Device



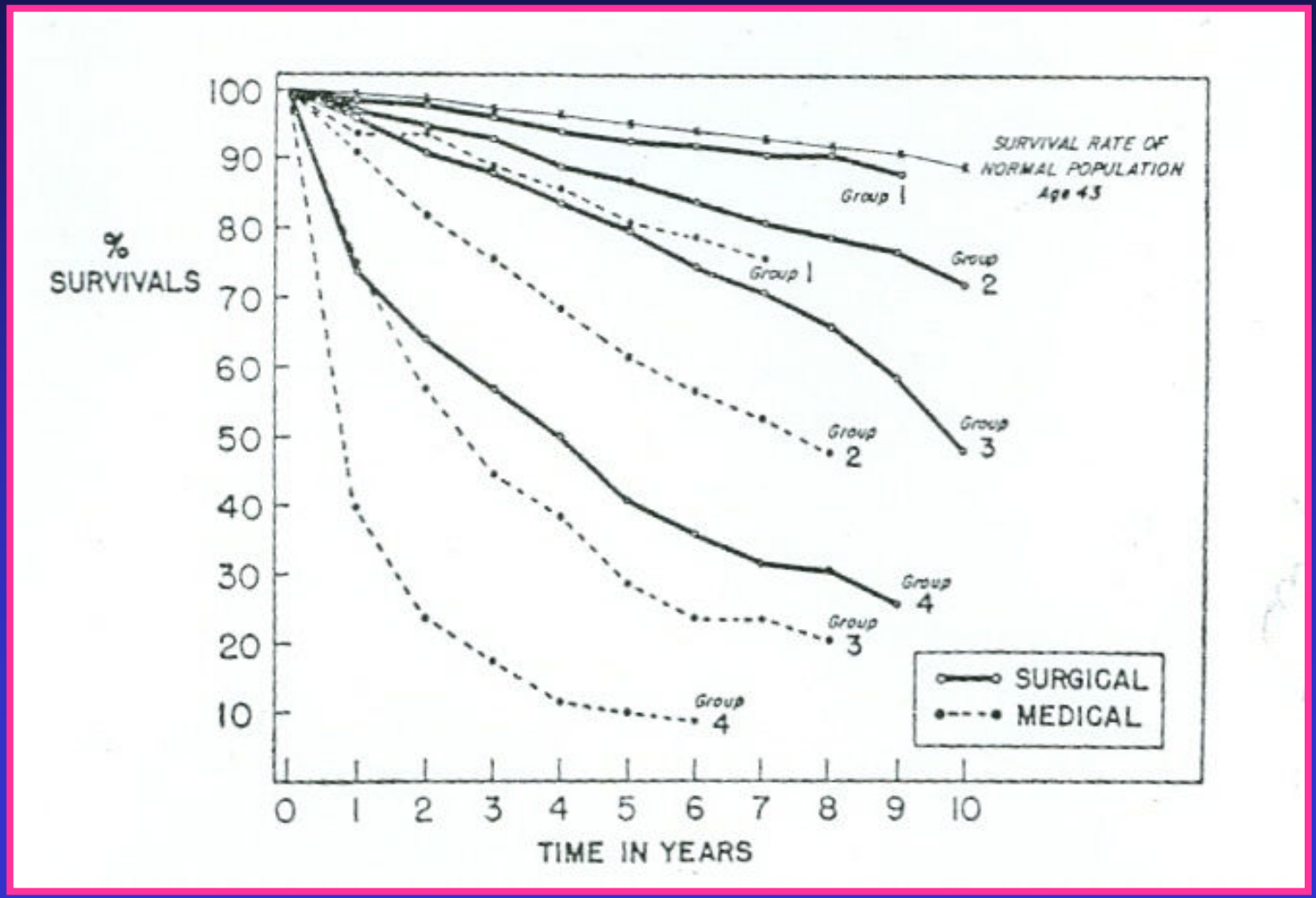
# Renal Sympathetic Activation & Chronic Heart Failure



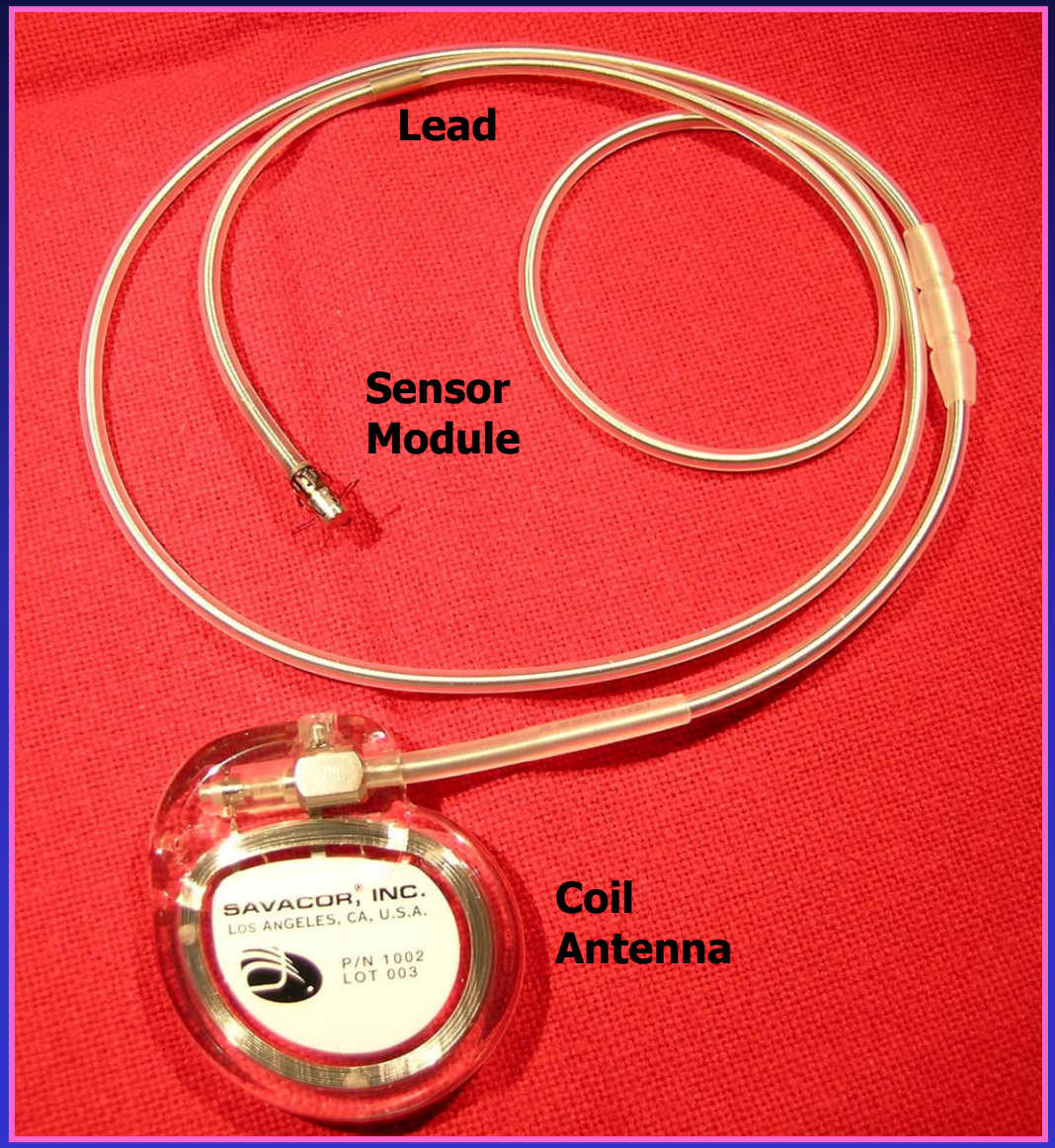
# Renal Denervation in CHF

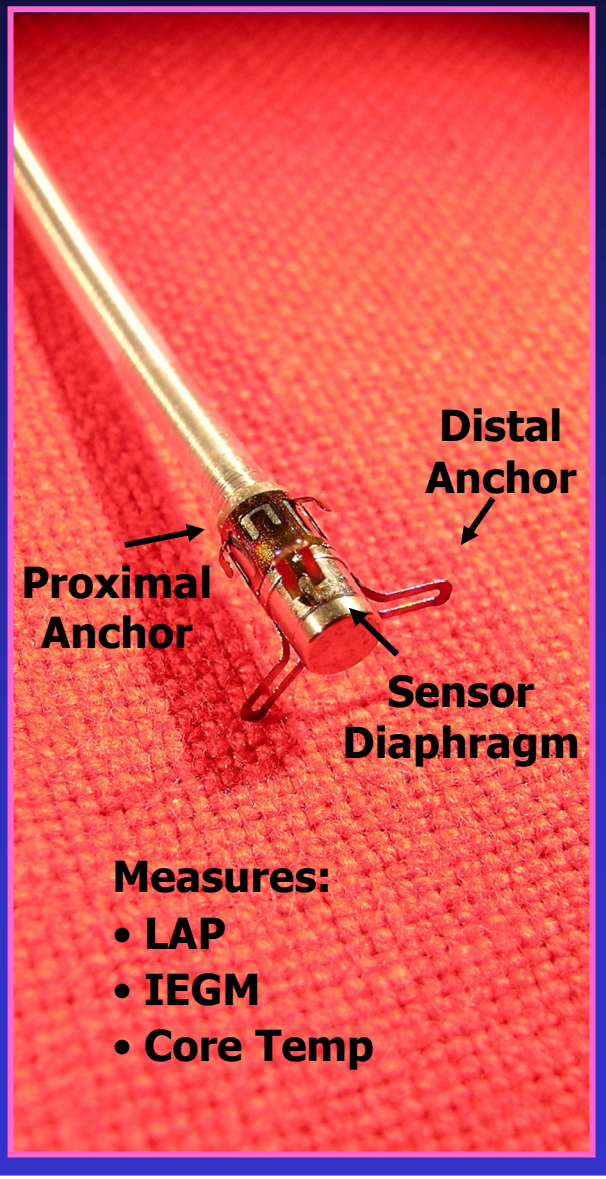
- Renal denervation in patients with hyperadrenergic states should result in:
  - Reduction of renin
  - Reduction of angiotensin II
  - Reduction of aldosterone
  - Improved natriuresis
  - Reduced central sympathetic “gain”
  - Improved renal blood flow
  - Reduction of blood pressure

# Renal Denervation in CHF Patients: Effects on Survival

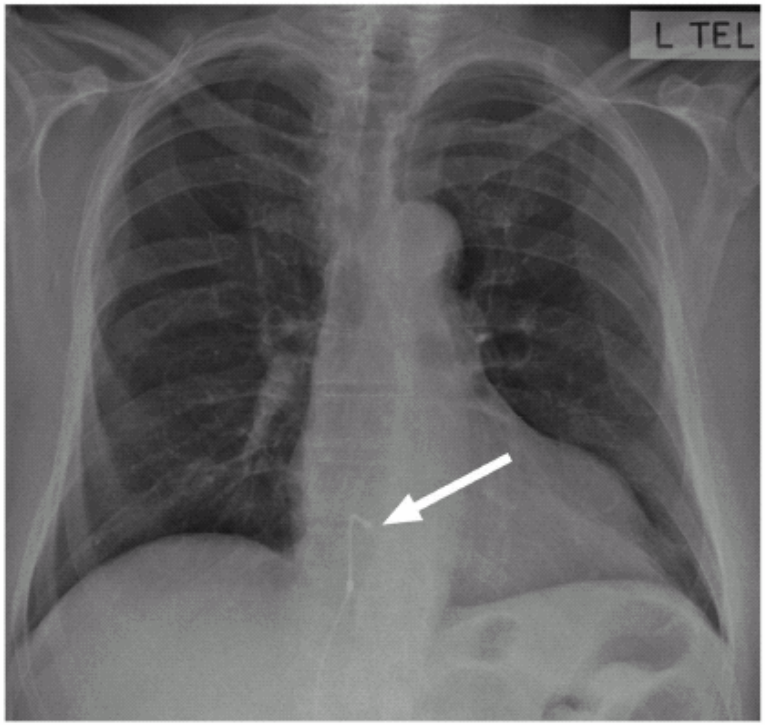


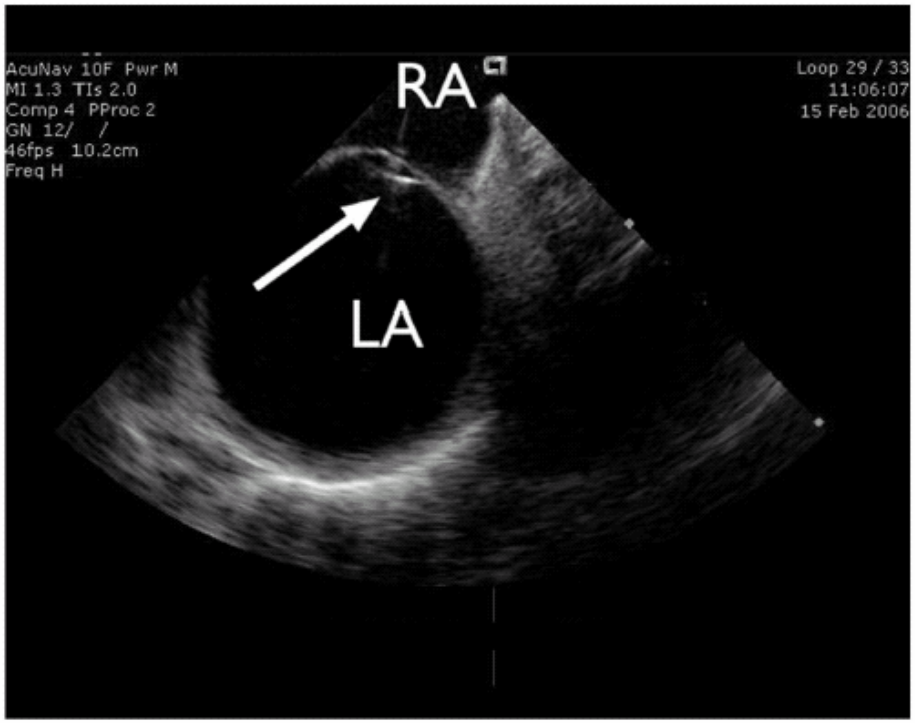
# HeartPOD LA Pressure Transducer



# LAP Device in Situ

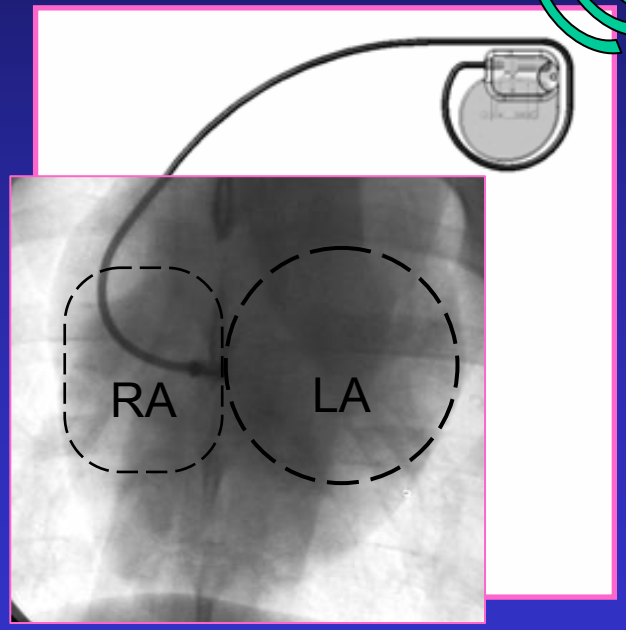


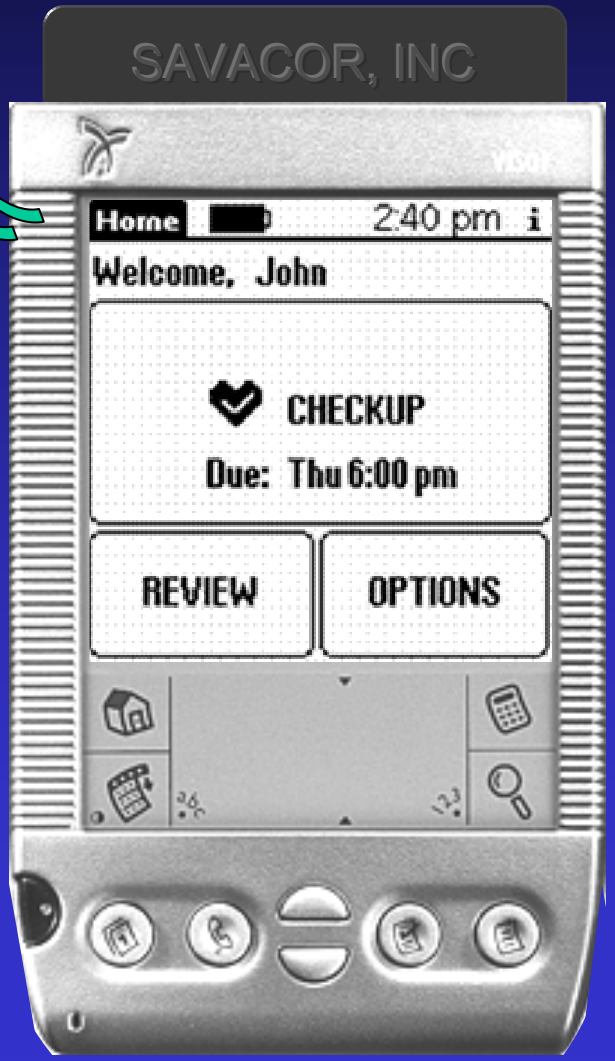




CCRE THERAPEUTICS

# HeartPOD LA Pressure Transducer

## *Patient Module*

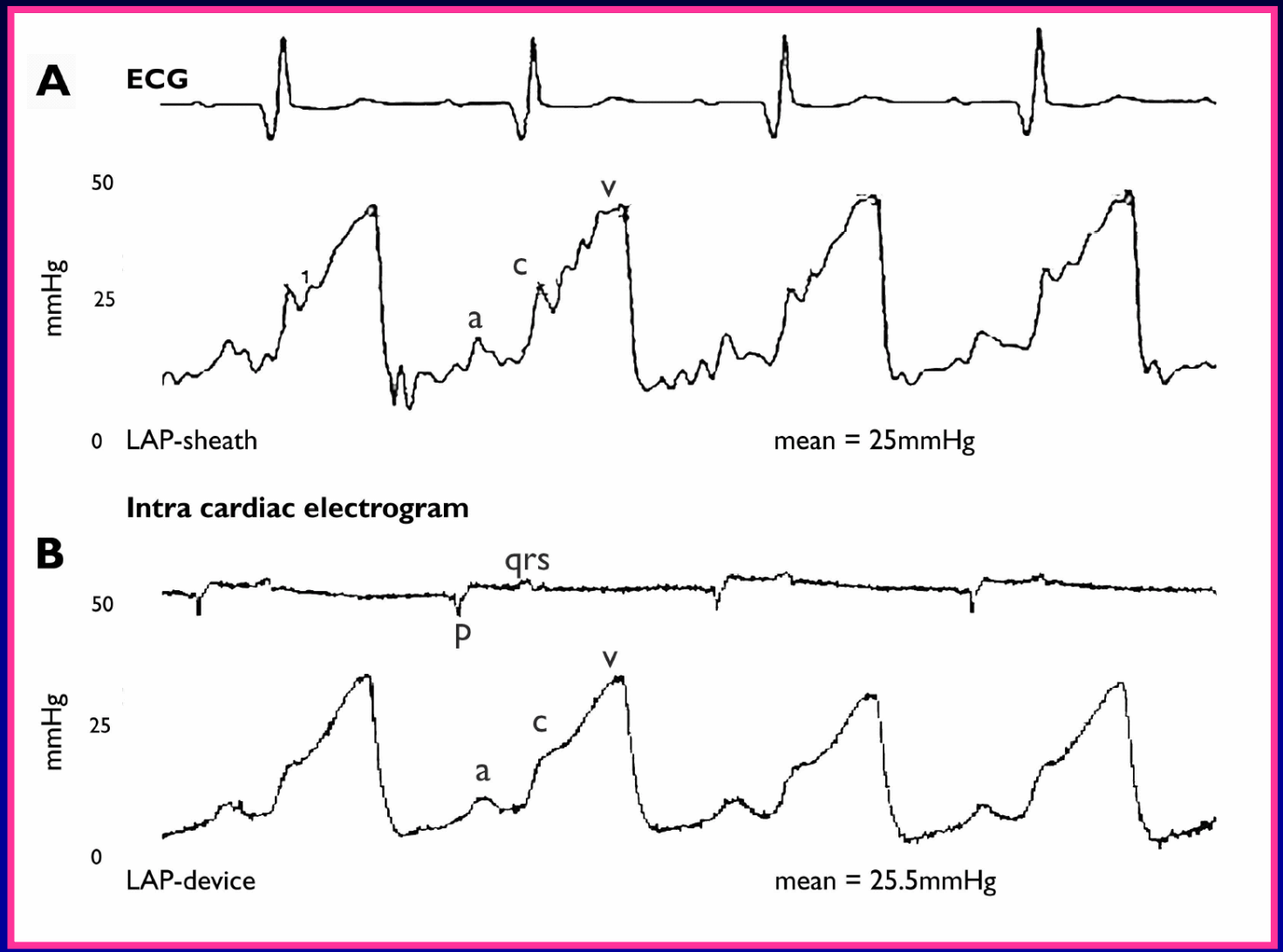



### Modified PDA

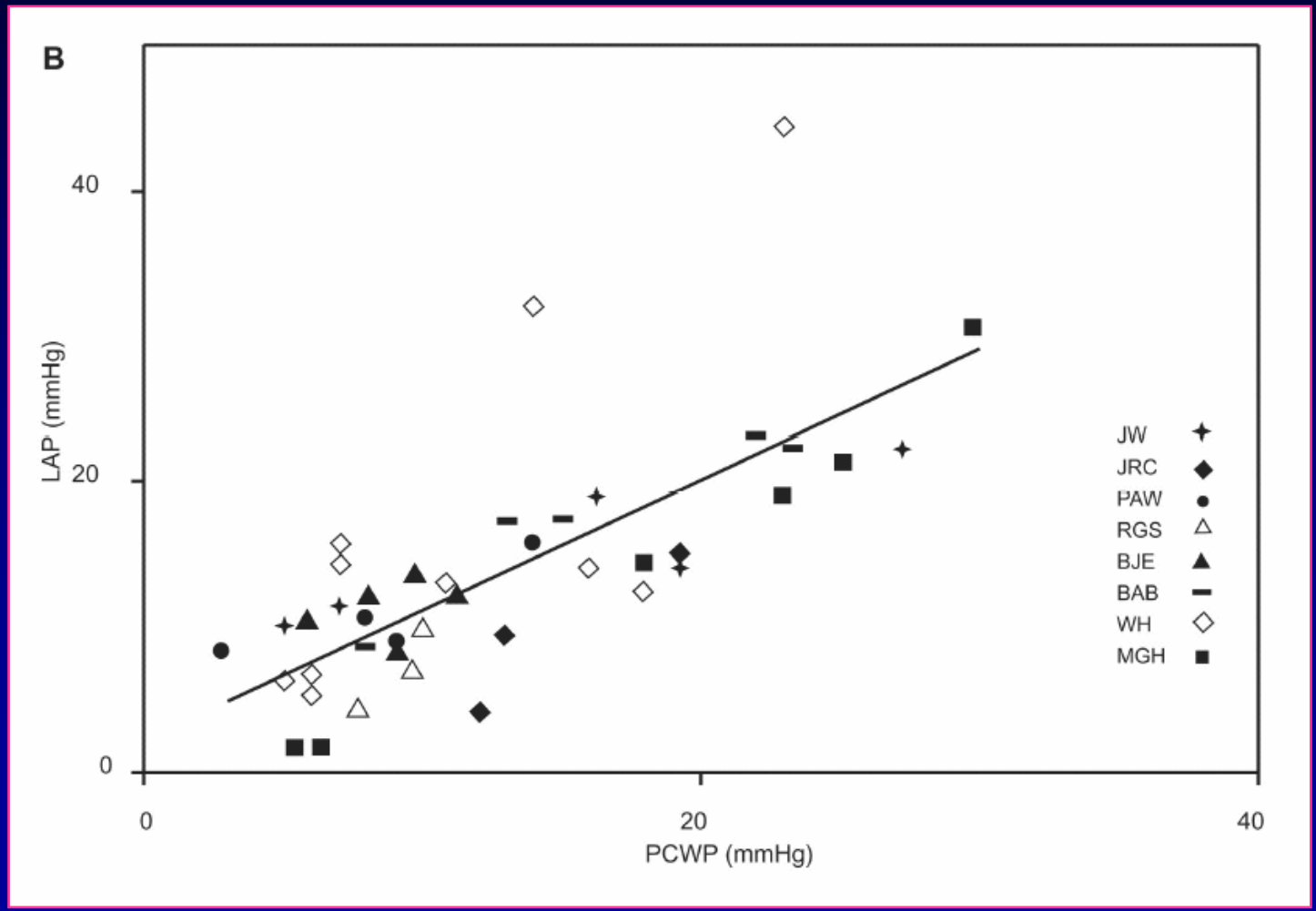
- Powers through clothing
- Atmospheric reference
- Stores telemetry
- Alerts patient to monitor
- Instructs patient re:
  - Medications
  - Activity
  - Clinician contact

# LAP Catheter vs LAP Device



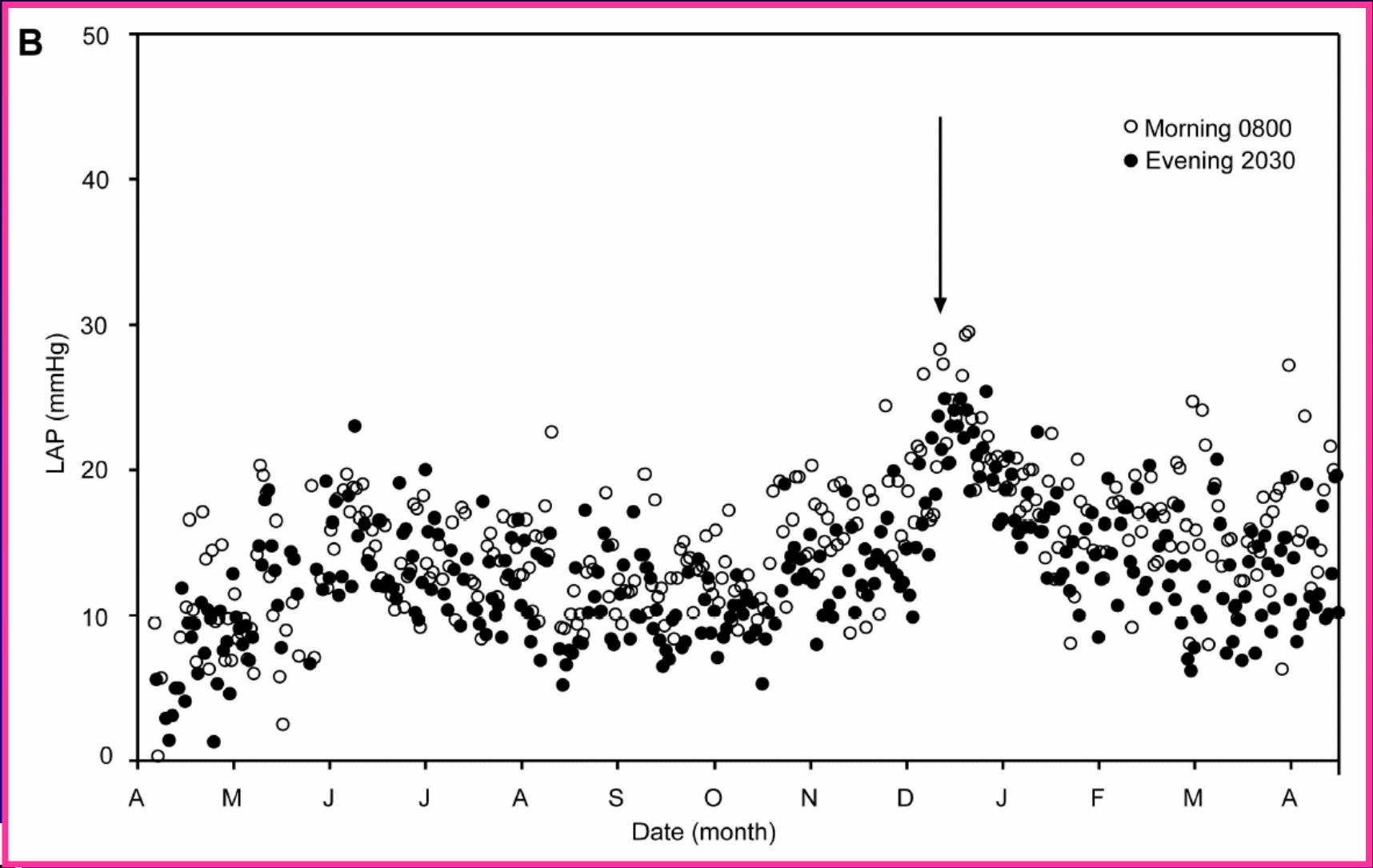

CCRE THERAPEUTICS

# LAP Device vs PCWP




CCRE THERAPEUTICS

# Individual LAP Device Readings




CCRE THERAPEUTICS

# Novel Therapies in Management of ADHF

***Summary***

- Cardiorenal syndrome assoc. with adverse clinical outcomes additional to the already high mortality of HF
- Conventional therapies all have adverse effects which may exacerbate problem
- Novel approaches may overcome these deficiencies in our current treatments

4TH ASIAN PACIFIC

# Congress of Heart Failure

Heart Failure in 3D - Drugs, Devices, Diagnostics

**31 January – 3 February 2008**

**Melbourne Exhibition & Convention Centre**

**Melbourne, Australia**

**REGISTER YOUR INTEREST NOW**

**www.apchf.com.au**

Hosted by: Endorsed by:

CCRE THERAPEUTICS

apsc

WHFS World Heart Failure Society

Heart Foundation