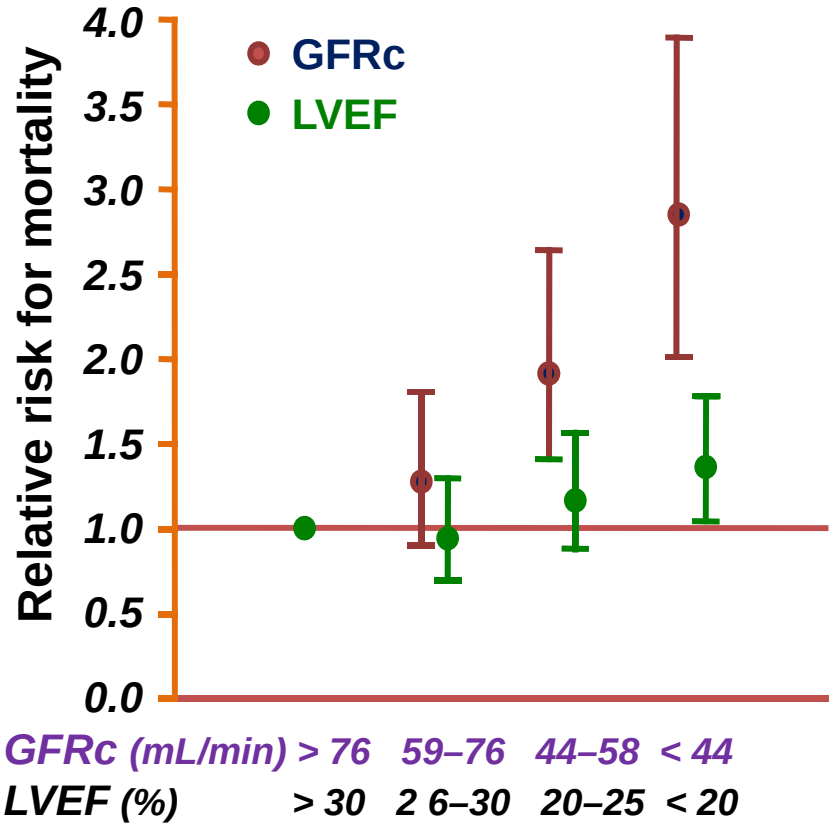
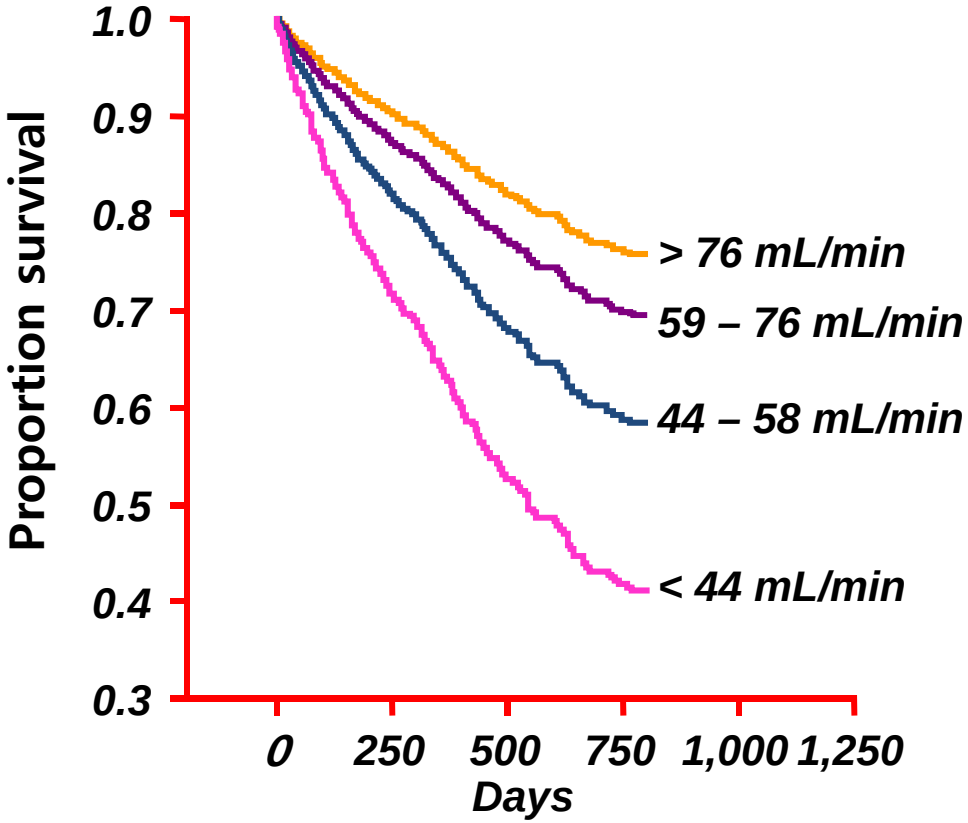
Effects of Neuro-hormonal System on Kidney

충남대병원 심장내과
정 진옥

Prognostic value of altered renal function in CHF





Hillege HL, et al. Circulation. 2000;102:203-210.

Pathophysiology of the Cardiorenal Syndrome

- Low-cardiac output
- Elevation of intra-abdominal and central venous pressures
- Electrolyte dysequilibration, volume overload
- **Neurohormonal and inflammatory activation**

Renal Hemodynamic Alteration in Heart Failure

Mechanisms that influence renal hemodnamics	Alterations in heart failure
Hydrostatic pressure gradients	
Cardiac output Renal vasoconstriction	Decreased Increased
Oncotic pressure gradients	
Solute concentration Relative permeability of the tubule	Increased No change
Permeability of the glomerular basement membrane	No change
Neurohormonal mechanisms	
Autonomic nervous system RAAS Arginine vasopressin Endothelin Natriuretic peptides	Increased Increased Increased Increased Increased

Underperfusion

- Acute decompensated heart failure

-> effective arterial filling volume감소

->renal blood flow, renal perfusion감소

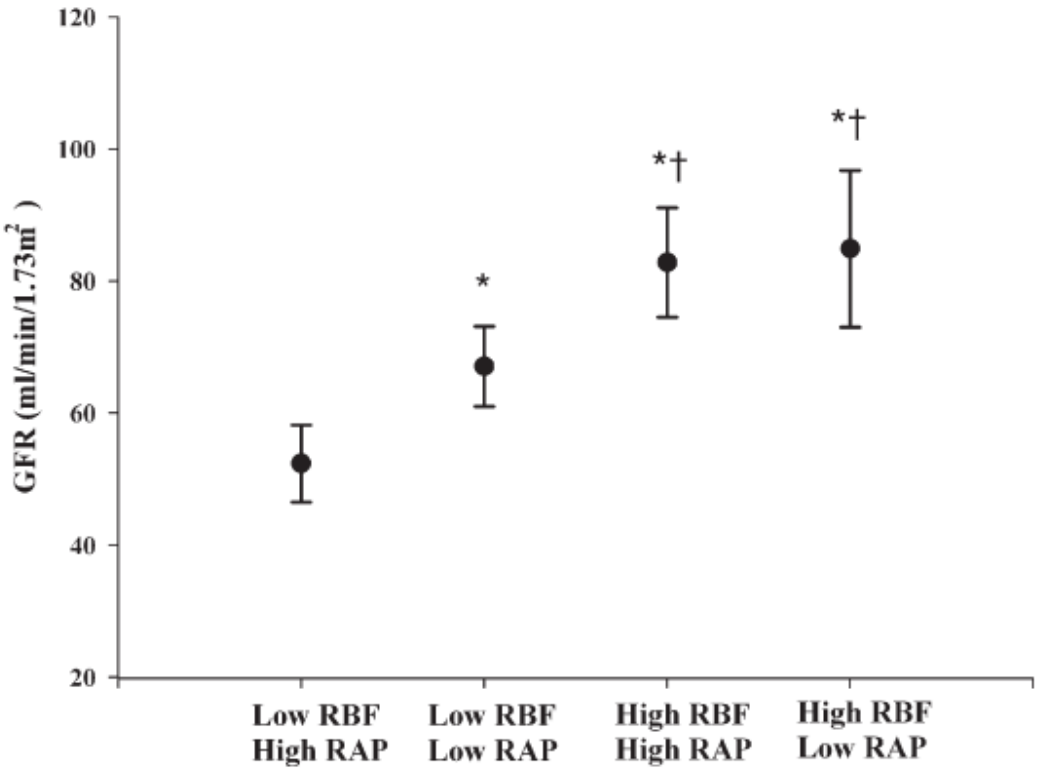
->RAAS, SNS(Nepi)활성화

- in the setting of low CO

-> renal blood flow감소, GFR감소

(NO, bradykinin, adenosine, PE)

Venous congestion



K. Damman et al. European Journal of Heart Failure 9 (2007) 872 – 878

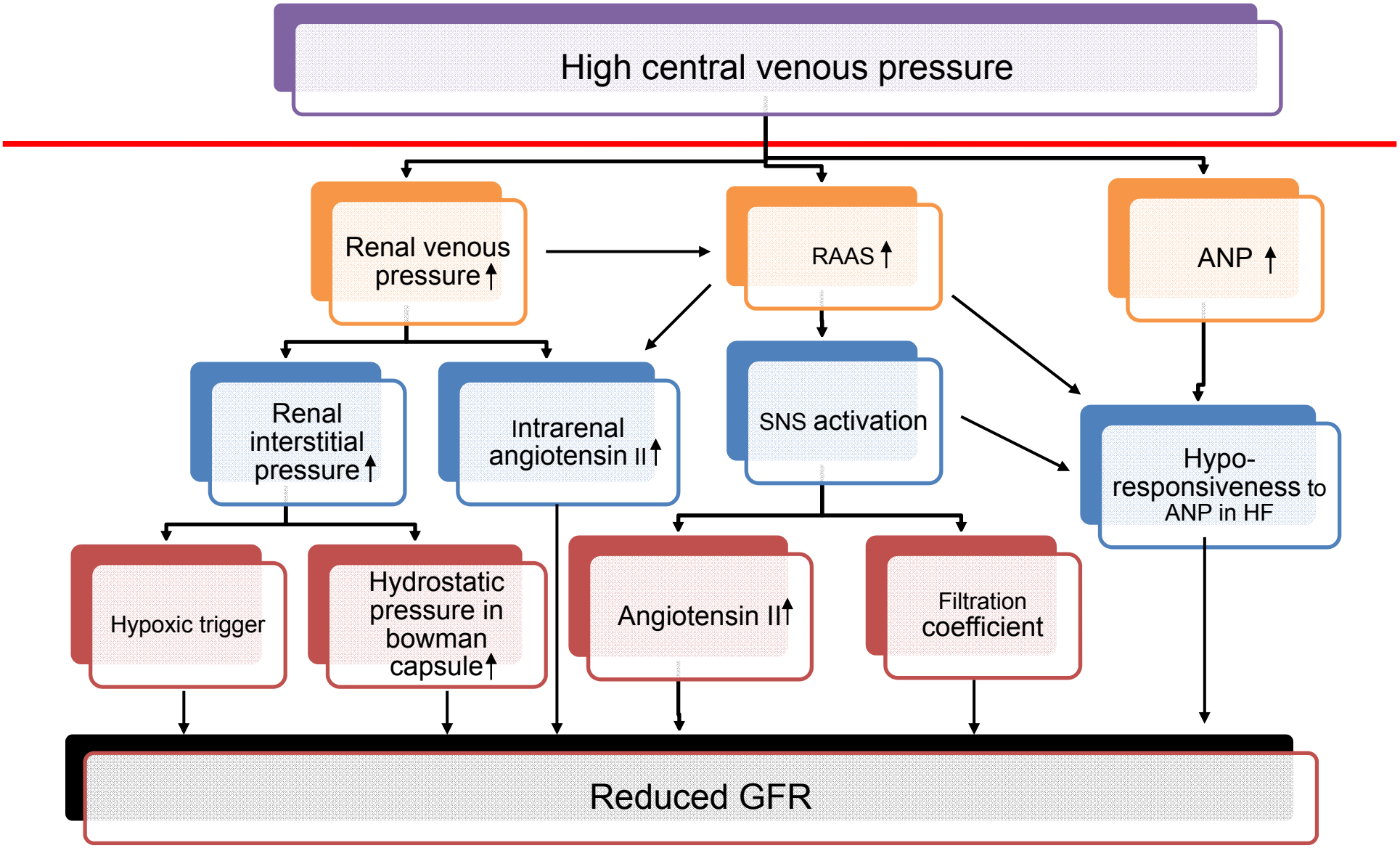
Venous congestion

Regression analysis for GFR

Variable	Univariate correlation coefficient	Univariate β	Multivariate correlation coefficient	Multivariate β	Multivariate *p*-value
Age	− 0.072	0.023			
Sex	− 0.218	− 0.028			
RBF	0.797	0.782	0.664	0.621	< 0.001
RAP	− 0.616	− 0.579	− 0.367	− 0.276	0.020
CI	0.404	0.396			
PVR	− 0.298	− 0.297			
Adjusted R^2			0.609		< 0.001

CI, cardiac index; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RBF, renal blood flow.

K. Damman et al. European Journal of Heart Failure 9 (2007) 872 – 878



K. Damman et al. European Journal of Heart Failure 9 (2007) 872 – 878

Intra-abdominal hypertension

- Increased intra-abdominal pressure from ascites and abdominal wall edema is prevalent in patient with ADHF
- Elevated renal venous congestion
- Worsening kidney function

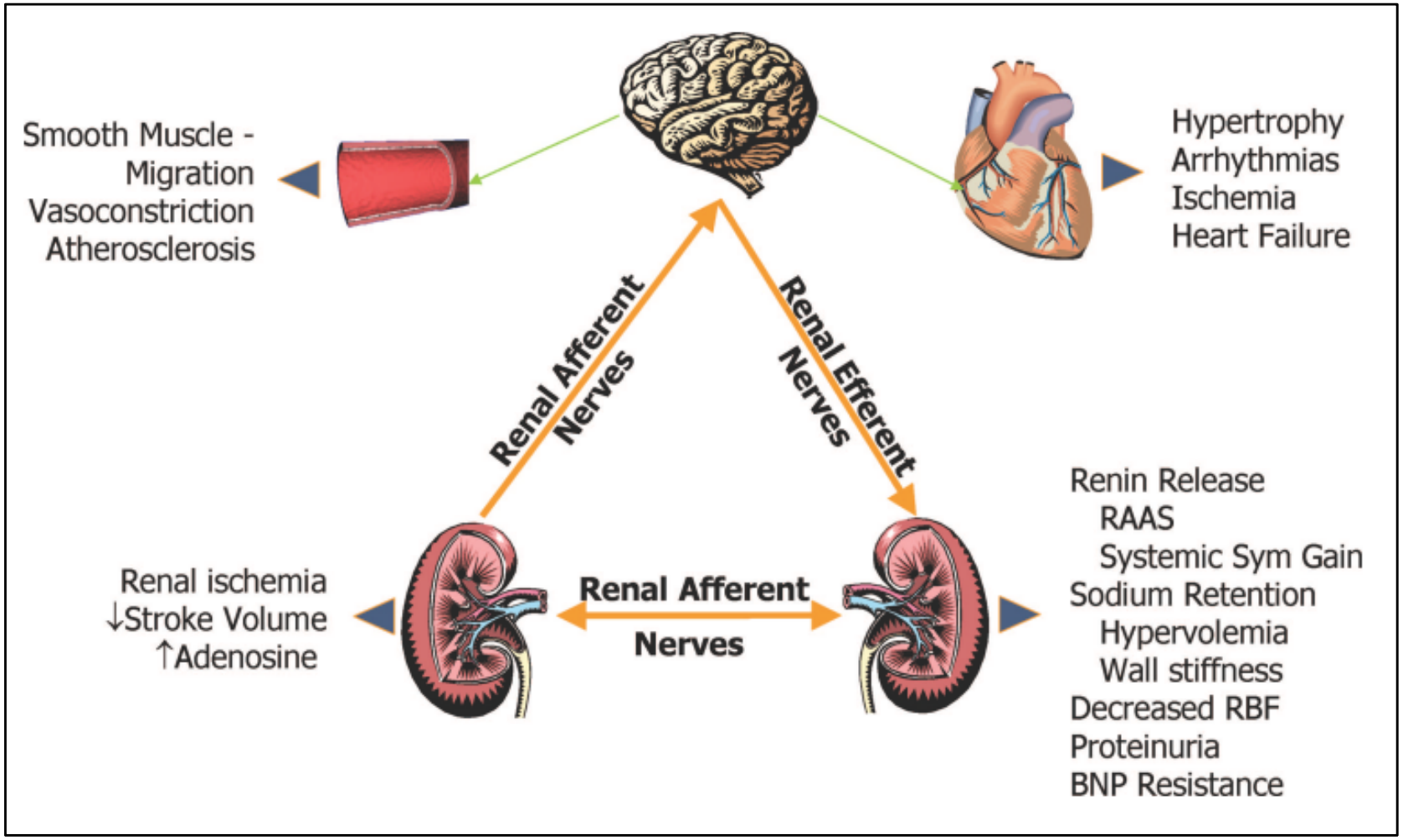
Types of the Cardiorenal Syndrome (CRS)

	Inciting event	Secondary disturbance
CRS type 1	Acute decompensated heart failure	Acute kidney injury
CRS type 2	Chronic heart failure	Chronic kidney disease
CRS type 3	Acute kidney injury	Acute heart failure
CRS type 4	Chronic kidney disease	Chronic heart failure
CRS type 5	Co-development of heart failure and chronic kidney disease	

Neuro-hormonal Systems of Kidney

- Autonomic nervous system
- Renin–angiotensin–aldosterone system (RAAS)
- Arginine vasopressin (AVP)
- Endothelin, nitric oxide
- Natriuretic peptide systems, including atrial and B-type natriuretic peptide (BNP)

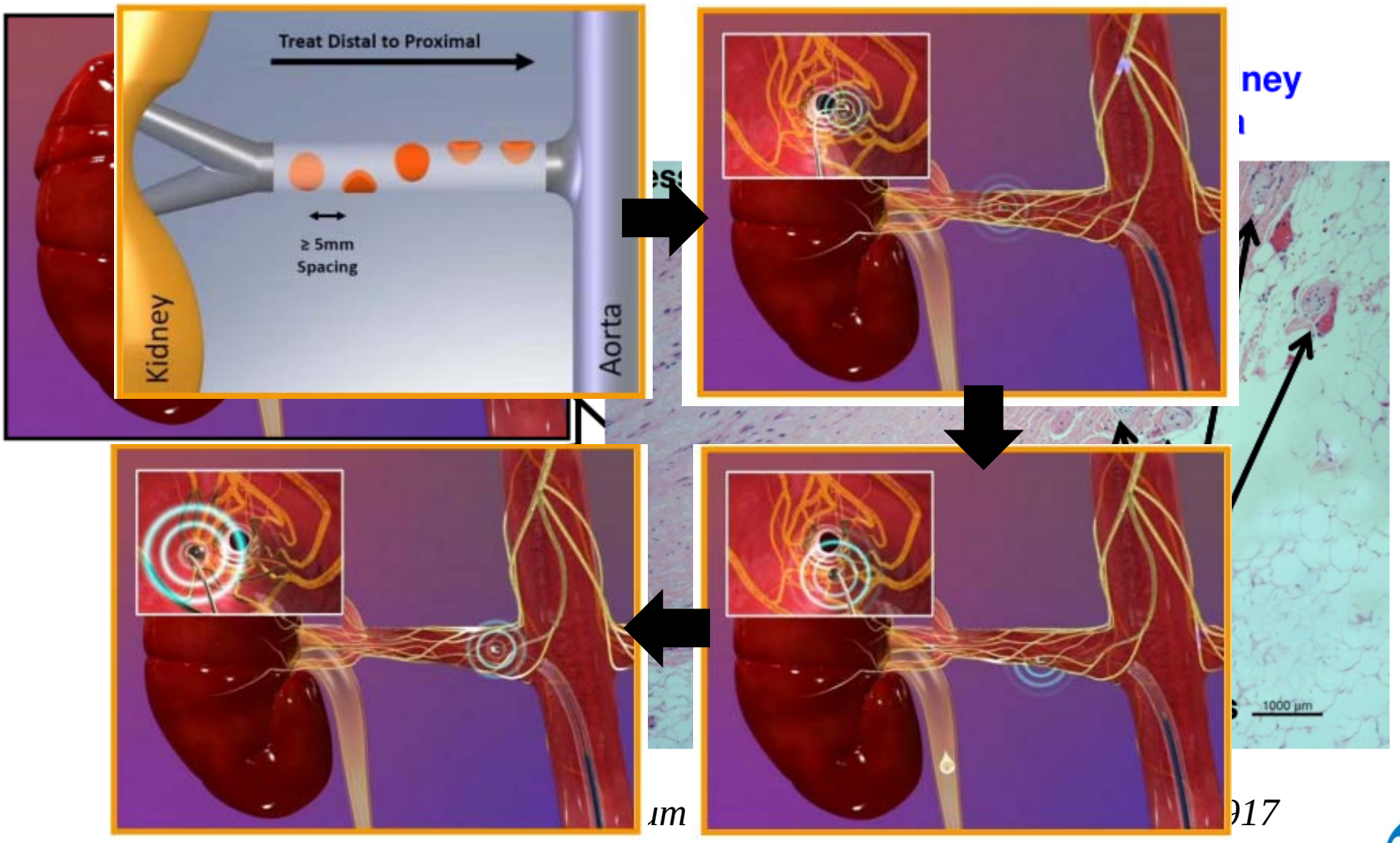
Sympatho-Renal Axis in Chronic Disease

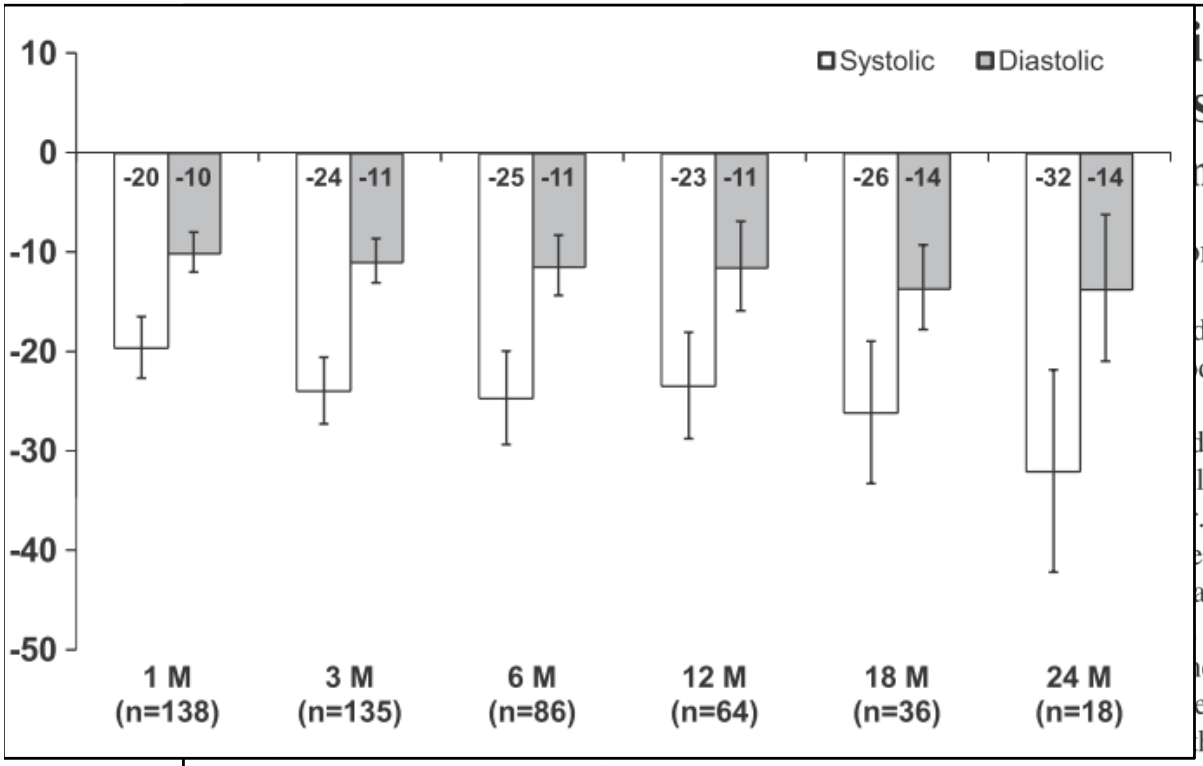


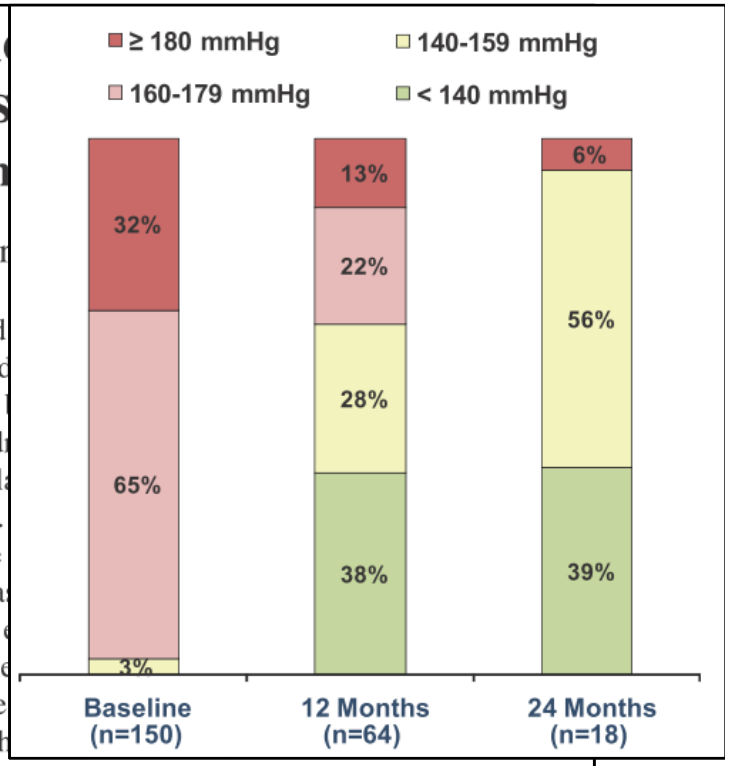
Krum et al. Circulation. 2011;123:209-215

Paul et al. Clin Res Cardiol (2011) 100:1049–1057

Catheter-Based Renal Sympathetic Denervation







reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively. In conclusion, in patients with resistant hypertension, catheter-based renal sympathetic denervation results in a substantial reduction in BP sustained out to ≥2 years of follow-up, without significant adverse events. (***Hypertension***. **2011;57:911-917.**)

Key Words: hypertension ■ blood pressure ■ renal sympathetic denervation

Krum et al. Hypertension. 2011;57:911-917

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

*Symplicity HTN-2 Investigators**

Summary

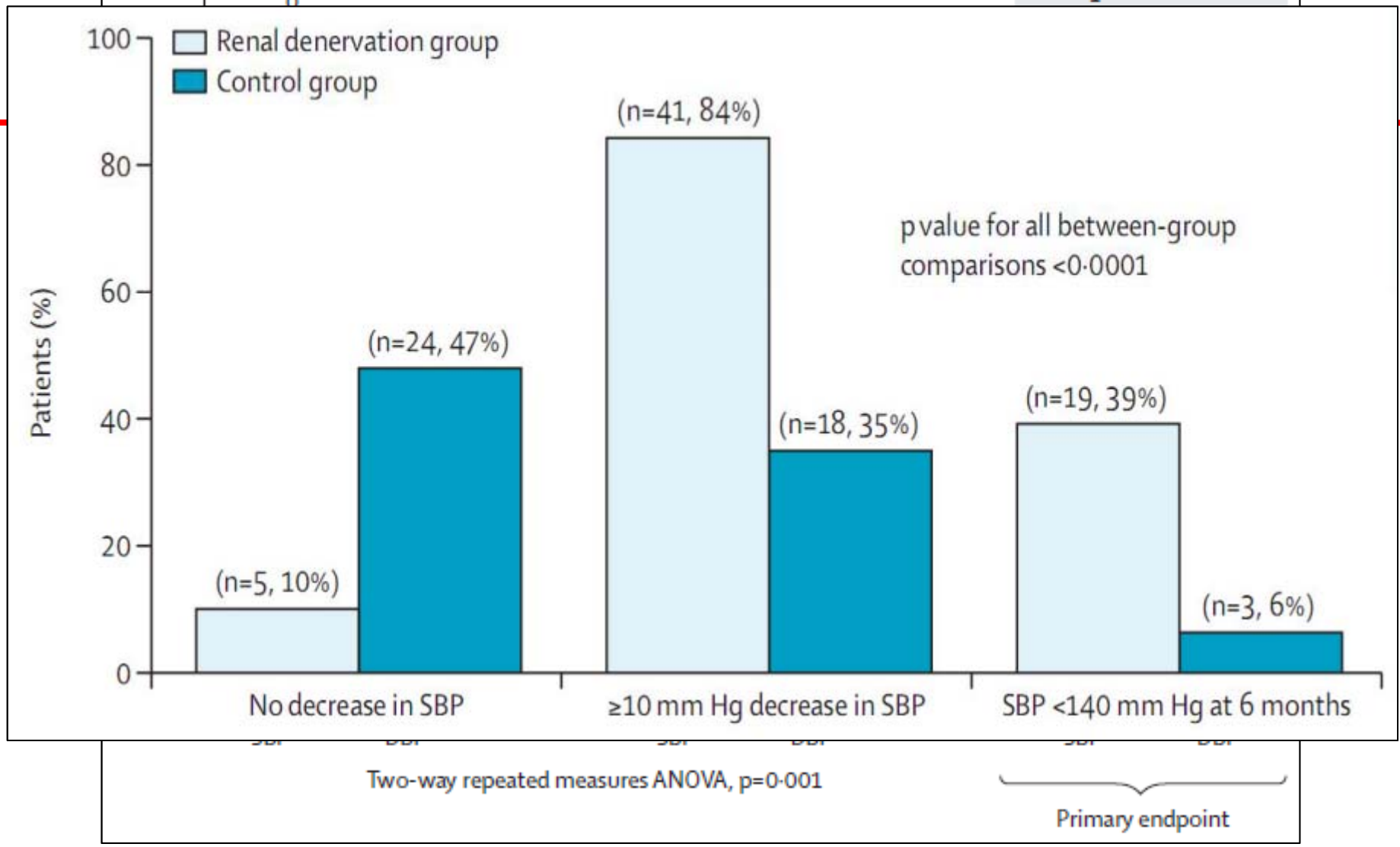
Background Activation of renal sympathetic nerves is key to pathogenesis of essential hypertension. We aimed to assess effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension.

Methods In this multicentre, prospective, randomised trial, patients who had a baseline systolic blood pressure of 160 mm Hg or more (≥150 mm Hg for patients with type 2 diabetes), despite taking three or more antihypertensive drugs, were randomly allocated in a one-to-one ratio to undergo renal denervation with previous treatment or to maintain previous treatment alone (control group) at 24 participating centres. Randomisation was done with sealed envelopes. Data analysers were not masked to treatment assignment. The primary effectiveness endpoint was change in seated office-based measurement of systolic blood pressure at 6 months. Primary analysis included all patients remaining in follow-up at 6 months. This trial is registered with ClinicalTrials.gov, number NCT00888433.

Findings 106 (56%) of 190 patients screened for eligibility were randomly allocated to renal denervation (n=52) or control (n=54) groups between June 9, 2009, and Jan 15, 2010. 49 (94%) of 52 patients who underwent renal denervation and 51 (94%) of 54 controls were assessed for the primary endpoint at 6 months. Office-based blood pressure measurements in the renal denervation group reduced by 32/12 mm Hg (SD 23/11, baseline of 178/96 mm Hg, p<0·0001), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg [21/10], baseline of 178/97 mm Hg, p=0·77 systolic and p=0·83 diastolic). Between-group differences in blood pressure at 6 months were 33/11 mm Hg (p<0·0001). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls (p<0·0001). We noted no serious procedure-related or device-related complications and occurrence of adverse events did not differ between groups; one patient who had renal denervation had possible progression of an underlying atherosclerotic lesion, but required no treatment.

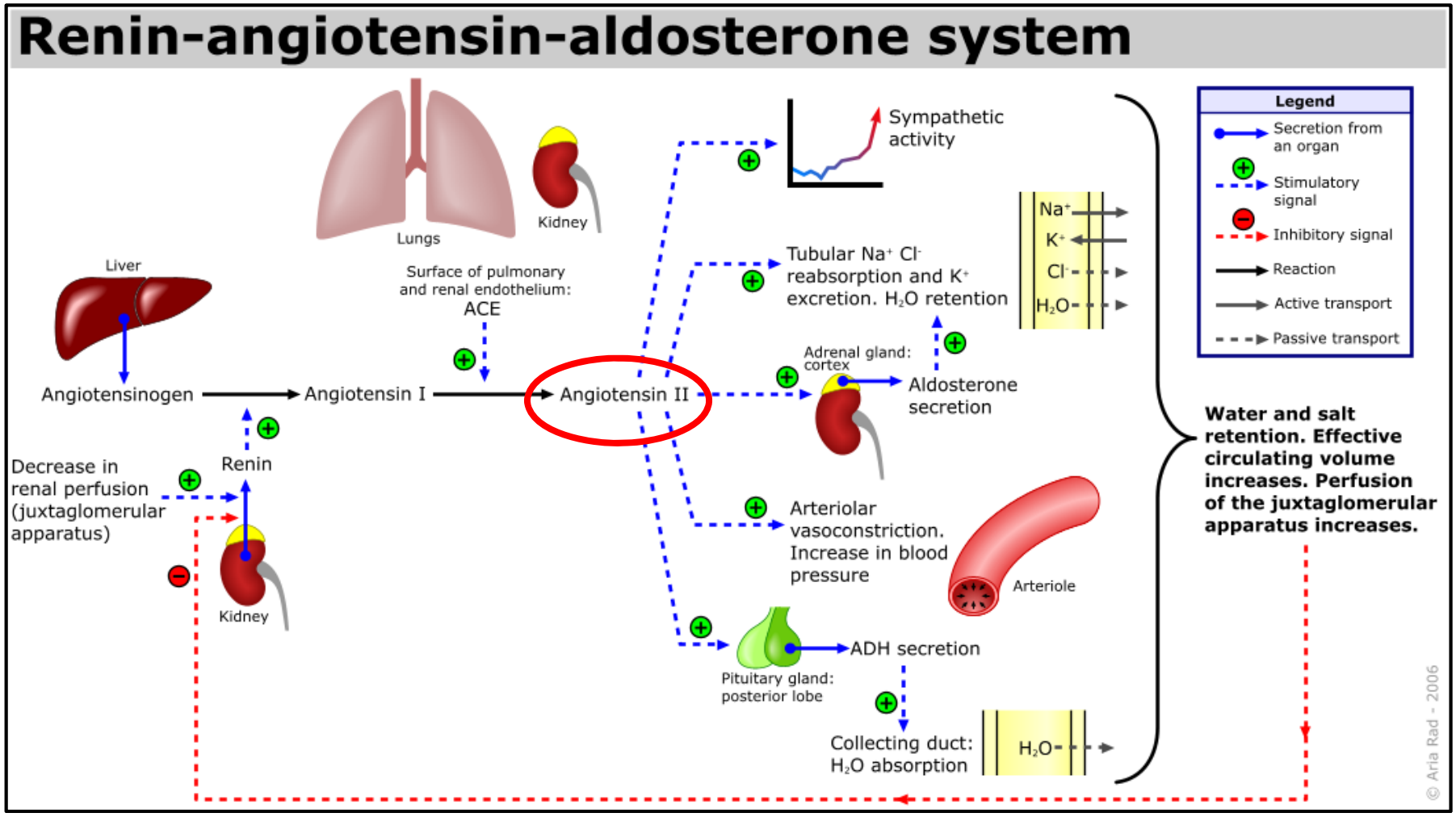
Interpretation Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients.

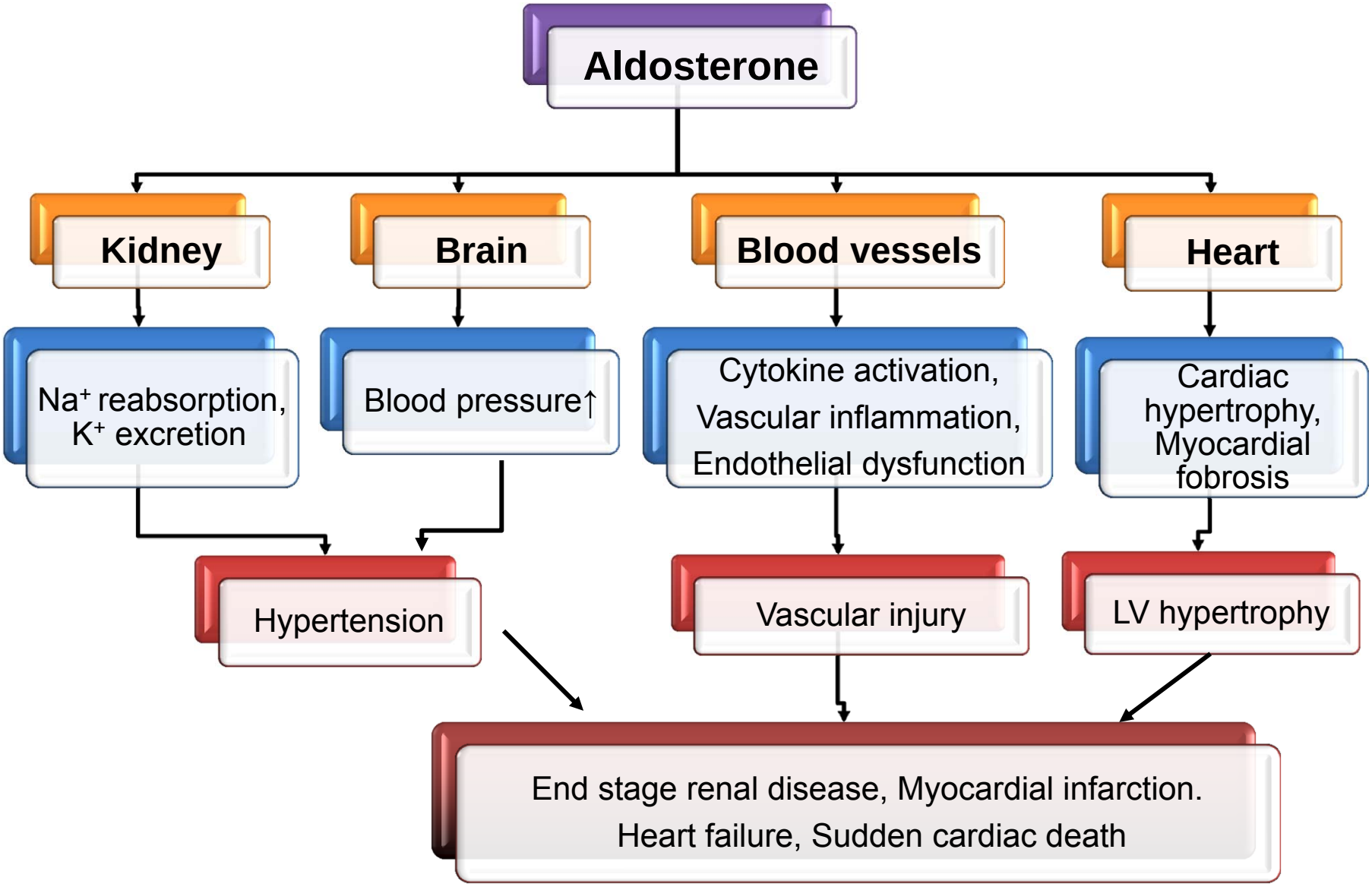
Murray et al. Lancet 2010; 376: 1903–09



Murray et al. Lancet 2010; 376: 1903–09

Renin–Angiotensin–Aldosterone System (RAAS)




Aldosterone
Kidney
Brain
Blood vessels
Heart
Na+ reabsorption, K+ excretion
Blood pressure↑
Cytokine activation, Vascular inflammation, Endothelial dysfunction
Cardiac hypertrophy, Myocardial fobrosis
Hypertension
Vascular injury
LV hypertrophy
End stage renal disease, Myocardial infarction. Heart failure, Sudden cardiac death

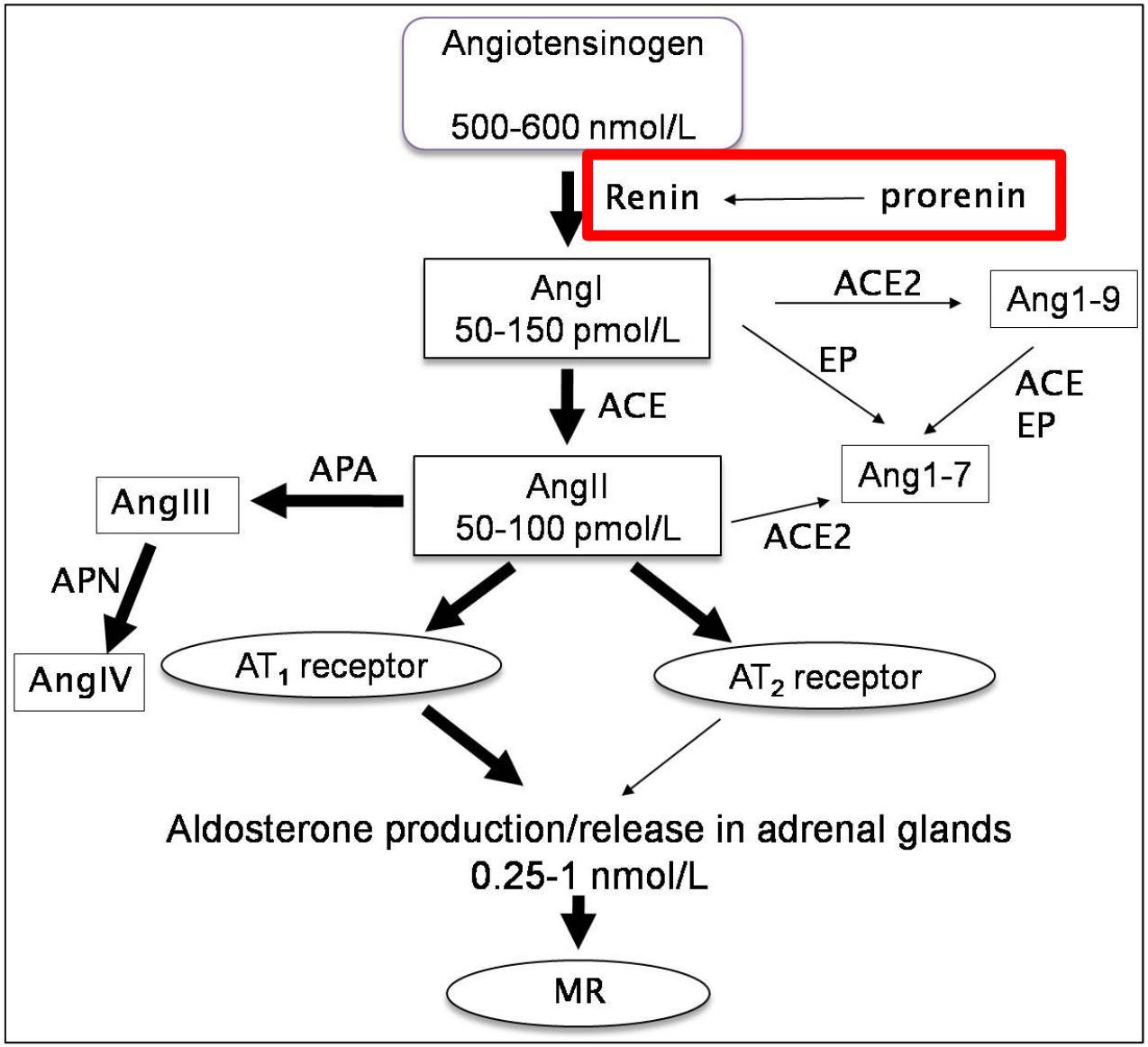
Cardinal role in the pathogenesis of cardiovascular disease

◆Block Angiotensin II

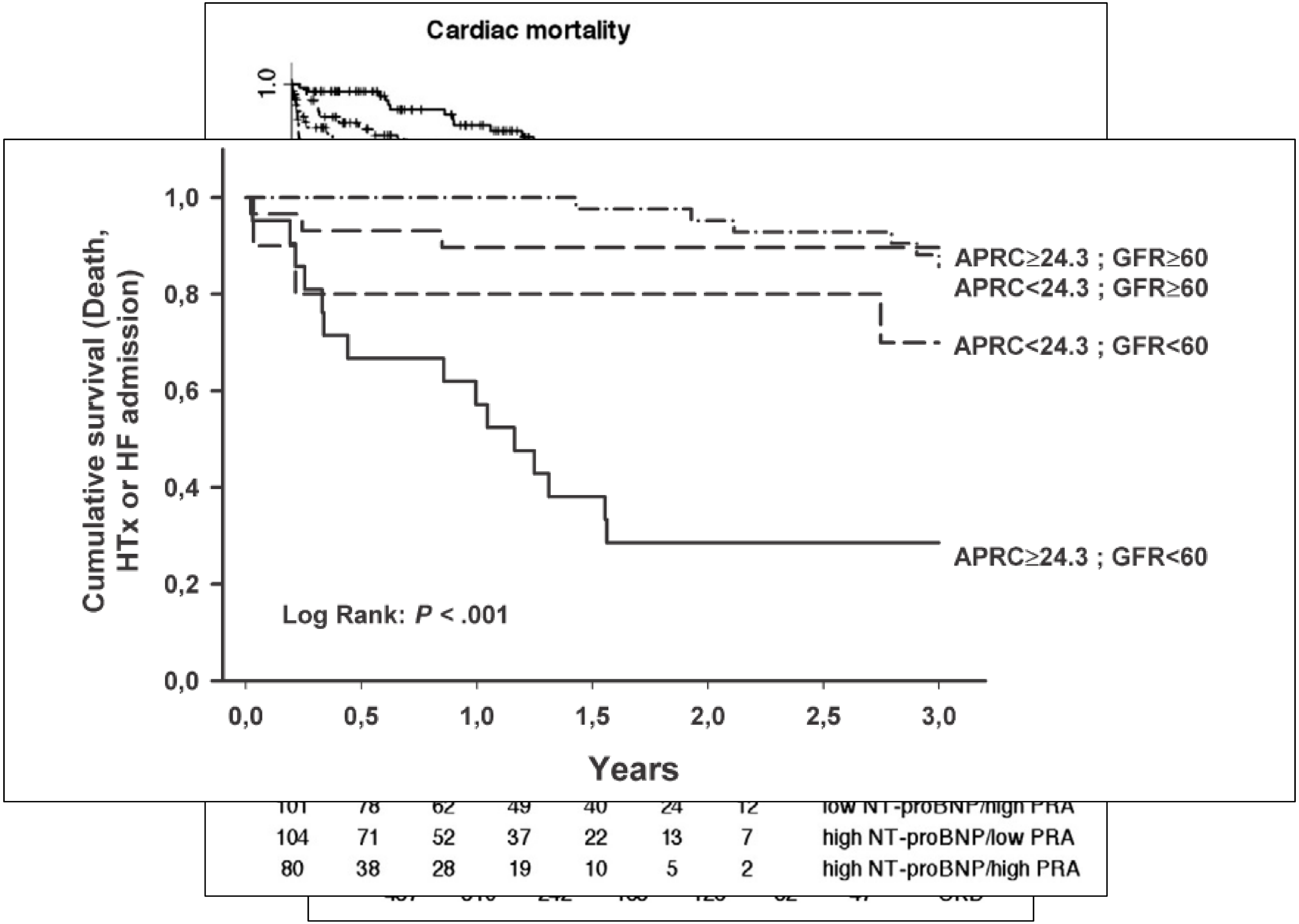
- Angiotensin-converting enzyme inhibitors (ACEIs)
- Angiotensin II type I (AT1)-receptor blockers (ARBs)

◆Block Aldosterone

- Spironolactone
- Eplerenone



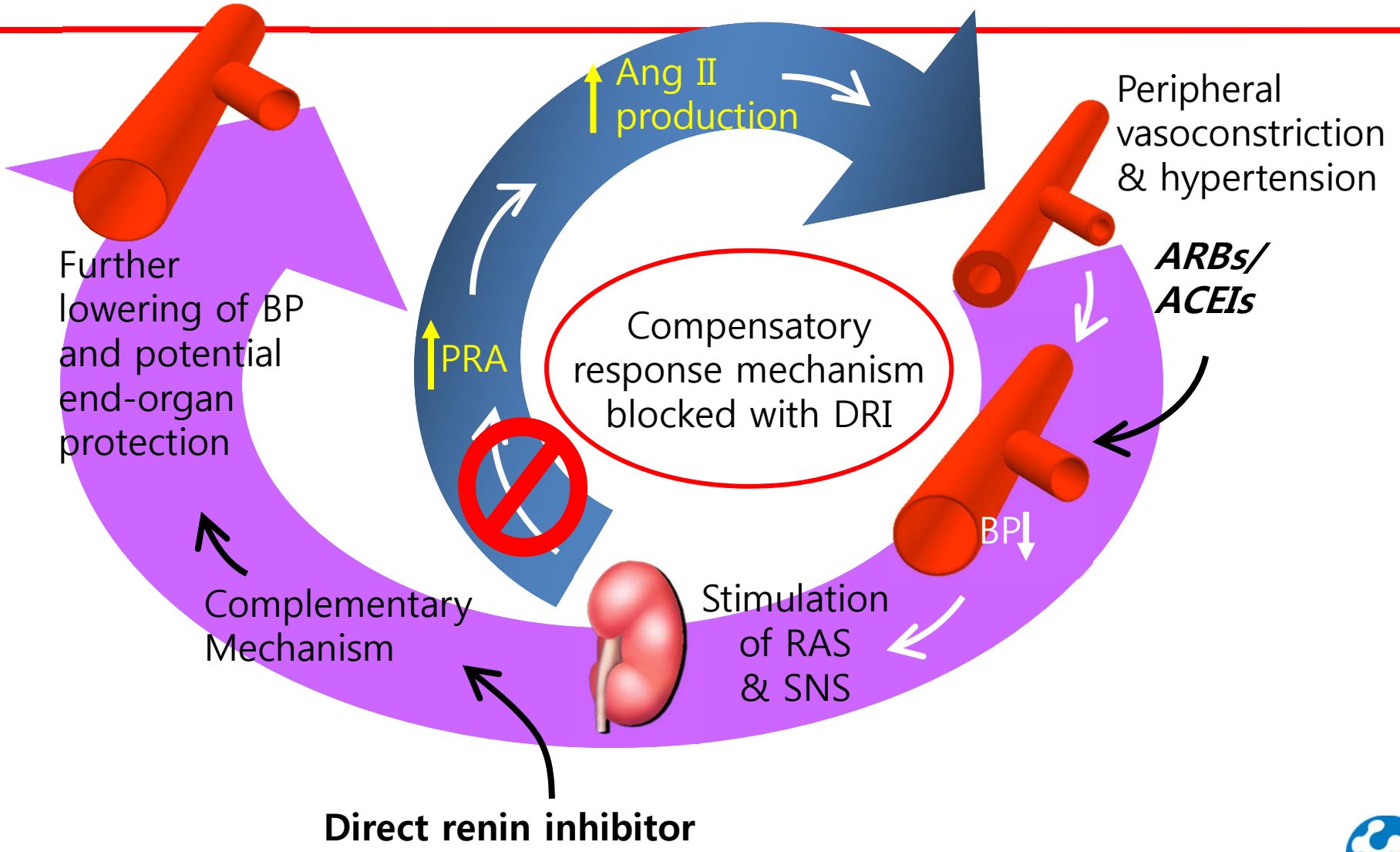
Nishiyama eet al. J Pharmacol Sci ***113, 289 – 291 (2010)***



Mariusz K et al. Am Heart J 2011;162:487-93

Poletti R, et al. Int J Cardiol (2012)

Direct Renin Inhibitor



Direct Renin Inhibitor

Neurohumoral effects of the new orally active renin inhibitor, aliskiren, in chronic heart failure

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Available online 18 October 2007

Rationale and design of the multicentre, randomized, double-blind, placebo-controlled Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT)

Mihai Gheorghiade[1]*, Mazen Albaghdadi[1], Faiez Zannad[2], Gregg C. Fonarow[3], Michael Böhm[4], Claudio Gimpelewicz[5], Jaco Botha[5], Shelley Moores[5], Eldrin F. Lewis[6], Henning Rattunde[5], and Aldo Maggioni[7] on behalf of the ASTRONAUT investigators and study coordinators

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Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE) study

Henry Krum[1*], Barry Massie[2], William T. Abraham[3], Kenneth Dickstein[4,5], Lars Kober[6], John J.V. McMurray[7], Ashkay Desai[8], Claudio Gimpelewicz[9], Albert Kandra[9], Bernard Reimund[9], Henning Rattunde[9], and Juergen Armbrecht[9], on behalf of the ATMOSPHERE Investigators

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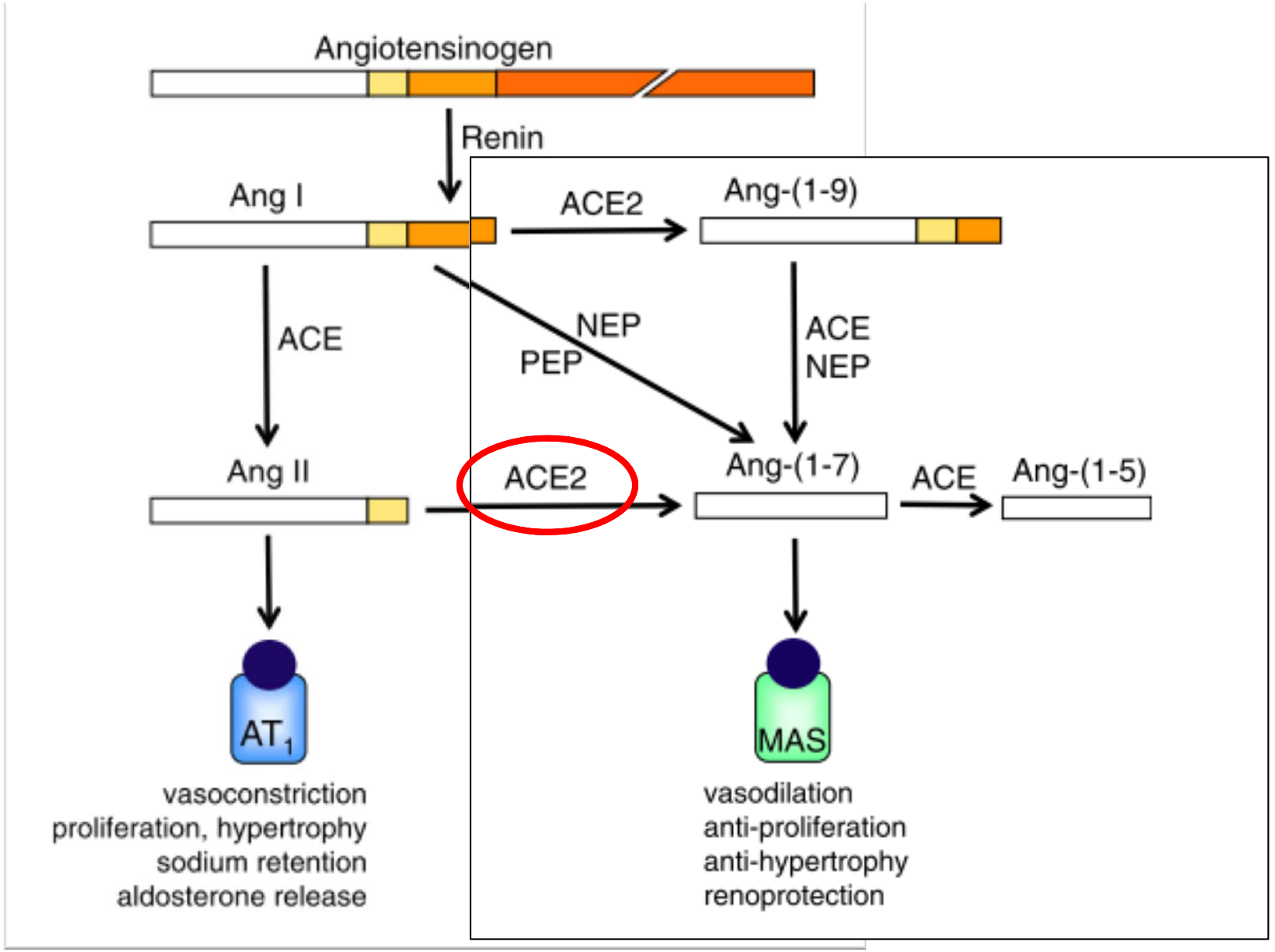
Received 10 August 2010; revised 15 September 2010; accepted 16 October 2010


Angiotensinogen
Renin
Ang I
ACE2
Ang-(1-9)
ACE
NEP
PEP
ACE
NEP
Ang II
ACE2
Ang-(1-7)
ACE
Ang-(1-5)
AT1
MAS
vasoconstriction
proliferation, hypertrophy
sodium retention
aldosterone release
vasodilation
anti-proliferation
anti-hypertrophy
renoprotection

Angiotensin-converting enzyme 2 (ACE2)

- ~40% homology with ACE
- Unblocked by ACE inhibitors
- Degradation of ANG II to ANG-(1-7) & ANGI to ANG-(1-9)
- **Protect against progressive CKD**

→ Kidney diseases is associated with a reduction in renal ACE2 expression

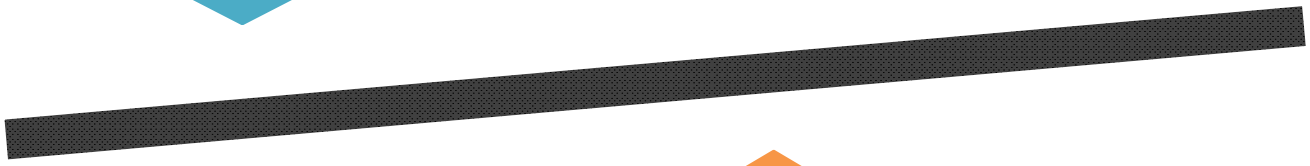
→ The reduction of ACE2 expression and activity leads to local elevation of Ang II concentrations and it contributes to development of renal damage

Angiotensin Fragments

Angiotensin-(1-7)	Angiotensin-(1-9)
Vasodilatation	Enhance bradykinin actions
Anti-proliferative	Nitric oxide and arachidonic acid release
Anti-thrombosis	Regulation of platelet function
Anti-fibrosis	Prothrombotic effects
Anti-arrhythmogenic	Maintenance of intraglomerular RAAS balance
Vasopressin release	
Baroreflex facilitation	
Modulation of sympathetic tone	
Increase in renal blood flow	
Modulation of sodium and water handling	

Renin–Angiotensin–Aldosterone system: Dual Function System

- prothrombotic
- profibrotic
- proliferative
- Pressor



- Anti-thrombotic
- Anti-fibrotic
- antiproliferative
- Vasodilatory

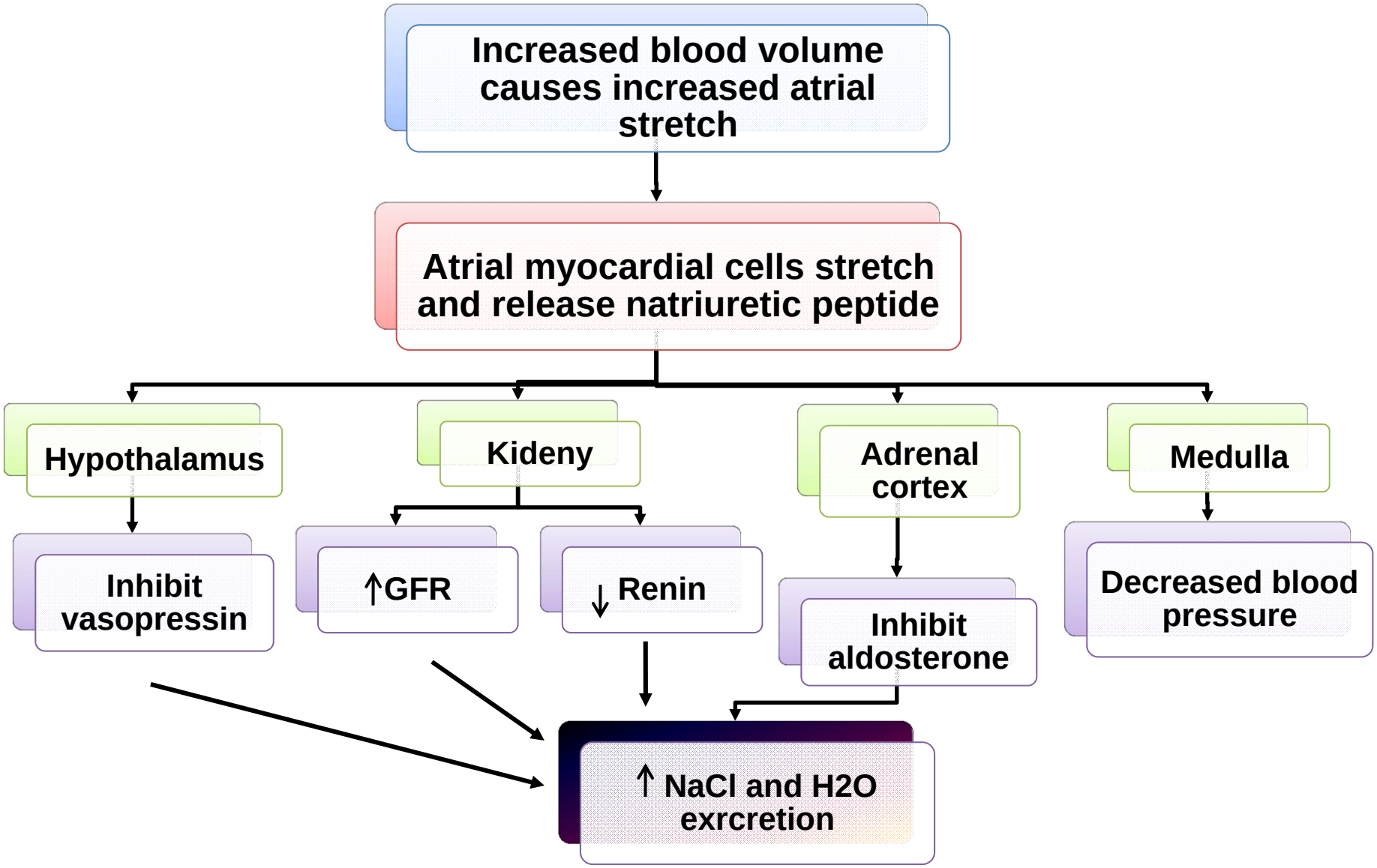
New pharmacological approach

Natriuretic Peptide

- Atrial natriuretic peptide
  - 28-amino-acid peptide
  - normally synthesized in the atria
  - In heart failure, plasma atrial natriuretic peptide concentrations rise as atrial pressures increase

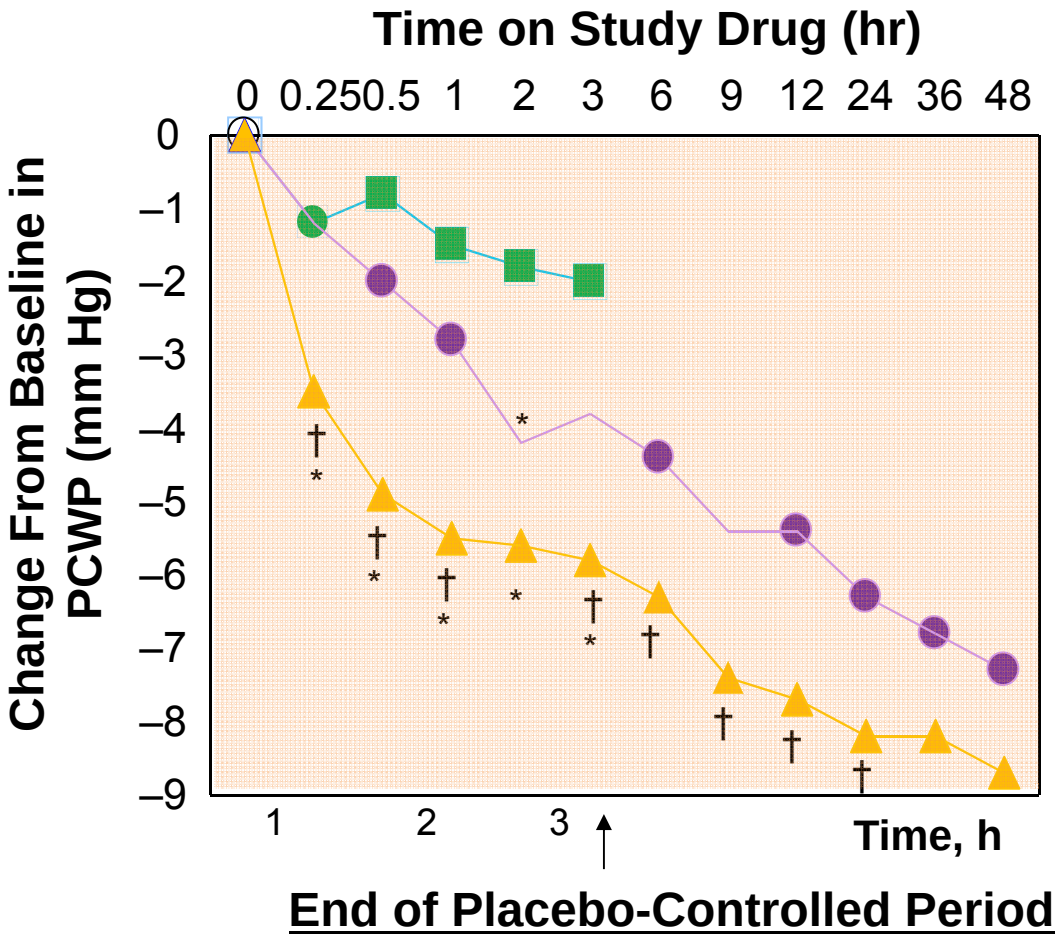
- B-type natriuretic peptide
  - 32-amino-acid peptide
  - synthesized primarily in the ventricles
  - sensitive diagnostic marker of heart failure as it increased in patients with early heart failure or left ventricular dysfunction

Natriuretic Peptide



BNP: Nesiritide

- Recombinant human brain, or B-type, natriuretic peptide
- Venous, arterial, and coronary vasodilatory properties that reduce preload and afterload
- Increase cardiac output without direct inotropic effects
- Not proarrhythmic effect



PCWP – Placebo
PCWP – IV NTG
PCWP – Nesiritide

During 3-hr placebo period
Placebo n = 62
IV NTG n = 60
Nesiritide n = 124

After 3-hr period
IV NTG n = 92
Nesiritide n = 154

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

JAMA. 2002;287:1531

ANP

- Urodilatin(recombinant ANP)

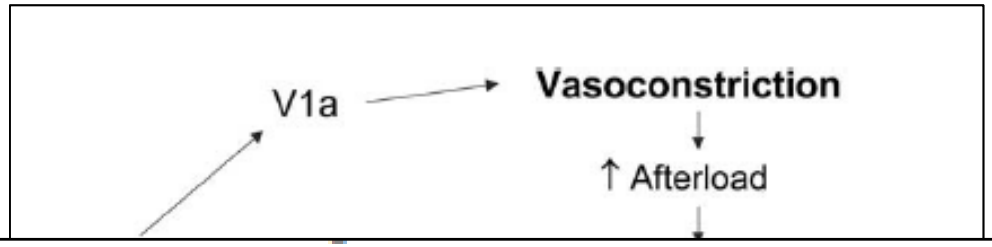
: increased natriuresis

- Neutral endopeptidase inhibitors

: reduce breakdown of ANP

: delayed onset of sodium retention

Arginine Vasopressin (AVP)

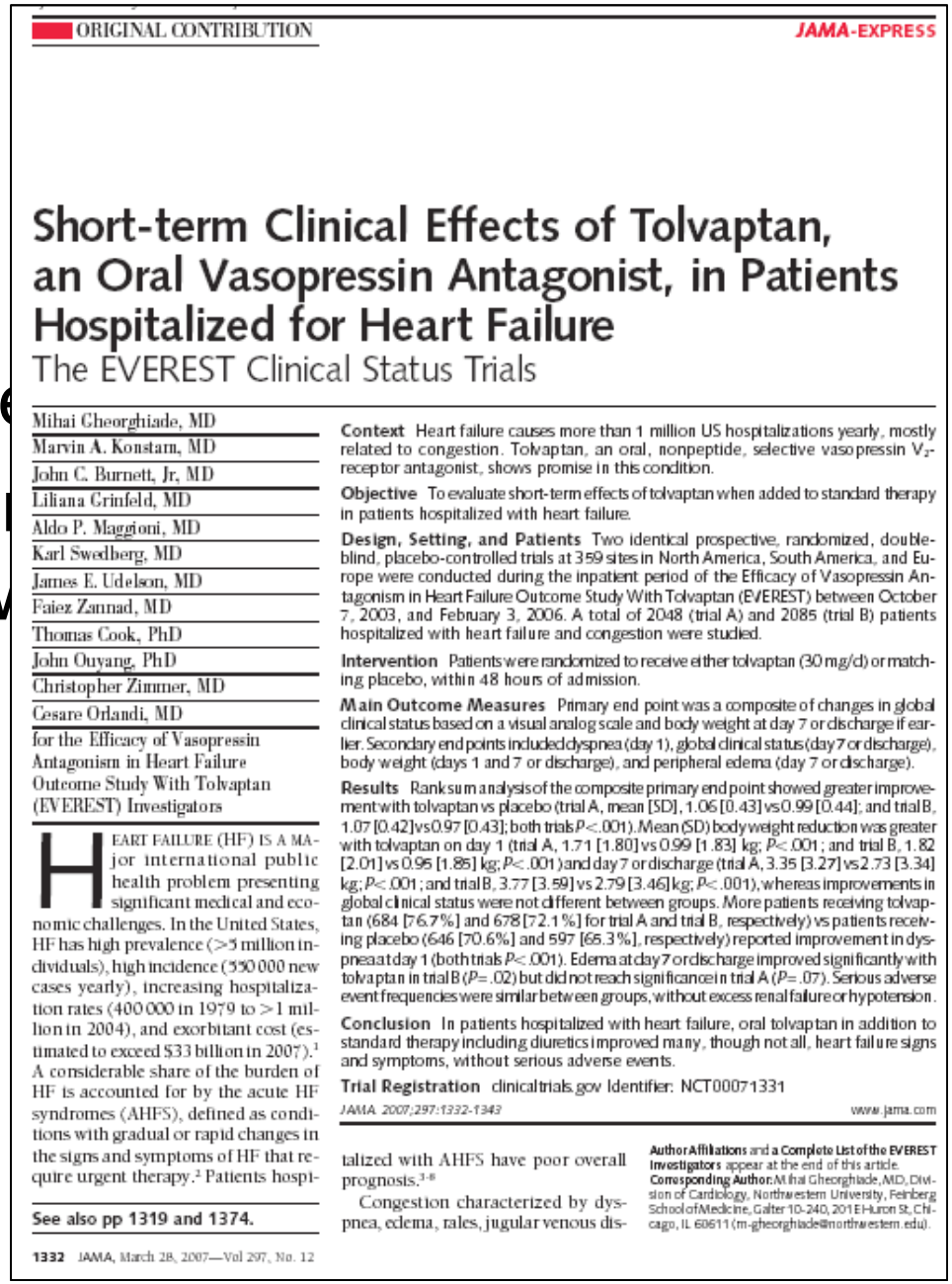


Receptor	Signaling	Location	Actions
V1a	G-protein, IP3	Blood vessels	Vasoconstriction
		Myocardium	Inotrope/mitogen
V2	Adenyl cyclase	Renal tubule	H_2O retention
		Endothelium	Vasodilation (high concentrations)

Tolvaptan

J Am Coll Cardiol. 2005;46:1785-1791

- Tolvaptan
  - Selective vasopre
  - Act on the distal
    electrolyte-free w
  - EVEREST trial



ORIGINAL CONTRIBUTION

JAMA-EXPRESS

Short-term Clinical Effects of Tolvaptan, an Oral Vasopressin Antagonist, in Patients Hospitalized for Heart Failure

The EVEREST Clinical Status Trials

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Thomas Cook, PhD
John Ouyang, PhD
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for the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators

Context Heart failure causes more than 1 million US hospitalizations yearly, mostly related to congestion. Tolvaptan, an oral, nonpeptide, selective vasopressin V_2-receptor antagonist, shows promise in this condition.

Objective To evaluate short-term effects of tolvaptan when added to standard therapy in patients hospitalized with heart failure.

Design, Setting, and Patients Two identical prospective, randomized, double-blind, placebo-controlled trials at 359 sites in North America, South America, and Europe were conducted during the inpatient period of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) between October 7, 2003, and February 3, 2006. A total of 2048 (trial A) and 2085 (trial B) patients hospitalized with heart failure and congestion were studied.

Intervention Patients were randomized to receive either tolvaptan (30 mg/d) or matching placebo, within 48 hours of admission.

Main Outcome Measures Primary end point was a composite of changes in global clinical status based on a visual analog scale and body weight at day 7 or discharge if earlier. Secondary end points included dyspnea (day 1), global clinical status (day 7 or discharge), body weight (days 1 and 7 or discharge), and peripheral edema (day 7 or discharge).

Results Rank sum analysis of the composite primary end point showed greater improvement with tolvaptan vs placebo (trial A, mean [SD], 1.06 [0.43] vs 0.99 [0.44]; and trial B, 1.07 [0.42] vs 0.97 [0.43]; both trials $P<.001$). Mean (SD) body weight reduction was greater with tolvaptan on day 1 (trial A, 1.71 [1.80] vs 0.99 [1.83] kg; $P<.001$; and trial B, 1.82 [2.01] vs 0.96 [1.85] kg; $P<.001$) and day 7 or discharge (trial A, 3.35 [3.27] vs 2.73 [3.34] kg; $P<.001$; and trial B, 3.77 [3.59] vs 2.79 [3.46] kg; $P<.001$), whereas improvements in global clinical status were not different between groups. More patients receiving tolvaptan (684 [76.7%] and 678 [72.1%] for trial A and trial B, respectively) vs patients receiving placebo (646 [70.6%] and 597 [65.3%], respectively) reported improvement in dyspnea at day 1 (both trials $P<.001$). Edema at day 7 or discharge improved significantly with tolvaptan in trial B ($P=.02$) but did not reach significance in trial A ($P=.07$). Serious adverse event frequencies were similar between groups, without excess renal failure or hypotension.

Conclusion In patients hospitalized with heart failure, oral tolvaptan in addition to standard therapy including diuretics improved many, though not all, heart failure signs and symptoms, without serious adverse events.

Trial Registration clinicaltrials.gov Identifier: NCT00071331

JAMA. 2007;297:1332-1343

www.jama.com

HEART FAILURE (HF) IS A MAJOR international public health problem presenting significant medical and economic challenges. In the United States, HF has high prevalence (>5 million individuals), high incidence (550 000 new cases yearly), increasing hospitalization rates (400 000 in 1979 to >1 million in 2004), and exorbitant cost (estimated to exceed $33 billion in 2007).[1] A considerable share of the burden of HF is accounted for by the acute HF syndromes (AHFS), defined as conditions with gradual or rapid changes in the signs and symptoms of HF that require urgent therapy.[2] Patients hospitalized with AHFS have poor overall prognosis.[3-6]

Congestion characterized by dyspnea, edema, rales, jugular venous dis-

See also pp 1319 and 1374.

Author Affiliations and a **Complete List of the EVEREST Investigators** appear at the end of this article.
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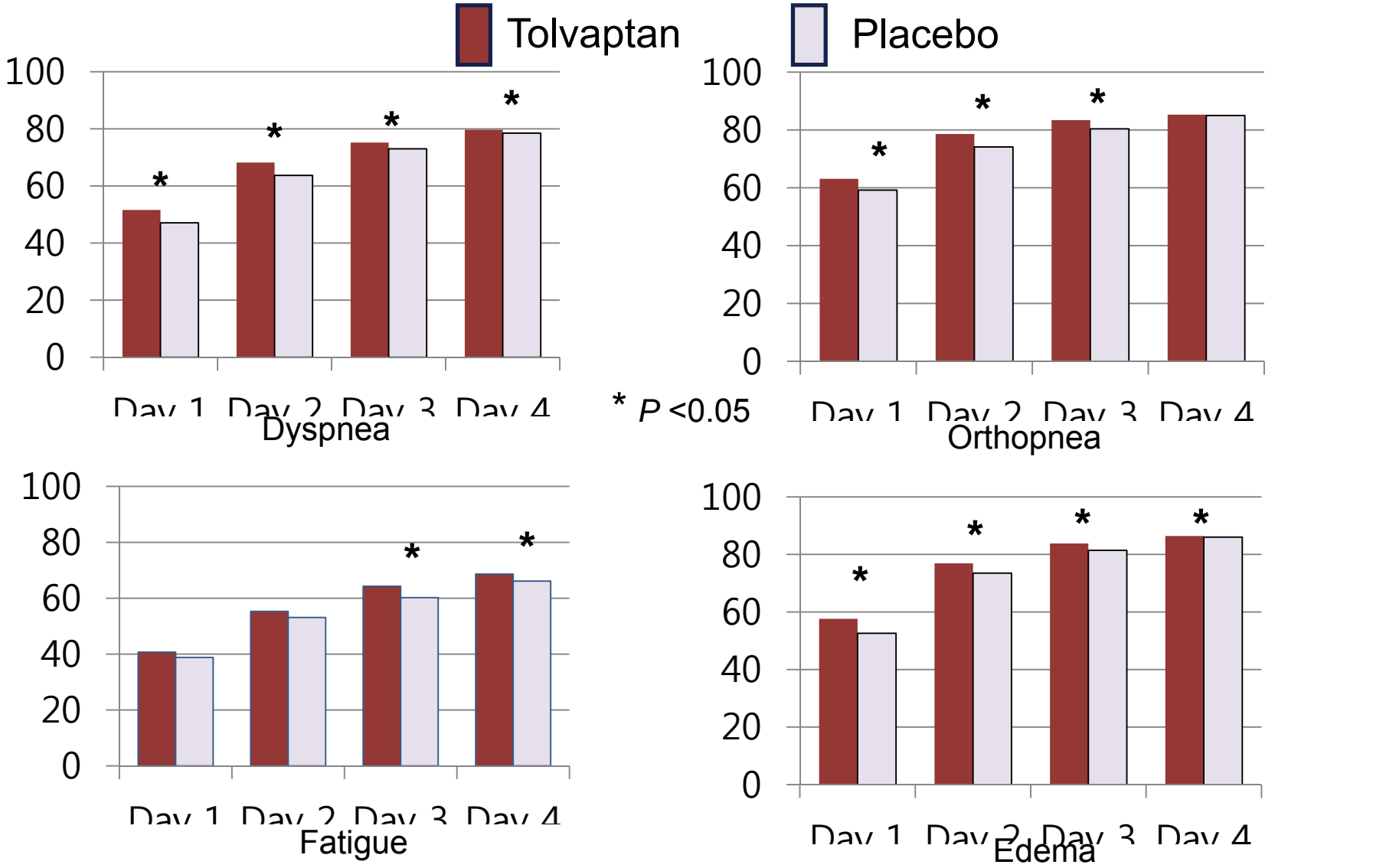
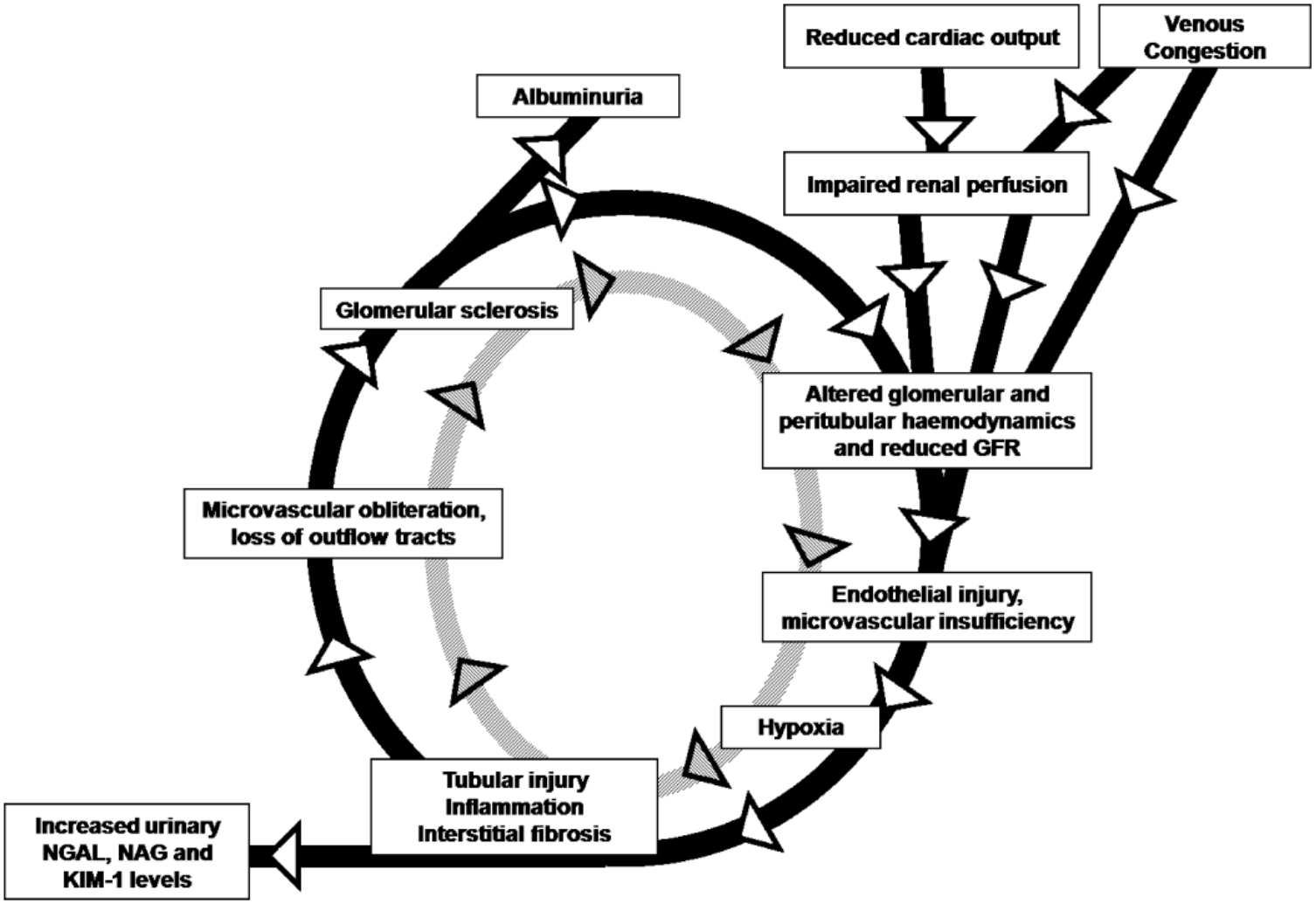
Physician-assessed Signs and Symptoms

(% Patients with Improvement)



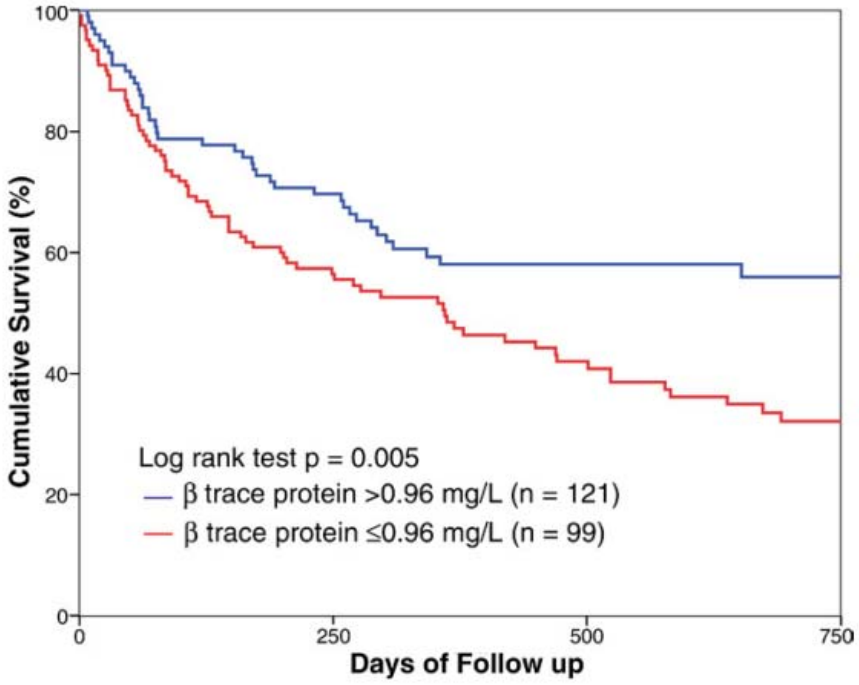
Everest trial. JAMA. 2007;297:1332-1343

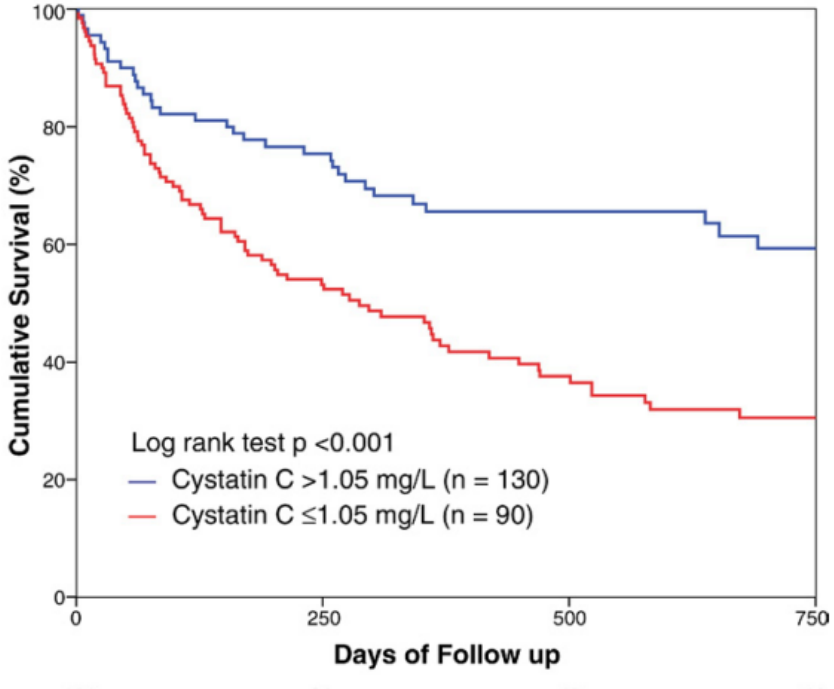
Vicious circle of decreased glomerular function, endothelial injury, tubular damage in heart failure



Norman et al. Cli Exp Pharmacology and Physiology 33, 989-996

Prognostic Importance of Biomarkers of Renal Dysfunction in Acutely Destabilized Heart Failure





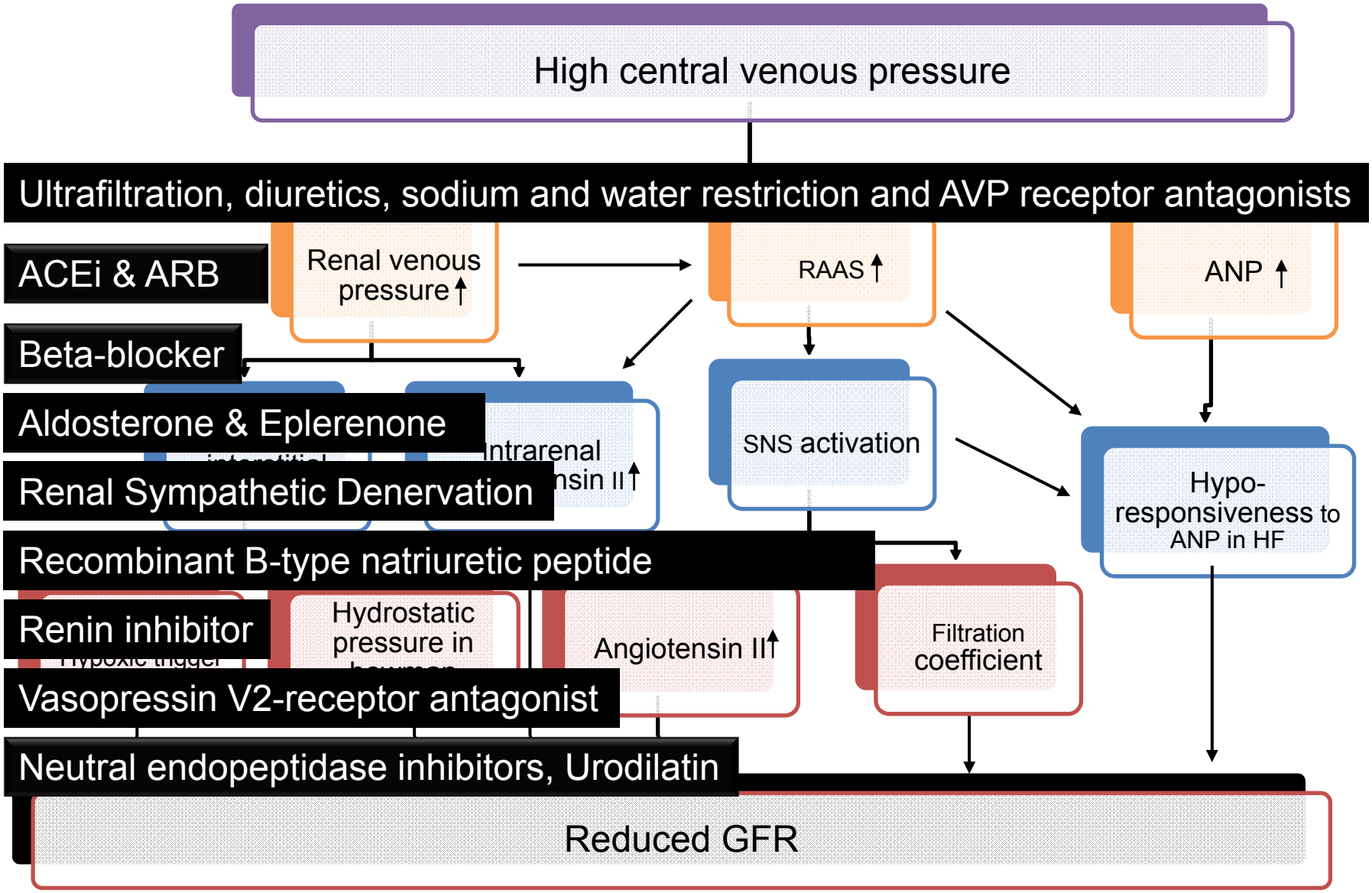
Manzano-Fernández et al. J Am Coll Cardiol 2011;57:849–58

Biomarkers for the Early Detection of Acute Kidney Injury

Table 1 Protein Biomarkers for the Early Detection of Acute Kidney Injury

Biomarker	Associated Injury
Cystatin C	Proximal tubule injury
KIM-1	Ischemia and nephrotoxins
NGAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Ischemia, pre-renal, post-renal AKI
Cytokines (IL-6, IL-8, IL-18)	Toxic, delayed graft function
Actin-actin depolymerizing F	Ischemia and delayed graft function
α-GST	Proximal T injury, acute rejection
π-GST	Distal tubule injury, acute rejection
L-FABP	Ischemia and nephrotoxins
Netrin-1	Ischemia and nephrotoxins, sepsis
Keratin-derived chemokine	Ischemia and delayed graft function

Ronco et al. J Am Coll Cardiol 2008;52:1527–39



K. Damman et al. European Journal of Heart Failure 9 (2007) 872 – 878

Conclusions

- Disruption of relationship between kidney and heart would be caused mainly by neurohormonal activation of kidney
- Identification of worsening kidney function using various biomarkers is cornerstone to diagnosis cardiorenal syndorme at an earlier time points.
- New drugs strategies are considered, and thereby effective control of neurohormonal system is most important to inhibit the aggravation of cardiorenal syndorme


감사합니다.