21ο ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ ΝΕΦΡΟΛΟΓΙΑΣ

29 ΜΑΪΟΥ έως 1 ΙΟΥΝΙΟΥ 2019

Μηχανισμοί νεφρικής βλάβης στην καρδιακή ανεπάρκεια

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Νεφρολογική Κλινική Α.Π.Θ., Ιπποκράτειο Νοσοκομείο

Καρδιακή Ανεπάρκεια και Νεφρική Βλάβη

Εισαγωγή

Καρδιονεφρικό Σύνδρομο: όρος 100 ετών

A Clinical Lecture

ON

PAROXYSMAL DYSPNOEA IN CARDIO-RENAL PATIENTS:

WITH SPECIAL REFERENCE TO "CARDIAC" AND "URAEMIC" ASTHMA.

Delivered at University College Hospital, London, November 12th, 1913.

By THOMAS LEWIS, M.D., D.Sc., F.R.C.P.,

ASSISTANT PHYSICIAN AND LECTURER IN CARDIAC PATHOLOGY, UNIVERSITY COLLEGE HOSPITAL; PHYSICIAN TO OUT-PATIENTS, CITY OF LONDON HOSPITAL.

those of a child; neither in the lips, tongue, ears, cheeks fingers, was there the faintest trace of cyanosis. U further examination the heart was found to be a little enlarg the pulse was at the rate of 92 per minute, occasional ex systoles interrupted its rhythm, and alternation in the force the pulse beats was seen. There were no murmurs. The ve pulsated freely and seemed a little engorged, but the liver not enlarged and there was no dropsy. The blood pressure 200 mm. Hg. He was passing from 600 to 2,000 c.cm. of urin day; sometimes a trace of albumin was present, and a granular casts were found. Over the lungs a few rhonchi w audible.

I take this as a type case and emphasize the follow features. The man presented some signs of a degener heart muscle, enlargement, and especially pulsus alterna he presented signs of renal involvement, the urine fl was, as a rule, increased, casts were present, the bl pressure was very high. He had urgent dyspnoea, yet

Καρδιονεφρικό Σύνδρομο στη σύγχρονη εποχή

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ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.07.051

STATE-OF-THE-ART PAPER

Cardiorenal Syndrome

Claudio Ronco, MD,* Mikko Haapio, MD,† Andrew A. House, MSc, MD,‡ Nagesh Anavekar, MD,§ Rinaldo Bellomo, MD¶

Vicenza, Italy; Helsinki, Finland; London, Ontario, Canada; and Melbourne, Australia

European Heart Journal (2010) **31**, 703–711
doi:10.1093/eurheartj/ehp507

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative

Claudio Ronco[1,2*], Peter McCullough[3], Stefan D. Anker[4,5], Inder Anand[6], Nadia Aspromonte[7], Sean M. Bagshaw[8], Rinaldo Bellomo[9], Tomas Berl[10],

Prof. Claudio Ronco

PubMed 3/3/2011:
1096 άρθρα με “cardiorenal”
308 άρθρα με “cardiorenal syndrome”

PubMed 19/5/2019:
2671 άρθρα με “cardiorenal”
827 άρθρα με “cardiorenal syndrome”

Cardiorenal Syndrome Types I-IV

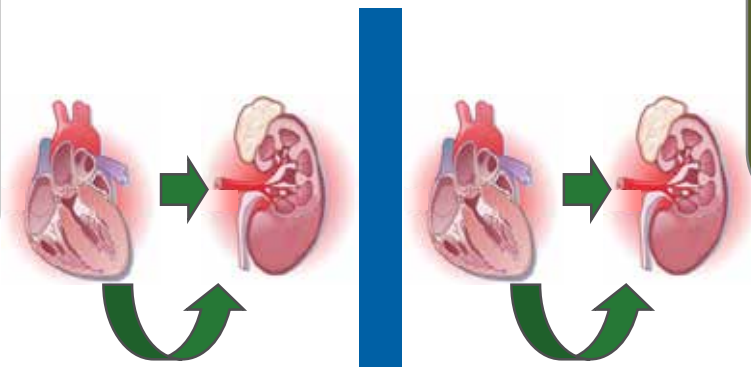
Type 1

AHF or ADHF leading to AKI
- Cardiac surgery/ cardiac procedures associated AKI
- CIN
- CPB
- Valve replacement

Cardiac dysfunction leading to renal disorder

Type 2

Chronic HF (Systolic or diastolic) leading to:
- CKD
- CKD progression
- Diuretic resistant oliguria



Acute

Chronic

Type 3

AKI leading to AHF
- Volume/uremia-induced AHF or ADHF
- Renal ischemia-induced AHF or ADHF
- Sepsis/cytokine-induced AKI and HF

Type 4

CKD increasing CV mortality.
CKD increasing CV morbidity.
Chronic HF progression due to CKD
- Uremia-related HF
- Volume-related HF

Renal dysfunction leading to CV disease

Haapio M, et al. J Am Soc Nephrol 2008;19:388A. F-PO1245; Ronco C, et al. J Am Coll Cardiol 2008;52:1527–39

Καρδιακή Ανεπάρκεια και Νεφρική Βλάβη

Ορισμοί

Box 1 | **Definitions of AKI and worsening renal function in HF**

AKI (KDIGO)

Stage 1

- *Serum creatinine*: 1.5–1.9 fold increase from baseline within 1–7 days or ≥26.5 μmol/l increase within 48 h
- *Urine output*: <0.5 ml·kg^{-1}/h for 6–12 h

Stage 2

- *Serum creatinine*: 2.0–2.9 fold increase from baseline
- *Urine output*: <0.5 ml·kg^{-1}/h for ≥12 h

Stage 3

- *Serum creatinine*: ≥3.0 fold increase from baseline or increase >354 μmol/l or initiation of renal replacement therapy
- *Urine output*: <0.3 ml·kg^{-1}/h for ≥24 h or anuria ≥12 h

Worsening renal function (HF literature)

Definitions based on creatinine level

- ≥26.5 μmol/l increase; ≥26.5 μmol/l and ≥25% increase; ≥44 μmol/l increase ≥1.5 times baseline; ≥25% increase and above 176 μmol/l

Definitions based on cystatin C

- >0.3 mg/l increase

Definitions based on eGFR

- ≥20% decrease; ≥25% decrease; >5 ml·min^{-1} per year decrease

Worsening renal function in chronic HF or AKI in acute HF (suggested definitions)

Worsening renal function in chronic HF[*]

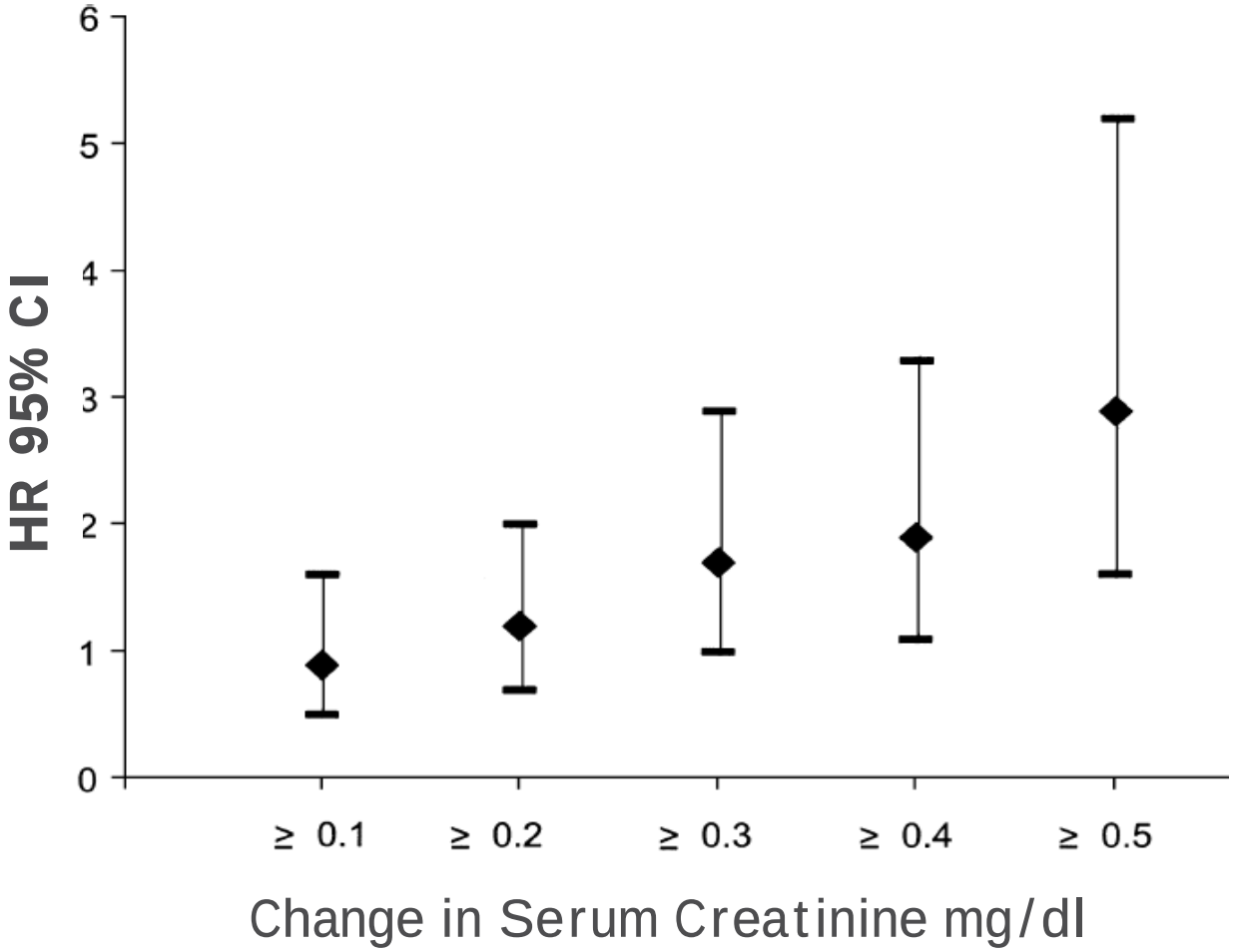
- ≥26.5 μmol/l and ≥25% increase in serum creatinine[‡] or ≥20% decrease in eGFR over 1–26 weeks
- *Additional criteria*: deterioration in HF status but not leading to hospitalization

AKI in acute HF[*]

- Increase 1.5–1.9 times baseline serum creatinine level within 1–7 days before or during hospitalization or ≥26.5 μmol/l increase in serum creatinine[‡] within 48 h or urine output <0.5 ml·kg^{-1}/h for 6–12 h
- *Additional criteria*: deterioration in HF status or failure to improve or need for inotropes, ultrafiltration or renal replacement therapy

Schefold et al.
Nature Rev Cardiol 2016

Change in Screatinine During Hospitalization of Patients with HF and Prognosis



Smith GL et. al. February 2003 vol 9, 13-25

Βασική Τυπολογία και Παθοφυσιολογία Καρδιακής Ανεπάρκειας

Τύποι Καρδιακής Ανεπάρκειας

- Chronic Heart Failure (CHF)
- Acute Heart Failure (Cardiogenic Shock)
- Systolic Failure (LVSD) – Reduced EFHF
- Diastolic Heart Failure (LVDD) – NEFHF
- Left Heart Failure (LVF)
- Right Heart Failure (Congestive CCF)
- Forward Failure and Backward Failure
- High output failure -Thyrotoxic, Paget's, Anemia, Pregnancy, A-V fistula
- Low output failure – 95% of HF is this

European Heart Journal
doi:10.1093/eurheartj/ehw128

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL.

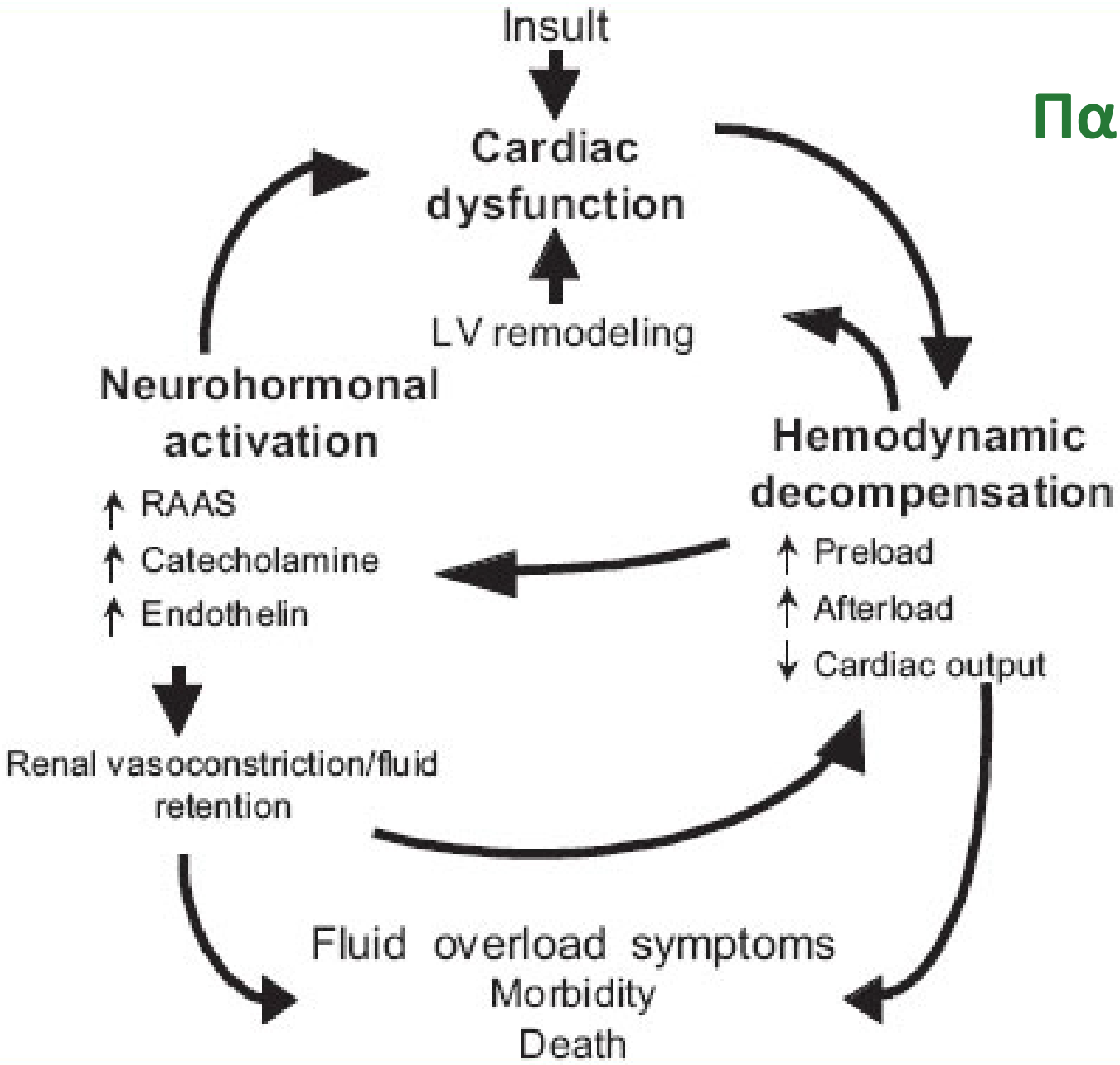
Οξεία Καρδιακή Ανεπάρκεια

Κλινικοί «τύποι»

Clinical Presentation	Incidence*	Characteristics	Targets† and Therapies‡
Elevated BP (above 160 mm Hg)	~25%	Predominantly pulmonary (radiographic/clinical) with or without systemic congestion. Many patients have preserved EF.	**Target:** BP and volume management **Therapy:** vasodilators (e.g., nitrates§, nesiritide, nitroprusside) and loop diuretics
Normal or moderately elevated BP	~50%	Develop gradually (days or weeks) and are associated with systemic congestion. Radiographic pulmonary congestion may be minimal in patients with advanced HF.	**Target:** volume management **Therapy:** loop diuretics ± vasodilators
Low BP (<90 mm Hg)	<8%	Mostly related to low cardiac output and often associated with decreased renal function.	**Target:** cardiac output **Therapy:** inotropes with vasodilatory properties (e.g., milrinone, dobutamine, levosimendan); consider digoxin (intravenous and/or orally) ± vasopressor medications ± mechanical assist devices (e.g., IABP)
Cardiogenic shock	<1%	Rapid onset. Primarily complicating acute MI, fulminant myocarditis, acute valvular disease.	**Target:** improve cardiac pump function **Therapy:** inotropes ± vasoactive medications ± mechanical assist devices, corrective surgery
Flash pulmonary edema	3%‖	Abrupt onset. Often precipitated by severe systemic hypertension. Patients respond readily to vasodilators and diuretics.	**Target:** BP, volume management **Therapy:** vasodilators, diuretics, invasive or NIV, morphine¶
ACS and AHFS	~25% of ACS have HF signs/symptoms	Rapid or gradual onset. Many such patients may have signs and symptoms of HF that resolve after resolution of ischemia.	**Target:** coronary thrombosis, plaque stabilization, correction of ischemia **Therapy:** reperfusion (e.g., PCI, lytics, nitrates, antiplatelet agents)
Isolated right HF from pulmonary HTN or intrinsic RV failure (e.g., infarct) or valvular abnormalities (e.g., tricuspid valve endocarditis)	?	Rapid or gradual onset due to primary or secondary PA hypertension or RV pathology (e.g., RV infarct). Not well characterized with little epidemiological data.	**Target:** PA pressure **Therapy:** nitrates, epoprostenol, phosphodiesterase inhibitors, endothelin-blocking agents, coronary reperfusion for RV infarcts, valve surgery
Post-cardiac surgery HF	?	Occurring in patients with or without previous ventricular dysfunction, often related to worsening diastolic function and volume overload immediately after surgery and the subsequent early post-operative interval. Can also be caused by inadequate intra-operative myocardial protection resulting in cardiac injury.	**Target:** volume management, improve cardiac performance (output) **Therapy:** diuretic or fluid administration (directed by filling pressures and cardiac index), inotropic support, mechanical assistance (IABP, VAD)

Gheorghiade & Pang. J Am Coll Cardiol 2009

Παθοφυσιολογία ΚΑ



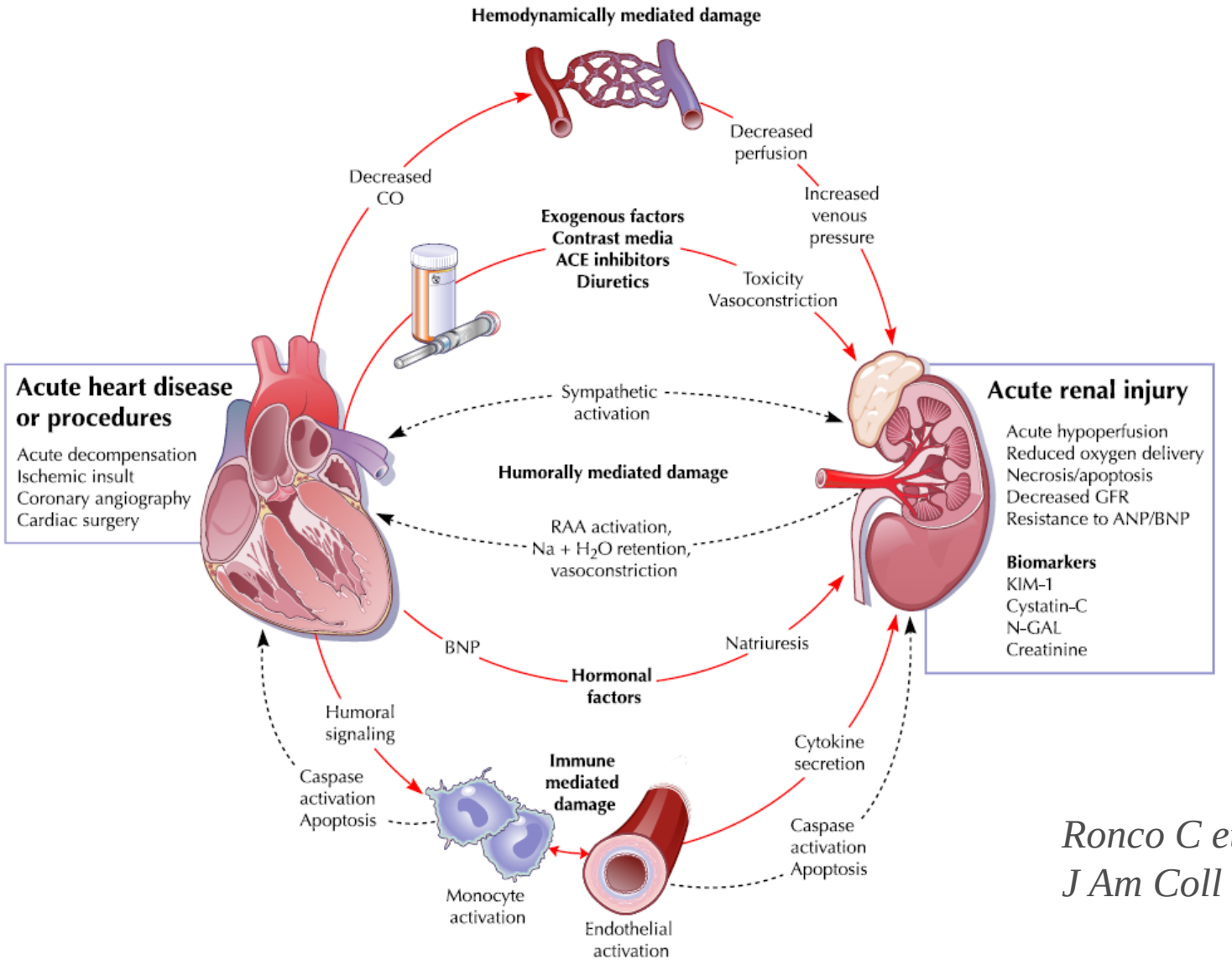
Ομάδες ασθενών με υψηλή συχνότητα νατριοευαισθησίας

- Fixed factors
  - Middle and older-aged persons
  - African-Americans
  - Individuals with:
    - Hypertension
    - Diabetes
    - Chronic Kidney Disease
- Modifiable
  - Low potassium intake
  - Poor quality diet

Sarafidis & Bakris. J Am Coll Cardiol 2008

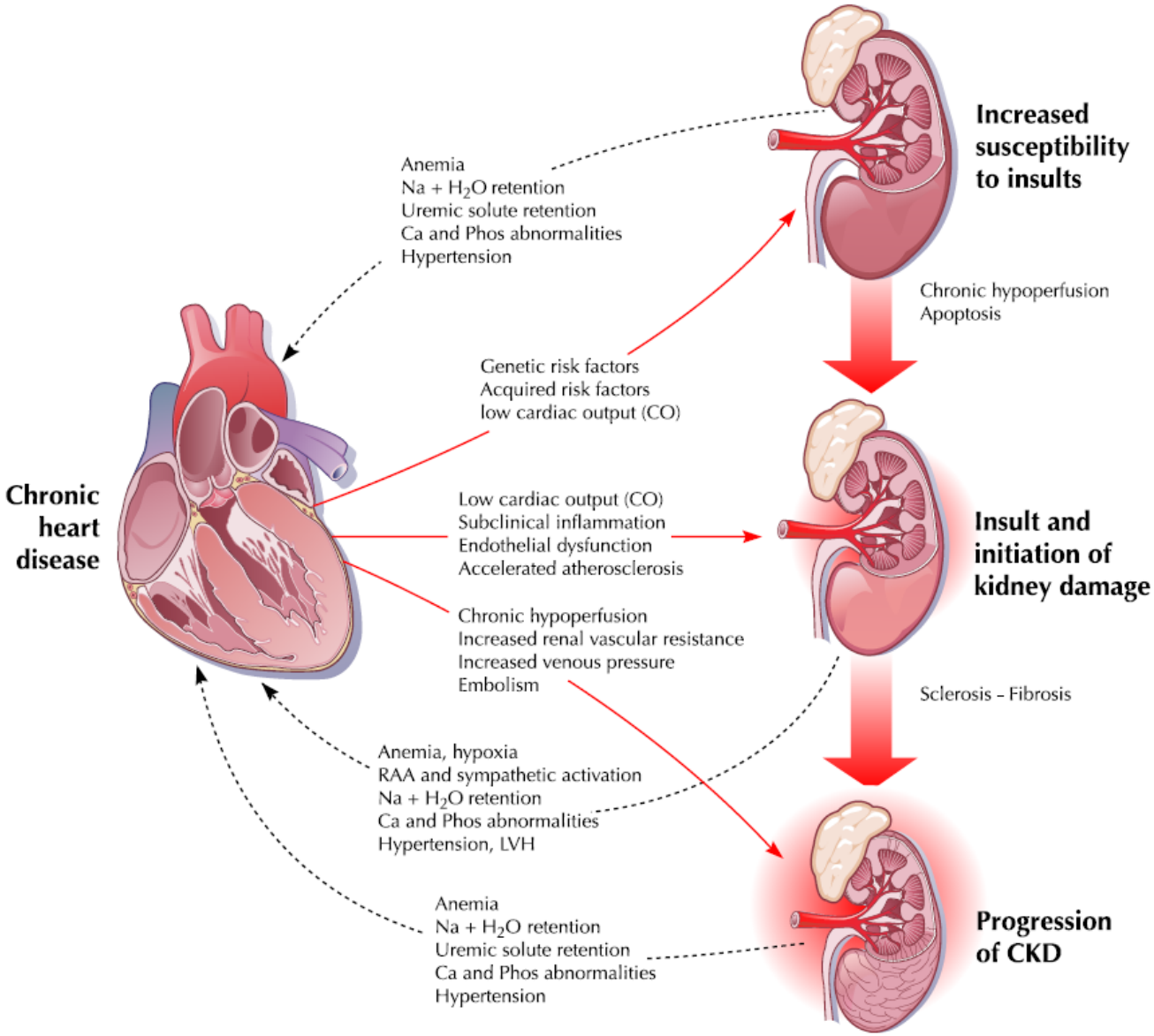
Οξύ και Χρόνιο Καρδιονεφρικό Σύνδρομο: Νεφρική Βλάβη

Καρδιονεφρικό Σύνδρομο Τύπου Ι: Οξύ Καρδιονεφρικό Σύνδρομο



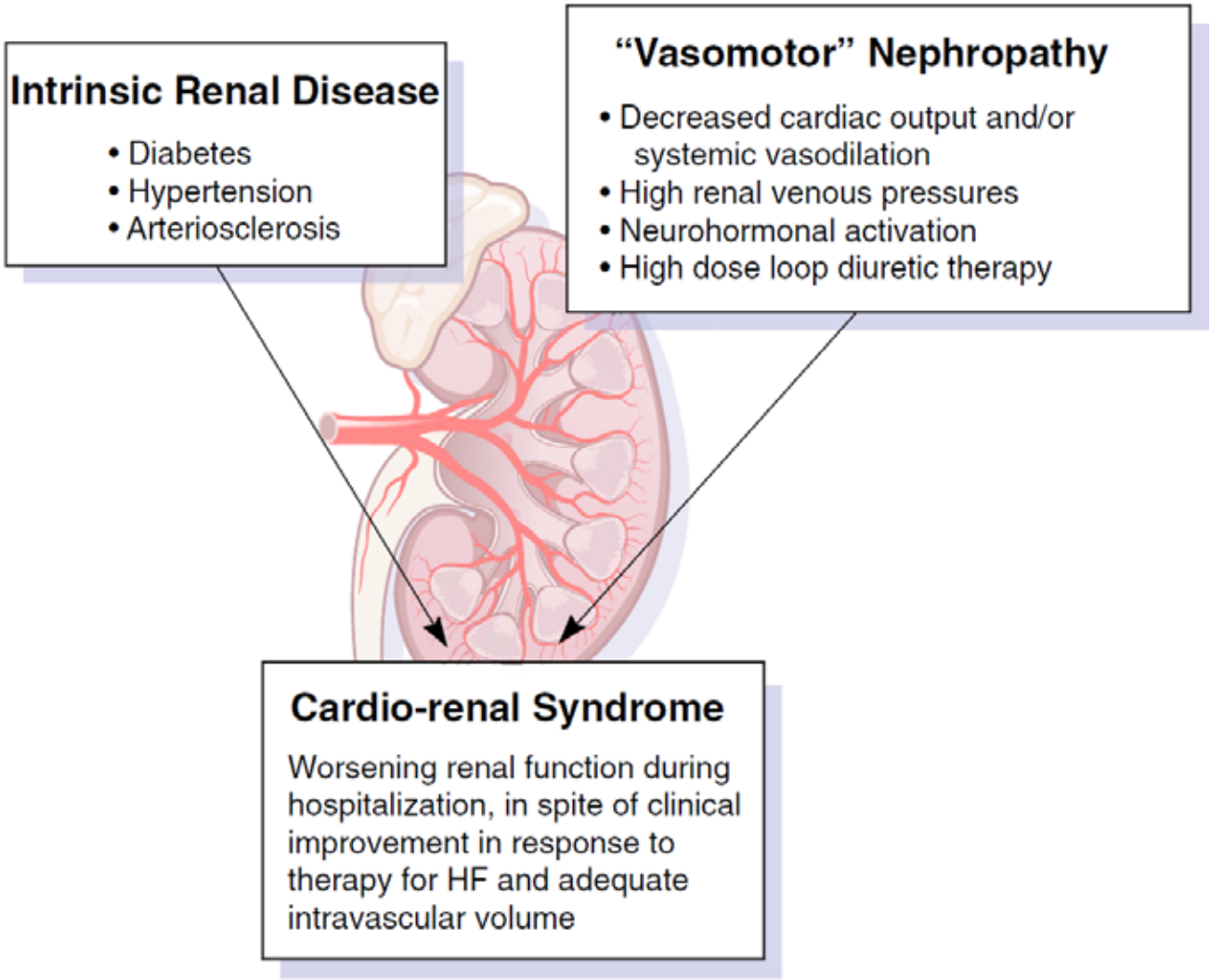
Ronco C et al,
J Am Coll Cardiol 2008

Καρδιονεφρικό Σύνδρομο Τύπου ΙΙ: Χρόνιο Καρδιονεφρικό Σύνδρομο



Ronco C et al, J Am Coll Cardiol 2008

Οξεία Καρδιακή Ανεπάρκεια και Νεφρική Βλάβη
Μηχανισμοί



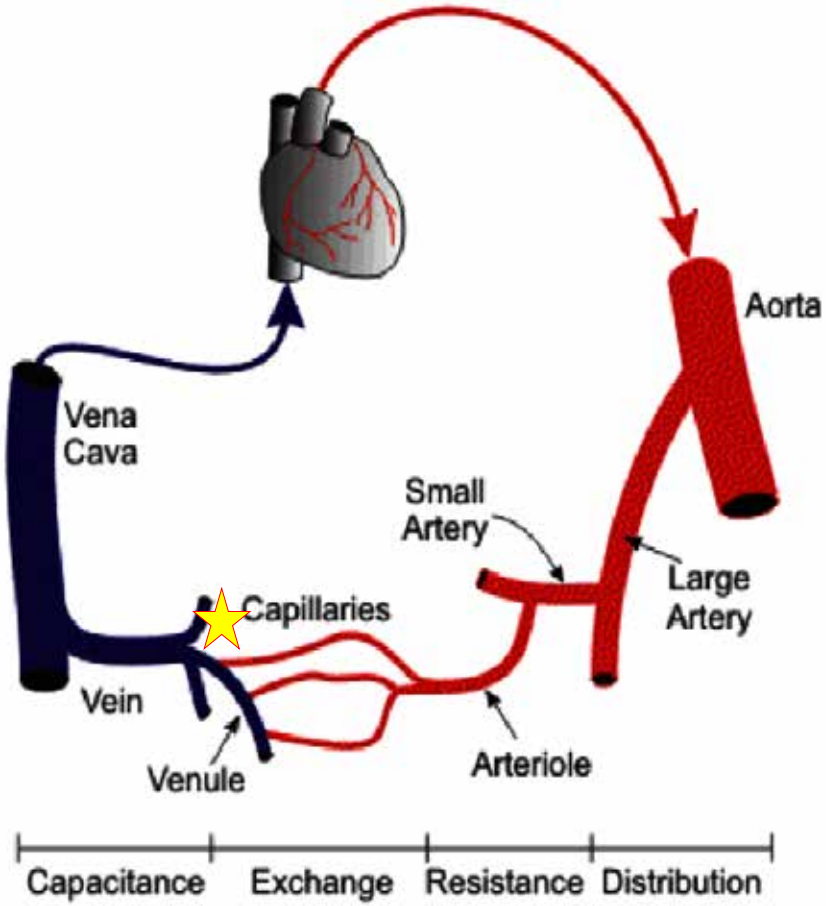
Gheorghiade M. J Am Coll Cardiol 2009

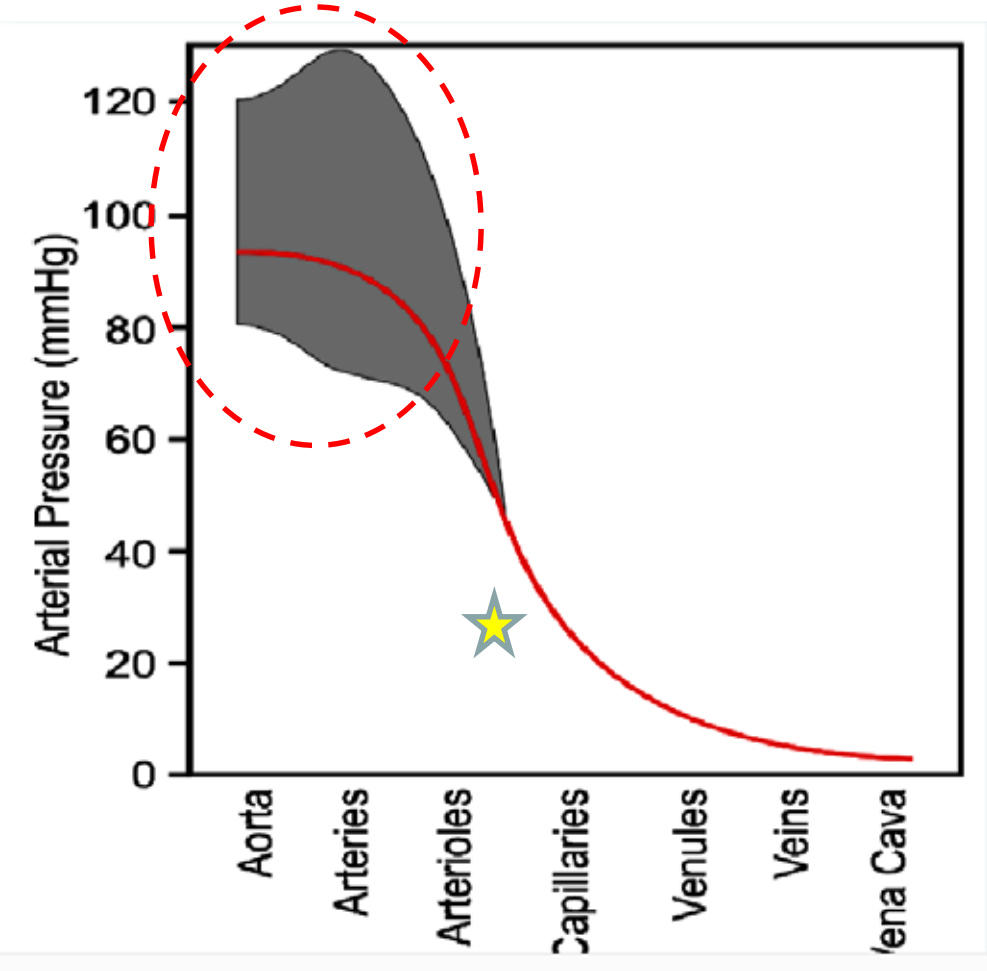
Μηχανισμοί Νεφρικής Βλάβης στην ΚΑ

Χαμηλή Παροχή

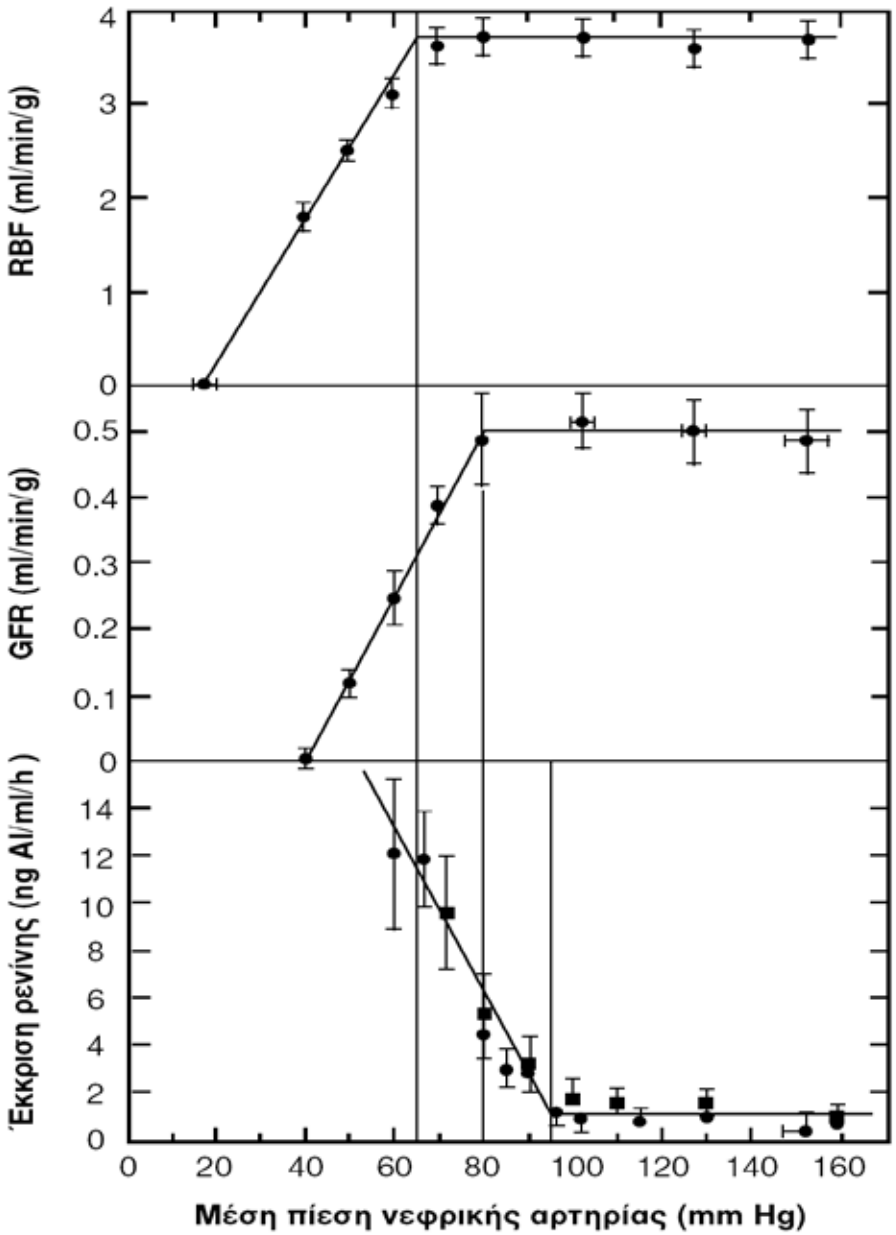
Global versus regional haemodynamics

13% blood volume





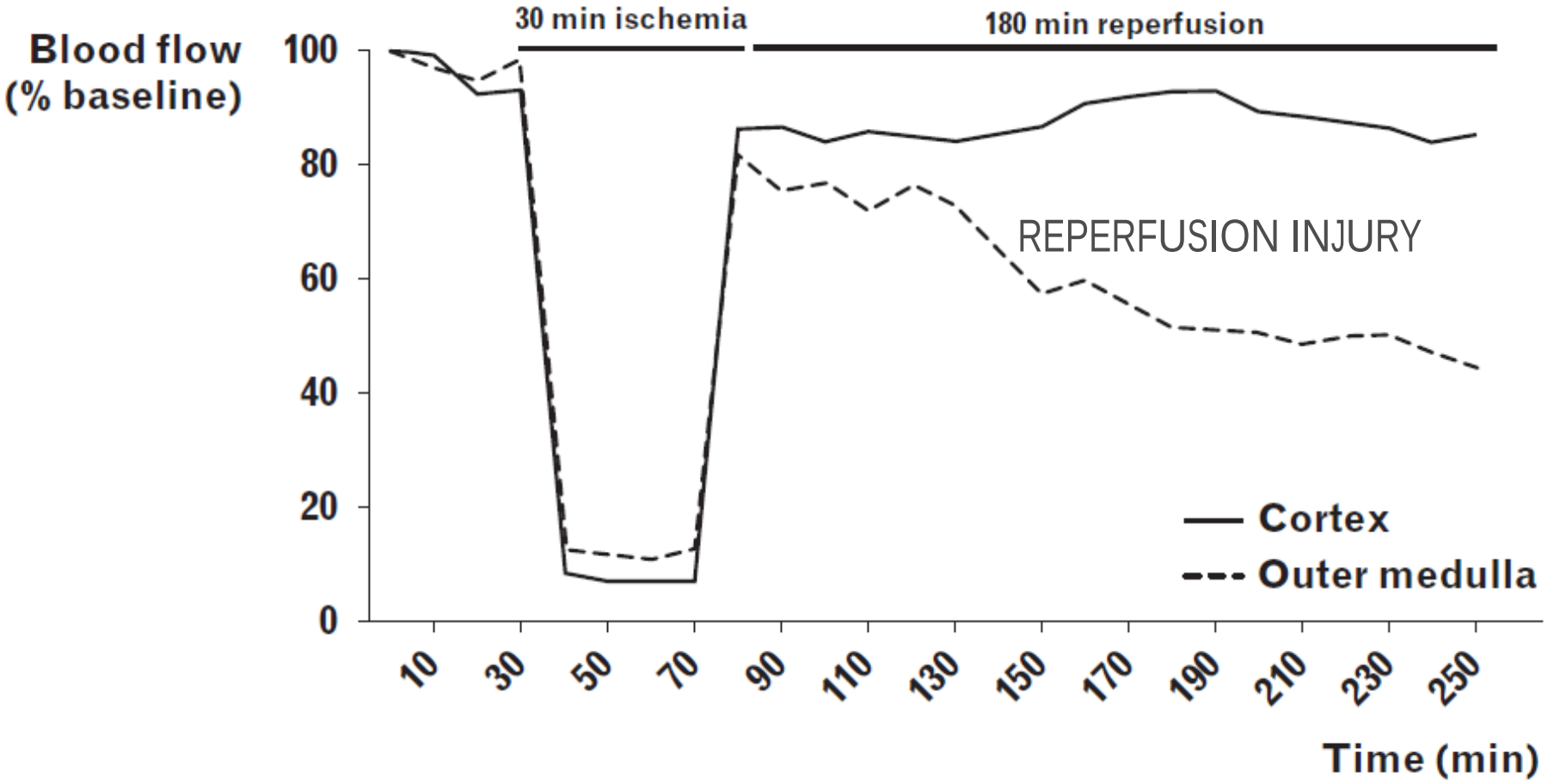
Αρτηριακή Πίεση και Προνεφρική ΟΝΑ



Η σχέση της πίεσης διήθησης του νεφρού με την νεφρική αιματική ροή (RBF), το ρυθμό σπειραματικής διήθησης (GFR) και την έκκριση ρενίνης σε κύνες. Η πίεση διήθησης ελεγχόταν με αεροθάλαμο που είχε τοποθετηθεί στη νεφρική αρτηρία. Οι μεταβολές της απεικονίζονται στο σχήμα με τις αντίστοιχες μεταβολές στη μέση πίεση της νεφρικής αρτηρίας. Πτώση στη μέση πίεση της νεφρικής αρτηρίας κάτω απ' το επίπεδο των 95 mmHg περίπου (threshold pressure) οδηγεί σε απότομη αύξηση της έκκρισης ρενίνης. Αν η πίεση συνεχίσει να υποχωρεί σε ακόμη χαμηλότερα επίπεδα, θα πέσει πρώτα ο GFR και στη συνέχεια η RBF. Τα δύο αυτά μεγέθη εμφανίζουν επίσης οξεία μεταβολή μετά από ένα ορισμένο επίπεδο πίεσης και τα τρία αυτά επίπεδα απέχουν περίπου 15 mmHg το ένα από το άλλο

Σαραφίδης Π και συν.,
Αρτηριακή Υπέρταση 2001

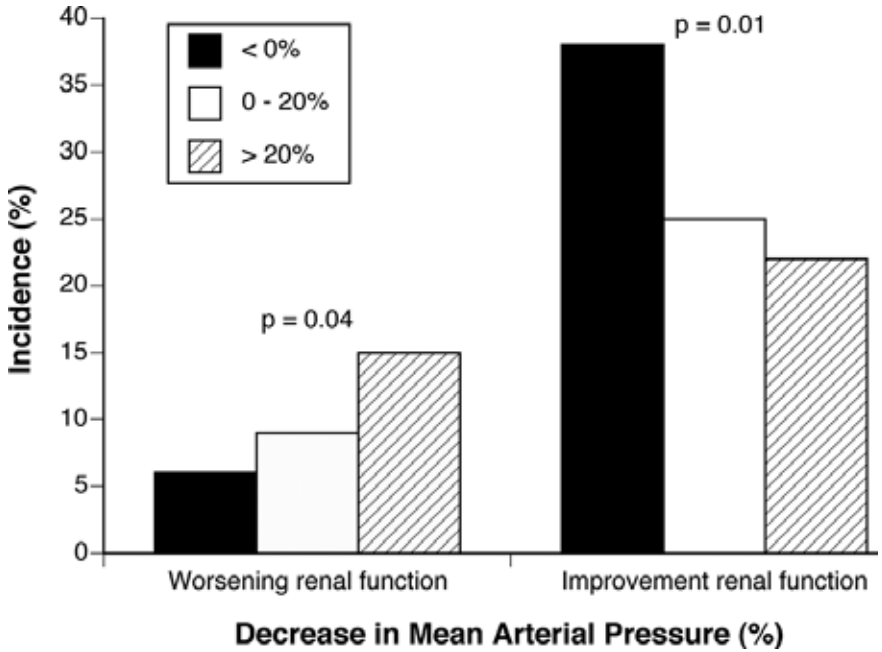
Renal medullary ischaemia

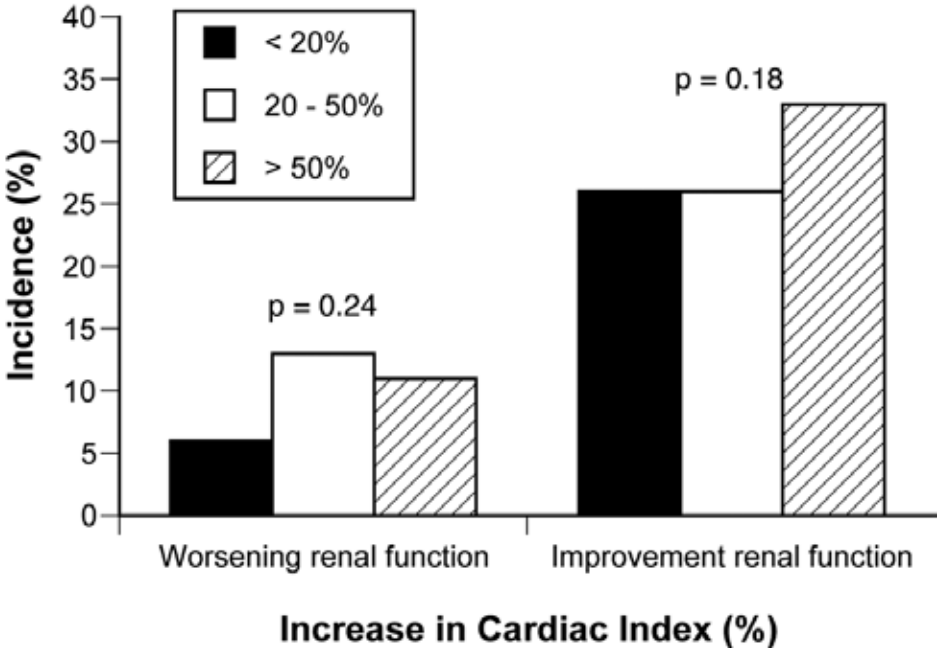


Regener Curr Opin Nephrol Hypertens. 2012 ; 21(1): 33–38

ΑΥ και ΟΝΒ στην Καρδιακή Ανεπάρκεια

443 patients treated for ADHF

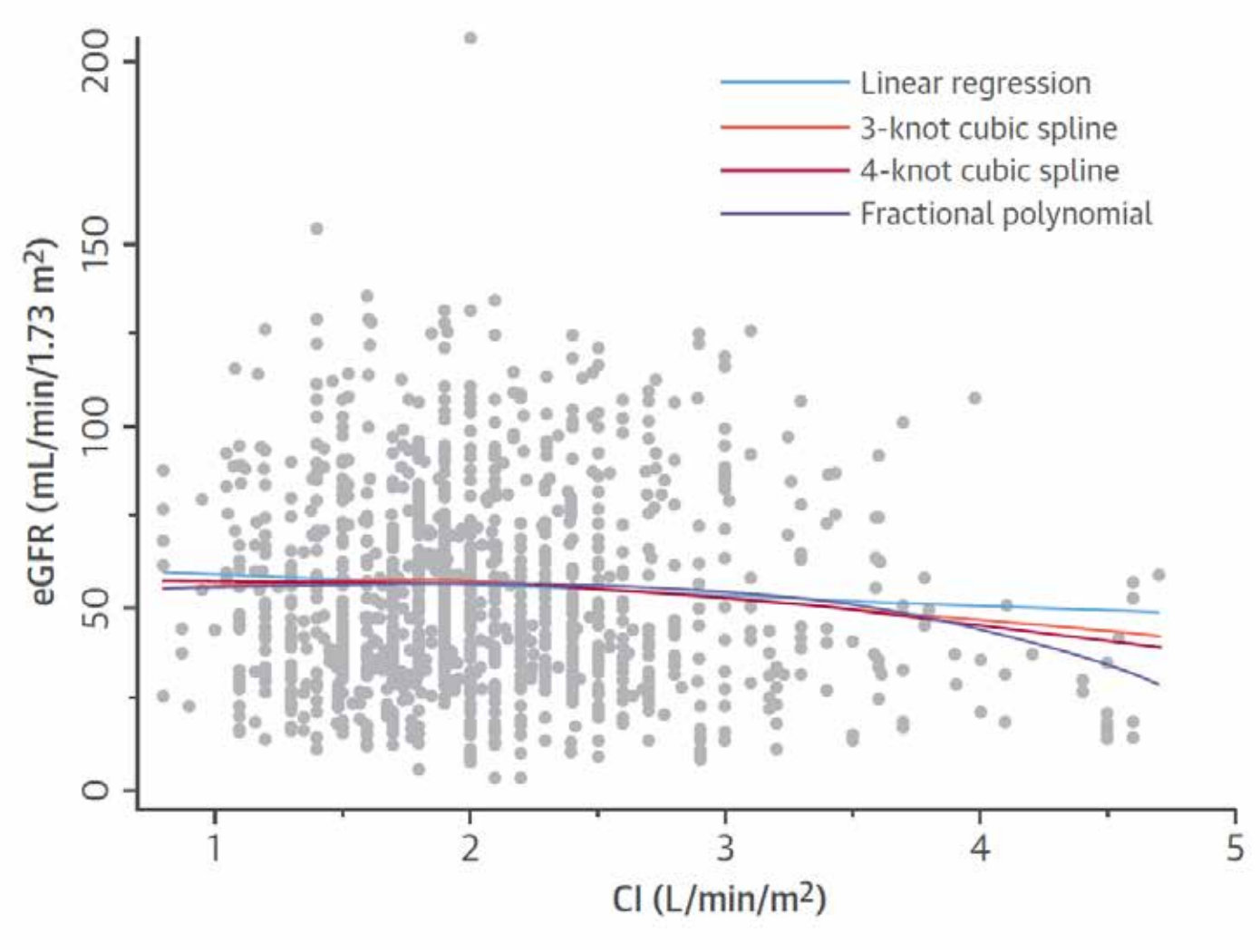




Dupont, et al.
Eur J Heart Fail 2013

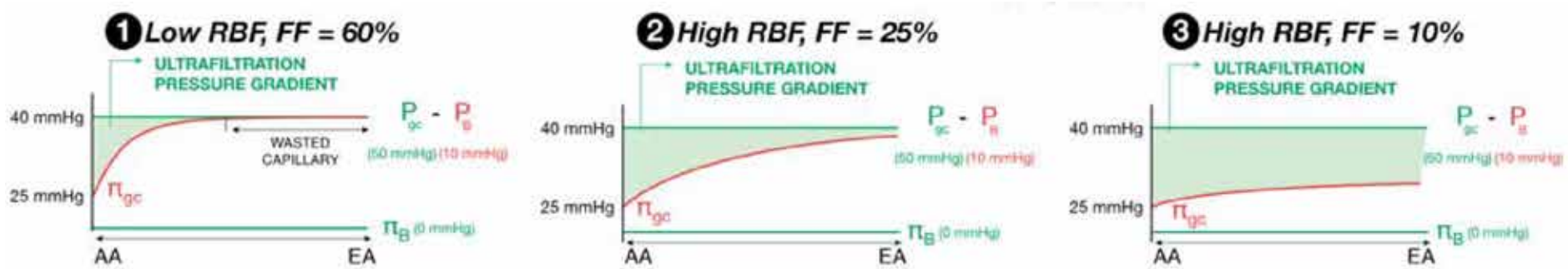
Καρδιακή παροχή και eGFR

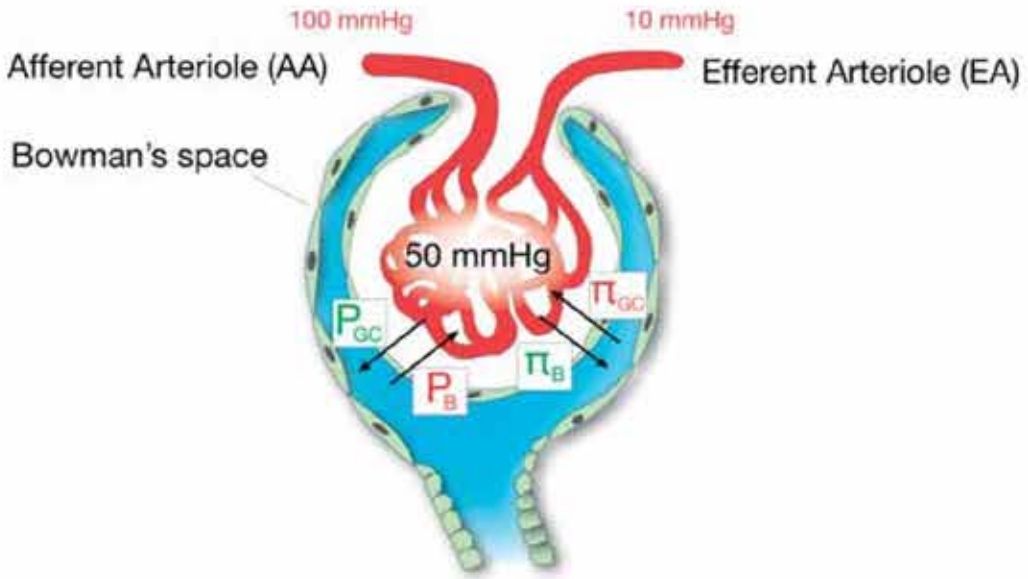
575 patients who underwent right PAC of the ESCAPE trial (mean EF 23±12%, CI 2.3±2.1 l/min/m^2 and a right atrial pressure of 14±9 mm Hg)



Hanberg, et al. J Am Coll Cardiol 2016

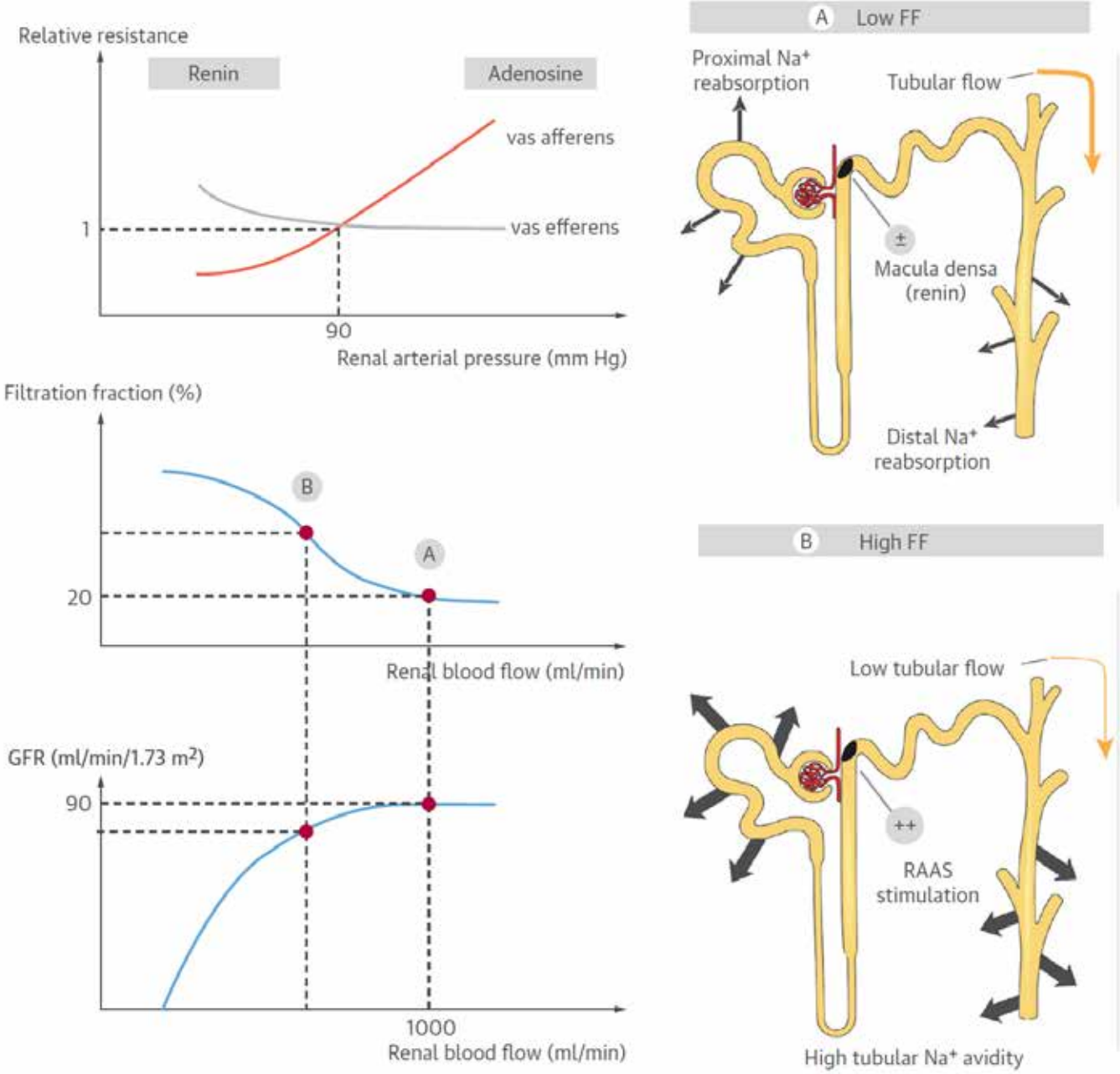
eGFR, RBF & Filtration Fraction





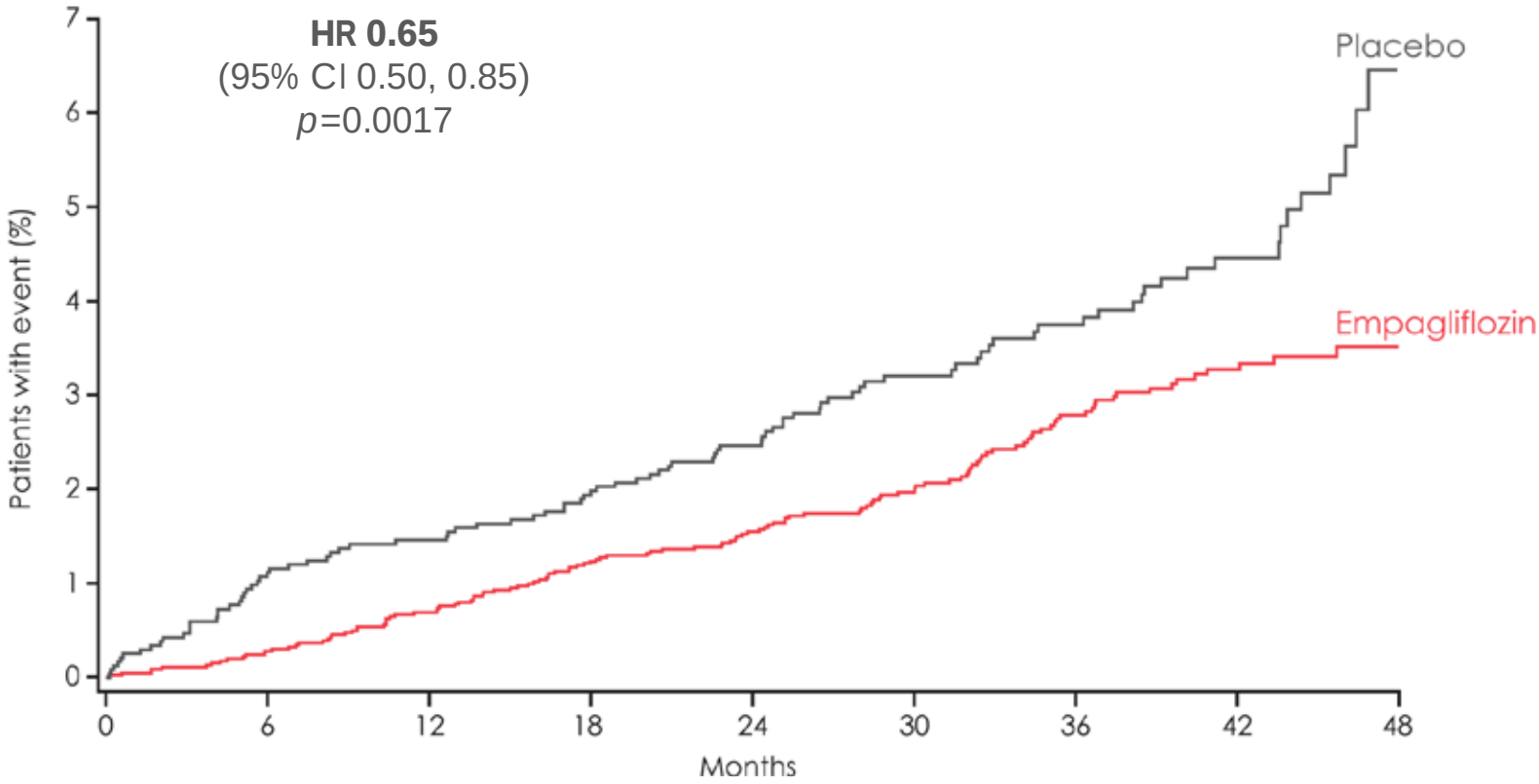
Verbrugge et al. Eur J Heart Failure 2013

eGFR, RBF & Filtration Fraction



Mullens & Nijst. J Am Coll Cardiol 2016

EMPAREG-OUTCOME
Νοσηλεία για Καρδιακή Ανεπάρκεια



No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function. HR, hazard ratio

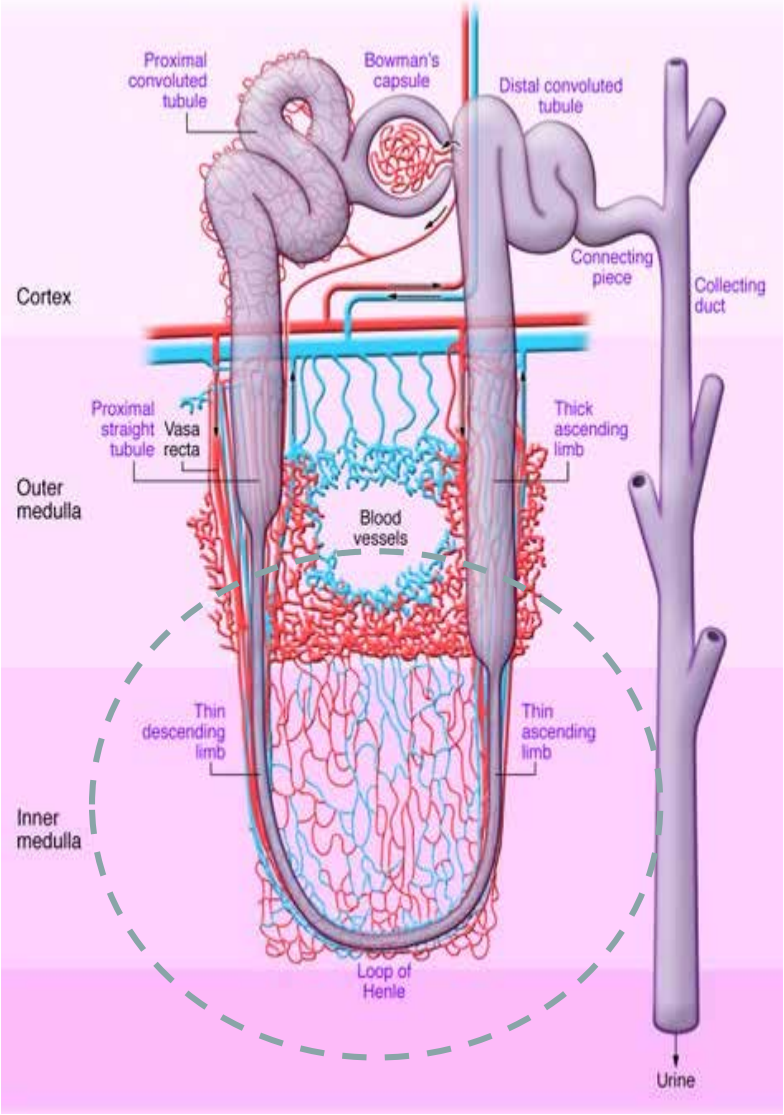
published Online, September 17, 2015, at NEJM.org. **DOI: 10.1056/NEJMoa1504720**

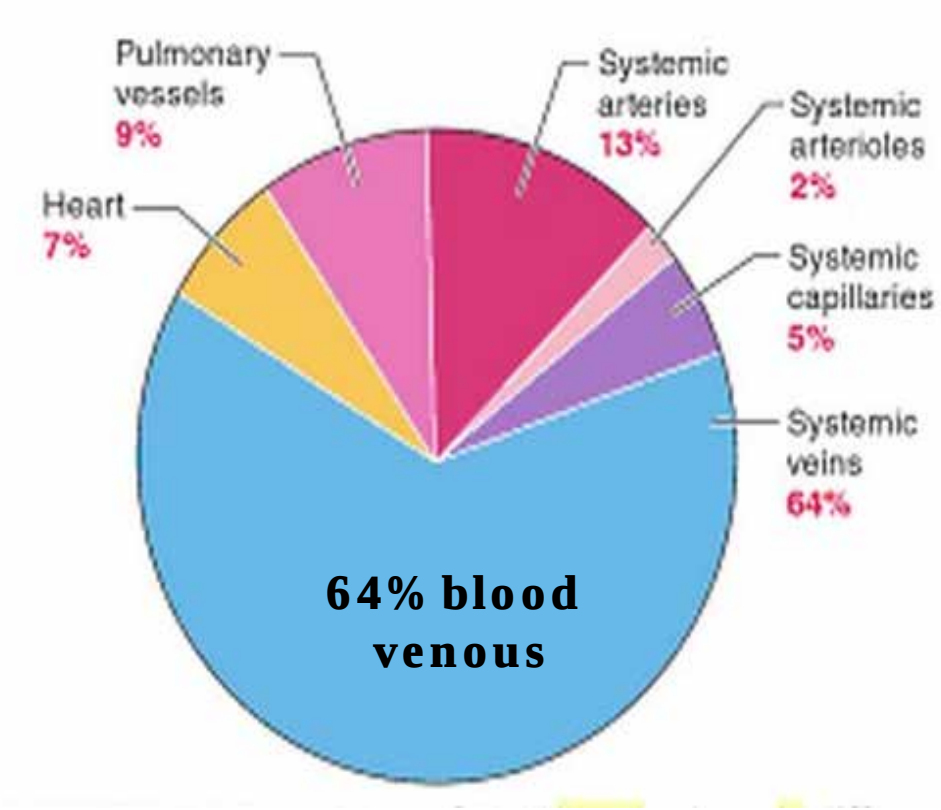
EMPA-REG OUTCOME®

Μηχανισμοί Νεφρικής Βλάβης στην ΚΑ

Φλεβική Συμφόρηση

Role of high CVP in AKI





J Clin Invest. 2011;121(11):4210-4221

Importance of Venous Congestion for Worsening of Renal Function in Advanced Decompensated Heart Failure

Wilfried Mullens, MD, Zuheir Abrahams, MD, PHD, Gary S. Francis, MD, FACC, George Sokos, DO, David O. Taylor, MD, FACC, Randall C. Starling, MD, MPH, FACC, James B. Young, MD, FACC, W. H. Wilson Tang, MD, FACC

Cleveland, Ohio

Objectives To determine whether venous congestion, rather than impairment of cardiac output, is primarily associated with the development of worsening renal function (WRF) in patients with advanced decompensated heart failure (ADHF).

Background Reduced cardiac output is traditionally believed to be the main determinant of WRF in patients with ADHF.

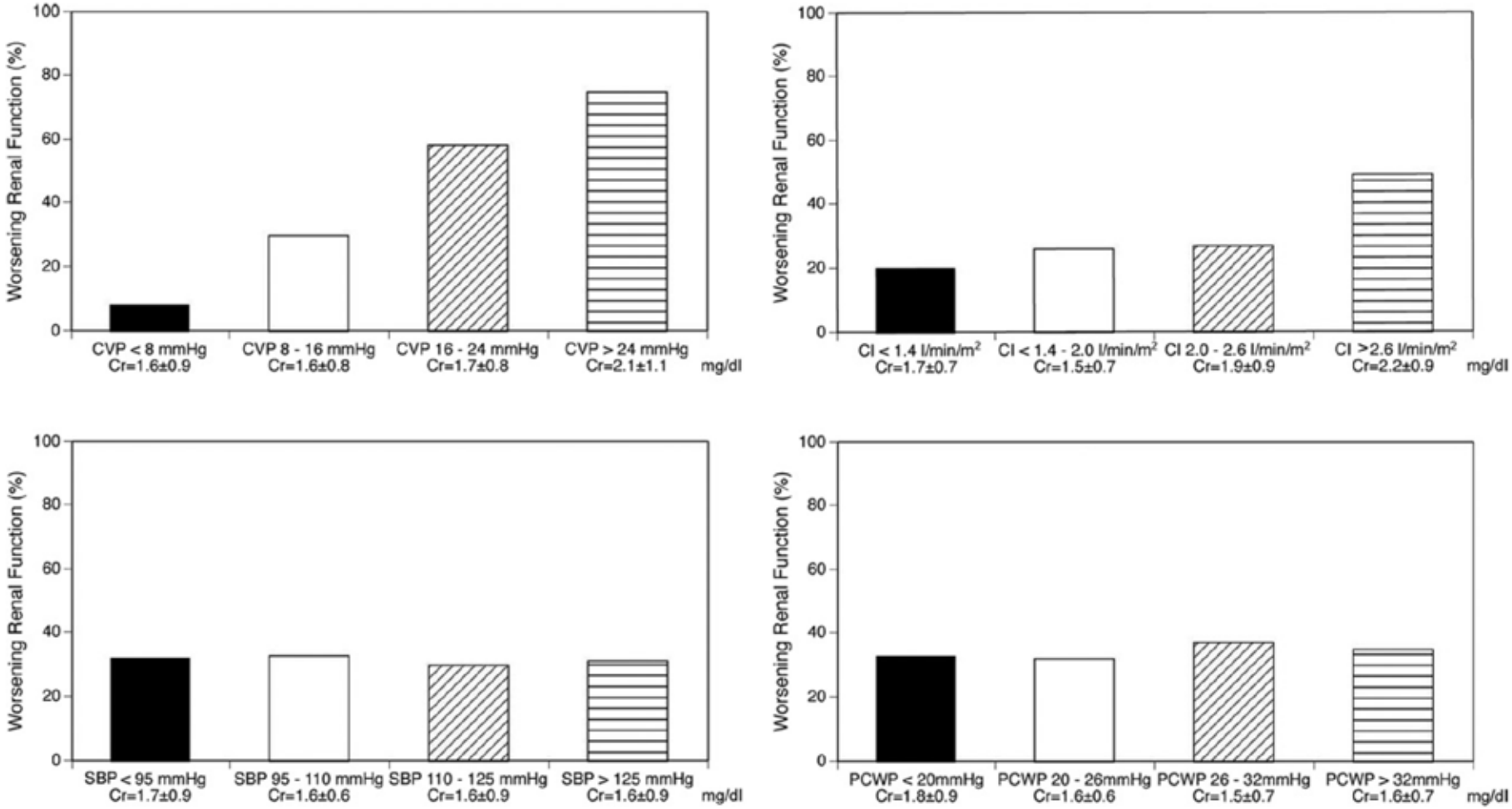
Methods A total of 145 consecutive patients admitted with ADHF treated with intensive medical therapy guided by pulmonary artery catheter were studied. We defined WRF as an increase of serum creatinine ≥0.3 mg/dl during hospitalization.

Results In the study cohort (age 57 ± 14 years, cardiac index 1.9 ± 0.6 l/min/m^2, left ventricular ejection fraction 20 ± 8%, serum creatinine 1.7 ± 0.9 mg/dl), 58 patients (40%) developed WRF. Patients who developed WRF had a greater central venous pressure (CVP) on admission (18 ± 7 mm Hg vs. 12 ± 6 mm Hg, $p < 0.001$) and after intensive medical therapy (11 ± 8 mm Hg vs. 8 ± 5 mm Hg, $p = 0.04$). The development of WRF occurred less frequently in patients who achieved a CVP <8 mm Hg ($p = 0.01$). Furthermore, the ability of CVP to stratify risk for development of WRF was apparent across the spectrum of systemic blood pressure, pulmonary capillary wedge pressure, cardiac index, and estimated glomerular filtration rates.

Conclusions Venous congestion is the most important hemodynamic factor driving WRF in decompensated patients with advanced heart failure. (J Am Coll Cardiol 2009;53:589–96)

Φλεβική Συμφόρηση στην Καρδιακή Ανεπάρκεια

145 patients admitted with ADHF (age 57±14 years, cardiac index 1.9±0.6 l/min/m^2, LVEF 20±8%, serum creatinine 1.7±0.9 mg/dl),



Mullens, et al. J Am Coll Cardiol 2009

Φλεβική Συμφόρηση στην Καρδιακή Ανεπάρκεια

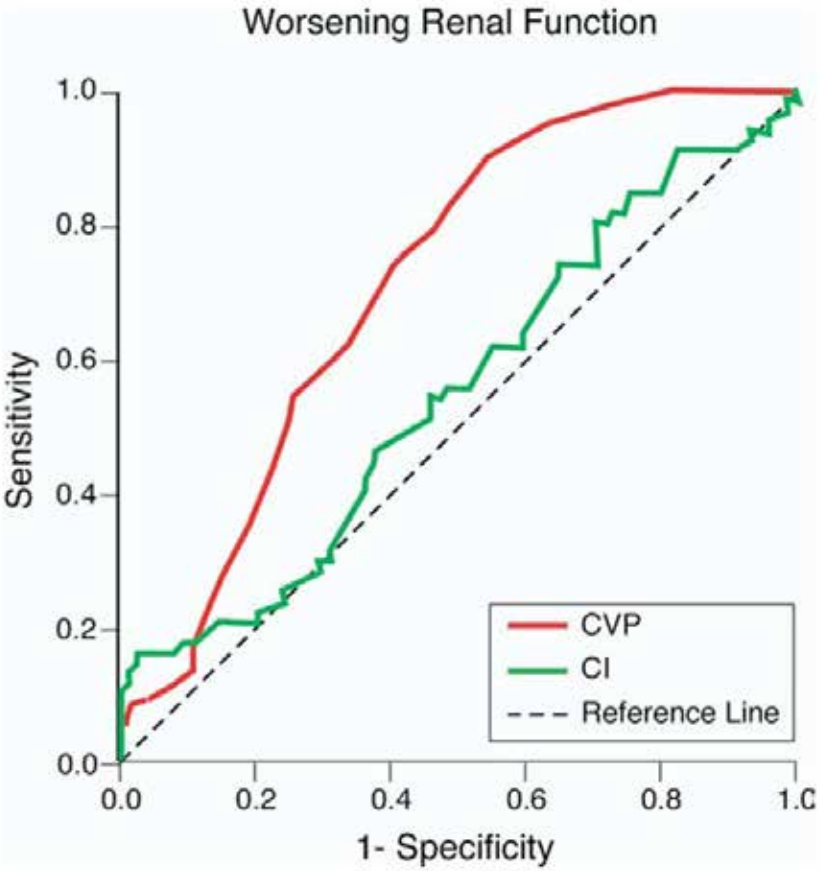


Figure 2 ROC Curves for CVP and CI on Admission for the Development of WRF

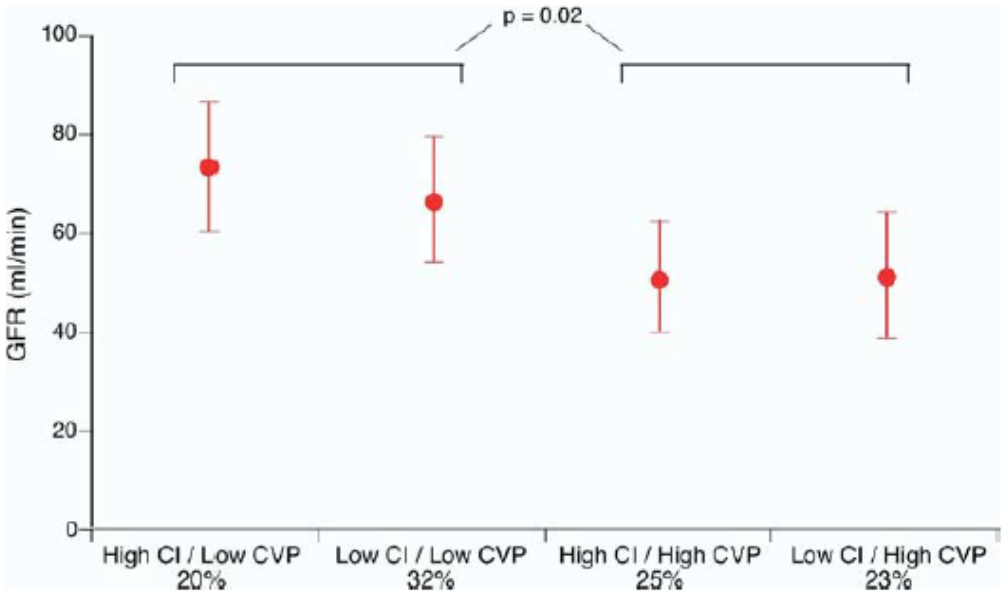


Figure 3 Relative Contributions of CVP and CI to GFR at Time of PAC Removal

Mullens, et al. J Am Coll Cardiol 2009

Φλεβική Συμφόρηση και eGFR

2,557 patients who underwent right heart catheterization (eGFR was 65±24 ml/min/1.73 m^2, cardiac index of 2.9 ± 0.8 l/min/m2 and CVP of 5.9 ± 4.3 mmHg)

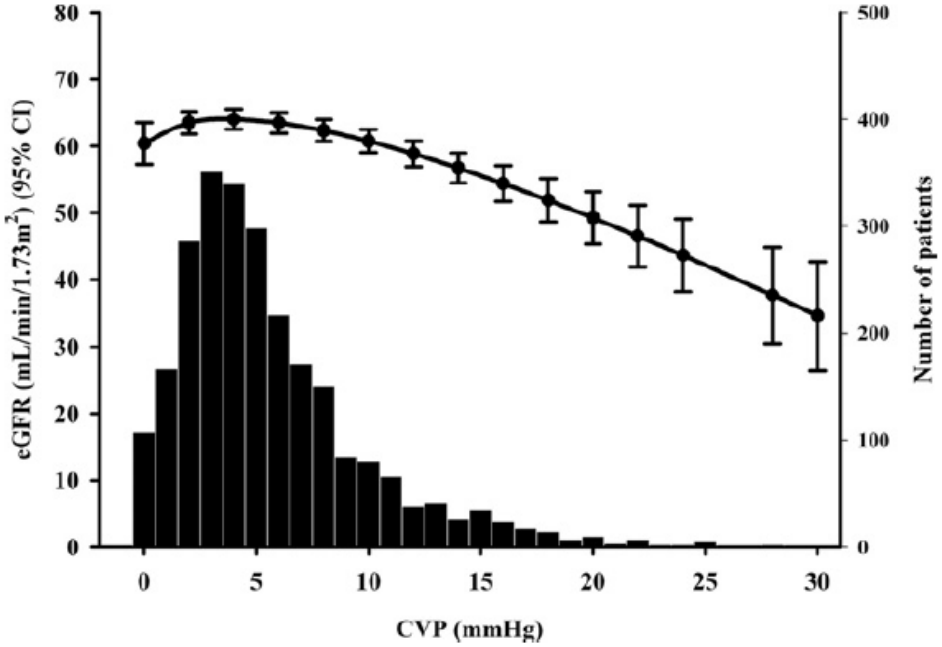


Figure 1 **Distribution of CVP and Curvilinear Relationship Between CVP and eGFR in the Study Population**

Adjusted for age, sex, and cardiac index. The curvilinear model had the following individual polynomial components for the relationship between CVP and eGFR: First order: $Y = -25.8 \cdot (CVP + 1)/10$ (Wald 28.2, $p < 0.0001$) and second order: $Y = 35.7 \cdot ([CVP + 1]/10)^{0.5}$ (Wald 17.4, $p < 0.0001$). CVP = central venous pressure, eGFR = estimated glomerular filtration rate.

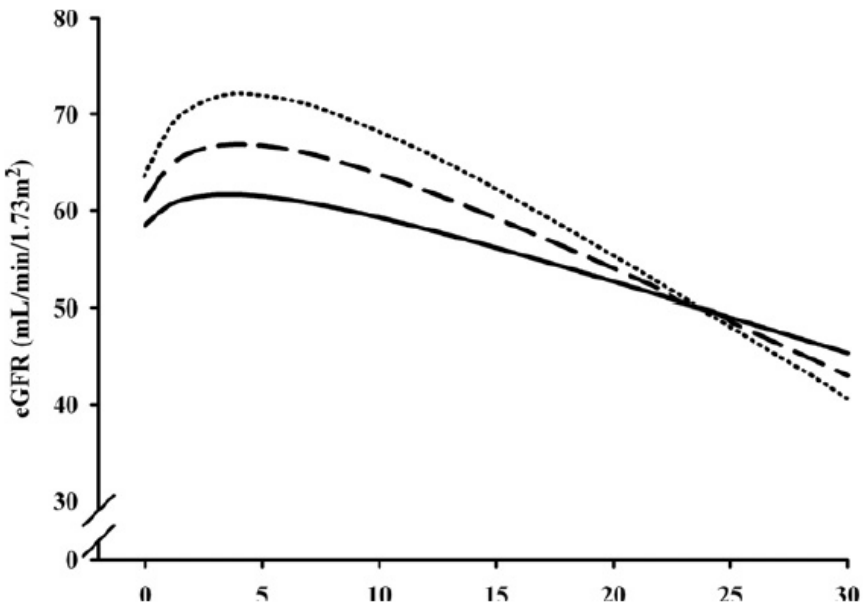
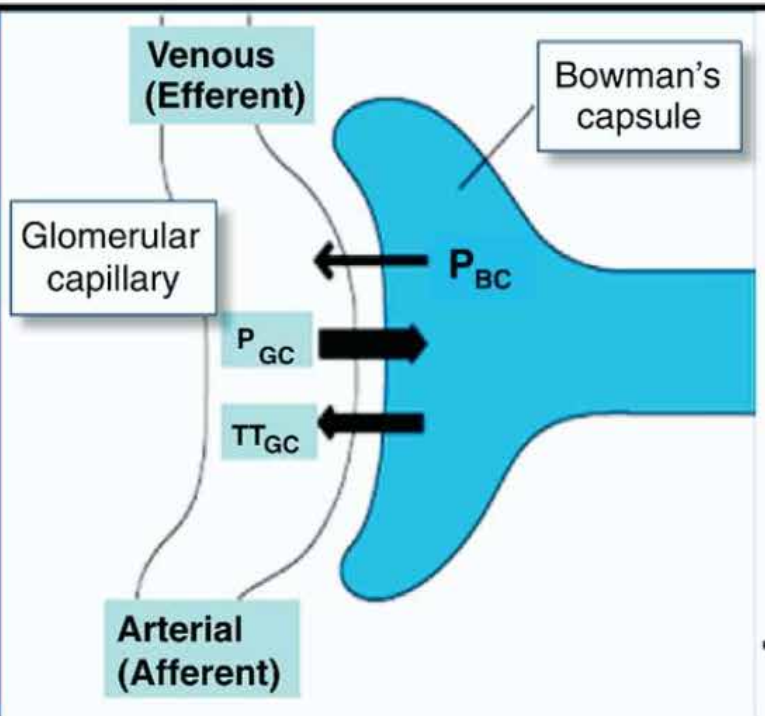


Figure 2 **Curvilinear Relationship Between CVP and eGFR According to Different Cardiac Index Values**

$p = 0.0217$ for interaction between cardiac index and CVP on the relationship with eGFR. **Solid line** = cardiac index <2.5 l/min/m^2; **dashed line** = cardiac index 2.5 to 3.2 l/min/m^2; **dotted line** = cardiac index >3.2 l/min/m^2. Abbreviations as in Figure 1.

Damman, et al. J Am Coll Cardiol 2009

Φλεβική Συμφόρηση και πίεση διήθησης



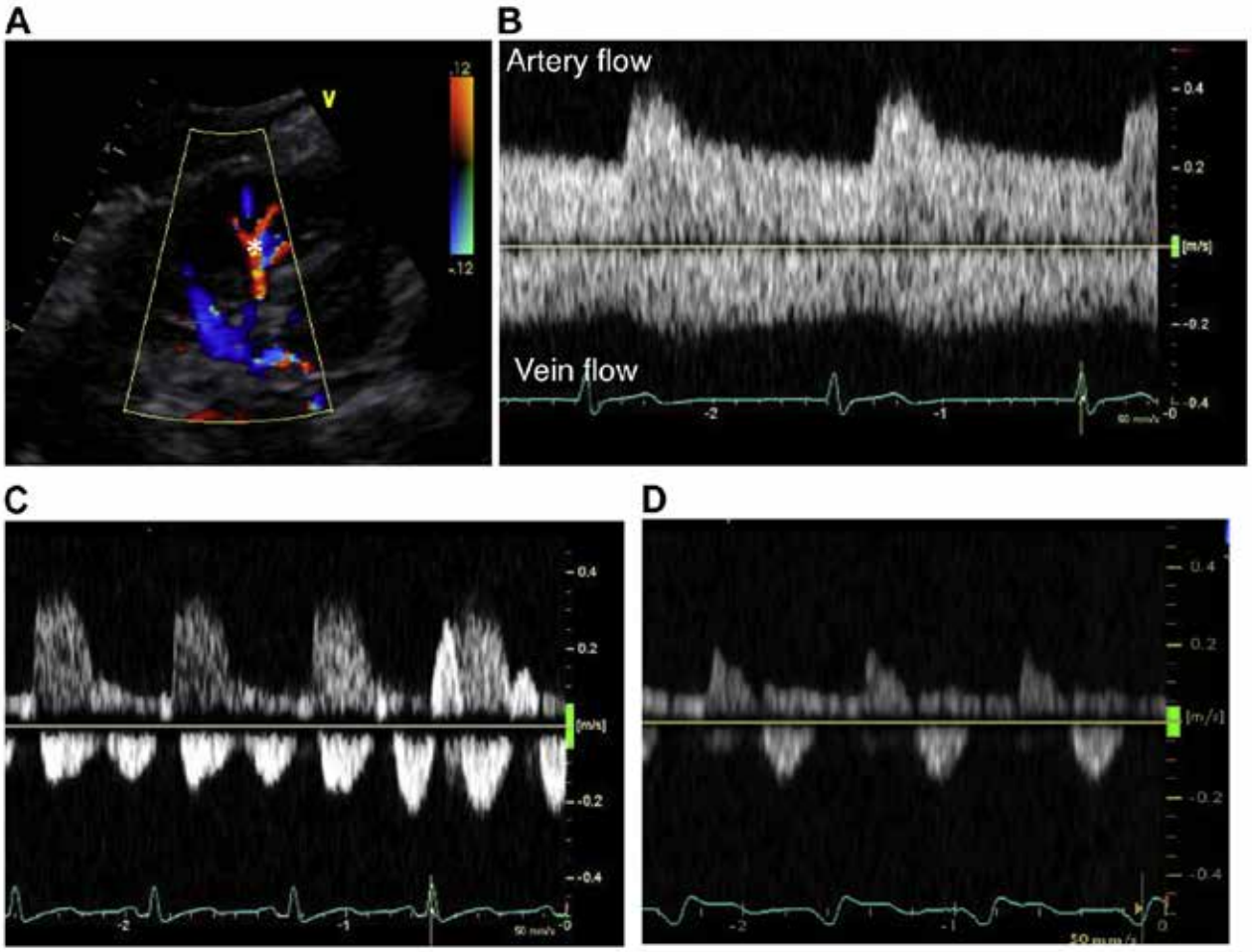
Forces	Normal: Afferent end of glomerular capillary (mmHg)	Normal: Efferent end of glomerular capillary (mmHg)	↑ RA pressure: Afferent end of glomerular capillary (mmHg)	↑ RA pressure: Efferent end of glomerular capillary (mmHg)
1. Favoring Filtration				
Glomerular-capillary hydrostatic pressure, P_{GC}	**60**	**58**	**55**	**63**
2. Opposing Filtration				
a. Hydrostatic pressure in Bowman's capsule, P_{BC}	**15**	**15**	**15**	**15**
b. Oncotic pressure in glomerular capillaries, π_{GC}	**21**	**33**	**21**	**33**
Net filtration pressure (1-2)	**24**	**10**	**19**	**15**
Filtration pressure:	*14 mmHg*		*4 mmHg*	

Figure 1 Impact of Venous Congestion on Glomerular Net Filtration Pressure

Jessup & Costanzo. J Am Coll Cardiol 2009

Φλεβική Συμφόρηση και Πρόγνωση ΚΑ

224 patients with HF were prospectively enrolled; IRD profiles of interlobar vessels assessing arterial resistance index (RI), venous impedance index (VII), and intrarenal venous flow (IRVF)

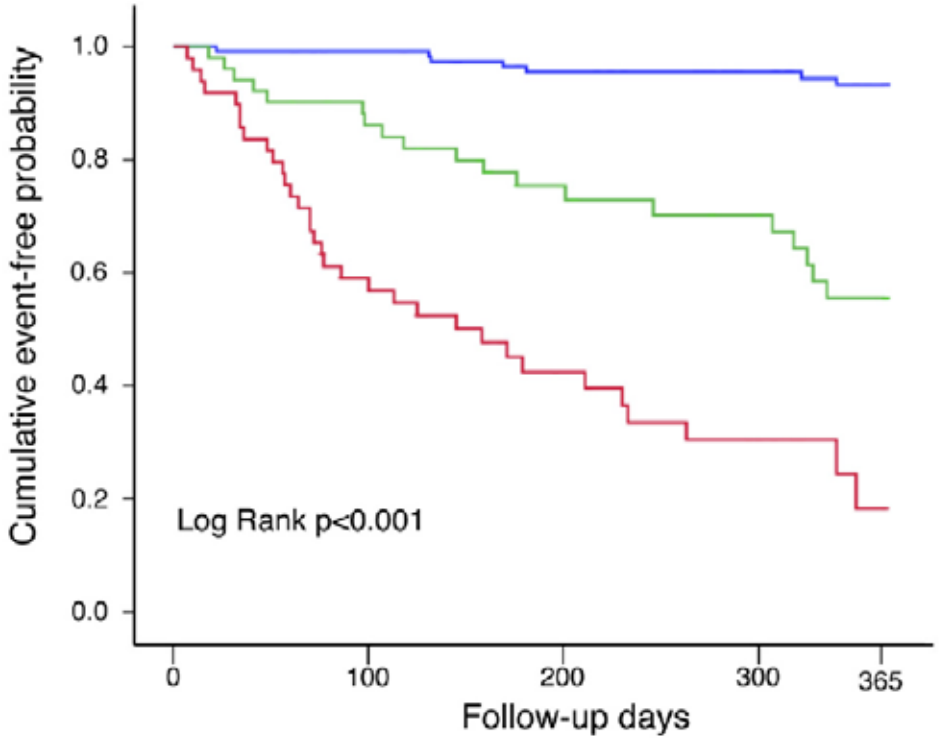


Color Doppler flow images from a right kidney. **(A)** *Doppler sample volume position in the interlobar vessels. Intrarenal artery flow (upward Doppler signals) and vein flow (downward Doppler signals) in **(B)** a continuous venous flow pattern, **(C)** a biphasic pattern, and **(D)** a monophasic pattern.

Iida, et al. J Am Coll Cardiol Heart Fail 2016

Φλεβική Συμφόρηση και Πρόγνωση ΚΑ

224 patients with HF were prospectively enrolled; IRD profiles of interlobar vessels assessing arterial resistance index (RI), venous impedance index (VII), and intrarenal venous flow (IRVF)



Number at risk					
Continuous flow	117	115	109	104	93
Biphasic flow	51	42	28	23	16
Monophasic flow	49	28	18	11	5

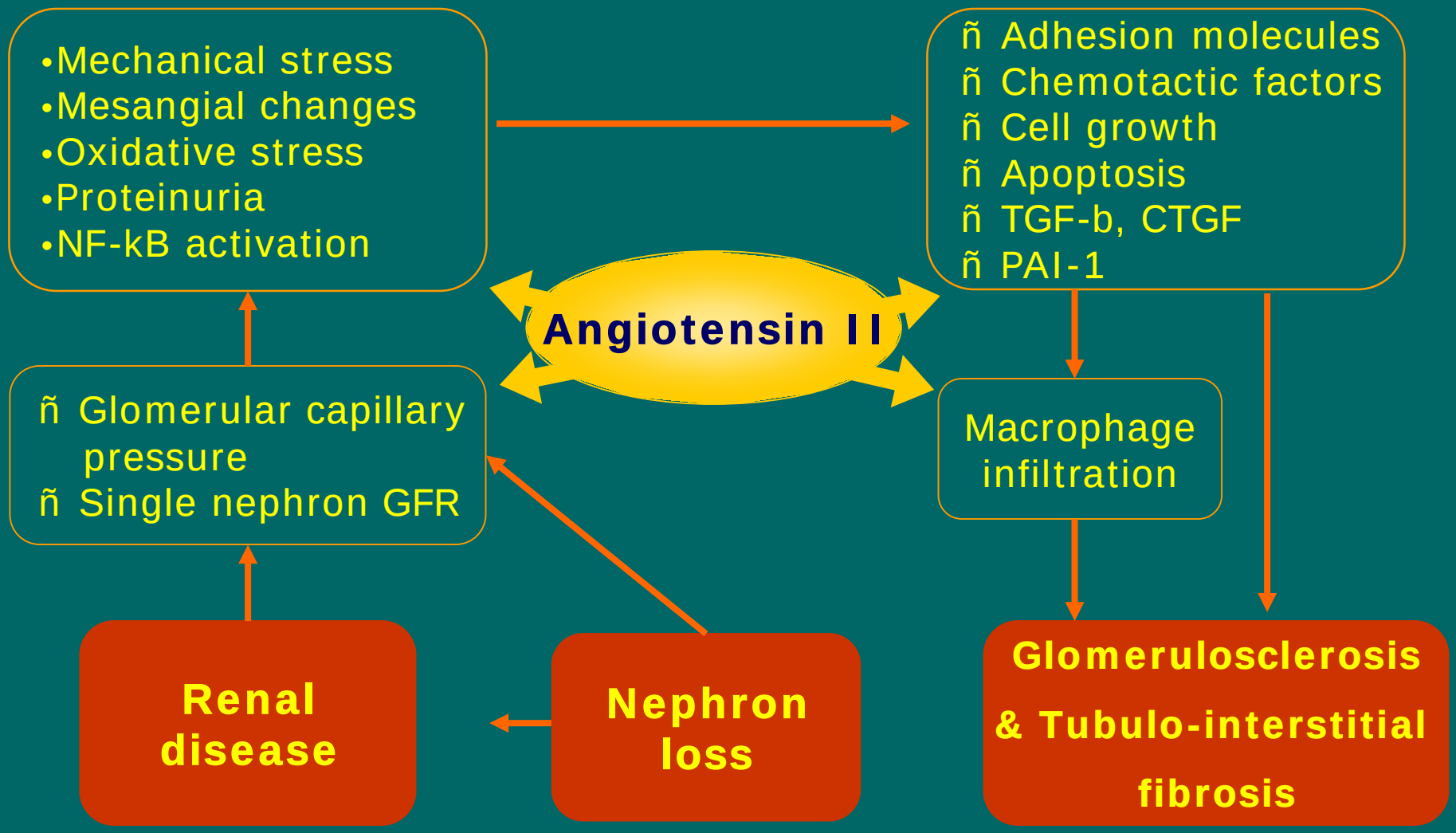
Kaplan-Meier curves at 1-year follow-up for the probability of freedom from death from cardiac causes and unplanned hospitalizations for heart failure of 3 classifications of intrarenal venous flow. IRVF = intrarenal venous flow.

Iida, et al. J Am Coll Cardiol Heart Fail 2016

Μηχανισμοί Νεφρικής Βλάβης στην ΚΑ

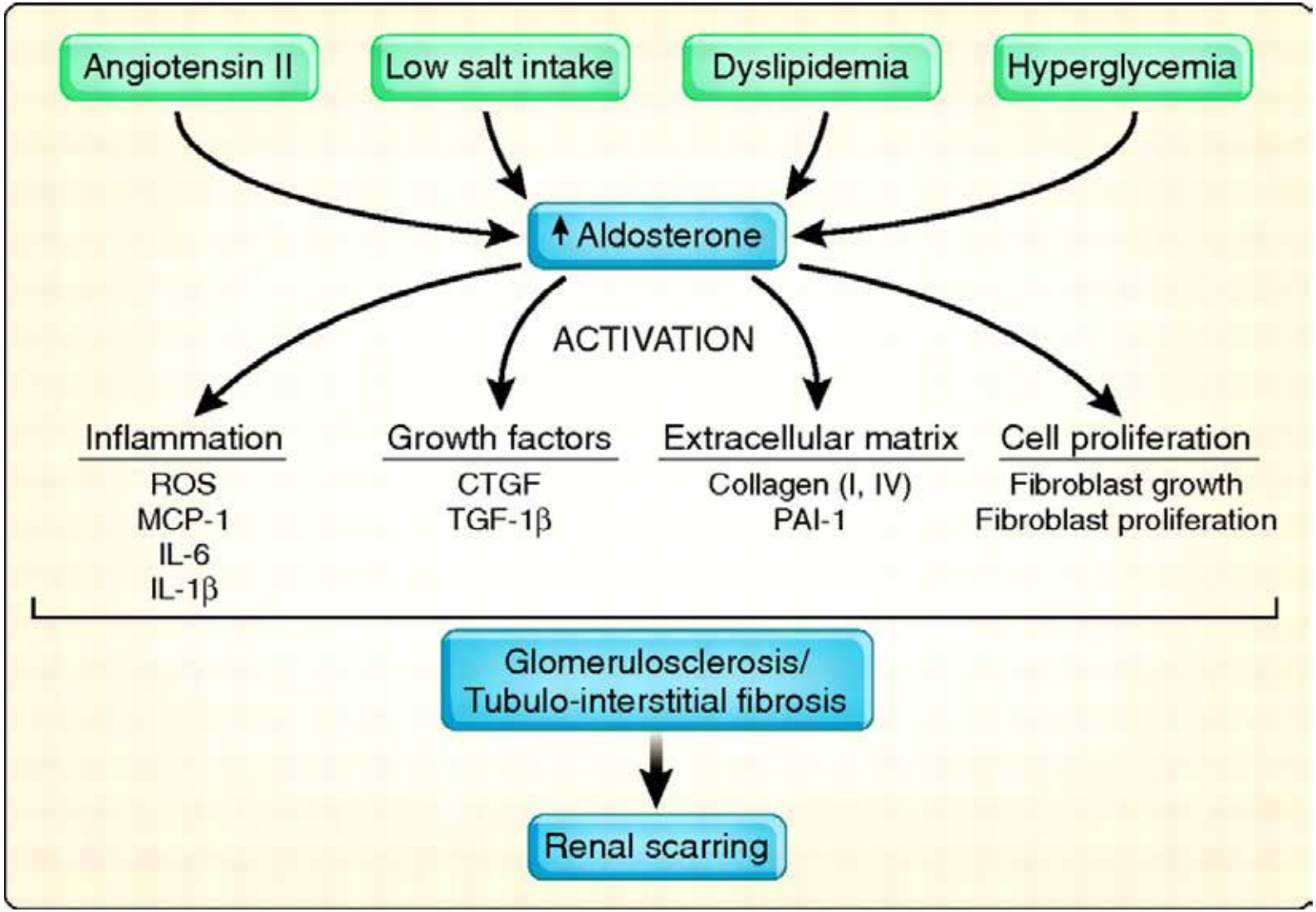
Νευροορμονική ενεργοποίηση

Ο ρόλος της AγγII στην εξέλιξη της ΧΝΝ



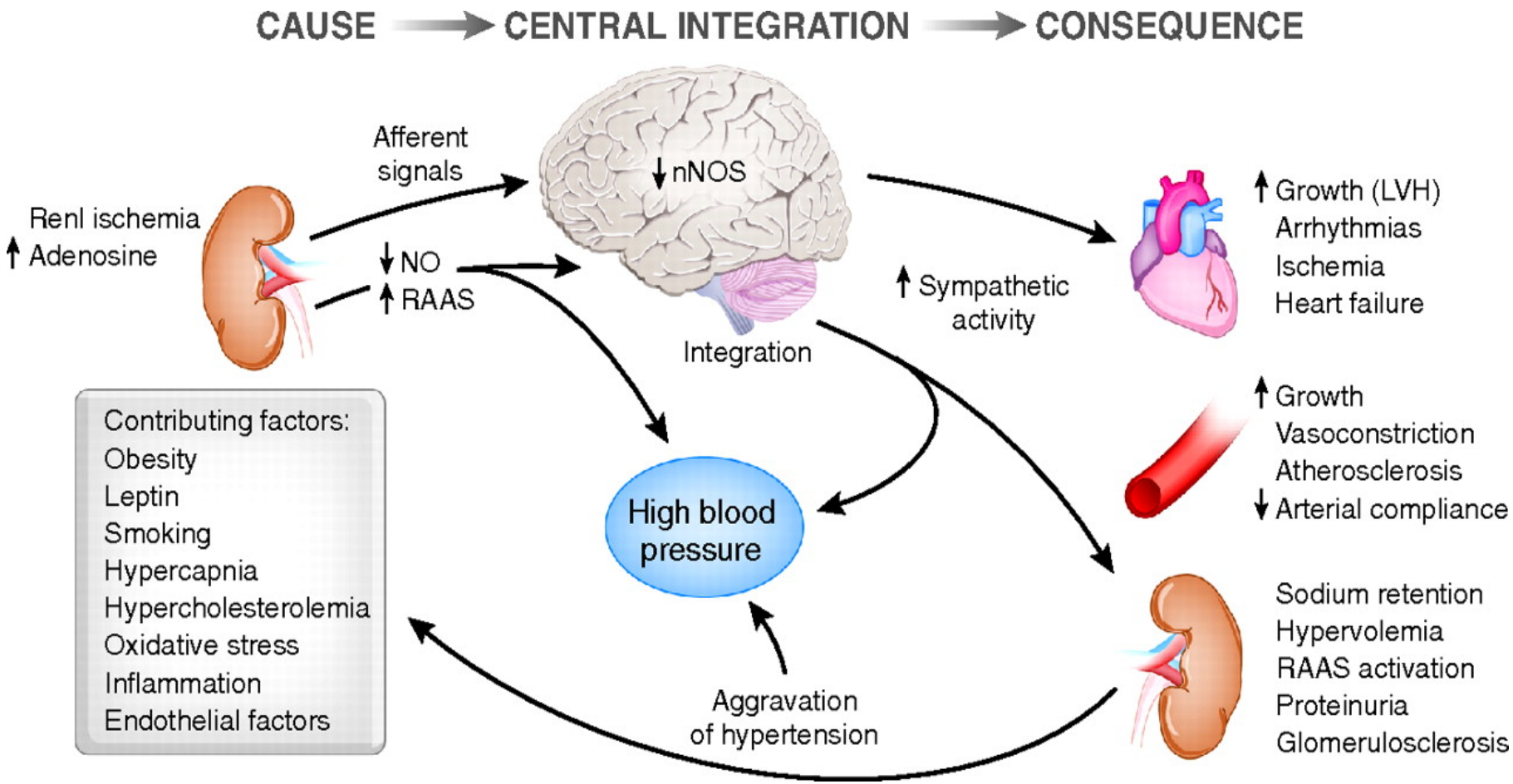
Adapted from Berk B. 2001.

Αλδοστερόνη και Νεφρική Βλάβη



Remuzzi et al. J Am Soc Nephrol 2008

ΣΝΣ και Νεφρική Βλάβη

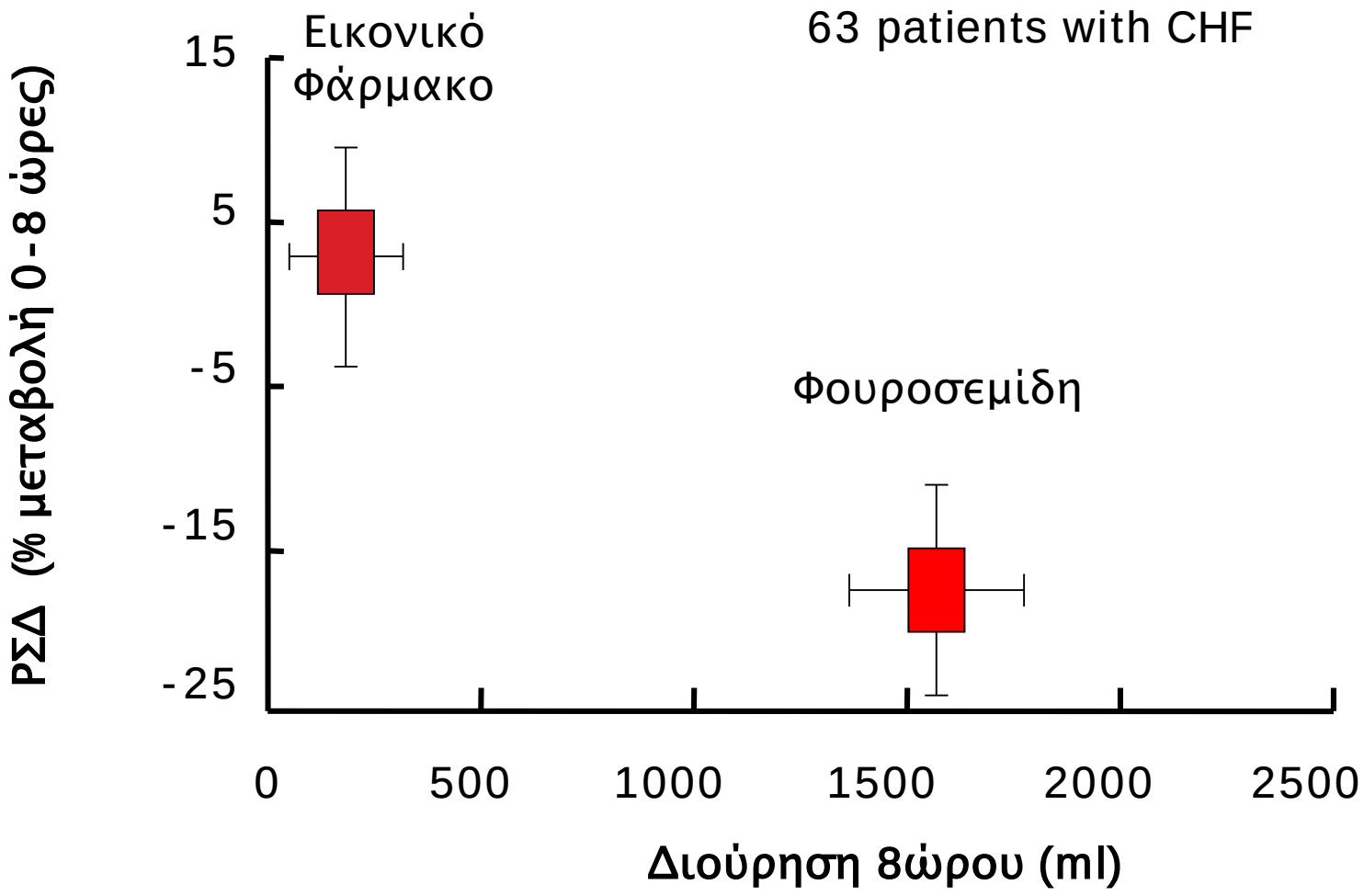


Schlaich et al. J Am Soc Nephrol 2009

Μηχανισμοί Νεφρικής Βλάβης στην ΚΑ

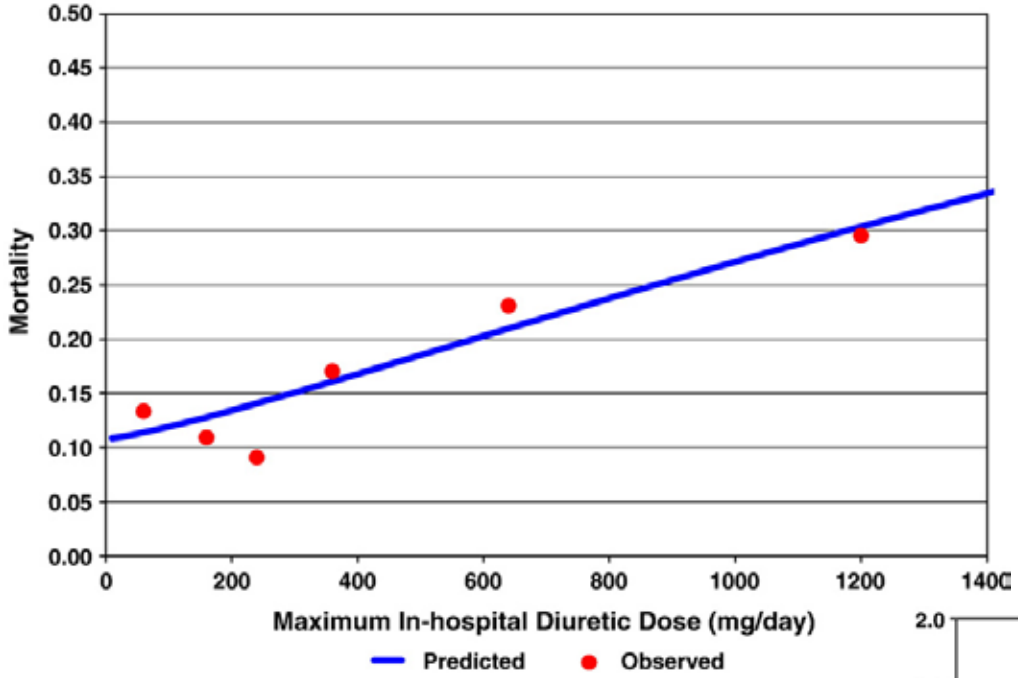
Τοξικότητα από Φάρμακα

Η φουροσεμίδη ελαττώνει το ρυθμό σπειραματικής διήθησης

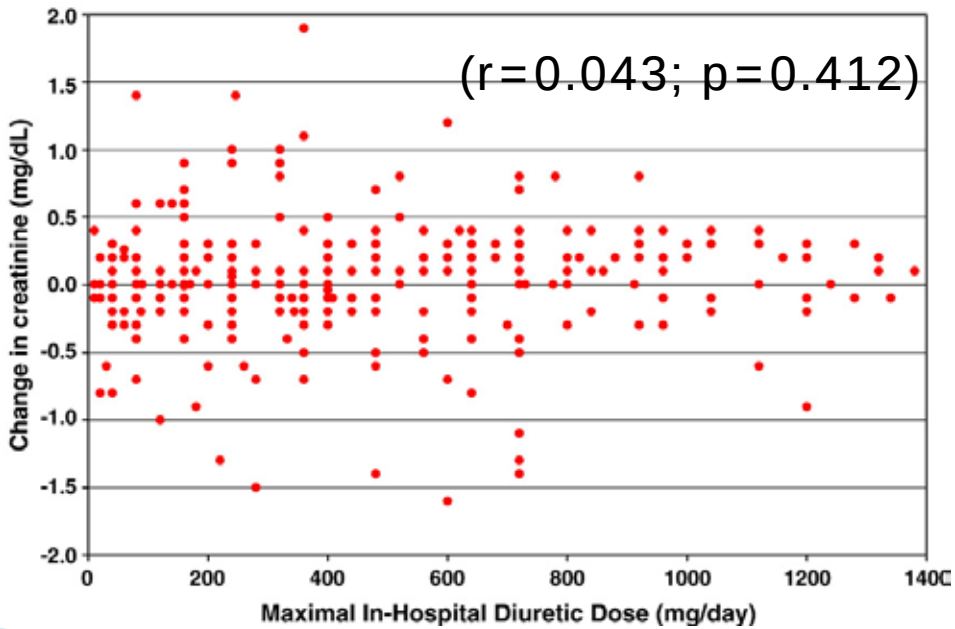


Gottlieb SS, et al. Circulation. 2002;105:1348-1353

Dose of loop diuretics and outcomes in HF

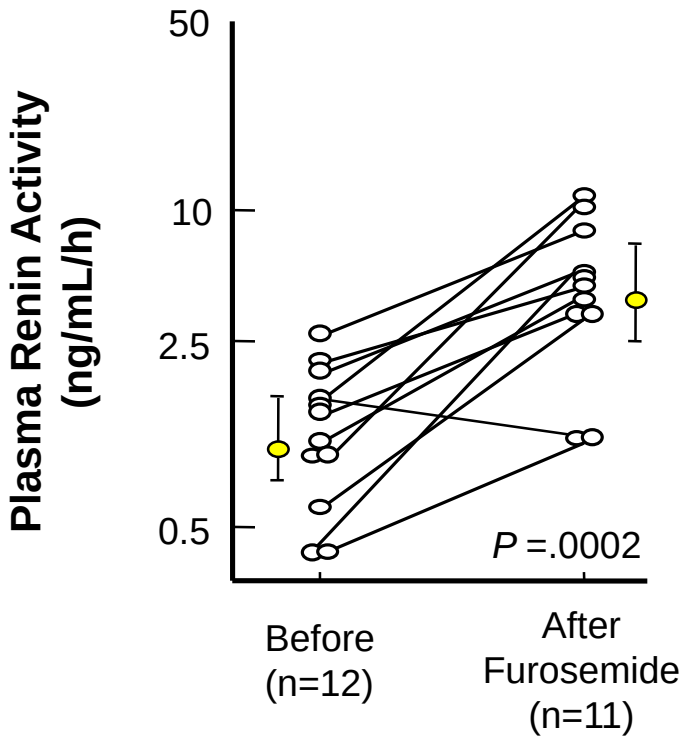


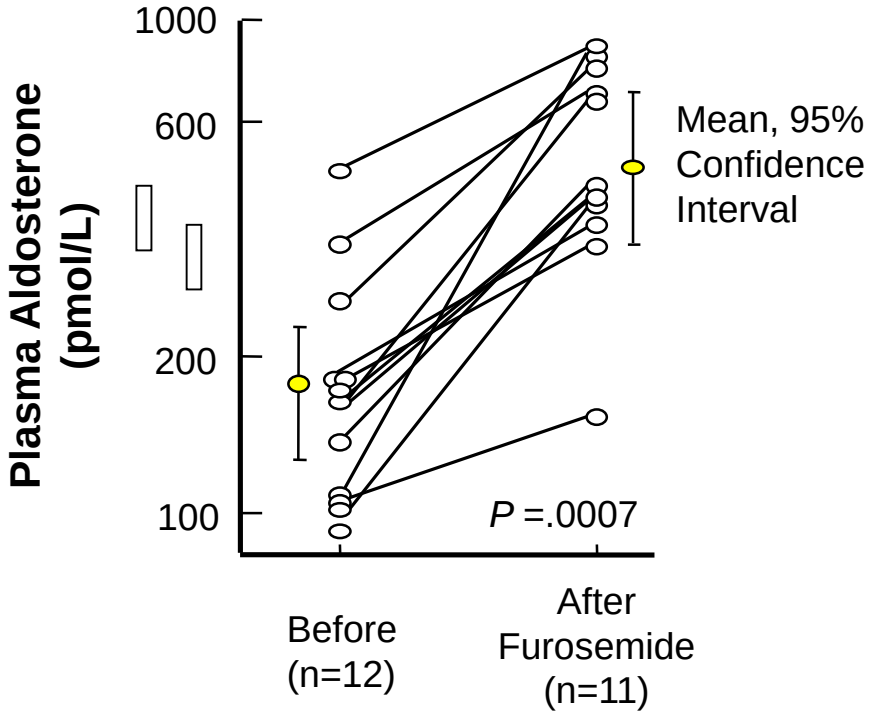
395 patients with HF that received diuretics



Hasselblad et al. Eur J Heart Fail 2007

Furosemide Activates Neurohormonal Systems in HF



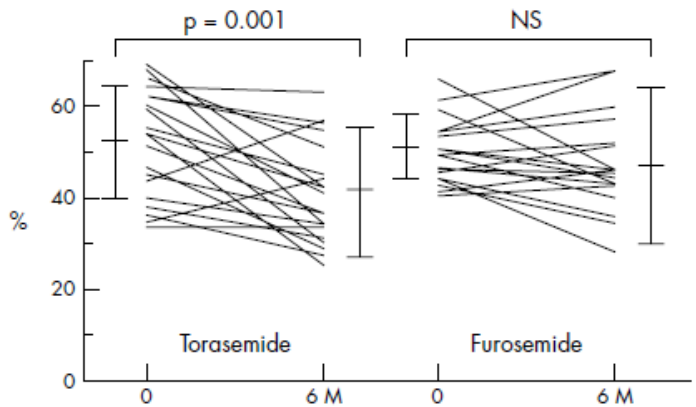


Bayliss et al. Br Heart J. 1987;57:17

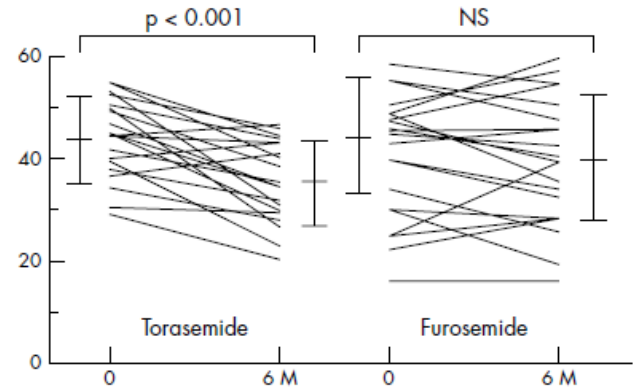
Effects of Torasemide vs. Furosemide on Cardiac Sympathetic Nerve Activity in CHF: ^{123}I-MIBG imaging

N=40 patients with non-ischaemic CHF, LVEF <45%, randomly assigned to:
A. **Torasemide** (4–8 mg/day; N=20) or B. **Furosemide** (20–40 mg/day; N=20)

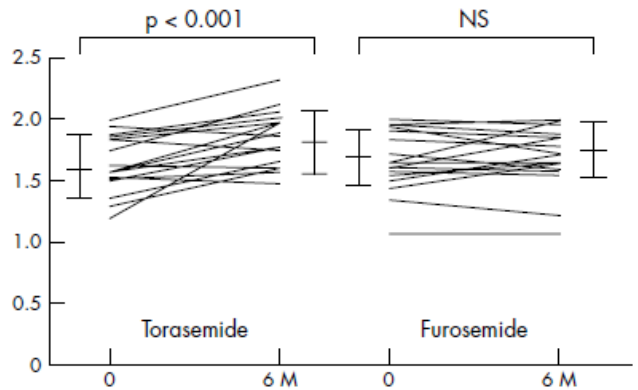
Washout rate (WR)



Total defect score (TDS)



Heart to mediastinum count (H/M)



Kasama, et al. Heart 2006;92:1434–1440

Nesiritide and Worsening Renal Function in ADHF

	Events, n/N (%)			
	Nesiritide	Control	RR_{MH} (95% CI)	*P*
Nesiritide ≤0.03 vs non-inotrope based controls	134/610 (22)	60/389 (15)	1.52 (1.16–2.00)	0.003
Nesiritide ≤0.03 vs all control therapies, including inotropes	163/772 (21)	69/472 (15)	1.54 (1.19–1.98)	0.001
Nesiritide ≤0.015 vs non-inotrope based controls	100/442 (23)	60/389 (15)	1.46 (1.09–1.95)	0.012
Nesiritide ≤0.015 vs all control therapies, including inotropes	99/464 (21)	69/472 (15)	1.47 (1.12–1.93)	0.006
Nesiritide ≤0.06 vs non-inotrope based controls	140/635 (22)	60/389 (15)	1.53 (1.16–2.00)	0.002
Nesiritide ≤0.06 vs all control therapies, including inotropes	169/797 (21)	69/472 (15)	1.54 (1.20–1.99)	0.001

Nesiritide doses refer to infusion rates ($\mu g \cdot kg^{-1} \cdot min^{-1}$) that followed bolus administration.

Sackner-Bernstein, et al. Circulation 2005

Φάρμακα για «άλλες» ενδείξεις

- **Metformin** (lactic acidosis and worsening heart function due to a negative inotropic effect).
- **Iodinated contrast** (transient vasoconstriction & direct tubular toxicity)
- **Antibiotics** (acute tubular necrosis, acute interstitial nephritis)
- **Chemotherapeutic agents** (acute tubular necrosis, acute interstitial nephritis, tumor lysis syndrome)

Ronco et al. J Am Coll Cardiol 2012

Μηχανισμοί Νεφρικής Βλάβης στην ΚΑ

Φλεγμονή και οξειδωτικό στρες

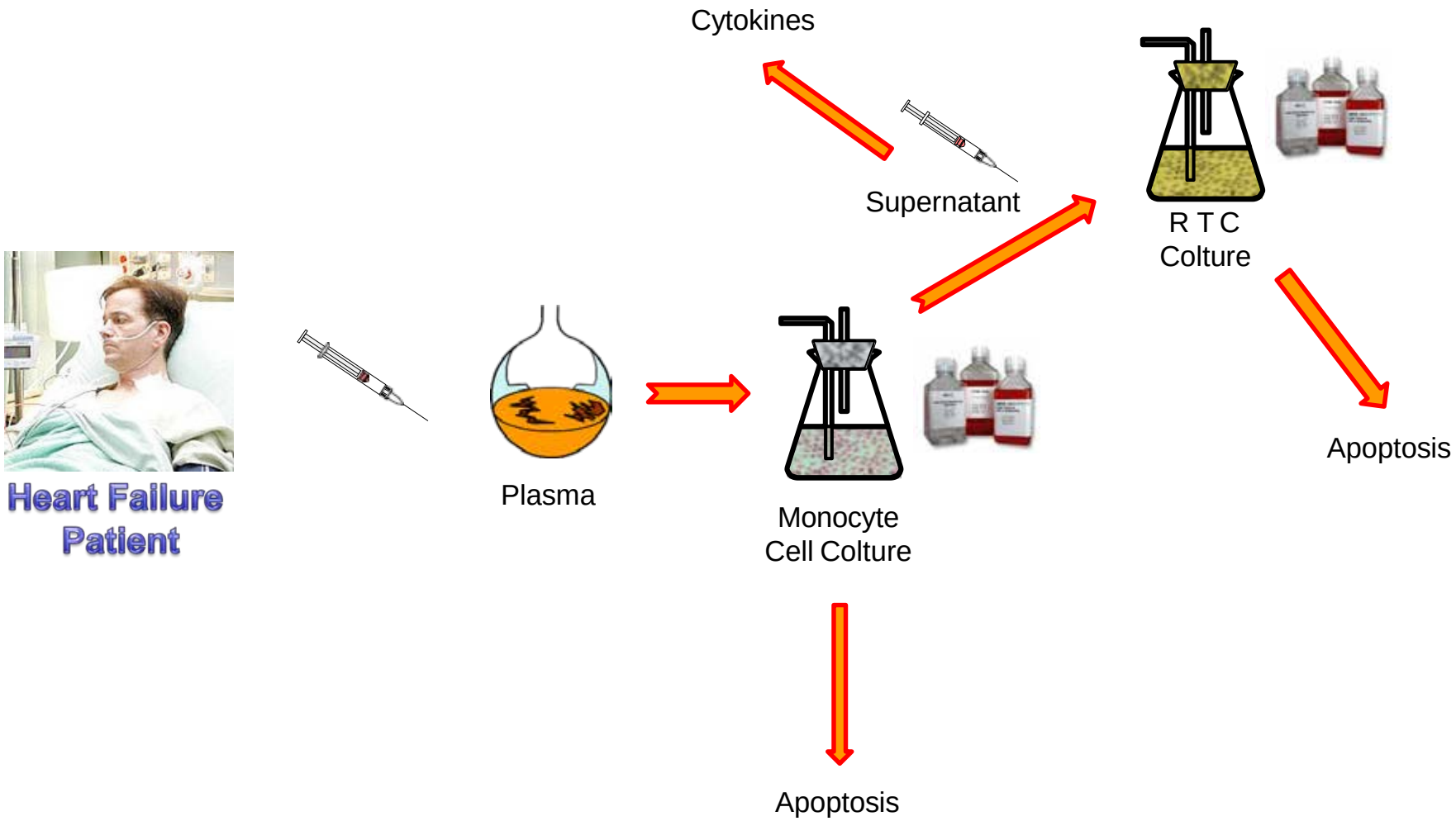
ΚΑ, Φλεγμονή και Νεφρική Βλάβη

- Patients with ADHF have excessive increase of proinflammatory cytokines and proapoptotic factors show and defective regulation of monocyte apoptosis
- Renal tubular epithelium is particularly vulnerable to ischemic injury resulting in cell death by apoptosis and necrosis
- During AKI with strong association between intra-renal inflammatory activity and renal cell apoptosis.
- Inflammation increases capillary permeability (pulmonary fluid overload, inadequate renal perfusion pressures, peritubular edema etc.)

Ronco et al. J Am Coll Cardiol 2012
Di Lullo et al. Ind Heart Journal 2017

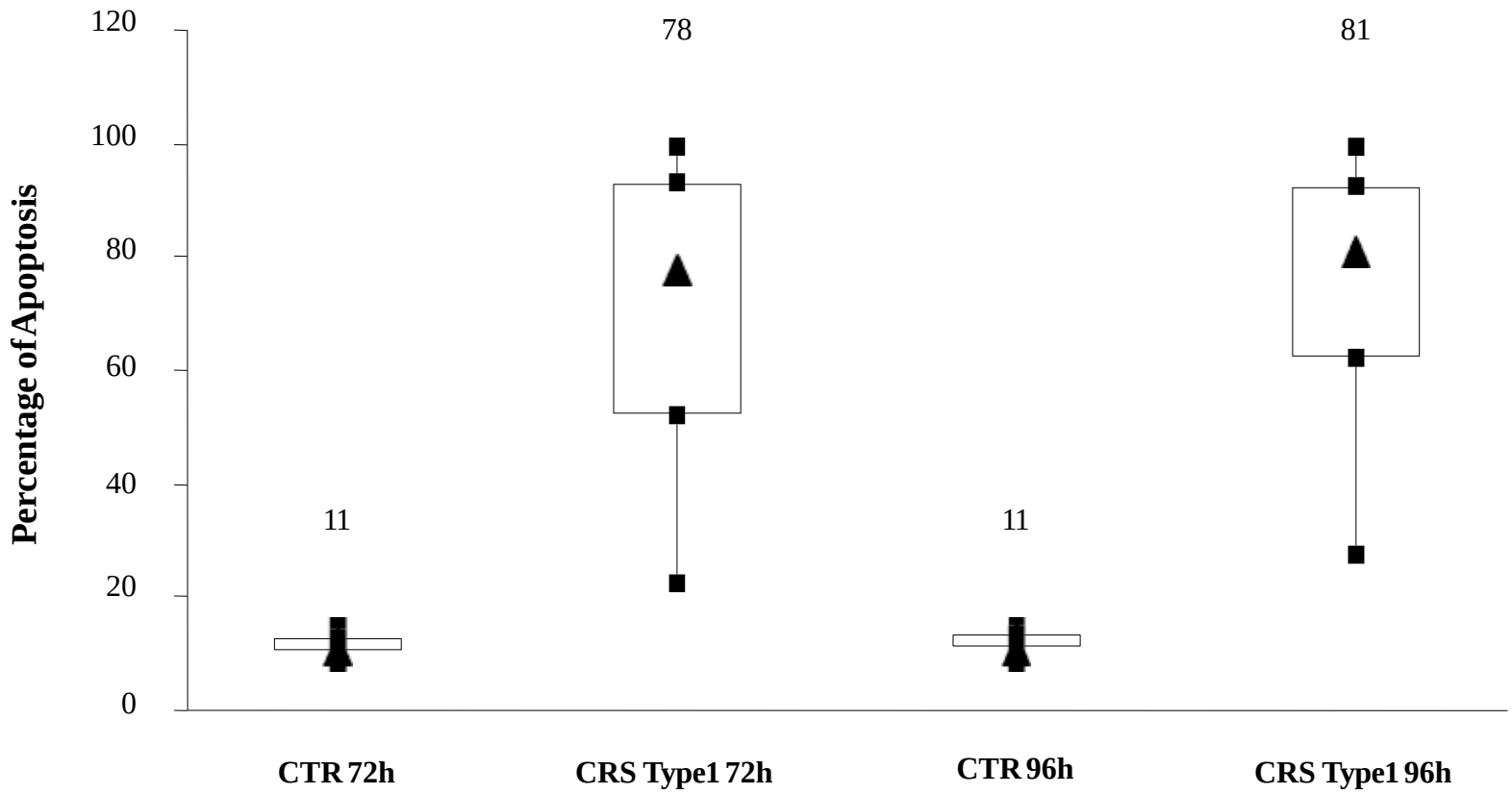
Cardio-Renal Syndrome Type 1

Inflammation/humoral theory



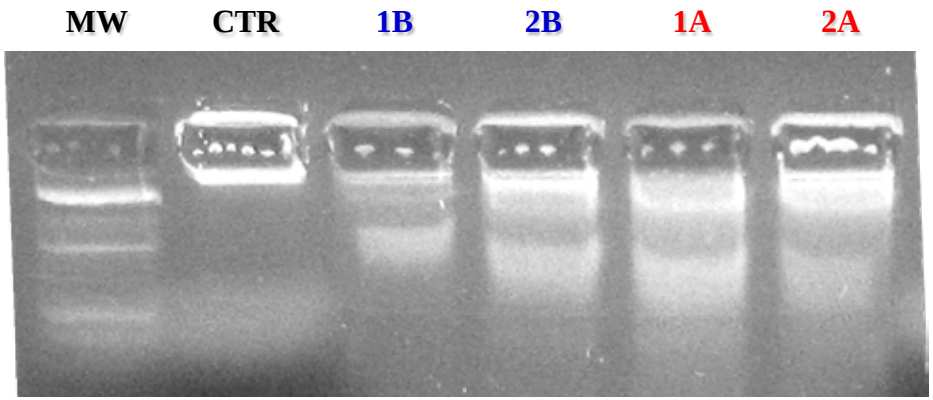
APOPTOSIS STUDY IN CRS T.1 and CONTROLS

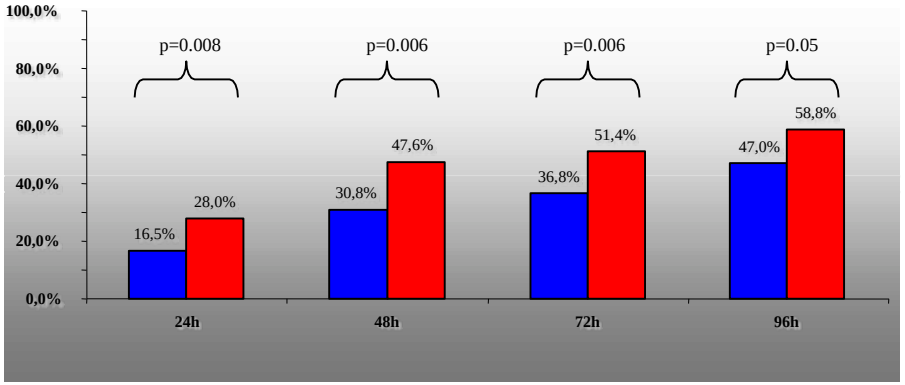
Evaluation of percentage of apoptosis in U937 cells after incubation with plasma from CRS Type 1 patients and healthy volunteers for 72h and 96h



APOPTOSIS STUDY IN HEART FAILURE

Evaluation of percentage of apoptosis in U937 cells after incubation with plasma from Heart Failure Patients developing CRS Type 1 (HF/AKI) or not (HF/No AKI)





HF/No AKI n.6

HF/AKI n.6

ΚΑ, Οξειδωτικό στρες και Νεφρική Βλάβη

- Oxidative stress is a final common pathway for cellular dysfunction, tissue injury, and organ failure.
- In type 1 CRS there is increase in circulating reactive oxygen species (ROS) and reactive nitrogen species (RNS), increased levels of NADPH oxidase and myeloperoxidase
- These enzymes promote hydrogen peroxide (H_2O_2) conversion into nitrogen dioxide (NO_2) and other species, leading to oxidative damage of several critical molecules implicated in the pathogenesis of AKI and CKD

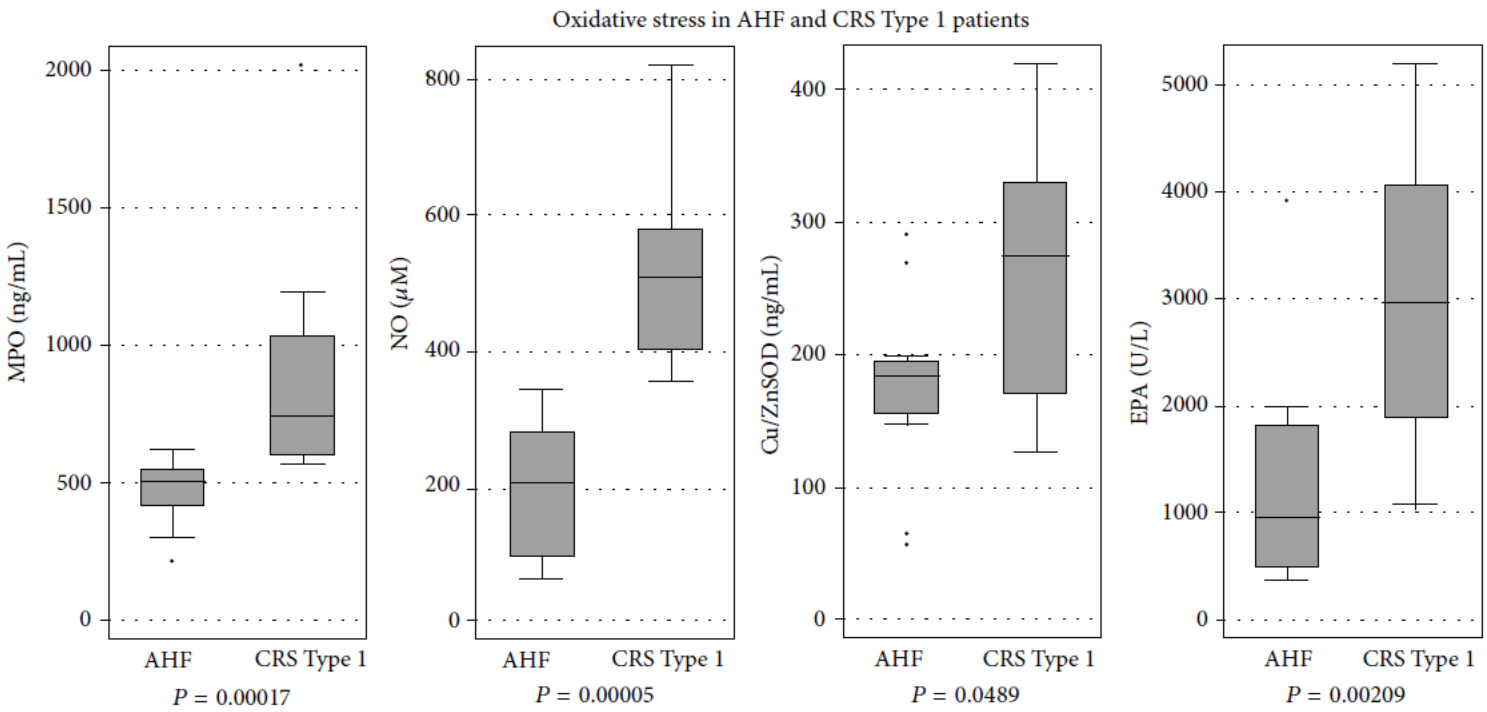
Ronco et al. J Am Coll Cardiol 2012
Di Lullo et al. Ind Heart Journal 2017

ΚΑ, Οξειδωτικό στρες και Νεφρική Βλάβη

Table 3: Oxidative stress and IL-6 levels in AHF, CRS Type 1 patients, and CTR.

	AHF	CRS Type 1	CTR	*P* value
MPO, pg/mL	505.6 (421.7–547.8)	746.9 (665.2–940.0)	10.1 (6.0–19.3)	<0.01
NO, μM	205.6 (95.0–277.5)	507.3 (404.7–557.3)	9.5 (6.1–12.2)	<0.01
Cu/ZnSOD, pg/mL	184.5 (160.5–192.0)	274.5 (191.8–326.8)	58.9 (51.7–70.9)	<0.01
EPA, U/L	274.5 (191.8–326.8)	2978.4 (2071.8–4069.9)	2.0 (0.9–3.9)	<0.01
IL-6, pg/mL	22.19 (16.6–24.6)	90.68 (59.9–105.3)	5.9 (3.4–7.6)	<0.01

Values denote medians (IQR).



Virzi et al. Oxid Med Cell Longevity 2015

Μηχανισμοί Νεφρικής Βλάβης στην ΚΑ

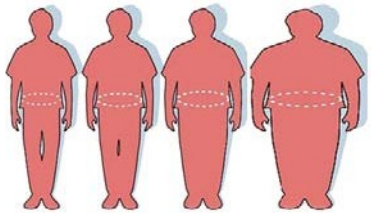
Άλλοι Παράγοντες

Παχυσαρκία και Καρδιονεφρικό Σύνδρομο

Diabetes

Sleep Apnea

Heart Disease

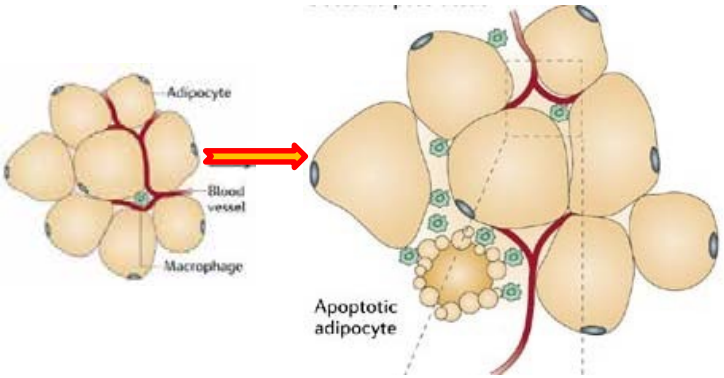


G.I. Tract Disorders

Kidney Disease

Obesity

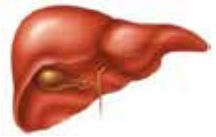
High Blood Pressure



Lean adipose tissue

Obese adipose tissue

TNF-a
IL-6



Inflammation
CRP

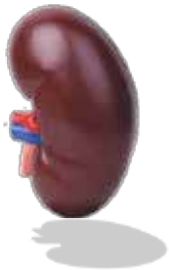
Coronary artery disease
Cardiac remodelling
LVH-Dilatation

F F A

Atherosclerosis

Crosstalk

Apoptosis

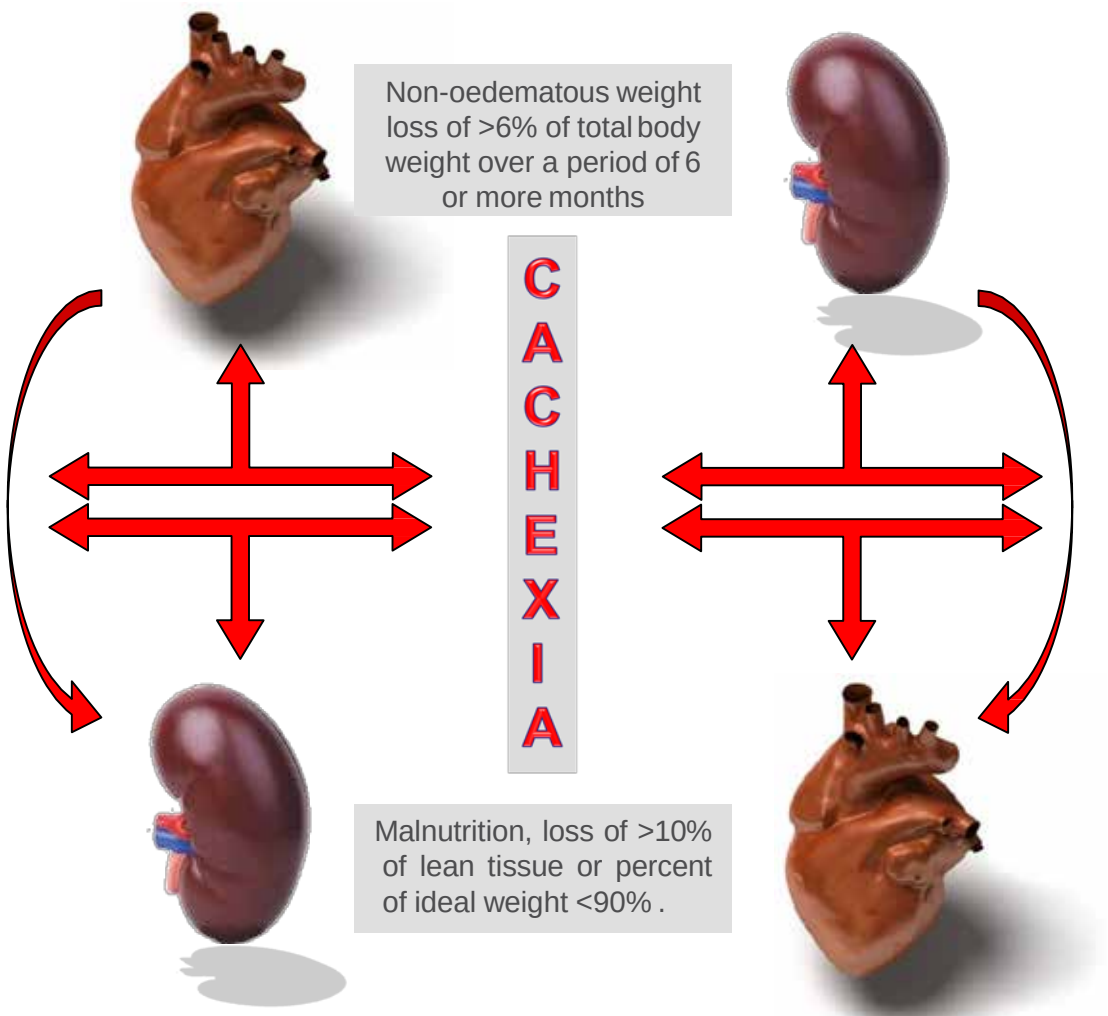


Chronic ischemia
CKD
Fibrosis-sclerosis

Leptin
Resistin
Adiponectin

Dysmetabolic syndrome

Καχεξία και Καρδιονεφρικό Σύνδρομο



CRS TYPES 1- 2

Low Cardiac output
Na and fluid overload
Chronic hypoperfusion
Embolism
Venous Congestion
Chronic inflammation
Cardiac Remodeling
Endothelial Dysfunction
Acceler. Atherosclerosis

CRS TYPES 3- 4

Na and fluid overload
Chronic inflammation
Uremic Toxins
Malnutrition
Anemia
EPO resistance
pH abnormalities
Ca-P abmormalities
Lack of VDR activation
Soft Tissue calcifications

CKD Progression, Apoptosis
Necrosis, Fibrosis, Sclerosis

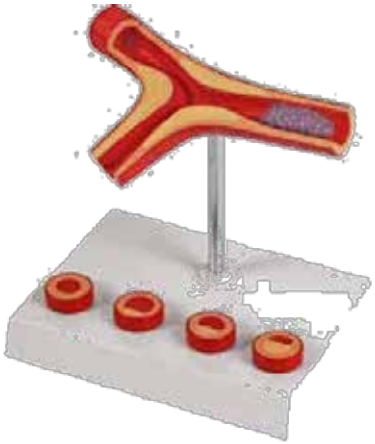
Heart Failure, Systolic/diastolic
dysfunction, Myoc.Remodelling

Anemia and Iron deficiency

AKI

CKD

Reduced Blood Viscosity
Decreased Oxygen Delivery
Increased Sympathetic Activity
Hyperdynamic circulation

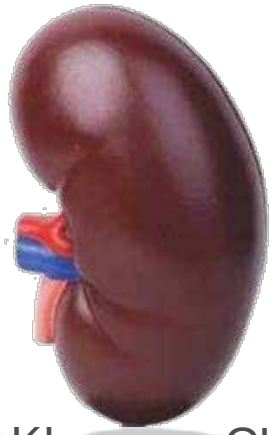


Ý **Cardiac Work**
Ý **Cardiac Output**

Ý Arterial diameter and volume

Ý Arterial wall tension

Eccentric remodelling of the arterial system



Ý Left ventricle hypertrophy

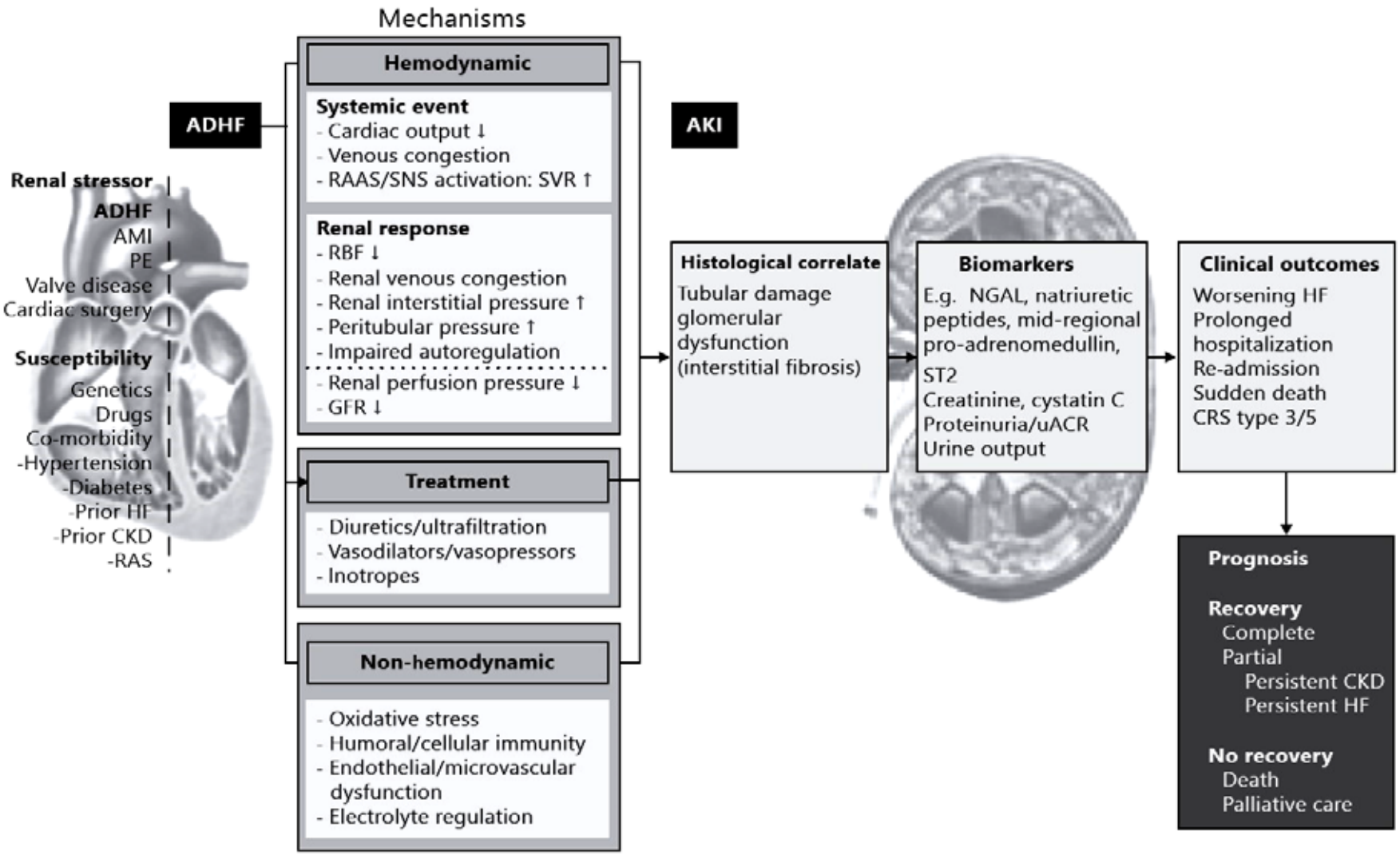
Ý Left Ventricle wall tension

Left ventricle eccentric remodelling

AKI

CKD

Μηχανισμοί Νεφρικής Βλάβης στην ΚΑ
Συμπεράσματα



Haase M, et.al. Contrib Nephrol 2013

Ευχαριστώ !