Cardiorenal Syndrome

a famous unknown cluster

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Overview

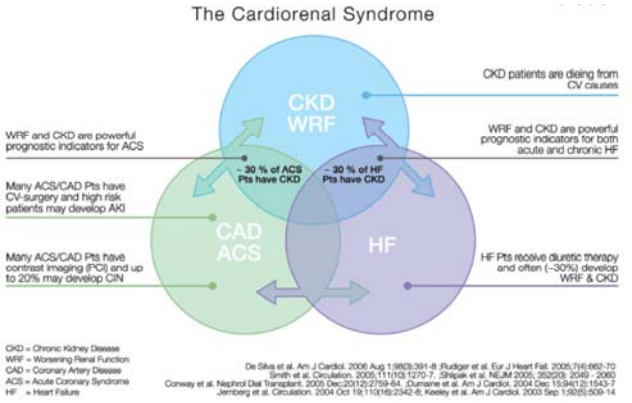
- Introduction
- Risk factors of CVD: Role of CKD
- CRS syndrome
  - Classification: definition and pathophysiology
  - Biomarkers – current and future
  - Preventive approaches
- Conclusions

CVD – cardiovascular disease, CKD – chronickidney disease, CRS – cardiorenal syndrome

Introduction

- The heart – kidney interaction is far more complex and intricate than that of a simple pump and filter
- Epidemiological data have demonstrated a close relationship between cardiorenal disease and clinical outcome

Nephrol Dial Transplant 2011; 26: 62–74



Nephrol Dial Transplant 2011; 26: 62–74

Introduction

- Chronic kidney disease (CKD) has remained largely a 'silent' epidemic
  - May be regarded as a clinical model of accelerated vascular disease and premature ageing, and
  - Risk-factor profile changes during the progression from mild/moderate CKD to ESRD

ESRD – End stage renal disease

J Intern Med 2010; 268: 456–467.

Introduction

- Cardiovascular disease remains the major cause of mortality and morbidity in patients with advanced CKD
  - The mechanisms for cardiotoxicity are multiple
  - Identifying high-risk patients remains a challenge

J Ren Care. 2010 May;36 Suppl 1:68-75

Introduction

- Given, the poor long-term outcome of dialysis patients who do not receive renal transplantation and the lower supply of donor kidneys relative to demand, optimal selection of renal transplantation candidates is crucial
  - This requires a clear understanding of the validity of cardiac tests in this patient group

J Ren Care. 2010 May;36 Suppl 1:68-75

Introduction

- Premature cardiovascular disease (CVD), including
  - stroke
  - peripheral vascular disease
  - sudden death
  - coronary artery disease and
  - congestive heart failure is

  a notorious problem in patients with chronic kidney disease

Clin J Am Soc Nephrol 2008;3: 505-521.

Introduction

- As recent data shows that CVD is independently associated with kidney function decline, it could be concluded that
  - The relationship between CKD and CVD is reciprocal or bidirectional and that this
  - Association leads to a vicious circle

Clin J Am Soc Nephrol 2008;3: 505-521.

Cardiovascular Risk Factors in CKD—A Complicated Puzzle with Many Pieces

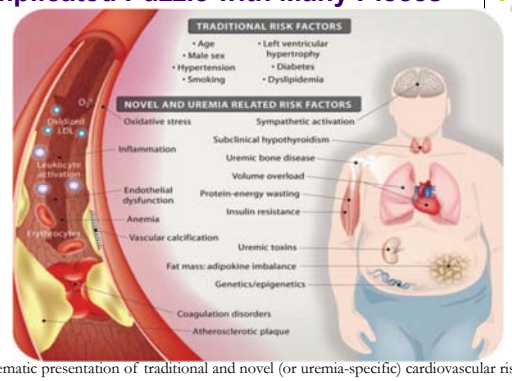


Figure . Schematic presentation of traditional and novel (or uremia-specific) cardiovascular risk factors in chronic kidney disease. *Clin J Am Soc Nephrol* 2008;3: 505-521.

List of cardiovascular risk factors in CKD (proven or hypothesized)

	Biochemical Risk Markers
Traditional risk factors	
Age	–
Male gender	–
Hypertension	–
Left ventricular hypertrophy	–
Smoking	–
Diabetes mellitus	HbA1c [52], glucose [53]
Dyslipidemia	Cholesterol [28], Lp(a) [189]

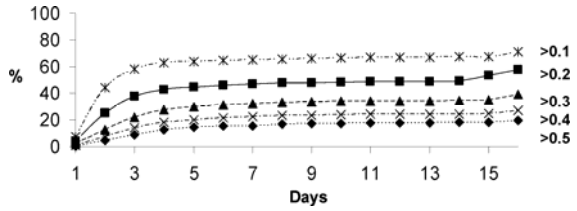
HbA1c, glycated hemoglobin; Lp(a), lipoprotein(a);

Clin J Am Soc Nephrol 2008;3: 505-521.

Novel risk and/or uremia-related risk factors	
Inflammation	IL-6 [37], IL-18 [38], S-albumin [39], WBC [40], fibrinogen [41], hyaluronan [42], MPO [43], CRP [44], PTX3 [45]
Oxidative stress	MPO [43], plasmalogens [127], oxLDL [125], AOPP [126]
Endothelial dysfunction	PTX3 [45], ADMA [79], tHcys [47], U-albumin [87], VCAM [97]
Protein-energy wasting	S-albumin [39], S-creatinine [39], prealbumin [50]
Sympathetic activation	Norepinephrine [51]
Coagulation/fibrinolysis disorders	Fibrinogen [41]
Insulin resistance	HOMA [54]
Genetics/epigenetics	SNPs [188], telomere attrition [190], DNA-methylation [198]
Vascular calcification	PO_4 [147], Ca [148], PTH [148], fetuin-A [156], OPG [162], OPN [163]
Classical uremic toxins	S-creatinine [39], P-cresol [76]
New uremic toxins	Proteomics [183]
Volume	NT-pro-BNP [48], troponin-T [49]
Subclinical hypothyroidism	fT3 [172], T3 [174]
Adipokines	Leptin [58], visfatin [59], adiponectin [66]
Anemia	Hemoglobin [55]

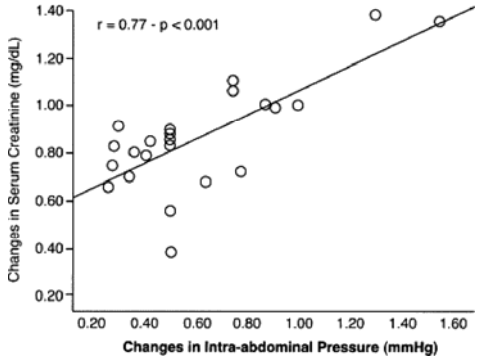
IL, interleukin; WBC, white blood cell count; MPO, myeloperoxidase; CRP, C-reactive protein; PTX3, pentraxin-3; ADMA, asymmetric dimethylarginine; oxLDL, oxidized LDL; AOPP, advanced oxidation protein products; tHcys, homocystine; U-alb, urinary albumin excretion; VCAM, vascular cell adhesion molecule; HOMA, homeostasis model assessment method; SNP, single nucleotide polymorphism; PTH, parathyroid hormone; OPG, osteoprotegerin; OPN, osteopontin; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; T3, triiodothyronine

Figure 1. The frequency and time course of developing an increase in creatinine in patients hospitalized with HF. The percent of patients with an increase (by that time in the hospitalization) in creatinine of at least the value indicated is shown.



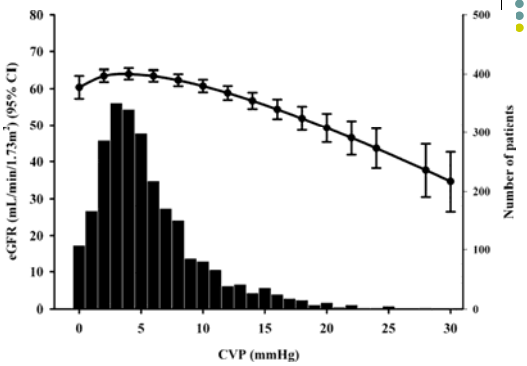
Bock J, Gottlieb S. Circulation 2010;121:2592-2600

Figure 2. The relationship between changes in IAP with diuresis and the change in serum creatinine.



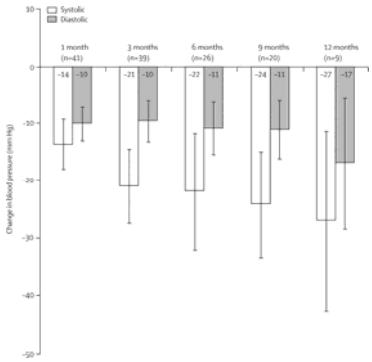
Bock J, Gottlieb S. Circulation 2010;121:2592-2600

Figure 3. Distribution of central venous pressure (CVP) and the relationship between CVP and estimated GFR in 2557 patients.



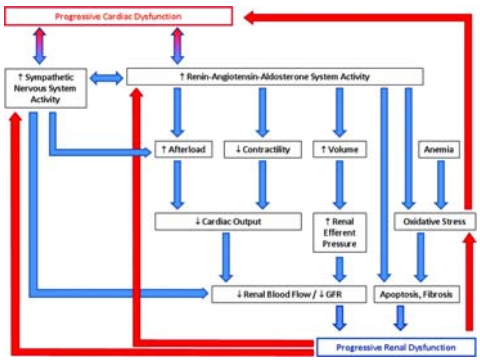
Bock J, Gottlieb S. Circulation 2010;121:2592-2600

Figure 4. The change in blood pressure after radiofrequency ablation of renal sympathetic nerves.



Bock J, Gottlieb S. Circulation 2010;121:2592-2600

Figure 5. Postulated mechanisms underlying the relationship between HF and renal dysfunction.



Bock J, Gottlieb S. Circulation 2010;121:2592-2600

Cardiorenal syndrome (CRS)

- CRS:
  - Conventionally defined as..
    - Condition characterized by the initiation and/or progression of renal insufficiency secondary to HF
  - Also used to describe the negative effects of reduced renal function on the heart and circulation (more appropriately named renocardiac syndrome)

Nephrol Dial Transplant 2011; 26: 62–74

Cardiorenal syndrome (CRS)

- Definitions..
  - However,
    - Older definitions of CRS have been challenged recently as advances in the basic and clinical sciences have changed our understanding of organ crosstalk and interactions
    - Of interest is that
      - Some therapies may have efficacy in the prevention and treatment of both cardiac and renal injury

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Cardiorenal syndrome (CRS)

- Definitions..
  - Recently,
    - A new definition has been proposed which focuses on the complexity of the interrelationship of heart and kidney,
      - including an emphasis on which organ is the initiator of functional damage and which organ is indirectly affected
    - To address the inherent complexity of cardiorenal functional deficits and to stress the bi-directional nature of these heart–kidney interactions,
      - This new classification of the CRS includes **five subtypes** whose terminology reflects
        - their primary and secondary pathology, time frame and simultaneous cardiac and renal dysfunction

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Cardiorenal syndrome (CRS)

- Definitions..
  - The CRS can thus be generally defined as a
    - Pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other…
  - **Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other**

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CRS: Types

- Type I: Definition
  - An abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive HF) leading to AKI..

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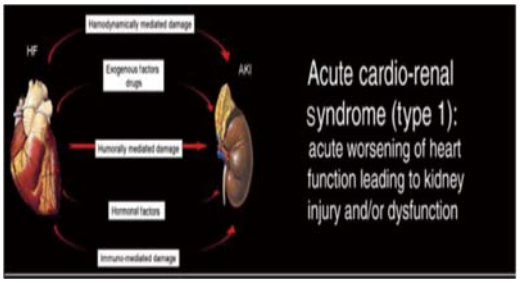
CRS: Types

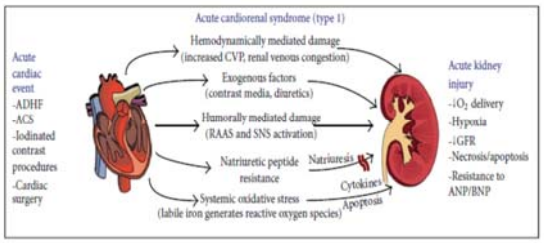
- Type I: Pathophysiology and definition



Circ J 2010; 74: 1274 – 1282

CRS: Types

- Type I: Pathophysiology



International Journal of Nephrology Volume 2011, Article ID 762590

CRS: Types

- Type II: Definition
  - Chronic abnormalities in cardiac function (e.g. chronic congestive HF) causing progressive chronic kidney disease...

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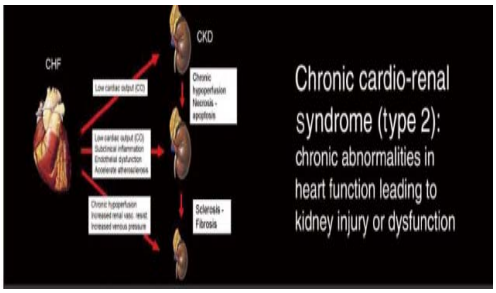
CRS: Types

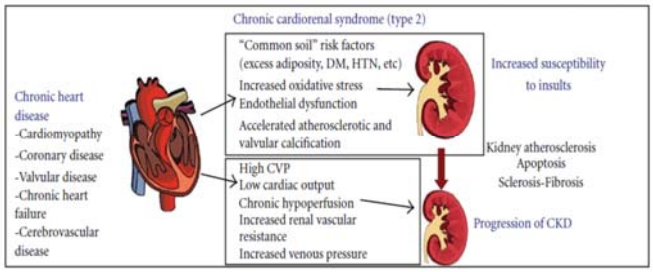
- Type II: Pathophysiology and definition



Circ J 2010; 74: 1274 – 1282

CRS: Types

- Type II: Pathophysiology



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CRS: Types

- Type III: Definition
  - An abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing an acute cardiac disorder (e.g. HF, arrhythmia, ischaemia).

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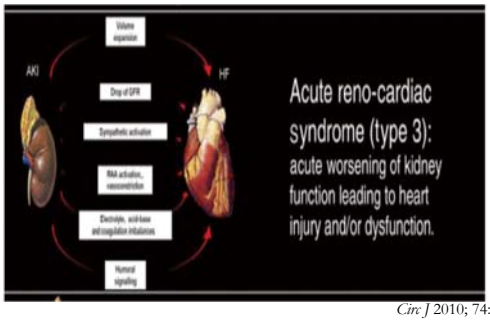
CRS: Types

- Type III: Pathophysiology and definition



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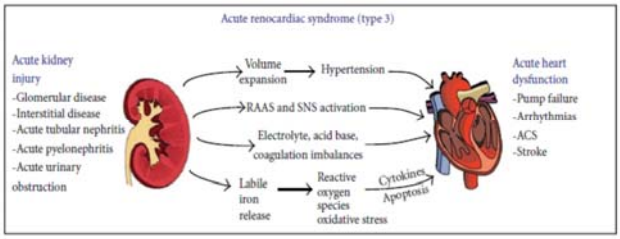
CRS: Types

- Type III: Pathophysiology



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CRS: Types

- Type IV: Definition
  - State of chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events

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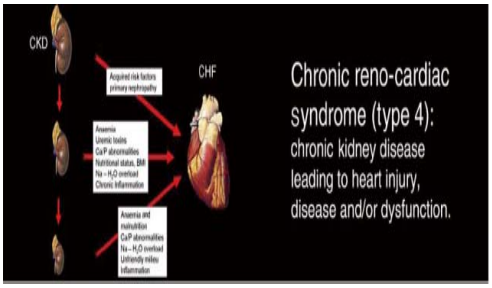
CRS: Types

- Type IV: Pathophysiology and definition



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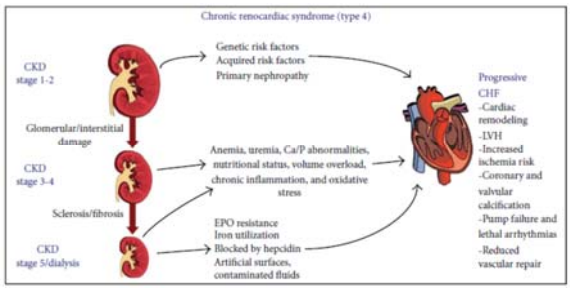
CRS: Types

- Type IV: Pathophysiology



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CRS: Types

- Type V: Definition
  - Systemic condition (e.g. sepsis) simultaneously causing both cardiac and renal dysfunction.

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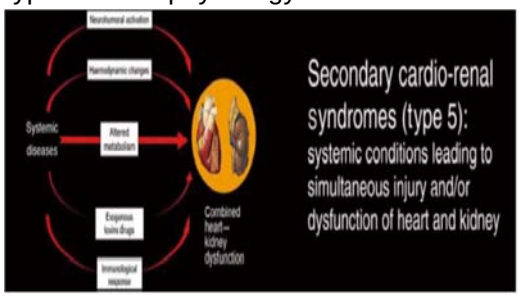
CRS: Types

- Type V: Pathophysiology and definition



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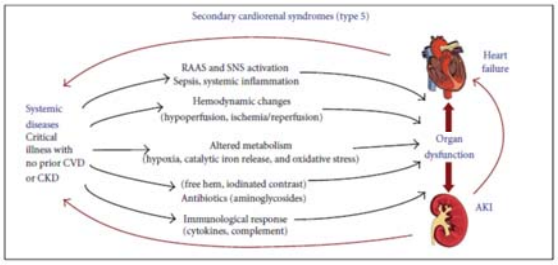
CRS: Types

- Type V: Pathophysiology



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The complicated puzzle of uremic CVD

Red- traditional (*i.e.*, Framingham) risk factors

Blue – inflammatory biomarkers

Green – endothelial dysfunction

Orange – vascular ossification

Brown – surrogate oxidative markers

Purple – adiopkines

Grey - others

Clin J Am Soc Nephrol 2008;3: 505-521.

Laboratory Biomarkers in Heart Failure

Neurohormones	**Matrix remodeling markers**
Natriuretic peptides (ANP, BNP, CNP, and related peptides)	Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs)
Markers of renin-angiotensin-aldosterone system activity	Telopeptides and propeptides of collagen type I and type III
Catecholamines	Osteopontin
Endothelins	Galectin 3
Arginine vasopressin and copeptin	**Inflammatory markers**
Adrenomedullin and mid-regional proadrenomedullin	C-reactive protein (CRP)
Cardiac injury (apoptosis and necrosis) markers	Cytokines and related receptors: IL-1, –2, –6, –8, –18, TNF-α, ST2, osteoprotegerin
Cardiac troponins (cTns)	Pentraxin 3
Heart-type fatty acid binding protein (H-FABP)	**Hormonal and other markers of cachexia**
Fas (APO-1)	Triiodothyronine
Growth differentiation factor-15 (GDF-15)	IGF-1 and GH
Oxidative stress markers	Cortisol
Oxidized low-density lipoproteins (oxLDL)	Adiponectin
Myeloperoxidase	Leptin
Isoprostanes	
Plasma malondialdehyde	
Serum uric acid	
Urinary biopyrrins	
Urinary biopyrrins	

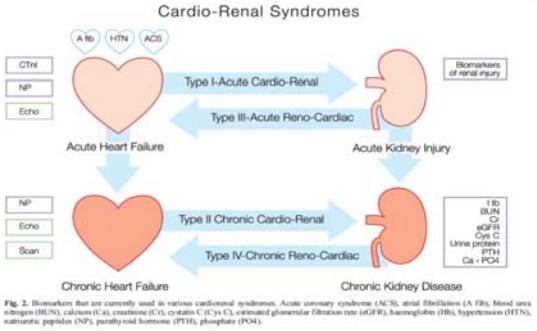
Circ J 2010; 74: 1274 – 1282

Cardiac biomarkers in CKD

- Identifying serum biomarkers that are useful in
- profiling cardiovascular risk and
- enabling stratification of early mortality and cardiovascular risk is

  an important goal in the treatment of patients with CKD

Current biomarkers in CRS



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BNP and NT-proBNP

- BNP belong to a family of vasopeptide hormones that have major role in regulating BP and volume through direct effects on the kidney and systemic vasculature and represent a favorable aspect of neurohumoral activation
- Three different families:
  - A-type (atrial) natriuretic peptide
  - B-type (brain) natriuretic peptide (BNP) and
  - C-type natriuretic peptide

Am Soc Nephrol 2008;19: 1643–1652

BNP and NT-proBNP

- BNP is synthesized as an amino acid precursor protein and undergoes intracellular modification to a prohormone (proBNP) that
  - Comprises 108 amino acids and is secreted from the left ventricle (LV) in response to increased myocardial wall stress
- On release into the circulation, proBNP is cleaved in equal proportions into
  - the biologically active 32–amino acid BNP, which represents the C-terminal fragment, and
  - the biologically inactive 76– amino acid N-terminal fragment (NTpro- BNP)

Am Soc Nephrol 2008;19: 1643–1652

BNP and NT-proBNP

- In the systemic circulation, BNP mediates different biologic effects through interactions with the natriuretic peptide receptor type A, causing intracellular cGMP production, and is eliminated from plasma by binding to the natriuretic peptide receptor type C or through proteolysis by neutral endopeptidases
  - Although these enzymes are found in the kidney, glomerular filtration has only a minor role in the elimination of BNP

Am Soc Nephrol 2008;19: 1643–1652

BNP and NT-proBNP

Table 2. BNP vs NT-proBNP

	BNP	NT-proBNP
Amino acids	32	76
Molecular weight (kDa)	3.5	8.5
Half-life (min)	20	60–120
Hormonal activity	Yes	No
Clearance	Renal, neutral endopeptidase clearance receptors (NPR-C)	Renal
Correlation with GFR	++	+++
Effect of renal function	++	++++
Removal by hemodialysis	~30%	~10%
Clinical range (pg/ml)	0–5,000	0–35,000
Approved cutoff value for heart failure diagnosis in normal renal function (pg/ml)	100	Age <50 years: 450/ Age ≥50 years: 900

BNP, B-type natriuretic peptide; GFR, glomerular filtration ratio
NT-proBNP, N-Terminal Pro-BNP.

Circ J 2010; 74: 1274 – 1282

Table 1. Summary of studies that evaluated the diagnostic potentials of BNP or NT-pro-BNP for LV disorders in CKD*

Author	No. of Patients	AUC for LVH, LVSD	Best Cutoff for LVH and LVSD
Mallamaci *et al.*,[33] 2000	212 HD and 34 PD	0.81, 0.78	LVH (BNP): 23.4 pmol/L (sens 62%, spec 88%, PPV 95%, NPV 61%) LVSD (BNP): 38.9 pmol/L (sens 74%, spec 76%, PPV 31%, NPV 95%)
Mark *et al.*,[42] 2006	55 HD	0.664, 0.532	LVH (BNP): ND (sens 68%, spec 67%, PPV 79%, NPV 53%)
David *et al.*,[44] 2007	62 HD	ND, 0.95	LVSD (BNP): ND (sens 94%, spec 21%, PPV 46%, NPV 83%)
deFilippi *et al.*,[27] 2005	207 with stages 1 through 5 CKD	0.73, ND (based on 99 patients)	LVSD (NT-pro-BNP): 7168 pg/ml (sens 98%, spec 79%) LVH (NT-pro-BNP): 271 pg/ml (sens 76%, spec 60%)
Khan *et al.*,[28] 2006	54 with CKD	0.72, ND (NT-pro-BNP)	LVH (NT-pro-BNP): 762 pg/ml (sens 63%, spec 67%, PPV 70%, NPV 57%)
		0.72, ND (BNP)	LVH (BNP): 200 pg/ml (sens 60%, spec 71%, PPV 72%, NPV 59%)

aAUC; area under the curve; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; ND, not documented; NPV, negative predictive value; PPV, positive predictive value; sens, sensitivity; spec, specificity.

Am Soc Nephrol 2008;19: 1643–1652

Diagnostic Utility of BNP and NT-pro-BNP in ESRD

Table 2. Summary of studies that evaluated the predictive value of BNP or NT-pro-BNP for coronary artery disease, hypervolemia, and mortality in CKD

Author	Patients	End Point	AUC	Best Cutoff
Goto *et al.*,[50] 2002	53 HD	Previous cardiac events	0.788	BNP: 390 pg/ml (sens 62%, spec 93%)
deFilippi *et al.*,[27] 2005	207 with stages 1 through 5 CKD	Previous coronary artery disease	0.69	NT-pro-BNP: 318 pg/ml (sens 78%, spec 56%)
Khan *et al.*,[28] 2006	54 with CKD	Coronary artery disease	0.80 (NT-pro-BNP) 0.82 (BNP)	NT-pro-BNP: 979 pg/ml (sens 79%, spec 70%, PPV 48%, NPV 90%) BNP: 228 pg/ml (sens 86%, spec 73%, PPV 52%, NPV 94%)
Takami *et al.*,[29] 2004	103 with CKD	LV overload	0.73	BNP: 150 pg/ml (sens 52%, spec 93%)
Sommerer *et al.*,[52] 2007	134 HD	Hypervolemia	0.815	NT-pro-BNP: 5300 pg/ml (sens 77%, spec 77%)
Madsen *et al.*,[32] 2007	109 HD	Death	0.718 (pre-HD) 0.729 (post-HD)	NT-pro-BNP: 4079 pg/ml (sens 82%, spec 61%)
Sharma *et al.*,[53] 2007	50 HD and 29 PD	Death	0.74	NT-pro-BNP: 350 pg/ml (sens 72%, spec 76%)

Am Soc Nephrol 2008;19: 1643–1652

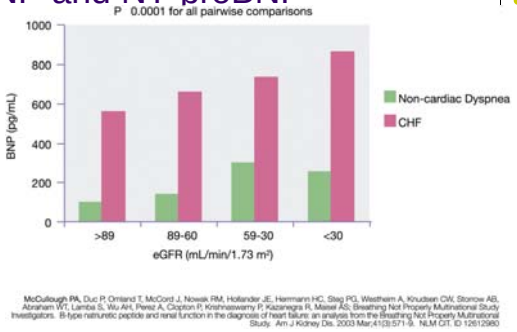
Table 3. Summary of studies that evaluated the prognostic value of BNP and NT-pro-BNP in ESRD*

Author	Patients	Follow-up	No. of Events	Outcome and HR (95% CI)
Studies using BNP				
Zoccali *et al.*,[34] 2000	212 HD and 34 PD	26 ± 10 mo	63 deaths, 74 CV events	Death: HR 1.62 (1.20 to 2.17), $P = 0.001$ for 1-unit increase in log-BNP CV death, T3 versus T1: HR 6.72 (2.44 to 18.54), $P = 0.0002$
Catalioti *et al.*,[37] 2001	112 HD	26 ± 10 mo	16 CV deaths	CV death: HR 2.18 (1.26–3.76), $P = 0.005$ for 1-unit increase in log-BNP
Naganuma *et al.*,[39] 2002	164 HD	36 mo	13 cardiac deaths	Cardiac death, Q4 versus Q1: HR 51.9 (6.5 to 416.3)
Goto *et al.*,[50] 2002	53 HD	11.3 ± 0.3 mo	13 CV events	CV events: HR not given ($P < 0.0001$)
Ruttan *et al.*,[51] 2006	68 PD	At least 18 mo	10 deaths	Death, BNP > median: HR 8.5 (1.0 to 73.8), $P = 0.05$
Studies using NT-pro-BNP				
Apple *et al.*,[31] 2004	399 HD	24 mo	101 deaths	Death, upper tertile: NT-pro-BNP >18,692 pg/ml increased mortality
Wang *et al.*,[35] 2007	240 PD	36 mo	66 deaths, 87 circulatory congestion, 43 CV deaths, 78 CV events	Death, Q4 versus Q1: HR 4.97 (1.35 to 18.28), $P = 0.016$ Circulatory congestion, Q4 versus Q1: HR 4.25 (1.56 to 11.62), $P = 0.005$ CV death – Q4 versus Q1: HR, 7.50 (1.36 to 41.39), $P = 0.021$ CV events, Q4 versus Q1: HR 9.10 (2.46 to 33.67), $P = 0.001$
Madsen *et al.*,[32] 2007	190 HD	24 mo	34 deaths	Death, pre-HD log-NT-pro-BNP: HR 1.42 (1.10 to 1.82), $P = 0.007$ Death, post-HD log-NT-pro-BNP: HR 1.52 (1.18 to 1.96), $P = 0.001$
Sommerer *et al.*,[52] 2007	134 HD	36 mo	74 deaths and CV events	Death and CV events: HR 3.2 (1.70 to 6.02), $P < 0.001$
Satyan *et al.*,[36] 2007	150 HD	24 mo	46 deaths, 26 CV deaths	Death, Q4 versus Q1: HR 4.03 (1.31 to 12.40), $P = 0.02$ CV death: HR 8.54 (1.04 to 69.98), $P = 0.05$
Sharma *et al.*,[53] 2007	50 HD and 29 PD	2.25 ± 0.71 yr	21 deaths	Death: HR 5.57 (3.14 to 8.21), $P = 0.02$ (univariate analysis)

*CI, confidence interval; CV, cardiovascular; HR, hazard ratio; Q, quartile; T, tertile.

Am Soc Nephrol 2008;19: 1643–1652

BNP and NT-proBNP



McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE, Herrmann HC, Steg PG, Westheim A, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS; Breathing Not Properly Multinational Study Investigators. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. Am J Kidney Dis. 2003 Mar;41(3):571-9. NLM CIT. ID 12612980

Mean BNP as it relates to GFR.

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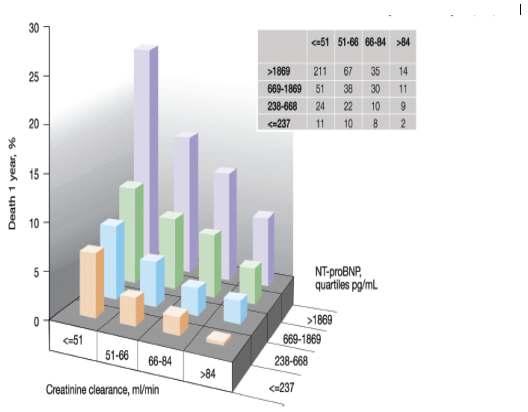

	<=51	51-66	66-84	>84
>1869	211	67	35	14
669-1869	51	38	30	11
238-668	24	22	10	9
<=237	11	10	8	2

Fig. 4. Mortality at 1-year follow-up among strata of patients, according to quartiles of NT-proBNP and quartiles of creatinine clearance.

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Cardiac troponins

- Troponins T, I, and C are components of the contractile apparatus of muscle
  - Specific forms of troponin T and I are present in the heart muscle, namely cTnT and troponin I (cTnI), and are released into the circulation with myocardial injury
    - Thus, measuring circulating cTnT and cTnI level using high-sensitivity assays has become the gold standard approach in diagnosing acute myocardial necrosis

Am Soc Nephrol 2008;19: 1643–1652

Cardiac troponins

- Levels of cardiac troponin are frequently elevated in the absence of acute coronary syndrome among patients with varying degrees of kidney disease, and
- cTnT is more frequently increased compared with cTnI in asymptomatic patients with ESRD

Am Soc Nephrol 2008;19: 1643–1652

Mechanisms of Elevated Cardiac Troponins in Patients with ESRD

- There is emerging evidence that
  - Increases in cTnT in asymptomatic patients with ESRD indicates subclinical myocardial necrosis or injury

Am Soc Nephrol 2008;19: 1643–1652

N-Acetyl-β-(D)Glucosaminidase (NAG)

- Recognized over thirty years ago, NAG is a lysosomal brush border enzyme found in proximal tubular cells
- It is a large protein (>130 kD) and is therefore not filtered through the glomerular membrane
- NAG has been shown to function as a marker of AKI, reflecting particularly the degree of tubular damage
- It is not only found in elevated urinary concentrations in AKI and CKD but also in diabetic patients, patients with essential hypertension and heart failure

International Journal of Nephrology 2011: Article ID 762590

Other markers

- The overproduction and release of pro-inflammatory cytokines, particularly tumour necrosis factor-alpha, interleukin (IL)-1 and IL-6, have been shown to exert an effect on ongoing myocardial cell injury
- However, due to the non-specific nature of many of these cytokines as well as difficulty in measurement, they are not routinely used in the clinical arena

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Other markers

- *Catalytic Iron*
- *Neutrophil Gelatinase-Associated Lipocalin (NGAL)*
- *Cystatin C*
- *Kidney Injury Molecule 1 (KIM-1)*
- *Liver Fatty Acid-Binding Protein (L-FABP)*
- *Tubular Enzymuria*

International Journal of Nephrology Volume 2011, Article ID 762590

Markers for AKI

- AKI may be
  - Primary event that leads to cardiac dysfunction (type III CRS), or
  - Result from acute cardiac dysfunction (type I CRS)
  - Condition with an increasing incidence in hospital and ICU patients
    - Using the recent RIFLE consensus definitions and its Injury and Failure categories, AKI has been identified in close to 9% of hospital patients and,
    - Large ICU database, AKI was observed in more than 35% of critically ill patients

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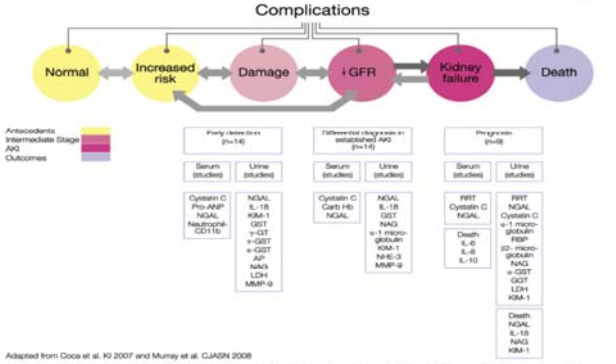
AKI: Pathophysiology and markers



Adapted from Coca et al. KI 2007 and Murray et al. CJASN 2008

Fig. 5. Acute kidney injury (AKI), blood urea nitrogen (BUN), fatty acid binding protein (FABP), glomerular filtration rate (GFR), glutamyl transpeptidase (GT), glutathione-s-transferase (GST), interleukin (IL), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), matrix metalloproteinase 9 (MMP-9), *N*-acetyl-β-D-glucosaminidase (NAG), natriuretic peptides (NP), neutrophil gelatinase-associated lipocalin (NGAL), renal replacement therapy (RRT), retinoid binding protein (RBP), sodium hydrogen exchanger (NHE).

Future Biomarkers

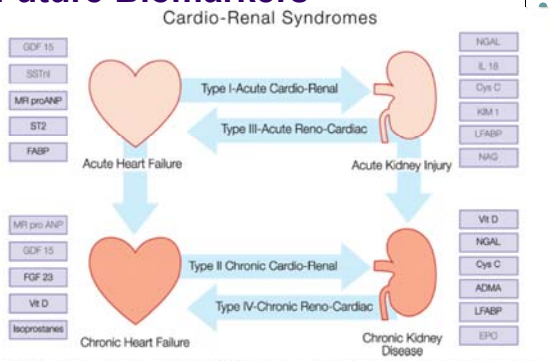


Fig. 6. Cystatin C (Cys C), erythropoietin (EPO), fatty acid binding protein (FABP), interleukin (IL), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), *N*-acetyl-β-D-glucosaminidase (NAG), natriuretic peptides (NP).

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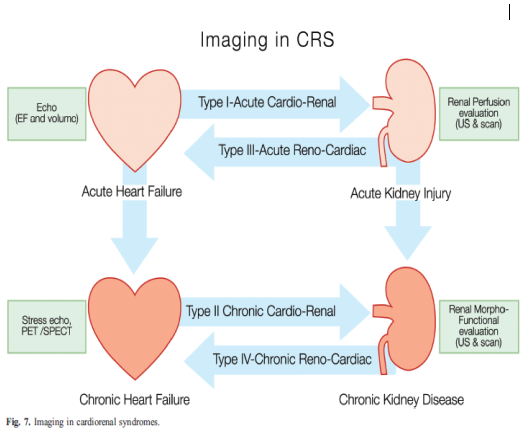

Fig. 7. Imaging in cardiorenal syndromes.

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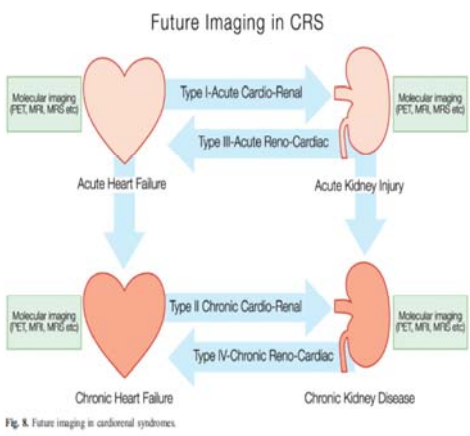

Fig. 8. Future imaging in cardiorenal syndromes.

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CRS: Preventive approaches

- Type I
  - The basic principles include
    - Avoidance of volume depletion,
    - Removal of superimposed renal toxic agents (nonsteroidal anti-inflammatory agents, aminoglycosides),
    - Minimization of the toxic exposure (iodinated contrast, time on cardiopulmonary bypass), and
    - Possibly the use of antioxidant agents such as
      - N-acetylcysteine (for contrast exposure) and B-type natriuretic peptide in the perioperative period after cardiac surgery

CRS: Preventive approaches

- Type I
- More broadly across all forms of CRSs Type I, consideration should be given for forms of
  - Continuous renal replacement therapy (CRRT) in the period of time surrounding the renal insult.
    - Conceptually, the use of CRRT provides 3 important protective mechanisms that cannot be achieved pharmacologically as follows:

(1) Ensures euvolemia and avoids hypo- or hypervolemia,

(2) Provides sodium and solute (nitrogenous waste products) removal, and

(3) by both mechanisms above, it may work to avoid both passive renal congestion and a toxic environment for the kidneys and allow their optimal function during a systemically vulnerable period

CRS: Preventive approaches

- Type I
- CRRT
  - Despite advantages, there remains a lack of clinical trial data supporting CRRT over other forms of extracorporeal solute removal
- Finally, for patients in whom anuria and serious renal failure have a high probability of occurring, the upstream use of CRRT
  - Removes the hazards around the critical period of initiation of dialysis including electrolyte imbalance, urgent catheter placement, and extreme volume overload

CRS: Preventive approaches

- Type II
- As a general axiom,
  - Pharmacologic therapies that have been beneficial for chronic CVD have been either neutral/favorable to the kidneys including use of
    - Renin angiotensin aldosterone system (RAAS) antagonists,
    - Beta-adrenergic blocking agents, and
    - Statins

CRS: Preventive approaches

- Type II
- Other strategies
  - Modestly beneficial from a cardiac perspective have even a larger benefit on microvascular injury to the kidneys includes
    - Glycemic control in diabetes and
    - Blood pressure control in those with hypertension

CRS: Preventive approaches

- Type II
- There is some support from clinical trials that
  - Fibric acid derivatives may preferentially reduce rates of microalbuminuria in patients with CKD
    - The long-term clinical implications of these observations are unknown

CRS: Preventive approaches

- Type III
- The major management principle concerning this syndrome is
  - Intra- and extravascular volume control with either
    - Use of diuretics and
    - Forms of extracorporeal volume and solute removal
      - CRRT, ultrafiltration, hemodialysis

CRS: Preventive approaches

- Type III
- In the setting of AKI,
  - Prevention of left ventricular volume overload is critical to
    - Maintain adequate cardiac output and systemic perfusion and
    - Avoid the viscous downward spiral in both cardiac and renal function

CRS: Preventive approaches

- Type IV
- Optimal treatment of CKD with
  - Blood pressure and glycemic control,
  - RAAS blockers, and
  - Disease-specific therapies, when indicated, are the best means of preventing this syndrome

CRS: Preventive approaches

- Type IV
  - Morbidities of CKD, including
    - Bone and mineral disorder and anemia, should be managed according to CKD guidelines; however,
    - Clinical trials have failed to demonstrate that treatment of these problems influences CVD outcomes

CRS: Preventive approaches

- Type V
  - There are no proven methods to prevent or ameliorate this form of CRSs at this time
  - Randomized trials of early versus later intervention with CRRT have shown no differential benefit
  - Supportive care with a judicious intravenous fluid approach and the use of pressor agents as needed to avoid hypotension are reasonable but
    - Cannot be expected to avoid AKI or cardiac damage

Conclusions

- We summarized a newly proposed framework for CRSs in order to better understand five possible subtypes
- A description of possible heart-kidney interactions is critical to our understanding and will guide future investigations into pathophysiology, screening, diagnosis, prognosis, and management

Conclusions

- Recent studies have identified and characterized several novel biomarkers for CRSs
- It is anticipated that these biomarkers will help make an earlier diagnosis of CRSs as well as identify its specific type and potentially its pathophysiology

Conclusions

- It remains to be seen whether or not effective prevention and treatment of CRSs will improve hard renal and cardiac outcomes including
  - ESRD, hospitalizations, and death