Cardiorenal Syndrome

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RHC

Definition of cardiorenal syndrome

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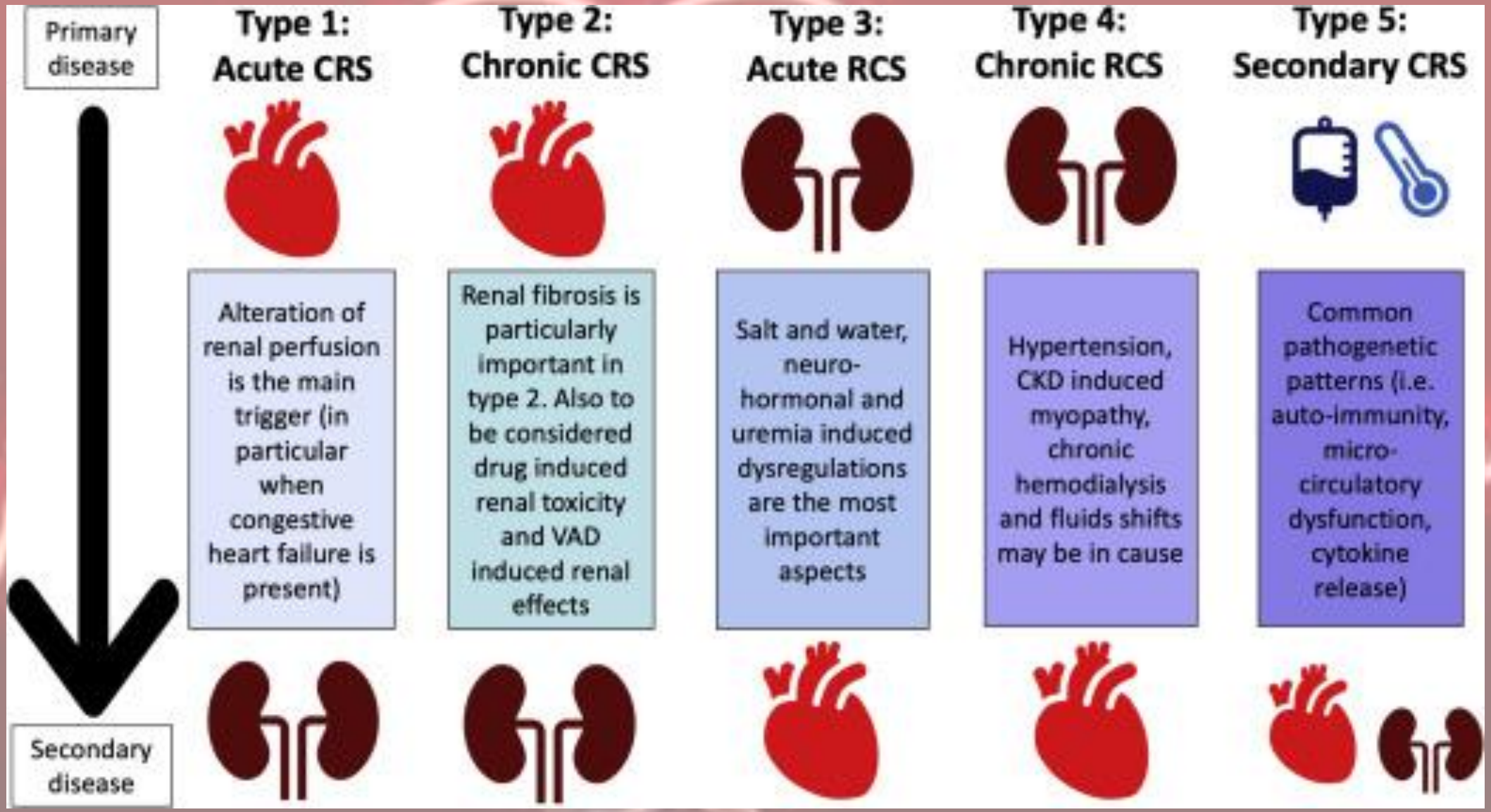
1. **The primary failing organ**
2. **The interaction being unidirectional or bidirectional**
3. **The nature of the disease affecting the organs**
4. **The pathophysiological mechanism (haemodynamic versus nonhaemodynamic)**
5. **The time course of development of the interaction (acute versus chronic)**


Primary disease
Secondary disease
Type 1: Acute CRS
Alteration of renal perfusion is the main trigger (in particular when congestive heart failure is present)
Type 2: Chronic CRS
Renal fibrosis is particularly important in type 2. Also to be considered drug induced renal toxicity and VAD induced renal effects
Type 3: Acute RCS
Salt and water, neuro-hormonal and uremia induced dysregulations are the most important aspects
Type 4: Chronic RCS
Hypertension, CKD induced myopathy, chronic hemodialysis and fluids shifts may be in cause
Type 5: Secondary CRS
Common pathogenetic patterns (i.e. auto-immunity, micro-circulatory dysfunction, cytokine release)

PATHOPHYSIOLOGICAL MECHANISMS IN CRS

CRS-1

- Renin-angiotensin-aldosterone system (RAAS)
  - Ang II:
    - vasoconstriction of renal efferent arterioles
    - lower hydrostatic pressure
    - Increased salt reabsorption in the proximal tubule and higher peritubular oncotic pressure
    - enhances the production of endothelin-1 (ET-1)
      - ET-1 is a powerful vasoconstrictor, proinflammatory, and profibrotic peptide
    - increases aldosterone-mediated salt reabsorption in the distal tubules
- Oxidative stress
  - volume expansion, sympathetic nervous system (SNS) and RAAS activation

CRS-2

- Both CKD and HF are chronic inflammatory diseases
  - production of pro-inflammatory molecules
  - Tissue injury in both systems
  - Fibrosis and cell death
- Oxidative stress and chronic inflammation have significant weight
  - TNF-alpha and IL-6 increase the production of monocyte chemotactic factors in the interstitium of the kidneys,
  - promoting the concentration of inflammatory cells in the interstitium.
  - TNF-alpha also causes mesangial cell death, which damages the glomerulus

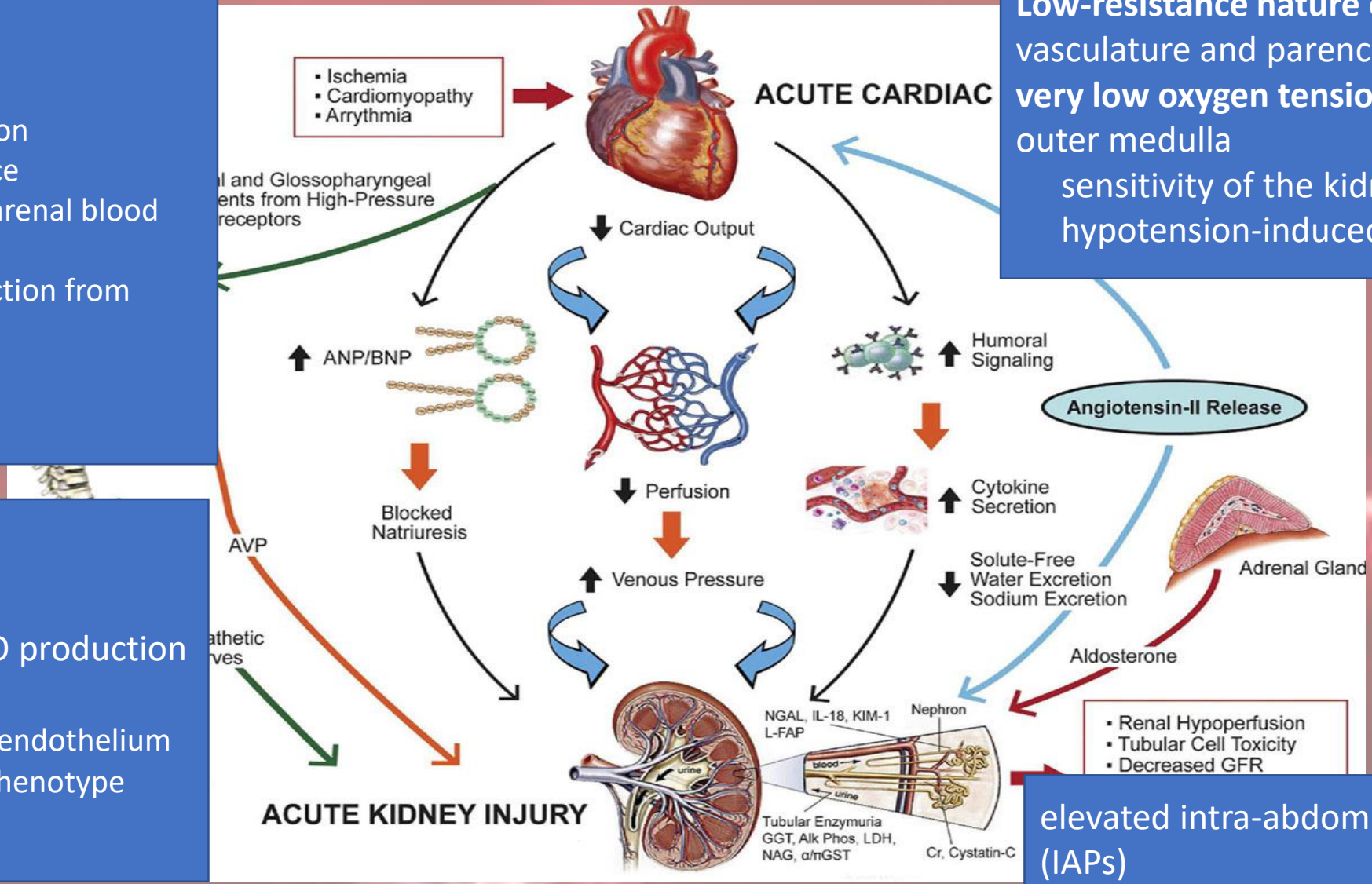
Elevated CVP
- renal venous hypertension
- increased renal resistance
- ultimately impaired intrarenal blood flow

Pre-glomerular vasoconstriction from extreme levels of RAAS

chronic inflammation
- imbalance in ROS/NO production

The endothelial stretch
- conversion of vascular endothelium to a proinflammatory phenotype

Low-resistance nature of the renal vasculature and parenchyma and **very low oxygen tension** in the outer medulla
- sensitivity of the kidneys to hypotension-induced injury



elevated intra-abdominal pressures (IAPs)
- renal compression and reduced perfusion

Janani Rangaswami. Circulation. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association, Volume: 139, Issue: 16, Pages: e840-e878, DOI: (10.1161/CIR.0000000000000664)

CRS-3

- Direct Effects of AKI on the Heart
  - neutrophil infiltration, inflammatory mediators, and cardiac apoptosis
    - Leukocyte activation and trafficking
    - After adherence and chemotaxis
    - Neutrophils release reactive oxygen species, proteases, myeloperoxidase, and other substances that directly damage the tissues via local or systemic effects or by stimulating the expression of cytokines

CRS-3

- Indirect Effects on the Heart
  - Oliguria can lead to fluid overload and sodium and water retention
    - Systemic edema, cardiac overload, hypertension, pulmonary edema, and myocardial dysfunction
  - electrolyte imbalances
    - Hyperkalemia: arrhythmias and even cardiac arrest
    - hyperphosphatemia and hypocalcemia: arrhythmias and depress the myocardial contractility
  - acidemia
    - disturb cardiac myocyte energy metabolism
    - pulmonary vasoconstriction
    - increased right ventricle afterload
    - negative inotropic effect
  - Acute accumulation of uremic toxins
    - affect myocardial contractility through the myocardia-depressant factors and cause pericarditis.
- sympathetic nervous system (SNS) and the RAAS

CRS-4

- Vasoconstriction
- Sodium and water reabsorption
- Oxidative stress
- RAAS and SNS activation
- PBUTs
  - increase oxidative stress in kidneys and heart
  - resulting in cardiorenal fibrosis
- Fibroblast growth factor-23 (FGF23)
  - are associated to left ventricular hypertrophy and death in those with severe CKD

Classification

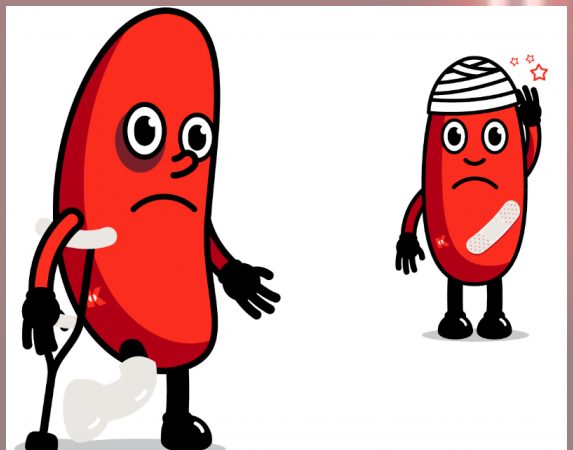
Table 1 | Proposed CRS classification based on putative pathophysiology and clinical applicability at time of patient evaluation

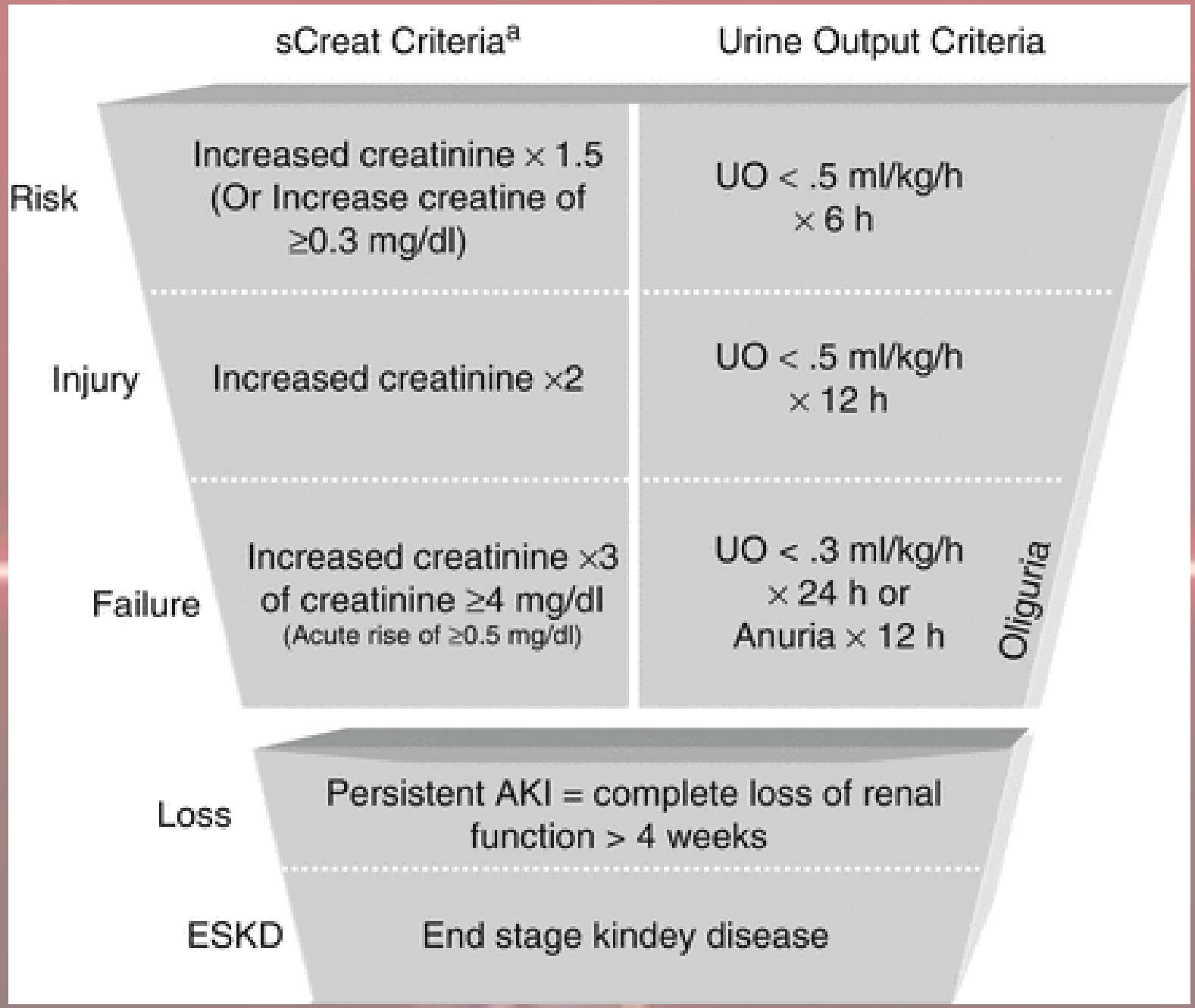
CRS category	Definition	Comments
1) Haemodynamic	Haemodynamic compromise is the major clinical manifestation	Can be subclassified as acute (1a) or chronic (1b)
2) Uraemic	Uraemic manifestations are the most prominent clinical appearances	Can be subclassified as acute (2a) or chronic (2b)
3) Vascular	Cardiovascular and/or renovascular manifestations are the most prominent clinical findings	Can be subclassified as acute (3a) or chronic (3b) and as atherosclerotic (as), thromboembolic (te) or endothelial dysfunction (ed)
4) Neurohumoral	Electrolyte disorders, acid–base disorders or dysautonomia is the most prominent finding	Can be subcategorized into acute (4a) or chronic (4b) and into electrolyte (el), acid–base (ab) or autonomic dysregulation (ad)
5) Anaemia and/or iron metabolism	Anaemia and/or iron metabolism dysregulation are the most prominent clinical manifestations	Can be subcategorized into acute (5a) or chronic (5b)
6) Mineral metabolism	Dysregulation of calcium and phosphorus and their regulators including vitamin D and FGF23 are the most prominent clinical manifestations	This category is mostly chronic by nature
7) Malnutrition–inflammation–cachexia	Malnutrition, cachexia and inflammatory state is the most prominent clinical manifestation	This category is mostly chronic by nature

Hatamizadeh, P. et al. Nat. Rev. Nephrol. 9, 99–111 (2013); published online 18 December 2012; doi:10.1038/nrneph.2012.279

AKI or Worsening renaL FUNCTION

- An increase in serum creatinine ≥0.2 mg/dL or a corresponding decrease in estimated glomerular filtration rate ≥5 mL·min·1.73 m^2 or > 20% decrease in eGFR from baseline [2,3].




sCreat Criteria[a]
Urine Output Criteria
Risk
Increased creatinine × 1.5
(Or Increase creatine of
≥0.3 mg/dl)
UO < .5 ml/kg/h
× 6 h
Injury
Increased creatinine ×2
UO < .5 ml/kg/h
× 12 h
Failure
Increased creatinine ×3
of creatinine ≥4 mg/dl
(Acute rise of ≥0.5 mg/dl)
UO < .3 ml/kg/h
× 24 h or
Anuria × 12 h
Oliguria
Loss
Persistent AKI = complete loss of renal
function > 4 weeks
ESKD
End stage kindey disease

Kidney Disease: Improving Global Outcomes (KDIGO)

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3 times baseline or ≥4.0 mg/dl (≥353.6 μmol/l) increase or initiation of RRT or in patients <18 years a decrease in eGFR <35 ml/min/1.73 m^2	<0.3 ml/kg/h for ≥24 h or anuria ≥12 h

Circulation

ORIGINAL RESEARCH ARTICLE

Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury

Editorial, see p 2029

BACKGROUND: Worsening renal function (WRF) in the setting of aggressive diuresis for acute heart failure treatment may reflect renal tubular injury or simply indicate a hemodynamic or functional change in glomerular filtration. Well-validated tubular injury biomarkers, *N*-acetyl-β-D-glucosaminidase, neutrophil gelatinase-associated lipocalin, and kidney injury molecule 1, are now available that can quantify the degree of renal tubular injury. The ROSE-AHF trial (Renal Optimization Strategies Evaluation–Acute Heart Failure) provides an experimental platform for the study of mechanisms of WRF during aggressive diuresis for acute heart failure because the ROSE-AHF protocol dictated high-dose loop diuretic therapy in all patients. We sought to determine whether tubular injury biomarkers are associated with WRF in the setting of aggressive diuresis and its association with prognosis.

METHODS: Patients in the multicenter ROSE-AHF trial with baseline and 72-hour urine tubular injury biomarkers were analyzed (n=283). WRF was defined as a ≥20% decrease in glomerular filtration rate estimated with cystatin C.

RESULTS: Consistent with protocol-driven aggressive dosing of loop diuretics, participants received a median 560 mg IV furosemide equivalents (interquartile range, 300–815 mg), which induced a urine output of 8425 mL (interquartile range, 6341–10 528 mL) over the 72-hour intervention period. Levels of *N*-acetyl-β-D-glucosaminidase and kidney injury molecule 1 did not change with aggressive diuresis (both $P>0.59$), whereas levels of neutrophil gelatinase-associated lipocalin decreased slightly (−8.7 ng/mg; interquartile range, −169 to 35 ng/mg; $P<0.001$). WRF occurred in 21.2% of the population and was not associated with an increase in any marker of renal tubular injury: neutrophil gelatinase-associated lipocalin ($P=0.21$), *N*-acetyl-β-D-glucosaminidase ($P=0.46$), or kidney injury molecule 1 ($P=0.22$). Increases in neutrophil gelatinase-associated lipocalin, *N*-acetyl-β-D-glucosaminidase, and kidney injury molecule 1 were paradoxically associated with improved survival (adjusted hazard ratio, 0.80 per 10 percentile increase; 95% confidence interval, 0.69–0.91; $P=0.001$).

CONCLUSIONS: Kidney tubular injury does not appear to have an association with WRF in the context of aggressive diuresis of patients with acute heart failure. These findings reinforce the notion that the small to moderate deteriorations in renal function commonly encountered with aggressive diuresis are dissimilar from traditional causes of acute kidney injury.

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Key Words: acute kidney injury ■ biomarkers ■ heart failure ■ renal insufficiency

Sources of Funding, see page 2027

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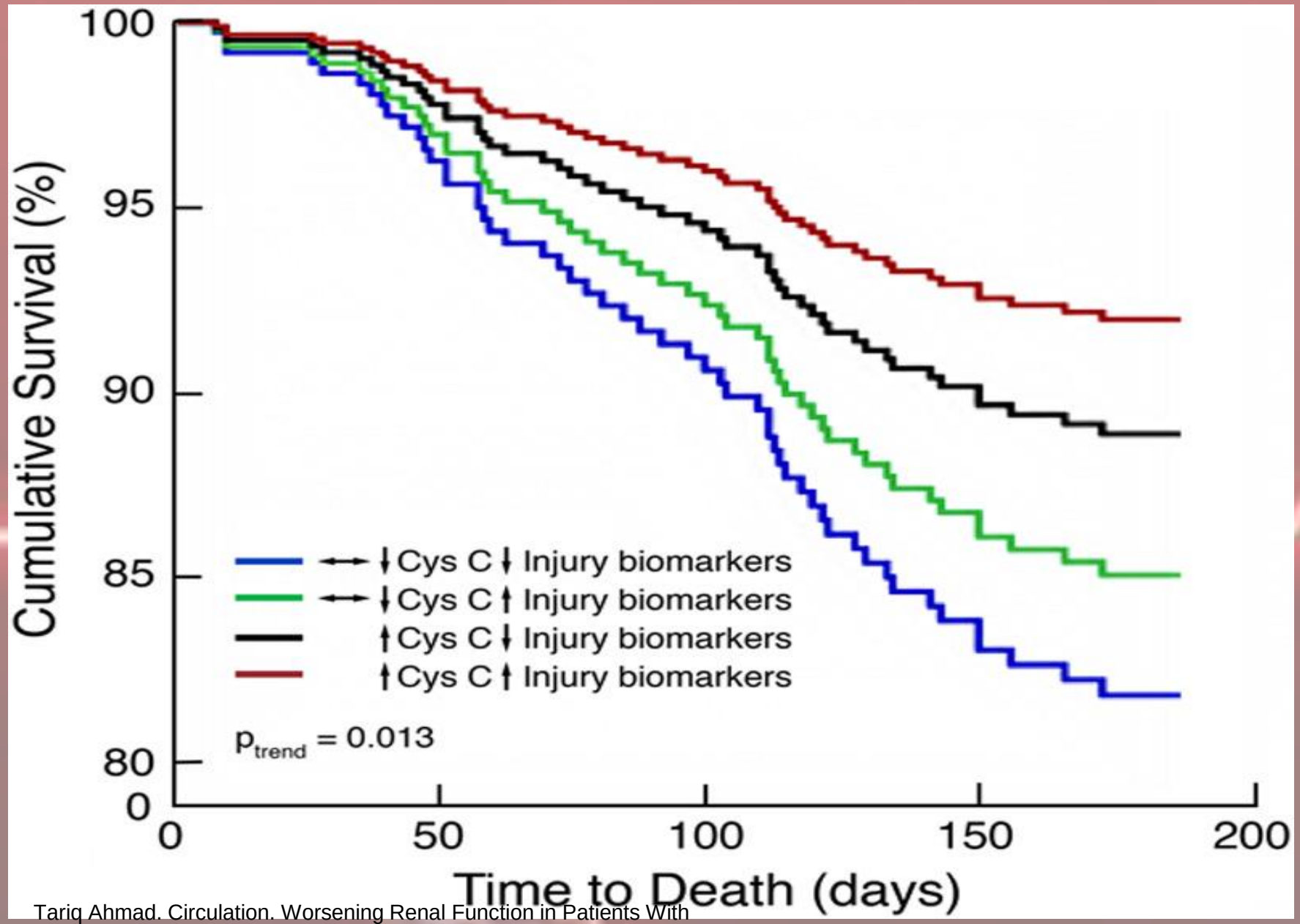


Tariq Ahmad. Circulation. Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury, Volume: 137, Issue: 19, Pages: 2016-2028, DOI: (10.1161/CIRCULATIONAHA.117.030112)

WRF OR Pseudo WRF

- Clinical assessment of perfusion status
- Relevant hemodynamic parameters (invasive and noninvasive),
- Detection of bedside markers of intrinsic renal injury evident on urine microscopy
- A thorough investigation of alternative explanations for worsening renal function.

DIAGNOSTIC STRATEGIES IN CRS

Is it true kidney injury?

Is it attributed to heart failure?

Biomarkers

Biomarkers

- Cardiac biomarkers
- AKI biomarkers
  - Potential for early detection of AKI
  - Potential for differential diagnosis of AKI
  - Potential for prognosis of AKI
  - Potential for inflammation and immune response

AKI biomarkers

- Neutrophil gelatinase associated lipocalin (NGAL)
  - Normally expressed at very low levels by neutrophils and by various epithelial cells including kidney, lung, stomach, and colon.
  - Have an important role in limiting oxidative damage in both acute and chronic diseases
  - One of the earliest kidney markers of ischemic or nephrotoxic injury models
- CysC
  - produced regularly and released into blood by all nucleated cells
  - not affected by age, sex, race, or muscle mass
  - is freely filtered at the glomerulus, reabsorbed completely by the proximal tubule
  - and not secreted into urine
  - serum levels of CysC reflect changes in GFR
  - the appearance in the urine may signal abnormal tubular cell function

AKI biomarkers

- **KIM-1**
  - transmembrane glycoprotein
  - not normally detectable in urine
  - may be detected after ischemic or nephrotoxic insults to proximal tubular cells.
  - seems to be highly specific for ischemic AKI and not for prerenal azotemia
  - may be an important biomarker for differentiating between subtypes of AKI.
- **IL-18**
  - a proinflammatory cytokine
  - detected in the urine after acute ischemic proximal tubular damage
  - has been associated with AKI mortality, and is significantly higher in patients with sepsis.
- **L-FABP**
  - A free fatty acid carrier protein produced mainly in the liver
  - Expressed in hepatocytes and proximal tubule of the kidney
  - Filtered through glomeruli and reabsorbed in the proximal tubule cells
  - When proximal tubular cells are injured, urine L-FABP levels rapidly increase.
  - An early accurate biomarker of AKI
  - Appears later than NGAL.

AKI biomarkers

- **Klotho**
  - a transmembrane protein
  - is present in the proximal tubule where it inhibits renal phosphate excretion
  - AKI is a state of acute reversible Klotho deficiency
  - a reduction in Klotho in the serum and urine occurs very rapidly after AKI
  - In ischemic-induced AKI, the administration of Klotho has a therapeutic potential
- **Netrin-1**
  - a laminin-like molecule protein
  - highly expressed in many organs including the kidney
  - is highly induced in tubular epithelial cells and is detected in urine as early as 1 to 3 hours after ischemia-reperfusion and other forms of AKI
- **Midkine**
  - a heparin-binding protein
  - increase expression in ischemic renal injury
  - a sensitive biomarker for early detection of AKI Importantly
- Many of the earlier- described markers, in particular NGAL and IL-18, are also makers of systemic inflammation and help characterize the substrate that results in CRS

Cardiac Biomarkers

- **BNP**
  - Synthesized and modified from a prohormone (proBNP)
  - released by cardiac
  - Myocytes in the left ventricle in response to wall stress
  - ProBNP is cleaved to biologically active BNP and NTproBNP
  - Glomerular filtration has only a minor role in the elimination of BNP
  - but principally clearance of NT-pro-BNP
  - best diagnosis and prognostic marker in patients with acute heart failure
  - NT-proBNP levels in patients with GFR less than 60 mL/min/1.7 m2 were still the strongest predictors of outcome
    - higher cut-off point for the diagnosis of heart failure
- BNP is reduced by dialysis with both high- and low-flux dialysis membranes
- NT-pro-BNP seems to be reduced significantly only by high-flux membranes.
- **ST2** (suppressor of tumorigenicity 2)
  - Is produced in response to biomechanical strain
  - results in myocyte dysfunction and tissue fibrosis
  - Is not affected by renal function
  - offer incremental value to natriuretic peptides

Cardiac biomarkers

- **Troponin**
  - a structural protein of cardiac and skeletal muscle
  - highly sensitive and specific biomarkers for ischemic myocardial injury
  - correlated with outcomes in the general population and in renal patients
  - In CKD, cTnI has been shown to be an important predictor of cardiac death
  - In AKI this is questionable.
- **Heart-FABP**
  - leak out of myocardial tissue and the concentration increases in plasma during cardiac ischemia
  - may have limited diagnostic value in renal failure
- **Catalytic iron**
  - potentially hazardous
  - powerful oxidant species

Biomarkers of both kidney and heart

- **CysC**
  - increased left ventricular mass and a concentric left ventricular hypertrophy
  - independent predictor of cardiovascular events at the 12-month follow-up evaluation of non-ST elevation ACS patients

- **IL-18**
  - associated with atherogenesis, coronary artery disease, plaque rupture leading to ACS, and myocardial IRI.
  - its levels were associated with mortality on follow-up evaluation in patients with ADHF
  - an independent predictor of cardiovascular events In post-ACS patients

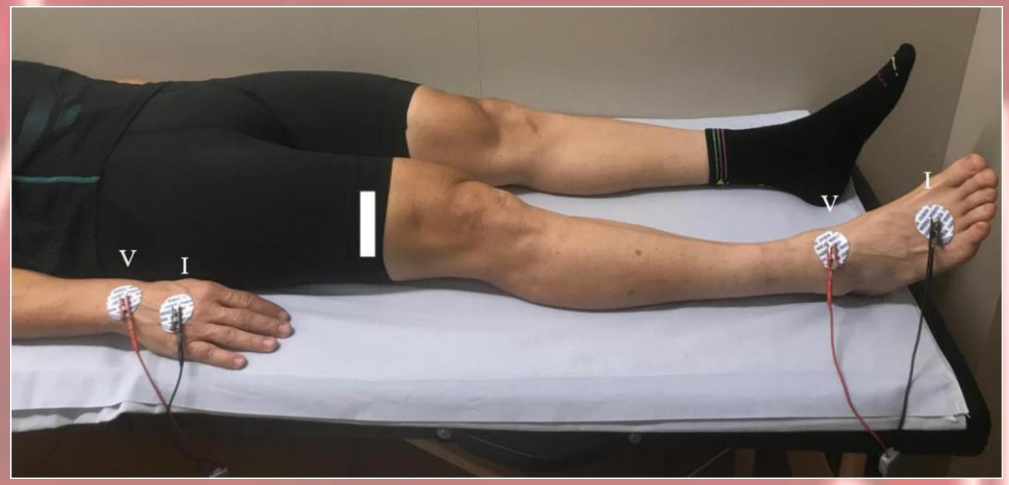
Imaging Modalities

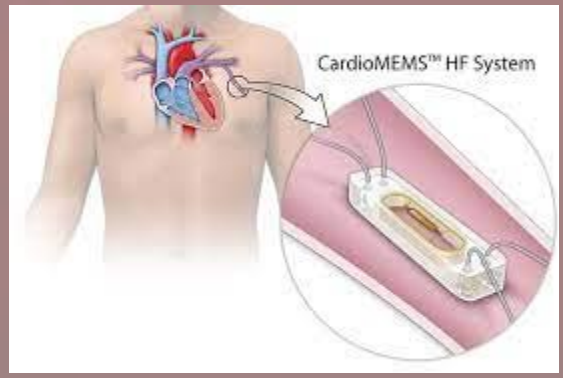
- Echocardiography
  - CVP
  - systolic PA pressure
  - CO
  - E/E' ratio

- Renal ultrasonography
  - intrarenal venous flow patterns
  - renal arterial resistive index?
  - renal perfusion index ?
  - information on the chronicity of the disease
    - Renal size
    - Echogenicity
    - Cortical thickness
    - Abnormal corticomedullary ratios

Volume Status Determination Strategies in CRS

- Bioimpedance Vector Analysis
- Measurement of IAP
- Implantable Hemodynamic Monitoring Devices
- Invasive Hemodynamic Monitoring in CRS





In Summary

- The cardiorenal syndrome is common and is associated with adverse clinical outcomes.
- The new focus should be to recognize the true kidney injury, attribute it to heart failure, and clear pathophysiological mechanisms.
- The optimization of heart failure therapy also preserves renal function.