Cardiorenal Syndrome and Renal Protection: Fact Vs Fiction

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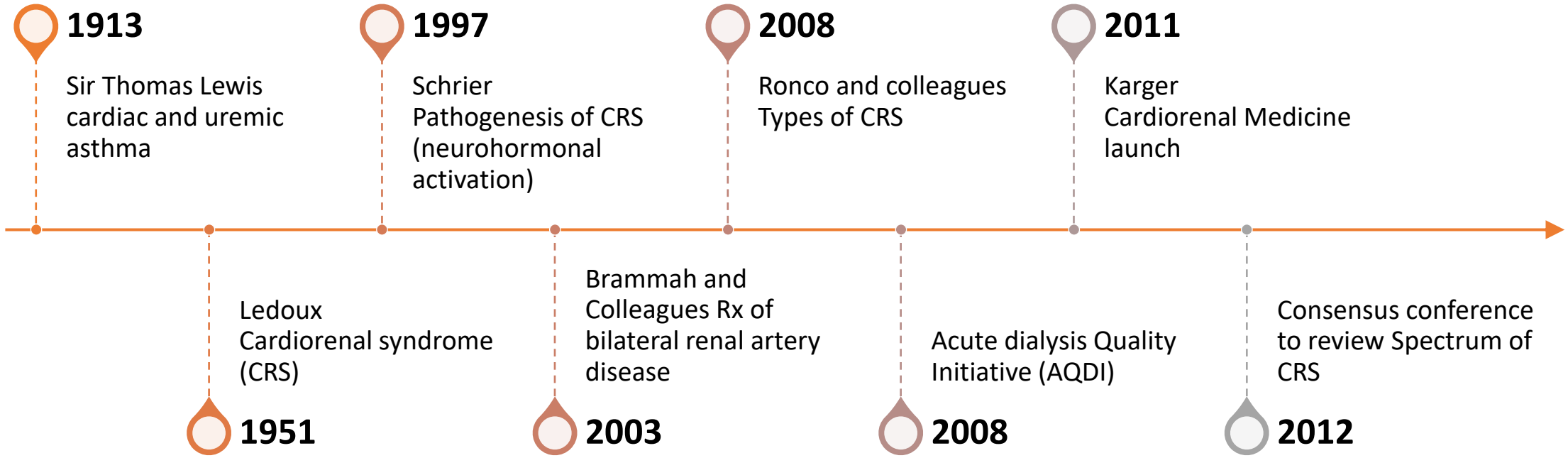
Disclosures

NONE RELVANT TO THIS TALK

Objectives

- Definition
- Epidemiology of Cardiorenal syndrome
- Review of Classification of Cardiorenal syndrome
- Pathogenesis of Cardiorenal syndrome
- Practical implications of the management of Cardiorenal syndrome
- Limitations of current approach

1868: Moxon: First noted description of Interaction Heart and Kidney Disease



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History and Timeline

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STATE-OF-THE-ART PAPER

Cardiorenal Syndrome

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

Nephrol Dial Transplant (2010) 25: 1416–1420
doi: 10.1093/ndt/gfq136
Advance Access publication 12 March 2010

NDT

Definition and classification of Cardio-Renal Syndromes: workgroup statements from the 7th ADQI Consensus Conference

Andrew A. House[1], Inder Anand[2], Rinaldo Bellomo[3], Dinna Cruz[4], Ilona Bobek[4], Stefan D. Anker[5], Nadia Aspromonte[6], Sean Bagshaw[7], Tomas Berl[8], Luciano Daliento[9], Andrew Davenport[10], Mikko Haapio[11], Hans Hillege[12], Peter McCullough[13], Nevin Katz[14], Alan Maisel[15], Sunil Mankad[16], Pierluigi Zanco[17], Alexandre Mebazaa[18], Alberto Palazzuoli[19], Federico Ronco[9], Andrew Shaw[20], Geoff Sheinfeld[21], Sachin Soni[22], Giorgio Vescovo[23], Nereo Zamperetti[24], Piotr Ponikowski[25], Claudio Ronco[4] and for the Acute Dialysis Quality Initiative (ADQI) consensus group

European Heart Journal

European Heart Journal
doi:10.1093/eurheartj/ehp507

CLINICAL RESEARCH

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], Ilona Bobek[1], Dinna N. Cruz[1,2], Luciano Daliento[11], Andrew Davenport[12], Mikko Haapio[13], Hans Hillege[14], Andrew A. House[15], Nevin Katz[16], Alan Maisel[17] Sunil Mankad[18], Pierluigi Zanco[19], Alexandre Mebazaa[20], Alberto Palazzuoli[21], Federico Ronco[11], Andrew Shaw[22], Geoff Sheinfeld[23], Sachin Soni[1,24], Giorgio Vescovo[25], Nereo Zamperetti[26], and Piotr Ponikowski[27] for the Acute Dialysis Quality Initiative (ADQI) consensus group

Blood Purification

Blood Purif 2009;27:114–126
DOI: 10.1159/000167018

The Cardiorenal Syndrome

Claudio Ronco[a] Chang-Yin Chionh[a] Mikko Haapio[b] Nagesh S. Anavekar[c]
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Circulation. 2019;139:e840–e878.

DOI:
10.1161/CIR.0000000000000664

Circulation

AHA SCIENTIFIC STATEMENT

Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies

A Scientific Statement From the American Heart Association

ABSTRACT: Cardiorenal syndrome encompasses a spectrum of disorders involving both the heart and kidneys in which acute or chronic dysfunction in 1 organ may induce acute or chronic dysfunction in the other organ. It represents the confluence of heart-kidney interactions across several interfaces. These include the hemodynamic cross-talk between the failing heart and the response of the kidneys and vice versa, as well as alterations in neurohormonal markers and inflammatory molecular signatures characteristic of its clinical

Janani Rangaswami, MD, Vice Chair
Vivek Bhalla, MD, FAHA
John E.A. Blair, MD
Tara I. Chang, MD, MS
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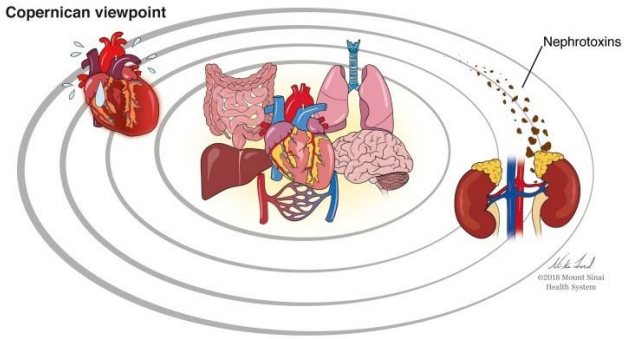
Krista L. Lentine, MD, PhD
Edgar V. Lerma, MD, FAHA

Cardiorenal Syndrome (CRS)



CRS encompasses spectrum of disorders involving both the heart and kidneys in which acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other organ

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Coca S. Ptolemy and Copernicus Revisited. The complex Interplay between the Kidneys and Heart Failure. Clin J Am Soc Nephrol. 2018 Jun 7: 13(6): 825-828
Rangaswami J et al., Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies. A scientific Statement From the American Heart Association. Circulation. 2019; 139: e840-e878.

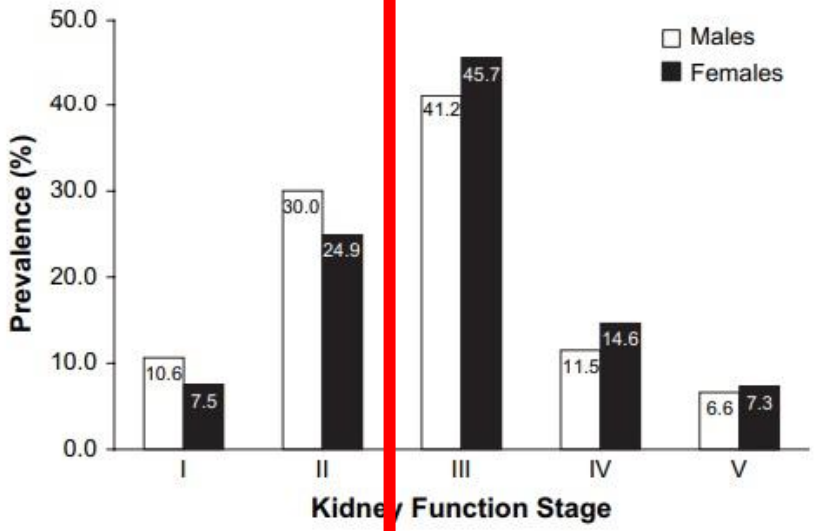
Renal dysfunction in HF Vs HF in CKD

- Acute Decompensated Heart Failure National Registry (ADHERE)
- 20-40% of patients hospitalized with Acute Decompensated Heart Failure (ADHF) are noted to have renal dysfunction
- NKF-KEEP examined > 100,000 individuals screened for kidney disease
  - HF Prevalence: 1.6% among eGFR > 120 Vs 14.9% with eGFR < 30
- The USRDS estimated that > 40% patients with CKD have HF Vs 18.5% of patients without CKD

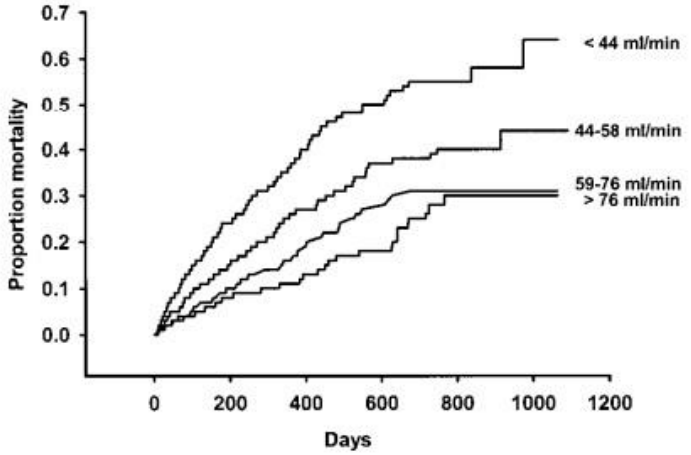
USRDS data 2011
Heywood, J Card Fail, 2007, 13:422

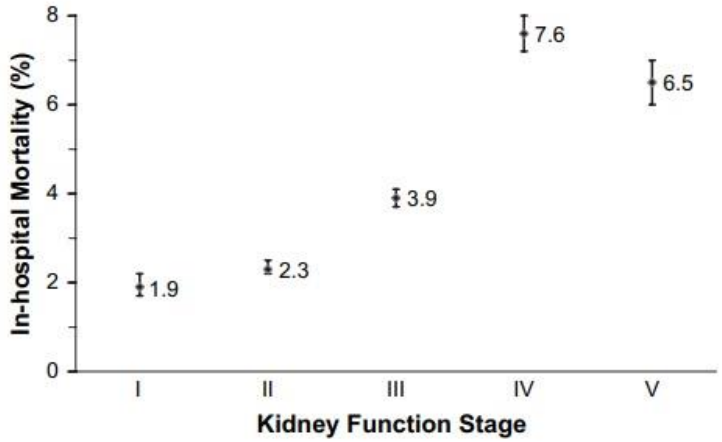
Renal dysfunction in Heart Failure

n = 118465



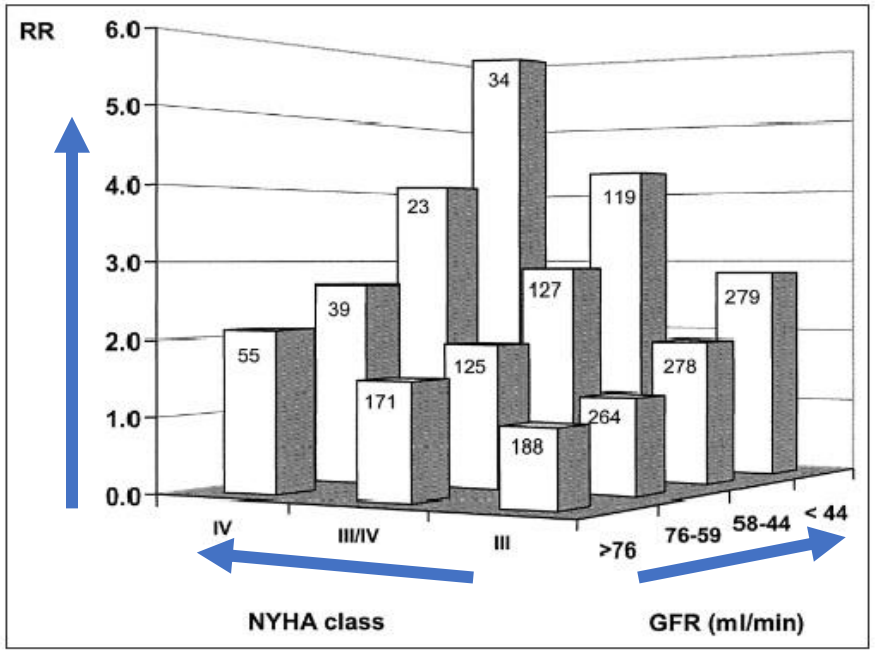
Journal of Cardiac Failure Vol. 13 No. 6 August 2007

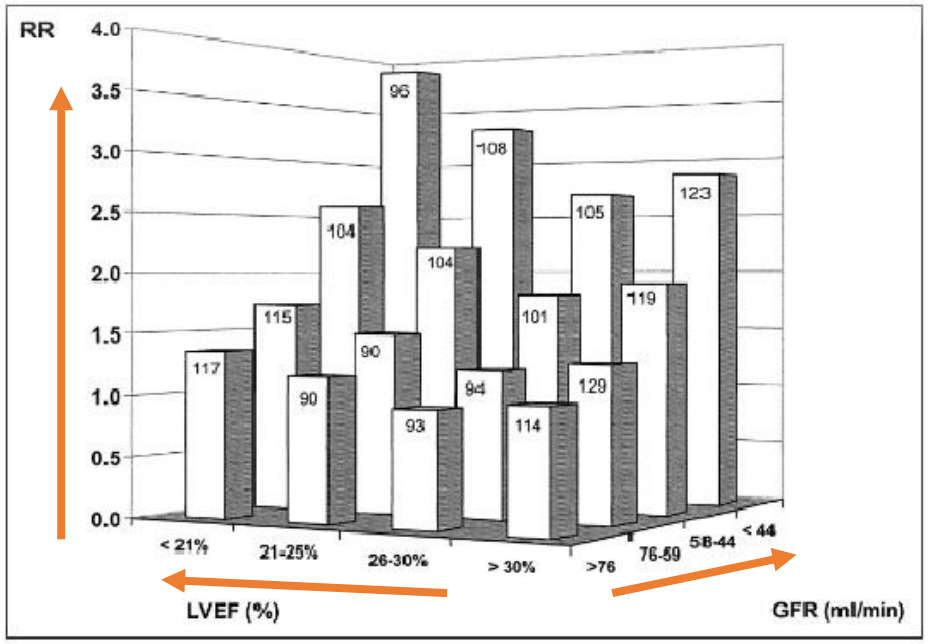




Heywood, J Card Fail, 2007, 13:422
Hillege et, Circulation 2000; 102: 203

Renal Function Is independent Mortality Predictor





Hillege HL Circulation 2000: 102: 203-210

Changes in Kidney Function (AKI Vs WRF)

Table 2 | Staging of AKI

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 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

Heart Fail Rev (2021) 26:487–496

Stage	Serum creatinine	Glomerular filtration rate	Urine output (mL/kg)
R: risk	1.5-fold increase	25% decrease	<0.5 in 6 h
I: injury	2-fold increase	50% decrease	<0.5 in 12 h
F: failure	3-fold increase or value ≥4 mg/dL	75% decrease	<0.3 in 24 h (oliguria) or anuria for 12 h
L: loss (of function)	Complete loss of renal function for ≥4 weeks, requiring dialysis		
E: end stage	Uremia or complete loss of renal function for ≥3 months, requiring dialysis		

Risk Injury-Failure-Loss-End-Stage (RIFLE) Criteria

Kidney Disease: Improving Global Outcomes (KDIGO) (2012) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2:1–138
Chua HR, Glassford N, Bellomo R (2012) Acute kidney injury after cardiac arrest. Resuscitation. 83:721–727

Worsening Renal Function

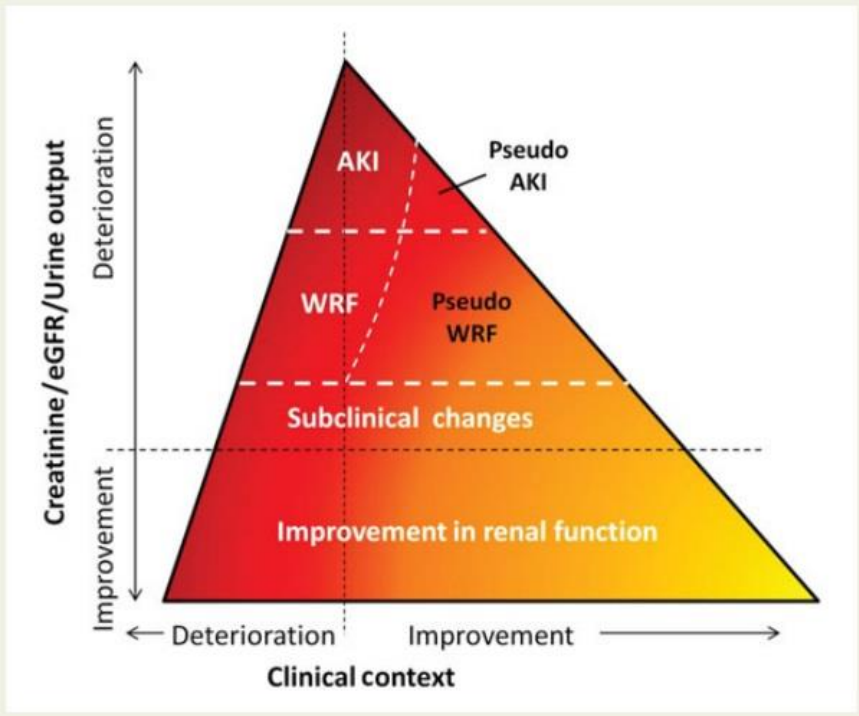
Table 3. Definitions of WRF as Specified in the Different Studies

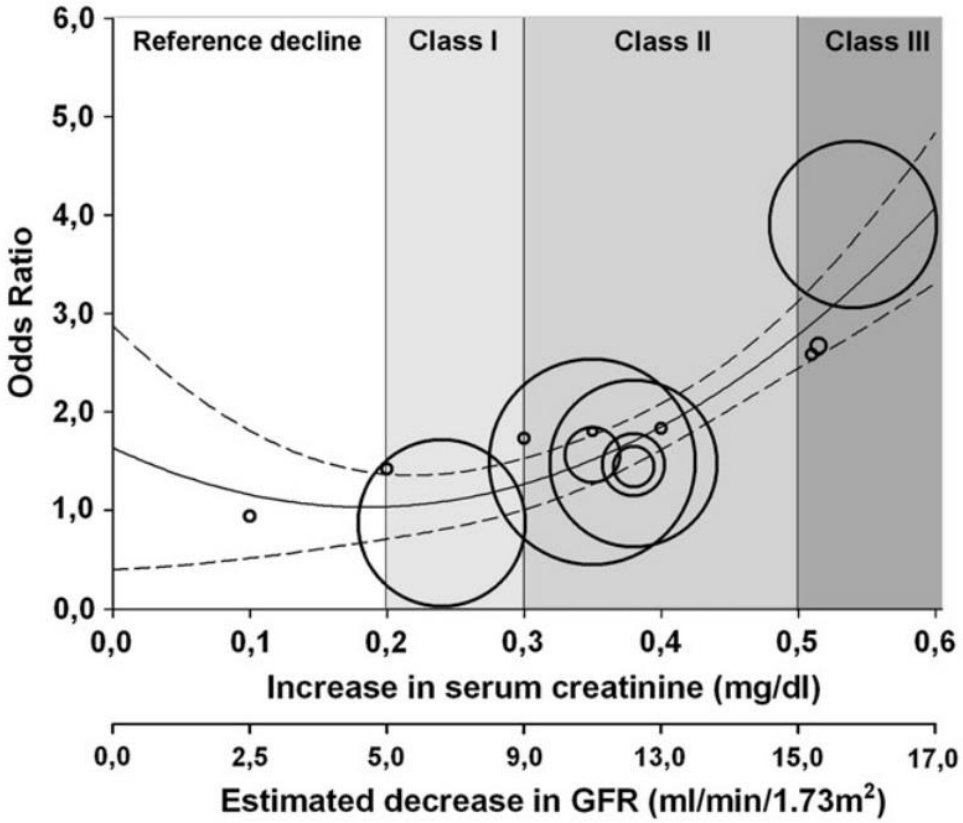
Study	General definition WRF	In Time	Stratified WRF	n Patients WRF	n Patients No WRF	Included in the Analysis as
Krumholz	>0.3 mg/dL increase*	During admission		469	1212	Class II WRF
Smith	Any increase*	During admission	>0.1 mg/dL increase*	103	309	Class I WRF
			>0.2 mg/dL increase*	173	239	Class I WRF
			>0.3 mg/dL increase*	227	185	Class II WRF
			>0.4 mg/dL increase*	280	132	Class II WRF
Akhter	>0.5 mg/dL increase*					
De Silva	>0.3 mg/dL increase*					
Khan	A decrease in eGFR of O 5 mL·min·1.73 n					
Cowie	>0.3 mg/dL increase*					
Jose	>0.3 mg/dL increase*					
Owan	>0.3 mg/dL increase*					

WRF, worsening renal function.

WRF Classification	Increase in Serum Creatinine	Decrease in eGFR
I (mild)	0.2 to 0.3 mg/dL	5 to 10 ml/min/1.73m^2
II (moderate)	0.3 to 0.5 mg/dL	11 to 15 ml/min/1.73m^2
III (severe)	> 0.5 mg/dL	> 15 ml/min/1.73m^2

Worsening Renal Function





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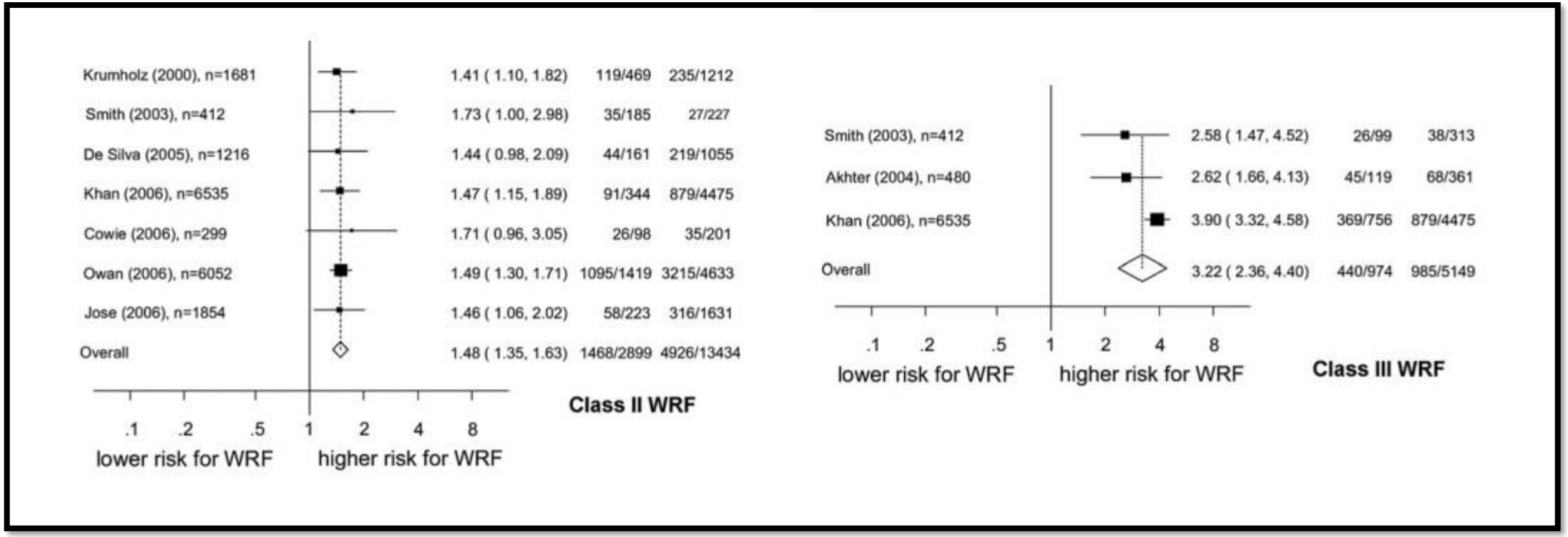
Worsening Renal Function in Heart Failure



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Damman K. J Card Failure 2007: 13: 599-608

Renal dysfunction in Heart Failure

- Renal dysfunction is independent risk factor for poor outcomes and all cause mortality in patients with Heart Failure
- Hospitalized HF patients with prolonged hospitalization, rehospitalization and death
  - Elevated serum creatinine on admission
  - Worsening creatinine during hospitalization

Classification of CRS

Phenotype	Nomenclature	Description	Clinical Examples
Type 1 CRS			HF resulting
Type 2 CRS			
Type 3 CRS			es in uremia
Type 4 CRS			athy
Type 5 CRS			

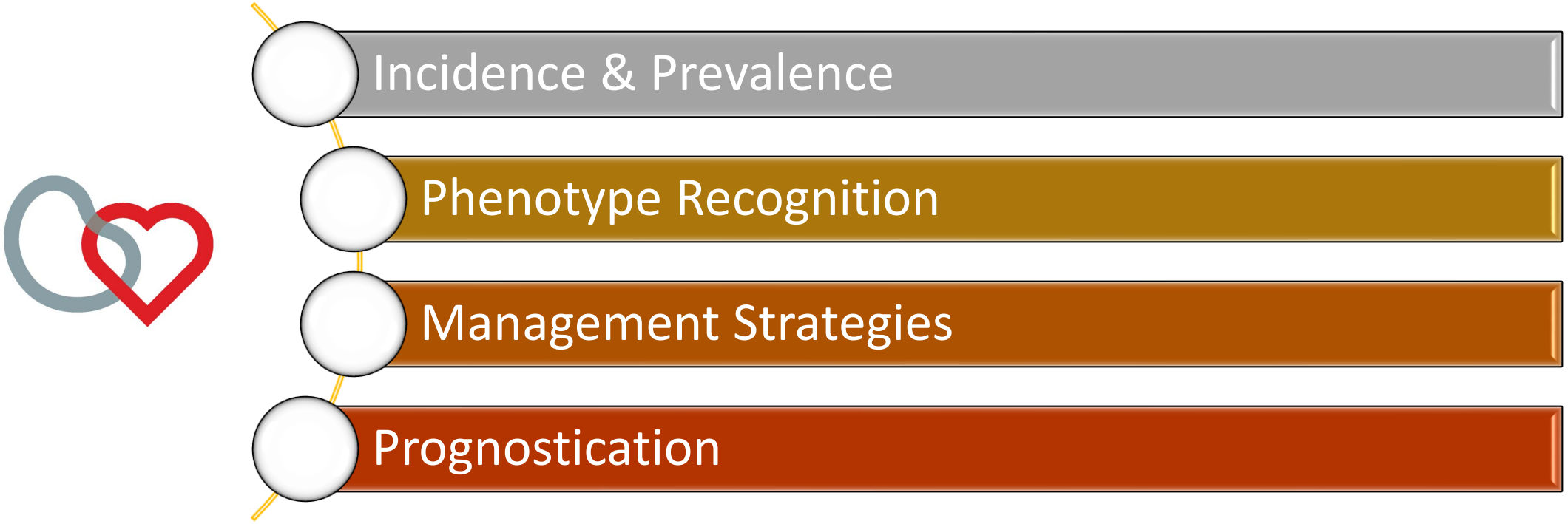
Ronco et al Classification

Type 1	Acute Cardiorenal	ACS, Cardiogenic Shock, ADHF
Type 2	Chronic Cardiorenal	Chronic Heart Failure
Type 3	Acute Renocardiac	Acute Renal Injury
Type 4	Chronic Renocardiac	Chronic Renal Disease
Type 5	Systemic CardioRenal	Sepsis, Non-Cardiogenic Shock

Classification of CRS Based on the Consensus Conference of the Acute Dialysis Quality Initiative

Rangaswami J et al., Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies. A scientific Statement From the American Heart Association. Circulation. 2019; 139: e840-e878.

Significance of Renal dysfunction in Heart Failure



Incidence of Type I CRS

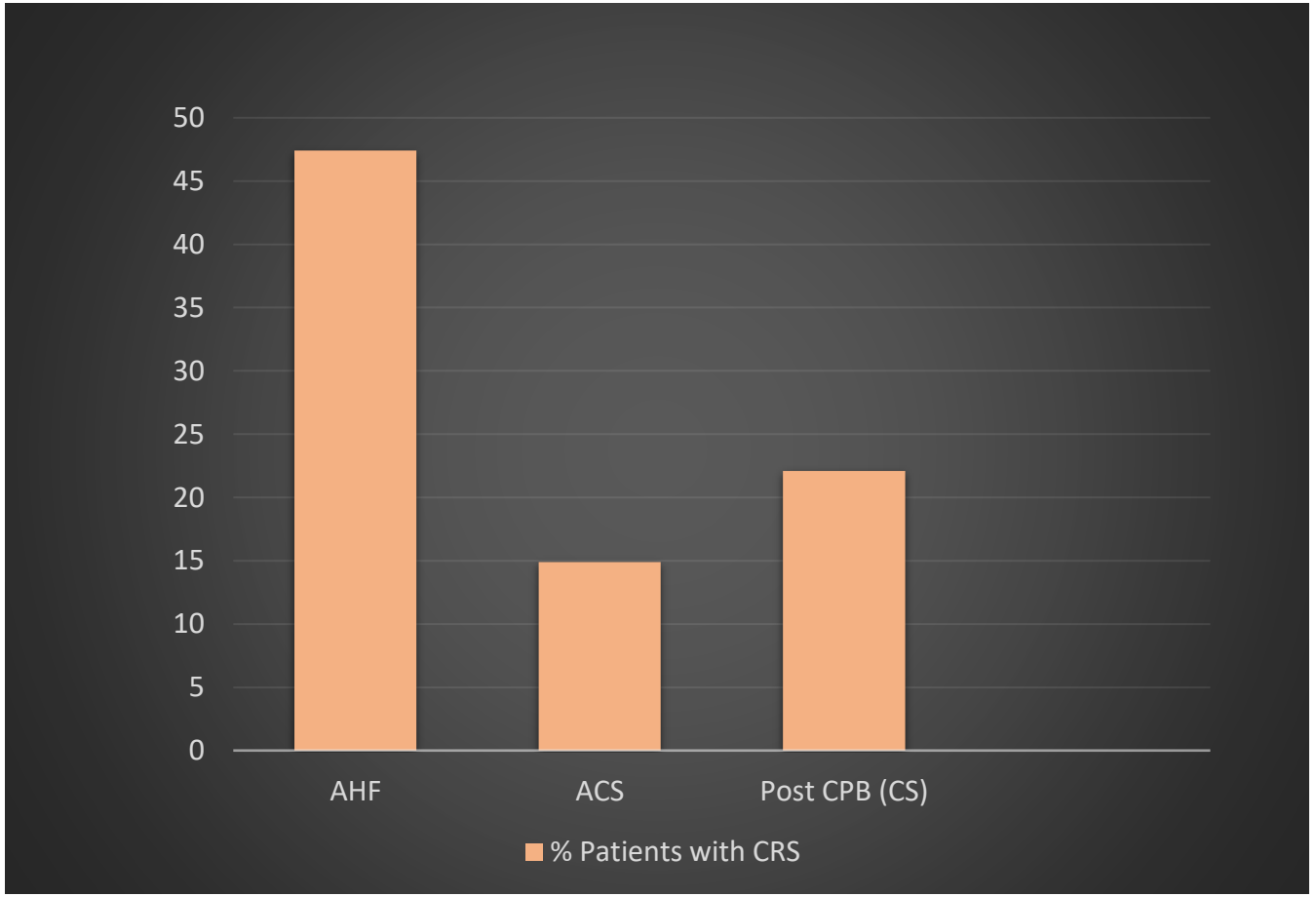
Acute Kidney Injury in Cardiorenal Syndrome Type 1 Patients: A Systematic Review and Meta-Analysis

Wim Vandenberghe[a] Sofie Gevaert[b] John A. Kellum[d, e] Sean M. Bagshaw[f] Harlinde Peperstraete[a] Ingrid Herck[a] Johan Decruyenaere[a] Eric A.J. Hoste[a, c, e]

Departments of [a]Intensive Care Medicine and [b]Cardiology, Ghent University Hospital, Ghent University, Ghent, and [c]Research Foundation-Flanders (FWO), Brussels, Belgium; [d]Centre for Critical Care Nephrology, University of Pittsburgh, and [e]The Clinical Research, Investigation, and Systems Modelling of Acute Illness (CRISMA) Centre, Department of Critical Care Medicine, University of Pittsburgh, School of Medicine, Pittsburgh, Pa., USA; [f]Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alta., Canada

Cardiorenal Med 2016;6:116–128
DOI: 10.1159/000442300
Published online: December 19, 2015

1664–3828/15/0062–0116$39.50/0
www.karger.com/crm



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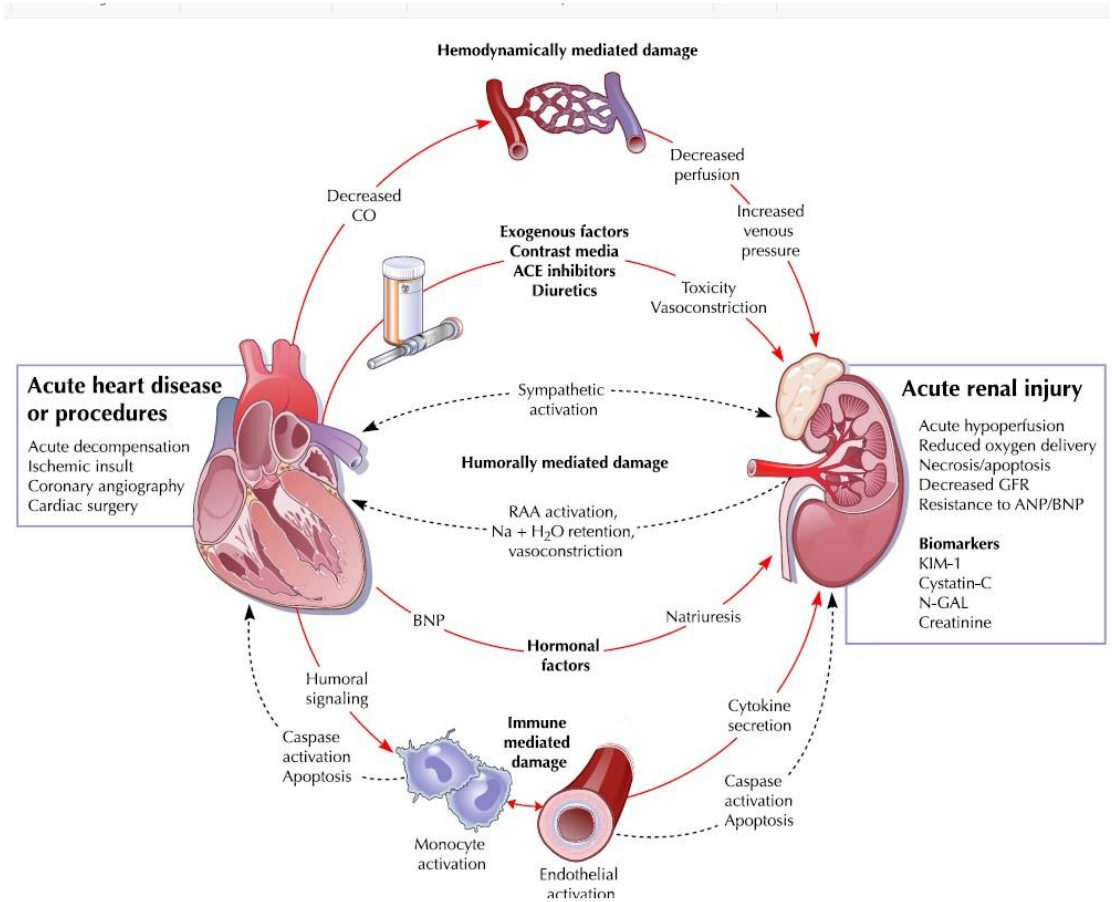

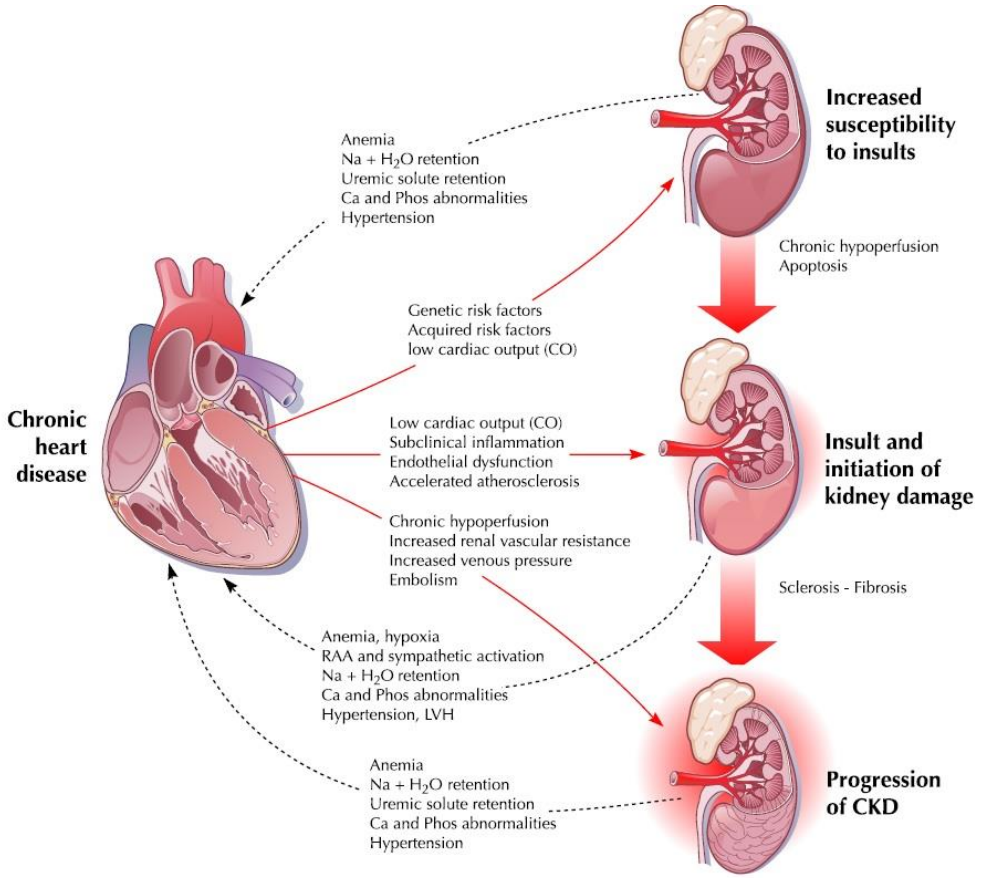

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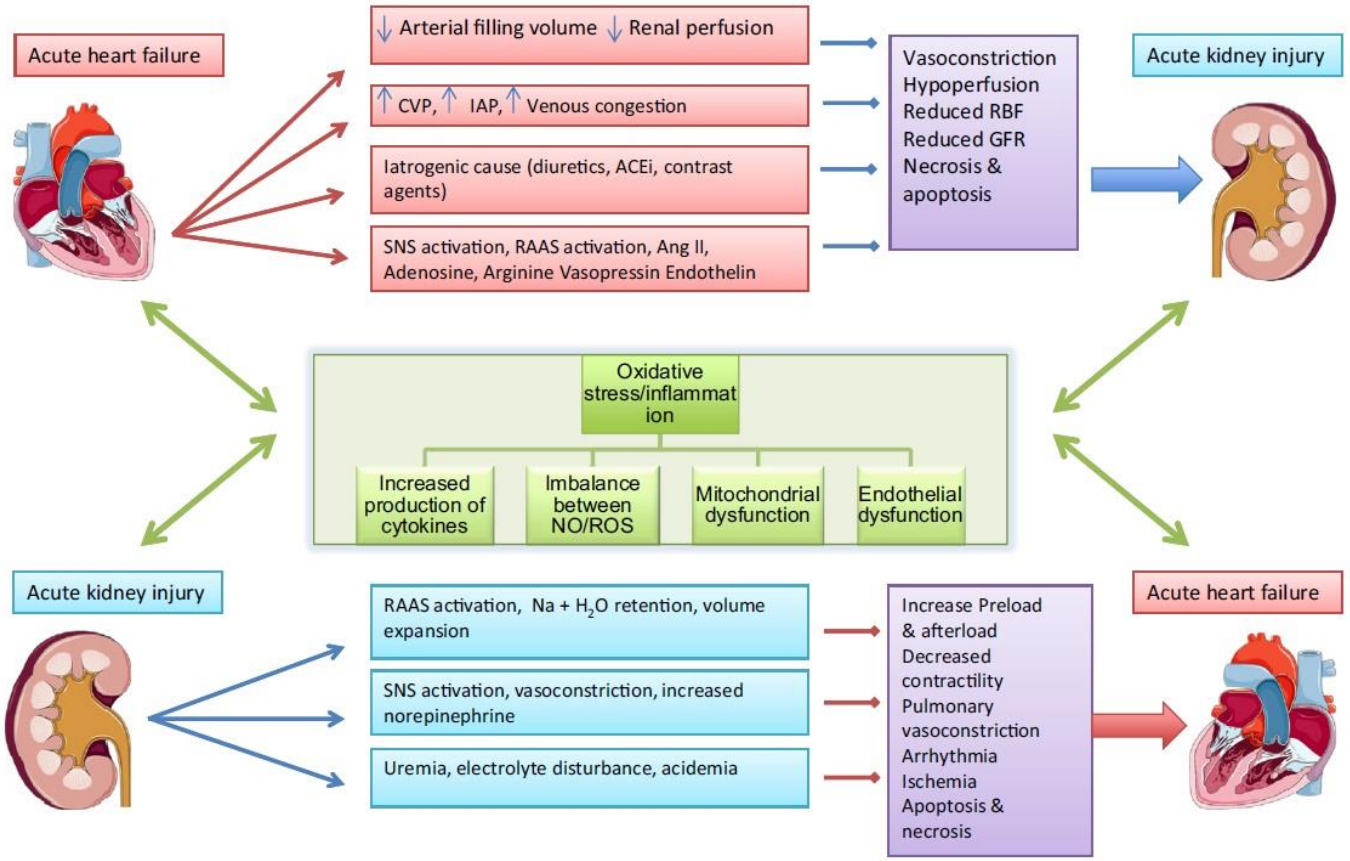
CRS Type I & Type II

Cardiorenal and Renocardiac Syndrome

- → Increased CVP
- → Increased intraabdominal pressure
- → Reduced Cardiac output
- → Neurohormonal dysregulation
  - → RAAS activation
  - → SNS activation
  - → Adenosine/AVP
- → Oxidative stress
- → Inflammatory mediators
- → Renal failure related mechanisms



Kumar U et al. Cardiorenal Syndrome Pathophysiology. Cardiol Clin 2019; 37: 251-265

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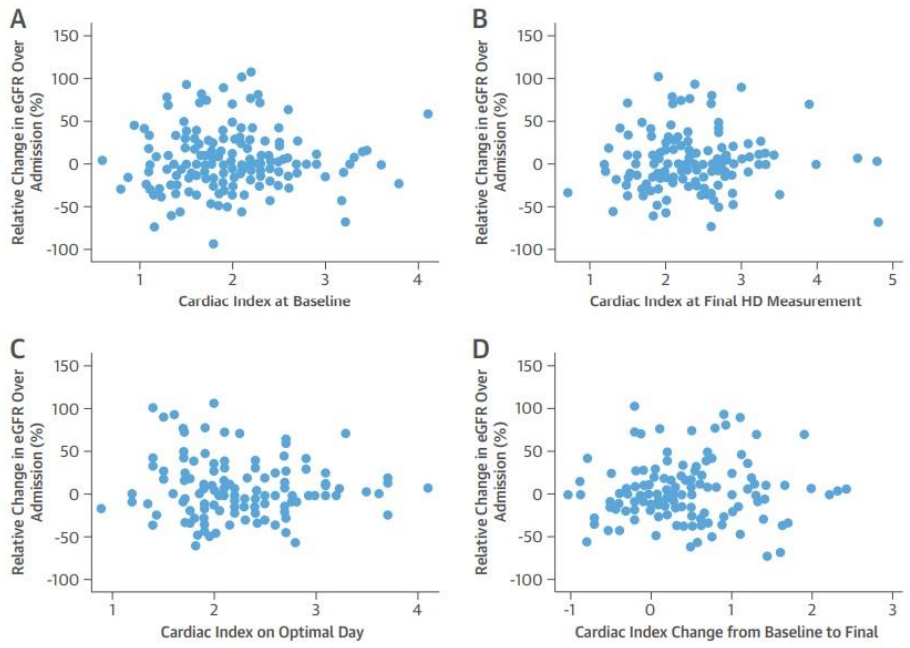
Driving Factor of Cardiorenal Syndrome



ORIGINAL INVESTIGATIONS

Reduced Cardiac Index Is Not the Dominant Driver of Renal Dysfunction in Heart Failure

Jennifer S. Hanberg, BA,[a] Krishna Sury, MD,[b] F. Perry Wilson, MD, MSCE,[a,b,c] Meredith A. Brisco, MD, MSCE,[d] Tariq Ahmad, MD, MPH,[b] Jozine M. ter Maaten, MD,[e] J. Samuel Broughton, BS,[a] Mahlet Assefa, BS,[a] W.H. Wilson Tang, MD,[f] Chirag R. Parikh, MD, PHD,[a,b,c] Jeffrey M. Testani, MD, MTR[a,b]

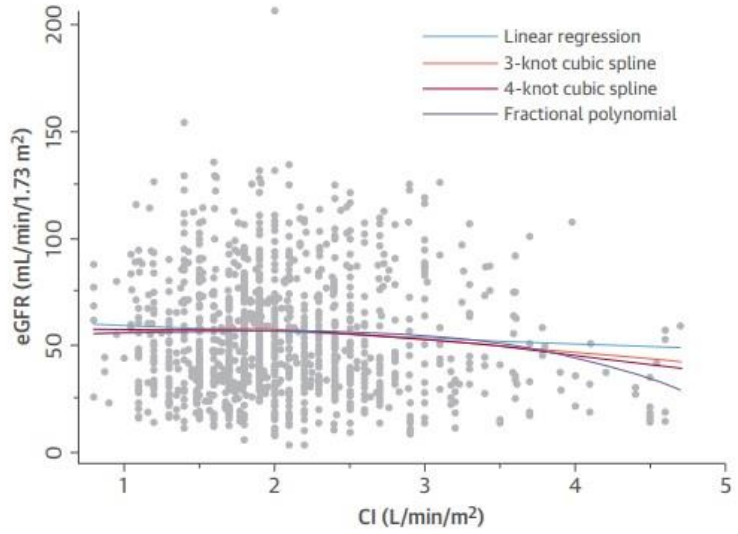
ABSTRACT

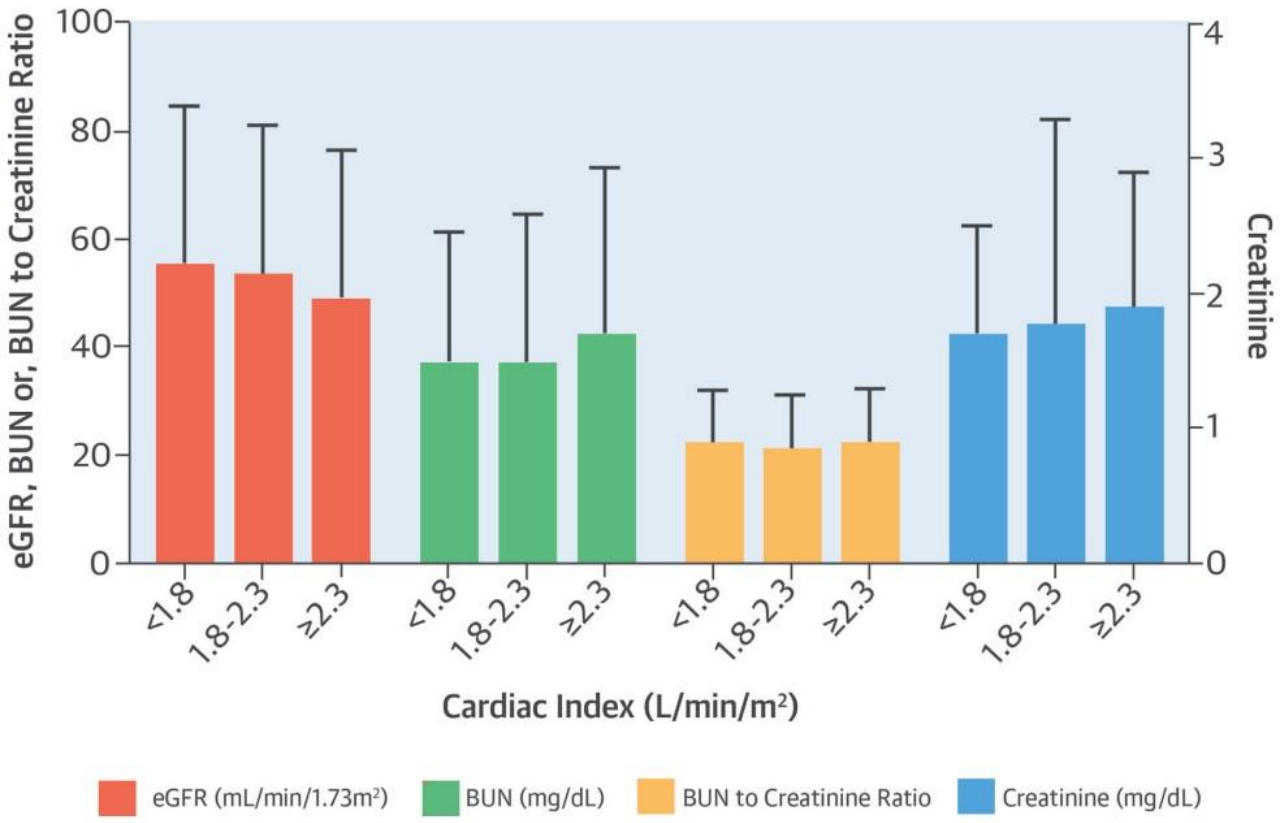
BACKGROUND It is widely believed that a reduced cardiac index (CI) is a significant contributor to renal dysfunction in patients with heart failure (HF). However, recent data have challenged this paradigm.

OBJECTIVES This study sought to determine the relationship between CI and renal function in a multicenter population of HF patients undergoing pulmonary artery catheterization (PAC).

METHODS Patients undergoing PAC in either the randomized or registry portions of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial were included (n = 575). We evaluated associations between CI and renal function across multiple subgroups and assessed for nonlinear, threshold, and longitudinal relationships.

Cardiac index or output is not the driving factor





Hanberg, J.S. et al. J Am Coll Cardiol. 2016;67(19):2199-208.

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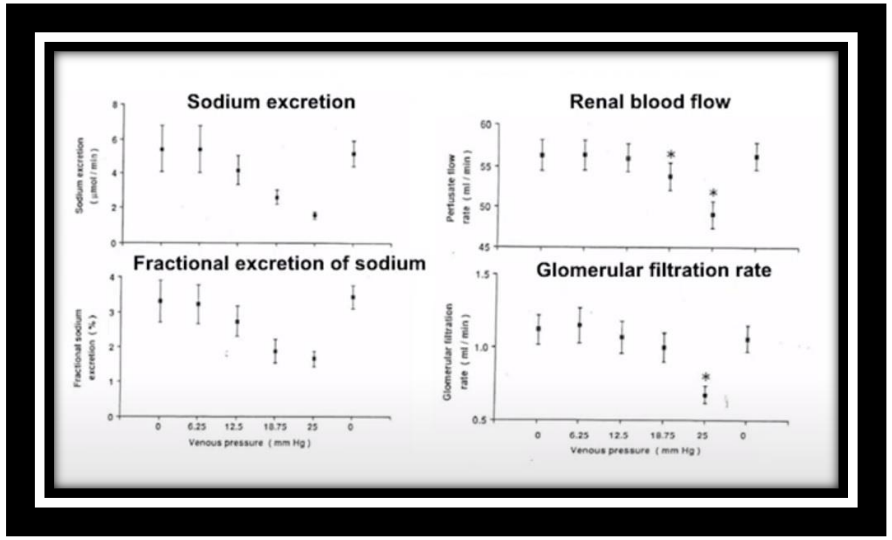
Hemodynamic determinants of WRF- ESCAPE



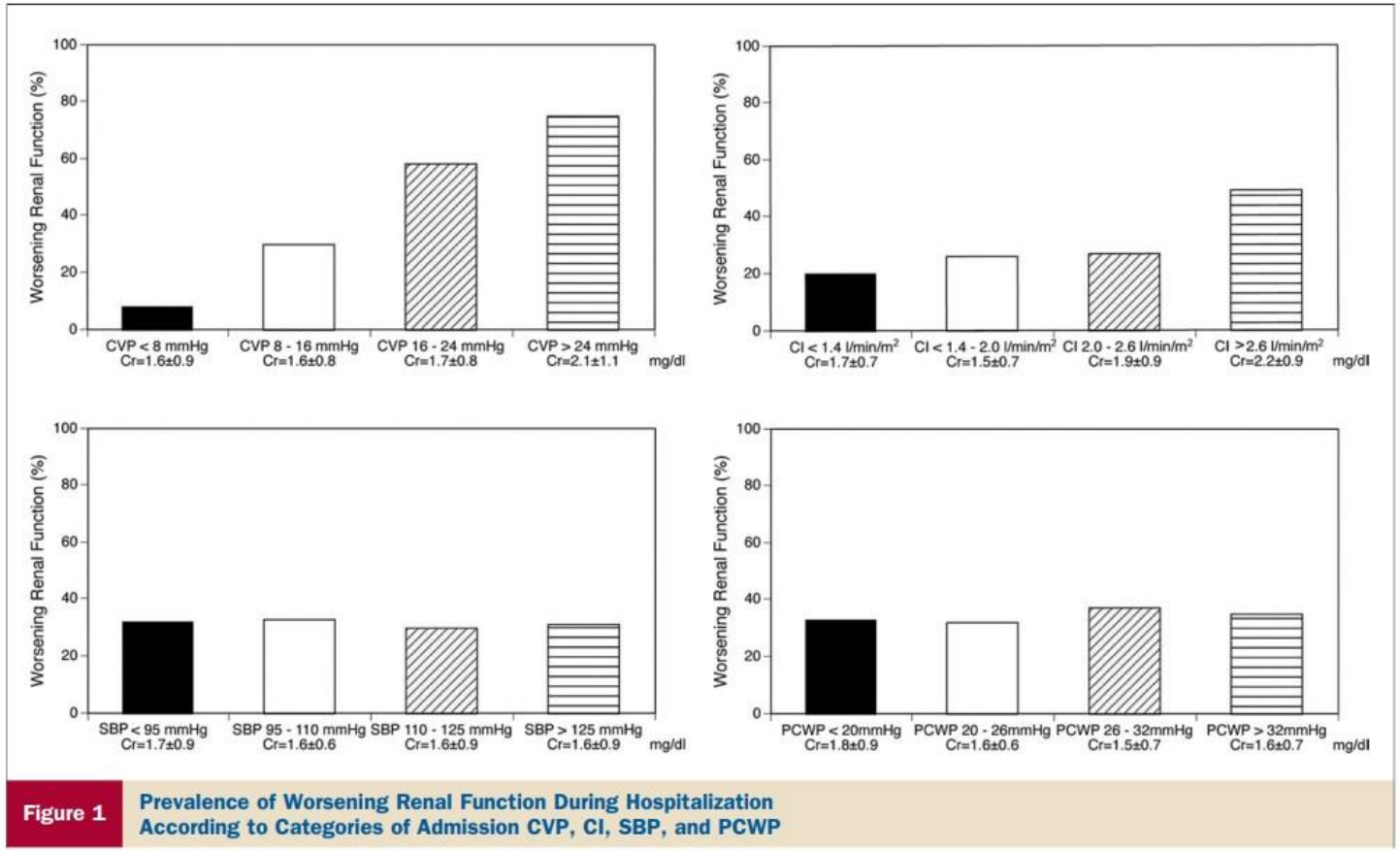
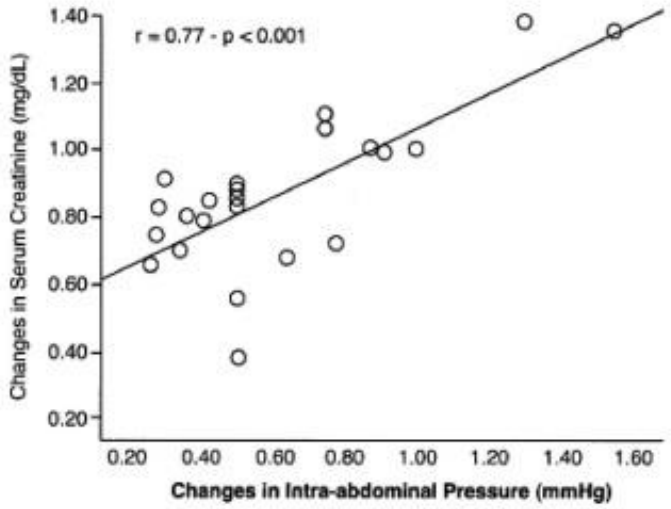
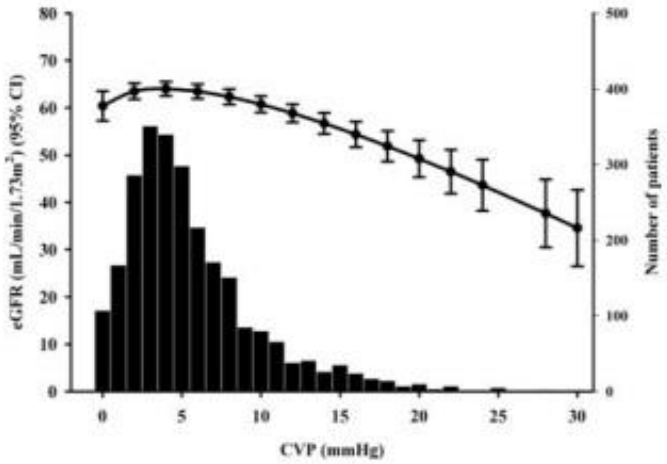


Figure 1 **Prevalence of Worsening Renal Function During Hospitalization According to Categories of Admission CVP, CI, SBP, and PCWP**

Mullens W et al., JACC 2009; 53: 589
Firth et al. Lancet 1988; 1:1033

Abdominal Pressure – Contributions to CRS





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STATE-OF-THE-ART PAPER

Abdominal Contributions to Cardiorenal Dysfunction in Congestive Heart Failure

Frederik H. Verbrugge, MD,*† Matthias Dupont, MD,* Paul Steels, MD,‡ Lars Grieten, PHD,*‡ Manu Malbrain, MD, PHD,§ W. H. Wilson Tang, MD,‖ Wilfried Mullens, MD, PHD*‡

Genk, Diepenbeek, and Antwerp, Belgium; and Cleveland, Ohio

Current pathophysiological models of congestive heart failure unsatisfactorily explain the detrimental link between congestion and cardiorenal function. Abdominal congestion (i.e., splanchnic venous and interstitial congestion) manifests in a substantial number of patients with advanced congestive heart failure, yet is poorly defined. Compromised capacitance function of the splanchnic vasculature and deficient abdominal lymph flow resulting in interstitial edema might both be implied in the occurrence of increased cardiac filling pressures and renal dysfunction. Indeed, increased intra-abdominal pressure, as an extreme marker of abdominal congestion, is correlated with renal dysfunction in advanced congestive heart failure. Intriguing findings provide preliminary evidence that alterations in the liver and spleen contribute to systemic congestion in heart failure. Finally, gut-derived hormones might influence sodium homeostasis, whereas entrance of bowel toxins into the circulatory system, as a result of impaired intestinal barrier function secondary to congestion, might further depress cardiac as well as renal function. Those toxins are mainly produced by micro-organisms in the gut lumen, with presumably important alterations in advanced heart failure, especially when renal function is depressed. Therefore, in this state-of-the-art review, we explore the crosstalk between the abdomen, heart, and kidneys in congestive heart failure. This might offer new diagnostic opportunities as well as treatment strategies to achieve decongestion in heart failure, especially when abdominal congestion is present. Among those currently under investigation are paracentesis, ultrafiltration, peritoneal dialysis, oral sodium binders, vasodilator therapy, renal sympathetic denervation and agents targeting the gut microbiota. (J Am Coll Cardiol 2013;62:485–95) © 2013 by the American College of Cardiology Foundation

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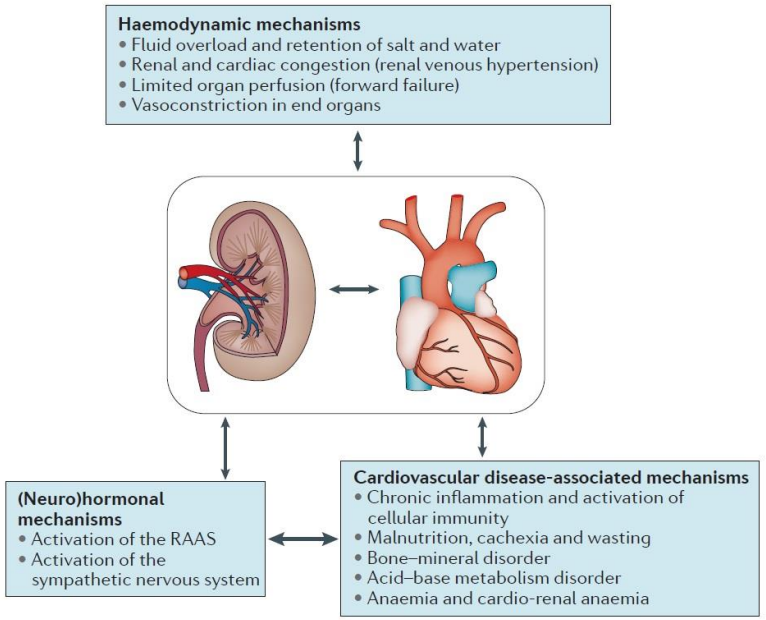
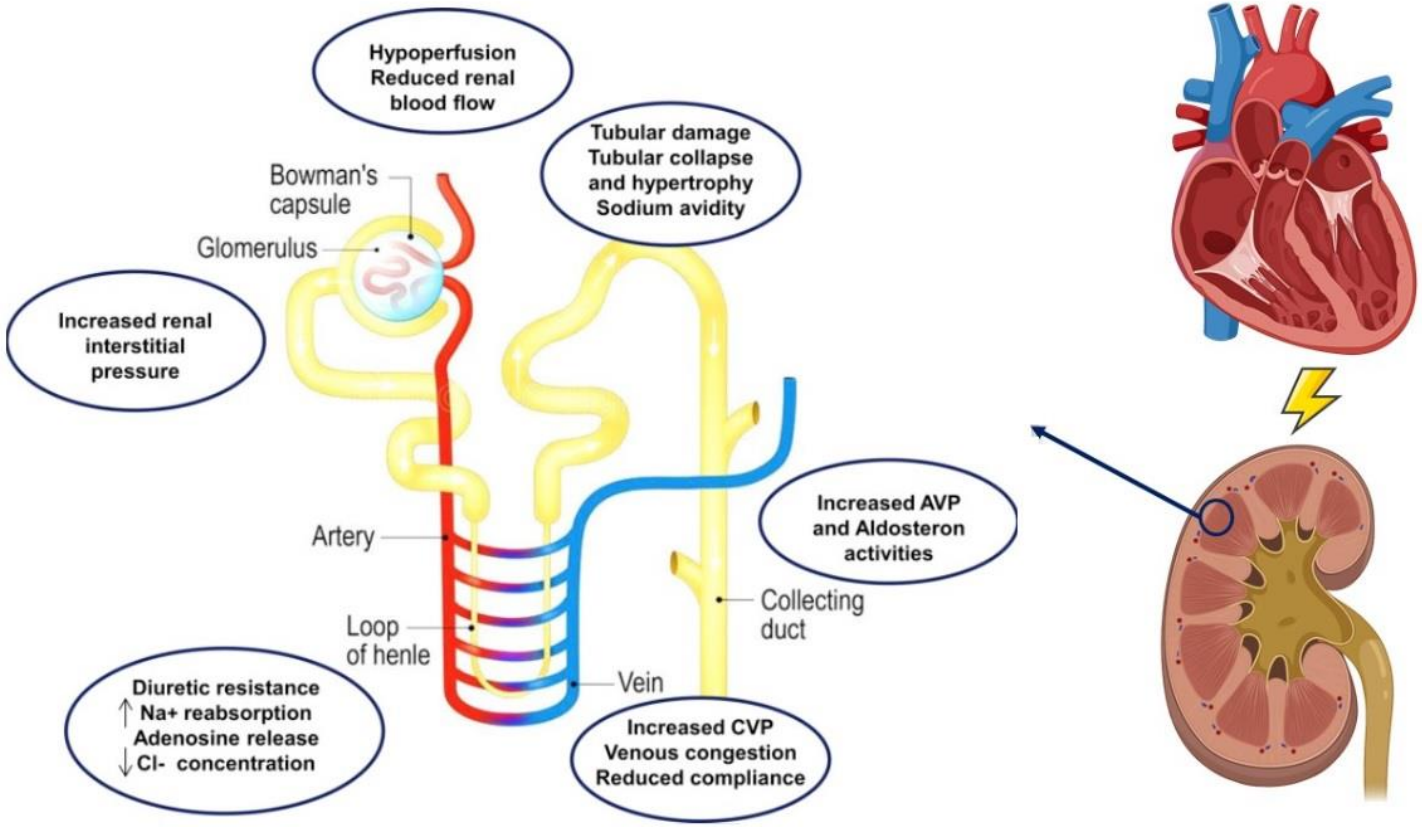
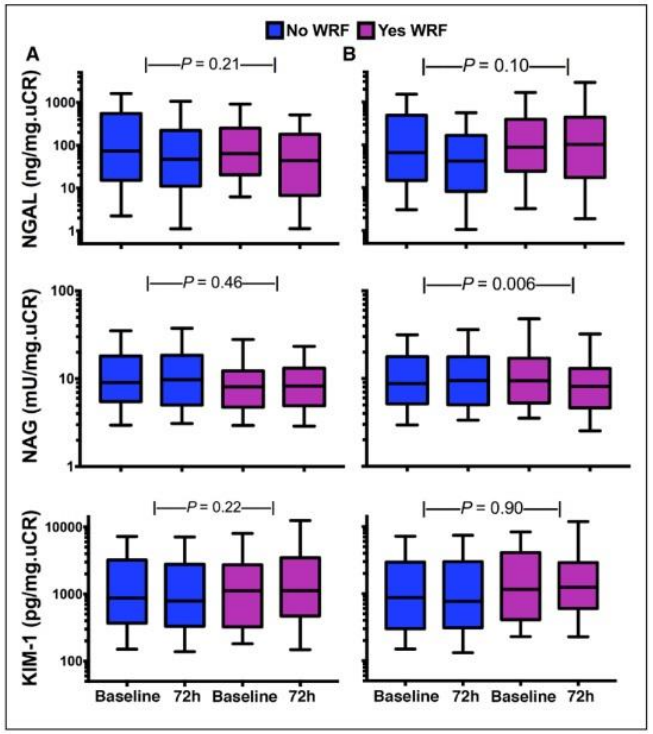
Renal Injury in Heart Failure





Shah BN and Greaves K. The Cardiorenal Syndrome: A review. International Journal of Nephrology 2011

Biomarkers of Renal Injury in CRS

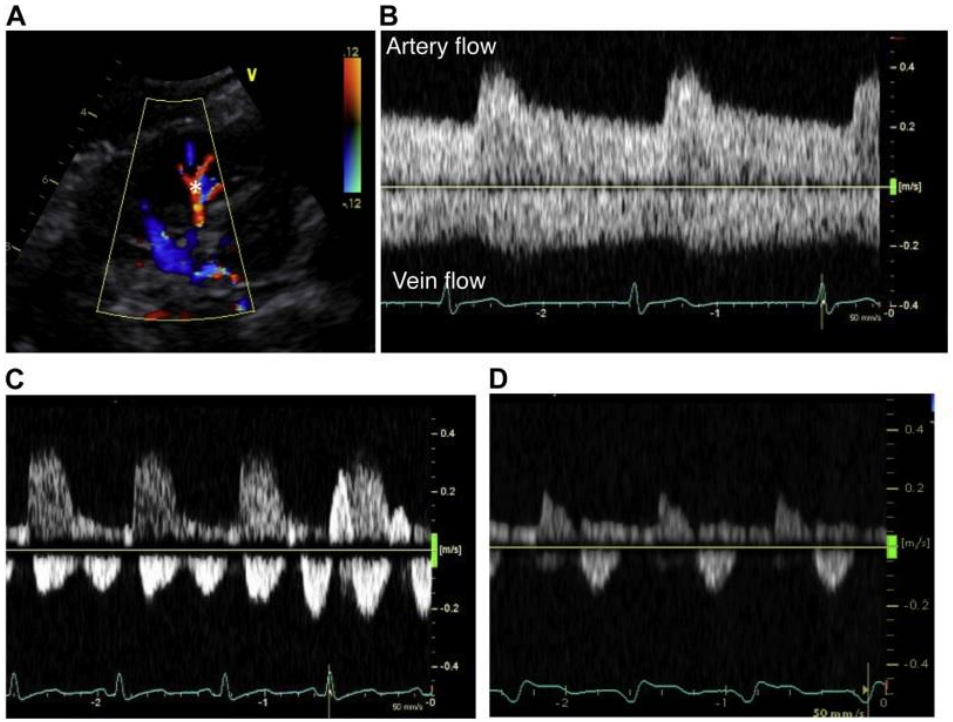


Rangaswami J et al., Circulation. 2019; 139: e840-e878
Ahmad T. Circulation 2018; 137: 2016-2028

Biomarkers	Characteristics/Site of Origin	Diagnostic Value	Prognostic Value
Cardiac biomarkers			
cTn	Marker of myocardial injury	ACS	ACS, HF, CKD
BNP	Marker of myocardial stretch	HF, ACS, CRS	HF, CRS
sST2	Member of IL-1 family of receptors	…	HF, CRS
Galectin-3	β-Galactoside binding lectin (intracellular and extracellular)	…	HF, CRS
Kidney biomarkers			
Biomarkers of glomerular integrity			
Serum creatinine	Skeletal muscle	AKI, CRS	HF, CRS
CysC	All nucleated cells	CRS	CRS
Albuminuria	Marker of glomerular integrity/PCT disruption	CRS	CRS
Biomarkers of tubular injury			
TIMP*IGFBP7	Involved in G1 cell cycle arrest; may stimulate renal epithelium in an autocrine and paracrine fashion and sensitize for upcoming insults	AKI	AKI recovery
Serum NGAL	25-kDa protein found in neutrophil granules; secreted by myocardium, renal tubules, activated immune cells, hepatocytes, lung, and colon	AKI	CRS
Urine NGAL	Loop of Henle, collecting ducts	AKI, CRS	CRS
NAG	PCT	CRS, AKI	CRS
KIM-1	Type 1 cell membrane glycoprotein expressed in regenerating PCT epithelium	AKI	CRS
IL-18	Cytokine mediating inflammation and AKI through the nuclear factor-κB pathway	AKI	CRS
L-FABP	Renal PCT	AKI	…
H-FABP	Cardiomyocytes, distal tubule	HF, CRS	…
Urine angiotensinogen	…	AKI, CRS	CRS
α-1 Microglobulin	Synthesized in liver; freely filtered through glomerular capillaries and reabsorbed by PCT	AKI	AKI recovery

Investigations

- Echocardiography
  - Right atrial Pressures
- Intrarenal Duplex US (IRD)
  - Interlobar vessels
  - Arterial resistance index
  - Venous impedance index
  - Intrarenal venous flow
- Measurement of IAP (intraabdominal Pressures)



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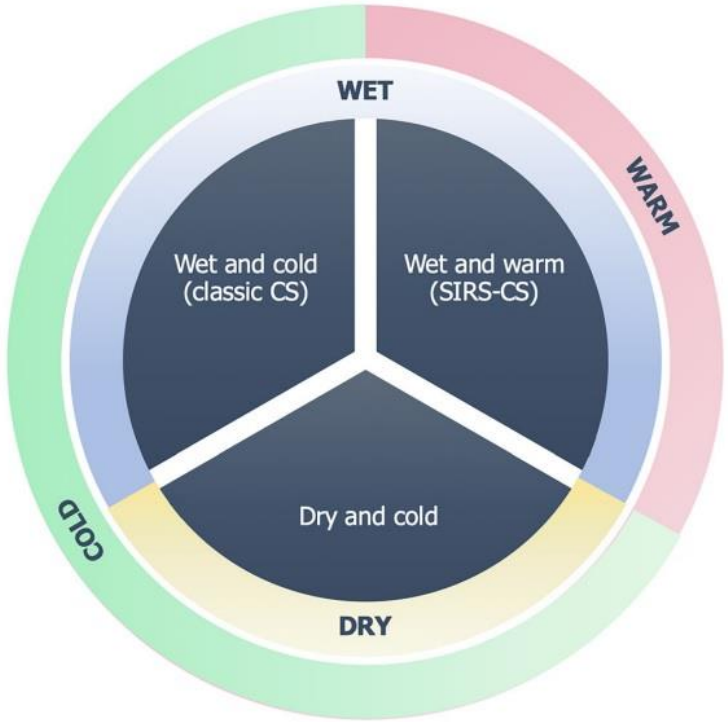
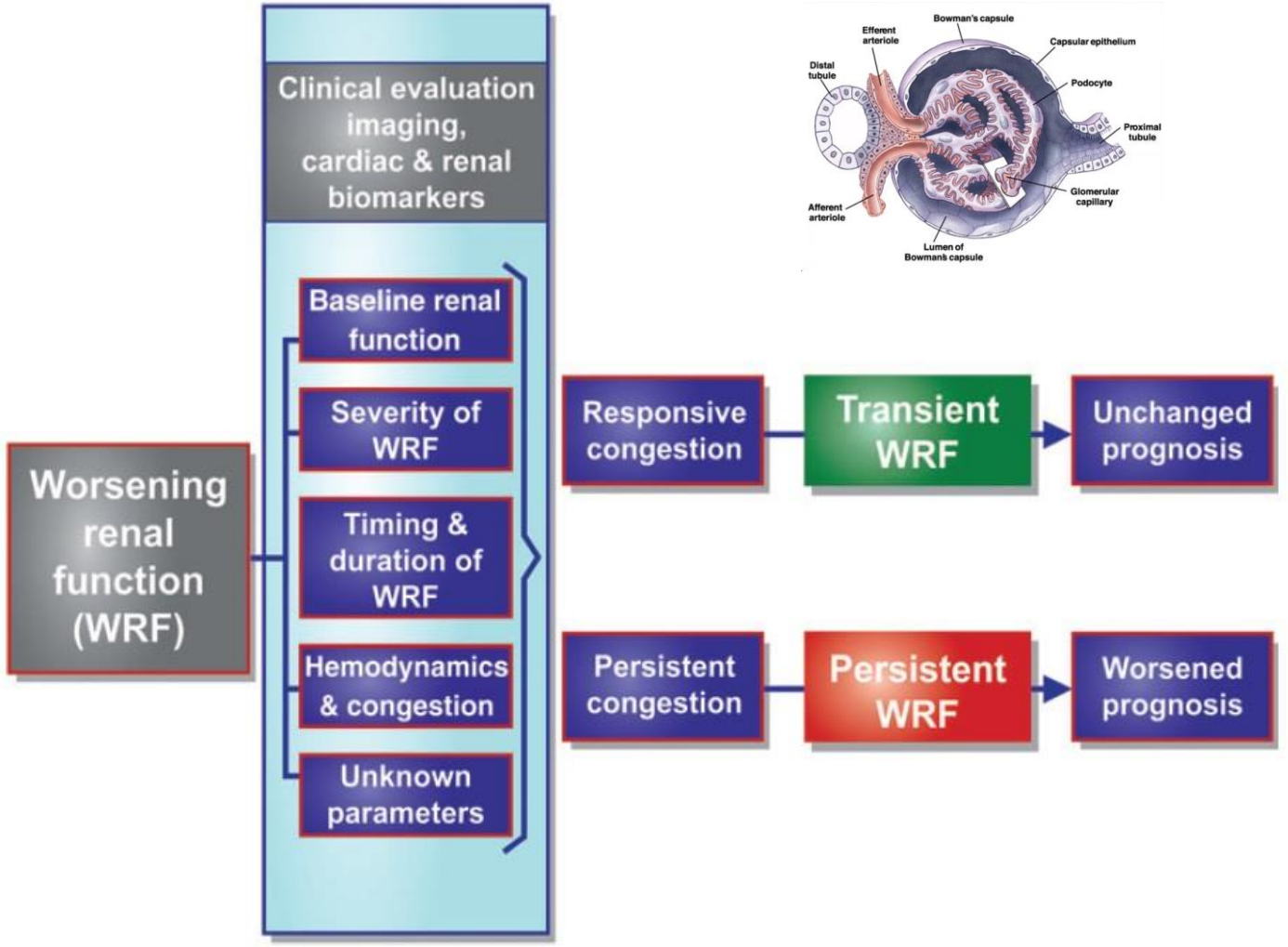
Clinical Implications of Intrarenal Hemodynamic Evaluation by Doppler Ultrasonography in Heart Failure

Noriko Iida, BA,[a] Yoshihiro Seo, MD,[b] Seika Sai, MD,[b] Tomoko Machino-Ohtsuka, MD,[b] Masayoshi Yamamoto, MD,[b] Tomoko Ishizu, MD,[b,c] Yasushi Kawakami, MD,[c] Kazutaka Aonuma, MD[b]





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What should we ask when we approach CRS?

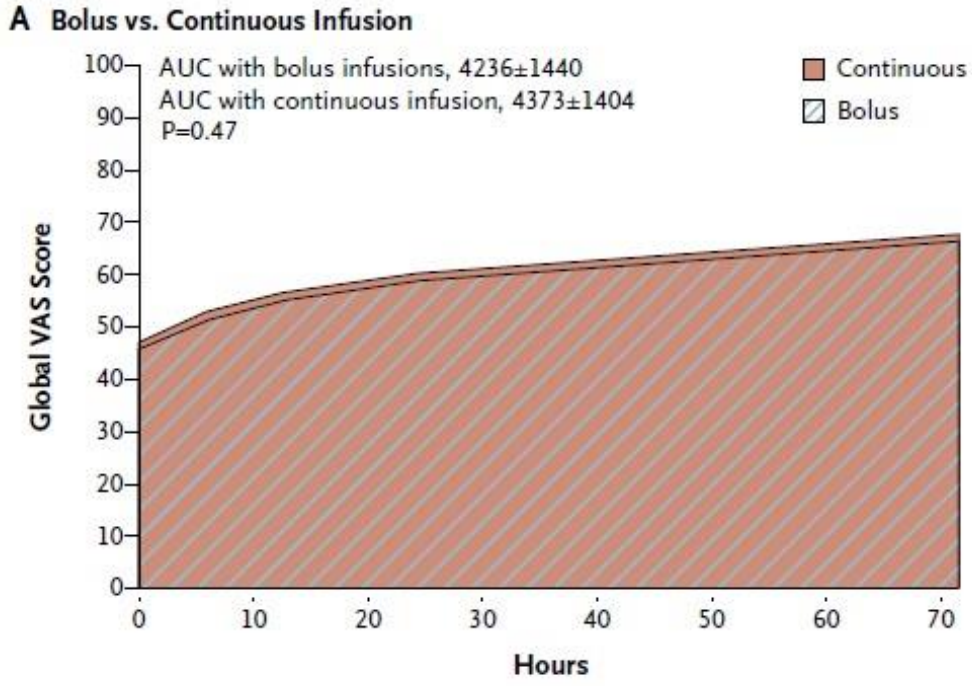
- Volume status of the patient?
- Is the Blood Pressure adequate for renal perfusion?
- What is the Cardiac output?
- What is the Central Venous Pressure? (JVP)
- Is there intrinsic renal disease?

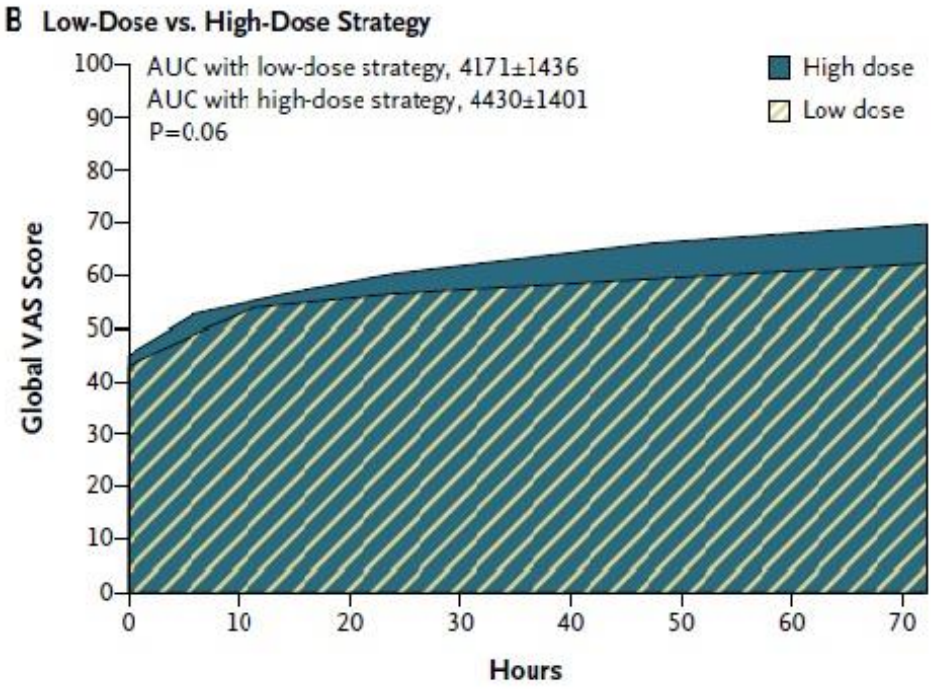
Heywood et al., The Cardiorenal Syndrome: A Clinician's Guide to Pathophysiology and Management 2011

Pre-diuretic Era

→Venesection
→Scarification
→Sweating utilizing hot air bath or warm water bath
→Schwartz in 1930 discovered that Sulfonamide has Na secretion property and used for edema in CHF

Diuretic Strategies in Patients with ADHF





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Aggressive diuresis Improved Survival

Heart Failure

(*Circulation*. 2010;122:265-272.)

Potential Effects of Aggressive Decongestion During the Treatment of Decompensated Heart Failure on Renal Function and Survival

Jeffrey M. Testani, MD; Jennifer Chen, BS; Brian D. McCauley, BS; Stephen E. Kimmel, MD, MSCE; Richard P. Shannon, MD

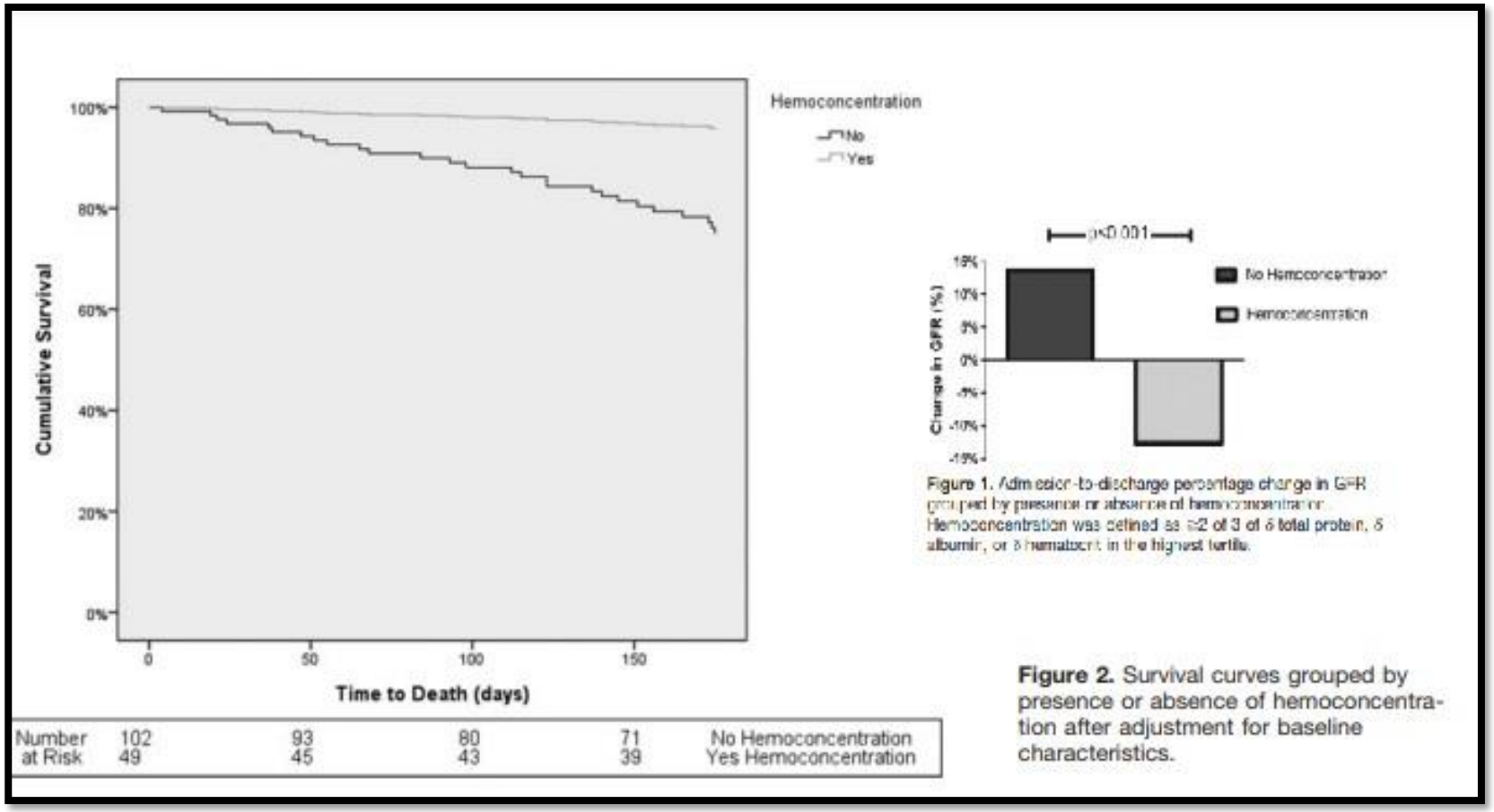

Figure 1. Admission-to-discharge percentage change in GFR grouped by presence or absence of hemoconcentration. Hemoconcentration was defined as ≥2 of 3 of ↓ total protein, ↓ albumin, or ↑ hematocrit in the highest tertile.

Figure 2. Survival curves grouped by presence or absence of hemoconcentration after adjustment for baseline characteristics.

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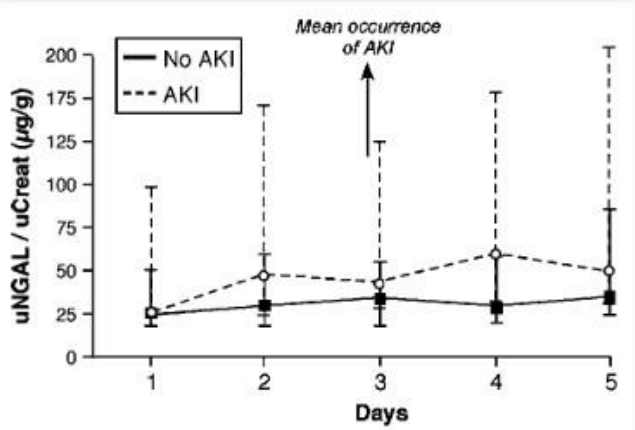
Aggressive Diuresis in ADHF



Lack of significant renal tubular injury despite acute kidney injury in acute decompensated heart failure

Matthias Dupont[1], Kevin Shrestha[1], Dhssraj Singh[1], Adiveh Awad[2], Cynthia Kovach[2], Mario Scarcipino[2], Anjli P. Maroo[2], and W.H. Wilson Tang[1]*

[1]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, OH 44195, USA; and [2]Fairview Hospital, Cleveland, OH, USA

Received 23 November 2011; revised 27 December 2011; accepted 19 February 2012; online publish-ahead-of-print 14 April 2012

Diuretic Resistance

No Consensus on definition of diuretic resistance

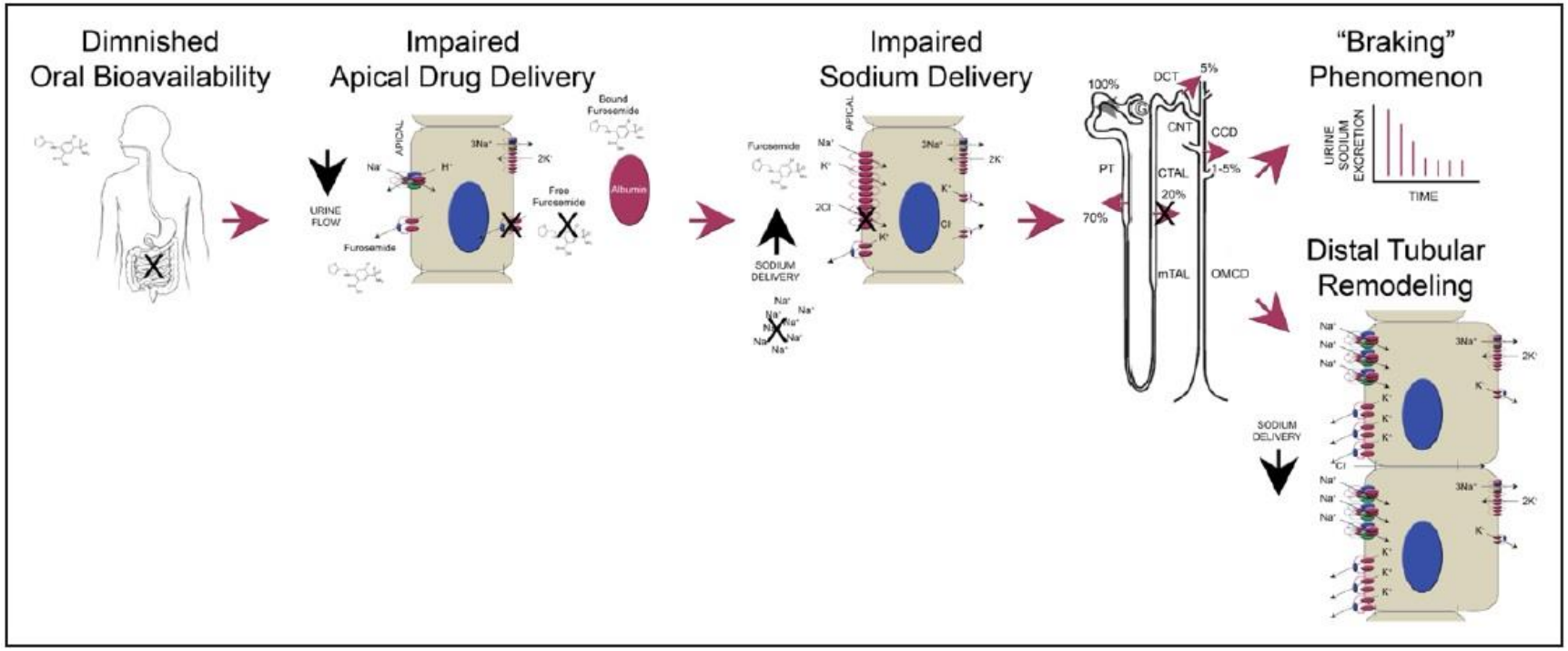
- → Poor response to diuretic therapy
- → Persistent Signs and symptoms despite diuretic therapy
- → Furosemide > 80 mg Vs 120 mg
- → Fractional Sodium Excretion < 0.2%
- → Failure to excrete at least 90 mmol of sodium within 72 hours of 160 mg oral Furosemide BID
- → Lack of Weight loss during IV loop diuretic therapy
- → Lack of negative fluid balance with Loop diuretic therapy

Management of Diuretic Resistance in Heart Failure

- Restriction of daily fluid intake (1.0 to 1.5 L) and moderate restriction of daily salt intake (<5 g)
- Avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs)
- Institution of ACE inhibition (start with small doses, such as captopril 6.25 mg three times per day, lisinopril or enalapril 2.5 mg daily, or ramipril 1.25 mg daily)
- Avoid overly aggressive vasodilator therapy that reduces mean arterial pressure below that necessary for renal perfusion
- Oral administration of a short-acting loop diuretic in several divided (and increasing) doses (eg, furosemide 40 to 80 mg two to three times per day), bolus intravenous administration (eg, furosemide 20 to 40 mg three times per day), or continuous intravenous infusion (furosemide 5 to 20 mg/hour)
- Sequential nephron blockade by combination of a loop diuretic and a thiazide (eg, hydrochlorothiazide 25 mg or metolazone 2.5 mg daily)
- Addition of small doses of spironolactone (12.5 to 25 mg/day) with ACE inhibitors, or larger doses (50 to 100 mg/day) in the absence of ACE inhibition
- Consider short-term addition of acetazolamide in selected patients

Kramer BK. Am J Med 1999; 106: 90-96

Mechanisms of diuretic Resistance



Rangaswami J et al., Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies. A scientific Statement From the American Heart Association. Circulation. 2019; 139: e840-e878.

Evidence Table of RCTs Comparing Pharmacological Therapy for Fluid Overload and Ultrafiltration in Patients With Acute Decompensated HF

Study	Subjects, n	Primary End Point	UF Protocol	Diuretics Protocol	Effect on Renal Function	Effect on Weight Loss	Adverse Events
RAPID-CHF[133]	40	Weight loss at 24 h	Single 8-h UF session to maximum rate of 500 mL/min per 1.73 m^2	Clinician based	NS	Similar in both groups; trend toward higher weight loss in UF arm	…
UNLOAD[134]	200	Weight loss and dyspnea at 48 h	Time and rate of UF flexible; maximum rate of 500 mL/min per 1.73 m^2	Clinician based	NS	UF>DT	…
CARRESS-HF[135]	188	Change in SCr and weight at 96 h	Fixed UF rate of 200 mL/min per 1.73 m^2	Prespecified stepped-up algorithm	Significant increase in SCr with UF	Similar in both groups	Higher SAEs in UF arm
CUORE[136]	56	Hospitalization for HF at 1 y	Time and rate of UF flexible; maximum rate of 500 mL/min per 1.73 m^2	Clinician based	Significant increase in SCr with DT at 6 mo	Similar in both groups	…
AVOID-HF*[137]	224	Time to HF <90 d after discharge	Time and rate of UF flexible; maximum rate of 500 mL/min per 1.73 m^2	Prespecified algorithm	NS	Similar in both groups	Higher SAEs in UF arm

Rangaswami J et al., Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies. A scientific Statement From the American Heart Association. Circulation. 2019; 139: e840-e878.

Ultrafiltration in Heart Failure

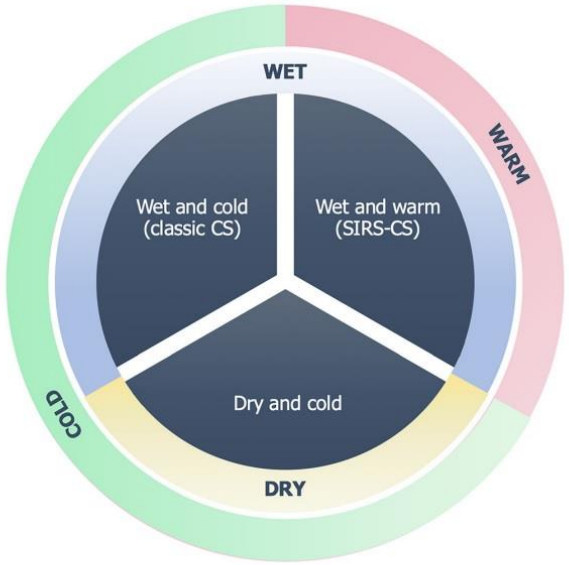
Vasoactive Agents in CRS

- Dopamine
  - ROSE-HF & DAD-HF II Showed no benefit of low dose Dopamine
- Nesiritide
  - ASCEND-HF showed no difference in WRF between Nesiritide and Placebo
- Dobutamine or Milrinone
  - No benefit shown in terms of diuresis or renal function

Vasoactive Agents in CRS

- Vasopressin Antagonist
  - EVEREST: similar rates of adverse events with greater degree of weight reduction in Tolvaptan arm
  - SECRET of CHF trial: No improvement in dyspnea
- Dobutamine or Milrinone
  - No benefit shown in terms of diuresis or renal function
- Levosimendan & Omecamptive Mecarbil
  - Insufficient or Limited data in the context of CRS

Clinical Phenotypes – AKI in Cardiogenic shock



Heart Failure Reviews (2021) 26:487-496
https://doi.org/10.1007/s10741-020-10034-0

Pre-Renal	Intrinsic	Post-renal
↓ Cardiac Output		↑ CVP Systemic Congestion
SNS: Vaso Constriction	SNS: RAAS activation	Papillary necrosis & Ureteral Obstruction

Mispositioning of devices
Contrast administration
Nephrotoxic agents
Excess Intrathoracic Pressure during Mechanical ventilation

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Predictors of severe acute kidney injury (logistic regression)

Characteristics	OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Age	1.00 (0.99-1.02)	.652		
BMI	1.02 (0.99-1.06)	.241		
Medical history				
CAD	1.30 (0.81-2.09)	.274		
HLD	1.39 (0.86-2.24)	.180	1.25 (0.68-2.27)	.474
HTN	1.51 (0.94-2.43)	.090	1.04 (0.57-1.92)	.893
DM	1.17 (0.70-1.94)	.551		
COPD	0.78 (0.32-1.89)	.583		
Prior CVA	4.08 (1.62-10.25)	**.003**	3.10 (1.14-8.42)	**.026**
CKD	1.92 (1.10-3.33)	**.021**	1.42 (0.74-2.73)	.290
Preoperative status				
Cause		.089		.367
1-PCS	Reference	-	Reference	-
2-AMI*	0.42 (0.22-0.80)	**.008**	0.45 (0.22-0.92)	.028
3-Graft*	0.73 (0.33-1.60)	.431	0.55 (0.23-1.35)	.195
4-ADHF*	0.51 (0.25-1.05)	.066	0.44 (0.19-1.02)	.056
5-Other*	0.60 (0.27-1.30)	.194	0.55 (0.23-1.30)	.172
MAP	0.99 (0.98-1.00)	.240		
Hemoglobin	0.83 (0.74-0.93)	**.001**	0.90 (0.80-1.03)	.130
Baseline creatinine	1.74 (1.29-2.35)	**.000**	1.53 (1.10-2.13)	**.012**
ALT	1.00 (1.00-1.00)	**.037**	1.00 (1.00-1.00)	.067
IABP	0.95 (0.59-1.52)	.827		
Active CPR	1.29 (0.72-2.34)	.392		
Device (CentriMag = 0, ECMO = 1)	1.72 (1.06-2.78)	**.028**	1.60 (0.93-2.75)	.087

Cardiogeni
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Andrew I. Ab
Jai Radhakris
Paolo Colomb
Hiroo Takaya

CrossMark

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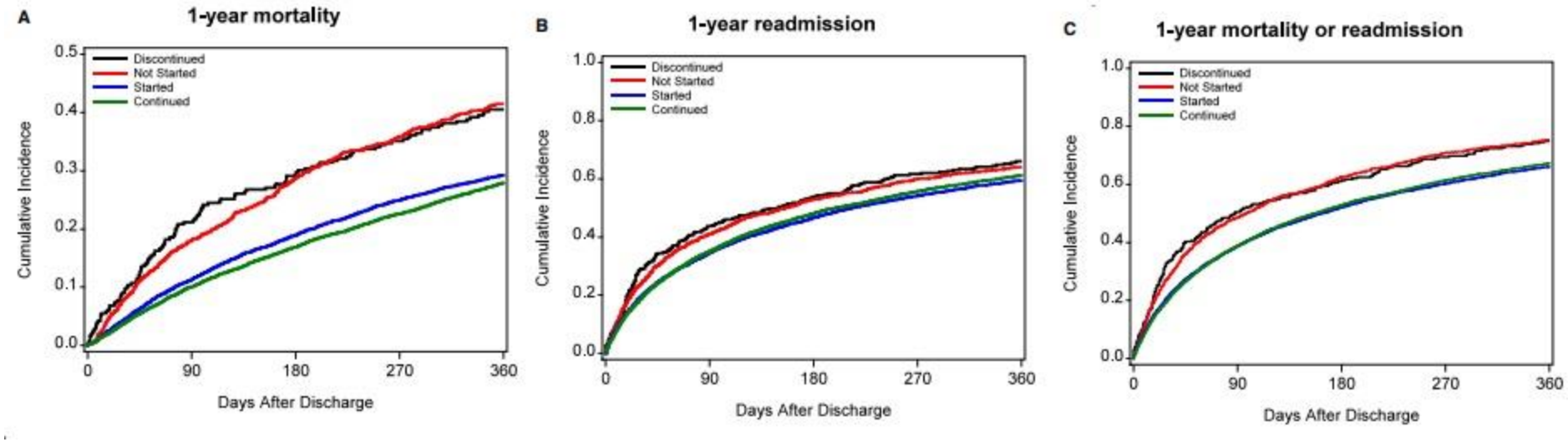
Initiation or Continuation of RAAS agents during ADHF

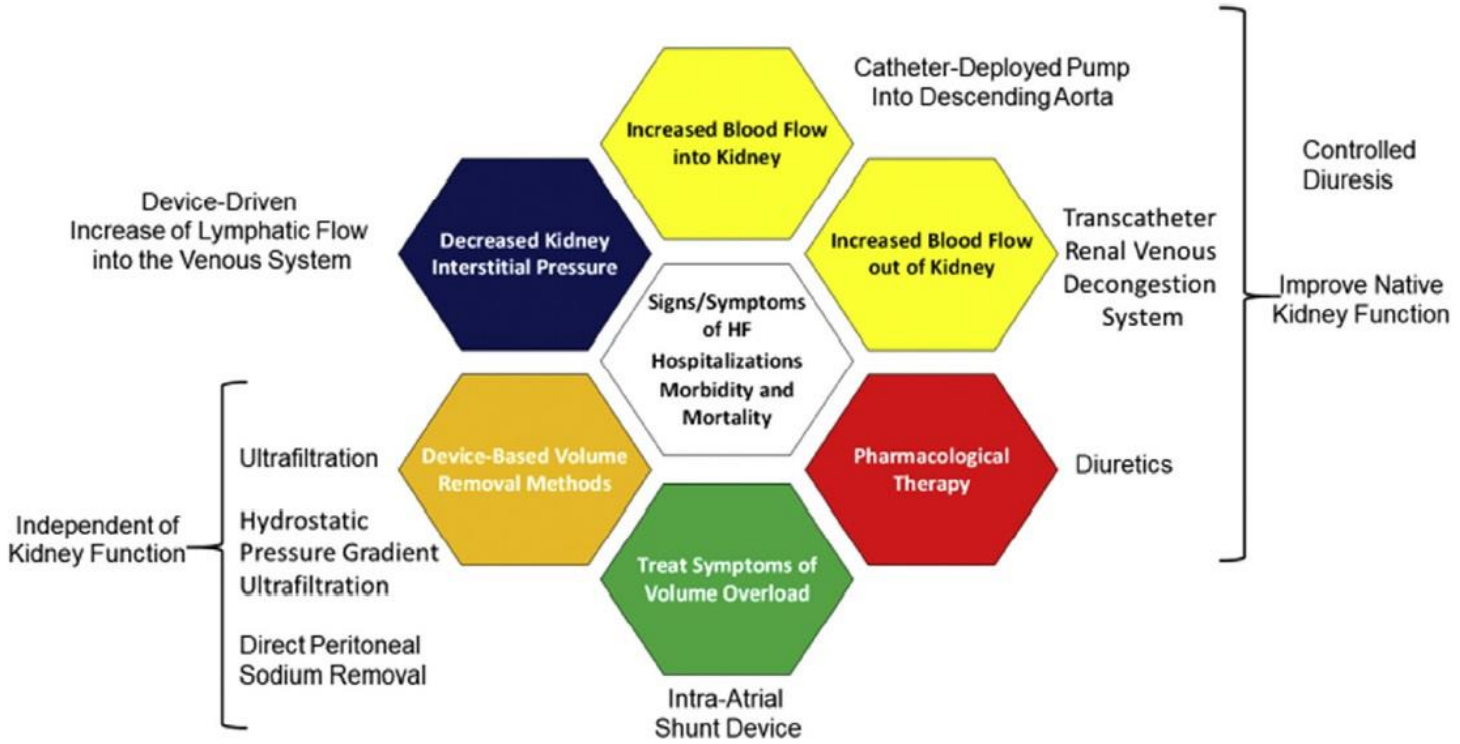


Gilstrap L et al., J Am Heart Assoc. 2017; 6: e004675

GDMT in HFrEF with Renal dysfunction

CRT	Strong	Strong	Absent
ICD	Strong	Strong	Weak
H-ISDN	Weak	Weak	Absent
Digoxin	Weak	Weak	Weak
Ivabradine	Moderate	Moderate	Absent
β-blocker	Strong	Strong	Moderate
MRA	Strong	Strong	Absent
ARNi	Strong	Strong	Absent
ACE inhibitor/ARB	Strong	Strong	Weak
Diuretics	Absent	Absent	Absent
	CKD 1 and 2	CKD 3	CKD 4 and 5

Future Directions



Costanza MR., The Cardiorenal Syndrome in Heart Failure. Cardiol Clin 40 (2022) 219–235
https://doi.org/10.1016/j.ccl.2021.12.010

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Conclusion

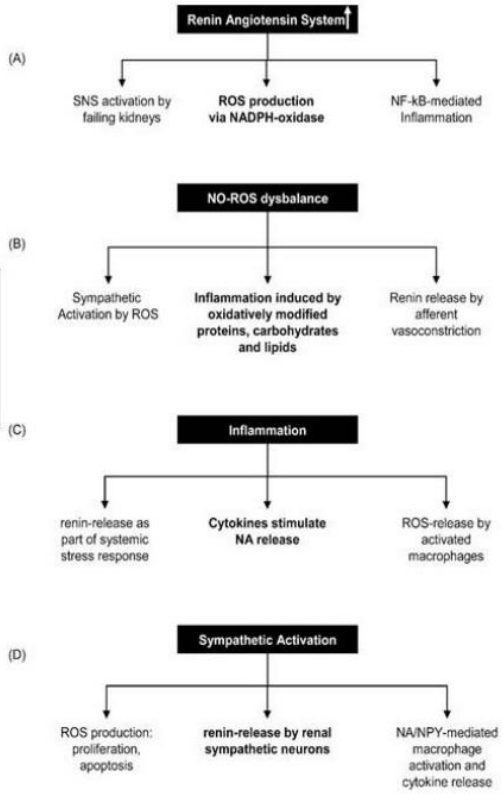
- Heart Failure and Renal disease frequently co-exist
  - Bidirectional
  - Temporally regulated
  - Mediated by multiple mechanisms
  - Heterogeneity in clinical manifestations
  - Functional Vs structural damage
  - May affect other organs
- Associated with poor prognosis
- Management is Challenging
- Recognition of this syndrome is essential for institution of appropriate management strategies

Guyton today

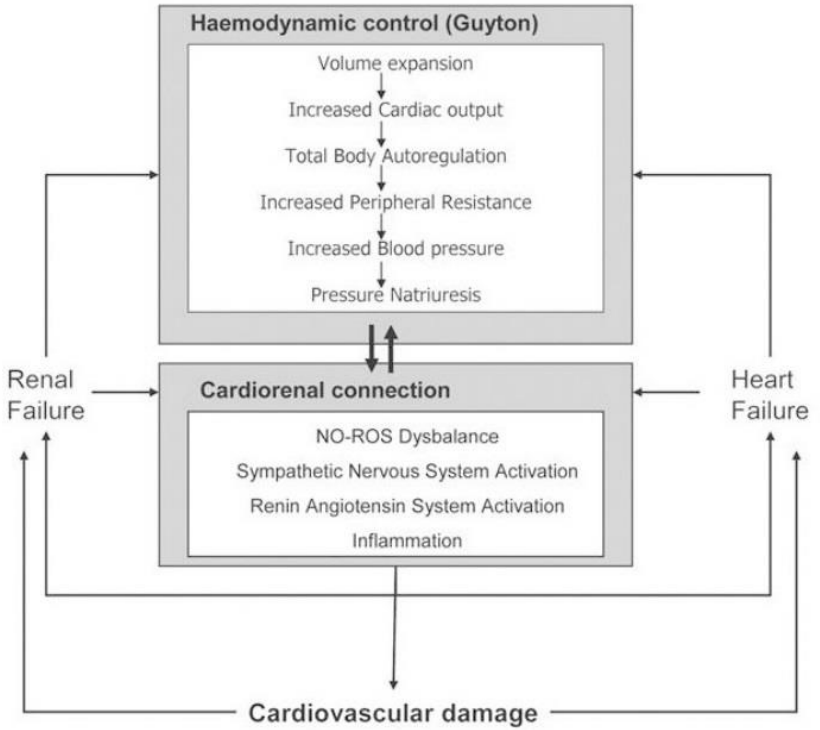
The severe cardiorenal syndrome:
'Guyton revisited'

Lennart G. Bongartz[1], Maarten Jan Cramer[1], Pieter A. Doevendans[1], Jaap A. Joles[2], and Branko Braam[2*]

European Heart Journal (2005) 26, 11–17
doi:10.1093/eurheartj/ehi020



Guyton, 1955 Guyton hypothesis



Limitations

- Significant inherent heterogeneity within the classes of CRS
- Lack of mechanistic framework