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Cardiorenal Syndrome: Do Changes in Creatinine Matter?

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Disclosures

None

Case Presentation

- A 52 year-old woman with a three year history of HFrEF from NICM presents with one week of worsening dyspnea on exertion, orthopnea and lower extremity swelling.
- Medical therapy includes furosemide 40 mg twice daily, lisinopril 10 mg daily, carvedilol 12.5 mg twice daily, and spironolactone 25 mg daily
- Exam shows JVD of 13 cm with HJR and 2+ edema
- Echo shows LVEF of 32%, moderate diastolic dysfunction, 2+ MR, IVC is 2.4 and <50% collapse
- Labs notable for a creatinine of 1.5 mg/dl from a previous value of 1.0 mg/dl one month prior

Case Presentation

- Patient admitted and started on furosemide 80 mg IV twice daily with poor urine output
- Over the next two days, escalated to a furosemide drip because of continued fluid overload and symptoms. Creatinine increasing to 2.1 mg/dl.
- Hospital day four, intravenous chlorothiazide added and creatinine now 3.3 mg/dl with continued poor urine output.
- Nephrology was consulted for dialysis and plan for right heart catheterization.
- What went wrong?

Case Conclusion

- Further history reveals patient taking ibuprofen 800 mg TID for seven days prior to admission because of back pain with her lisinopril and furosemide.
- Urinalysis reveals muddy brown casts consistent with ATN.

Outline

- Defining the syndrome
- Pathophysiology
- Epidemiology and Outcomes
- Paradoxes and Controversies
- New Paradigms in Acute Kidney Injury
- Biomarkers in Acute Heart Failure for Cardiorenal Syndrome

Defining the Syndrome

Importance of Cardiorenal Interactions Recognized for Over 30 years

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Renal Function: The Cinderella of Cardiovascular Risk Profile

Luis M. Ruilope, MD,* Dirk J. van Veldhuisen, MD, PHD, FACC,† Eberhard Ritz, MD, FRCP, FACP,‡ Thomas F. Luscher, MD, FRCP§

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Renal Function: The Cinderella of Cardiovascular Risk Profile

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- Hypertension
- Coronary Artery Disease
- Incident Heart Disease
- Congestive Heart Failure

Consensus Definition

- “Disorders of the heart and kidney whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other”
  - Eur Heart J 31: 703–711, 2010

- Basically dynamic pathophysiologic interplay between the two organs.

Framework for Classifying Interaction

CRS Type I (Acute Cardiorenal Syndrome)
Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury

CRS Type II (Chronic Cardiorenal Syndrome)
Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease

CRS Type III (Acute Renocardiac Syndrome)
Abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)

CRS Type IV (Chronic Renocardiac Syndrome)
Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events

CRS Type V (Secondary Cardiorenal Syndrome)
Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

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

Cardiorenal Syndrome Is Not Specific To Heart Failure

- Heart Failure, both acute and chronic
- Acute Coronary Syndrome
- Contrast Induced Nephropathy
- Cardiac Surgery
- Cholesterol Emboli Syndrome
- Hypertension

The Bidirectional Relationship
Kidney Disease Promotes Cardiovascular Disease

Sudden Cardiac Death and Dialysis Patients

Charles A. Herzog,*† J. Michael Mangrum,‡ and Rod Passman§
*Cardiovascular Special Studies Center, United States Renal Data System, Minneapolis, Minnesota, †Department of Medicine, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota, ‡Department of Medicine, University of Virginia, Charlottesville, Virginia, and §Department of Medicine, Northwestern University, Chicago, Illinois

- 43% of deaths in dialysis patients are from a cardiovascular cause
  - 62% of these are from arrhythmias

Predictors of Early Mortality among Incident US Hemodialysis Patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Brian D. Bradbury,* Rachel B. Fissell,† Justin M. Albert,‡ Mary S. Anthony,* Cathy W. Critchlow,* Ronald L. Pisoni,‡ Friedrich K. Port,‡ and Brenda W. Gillespie§
*Department of Global Epidemiology, Amgen, Inc., Thousand Oaks, California; †Department of Internal Medicine, Veteran's Affairs Medical Center, ‡Dialysis Outcomes and Practice Patterns Study (DOPPS), University Renal Research and Education Association and §Department of Biostatistics, University of Michigan, Ann Arbor, Michigan

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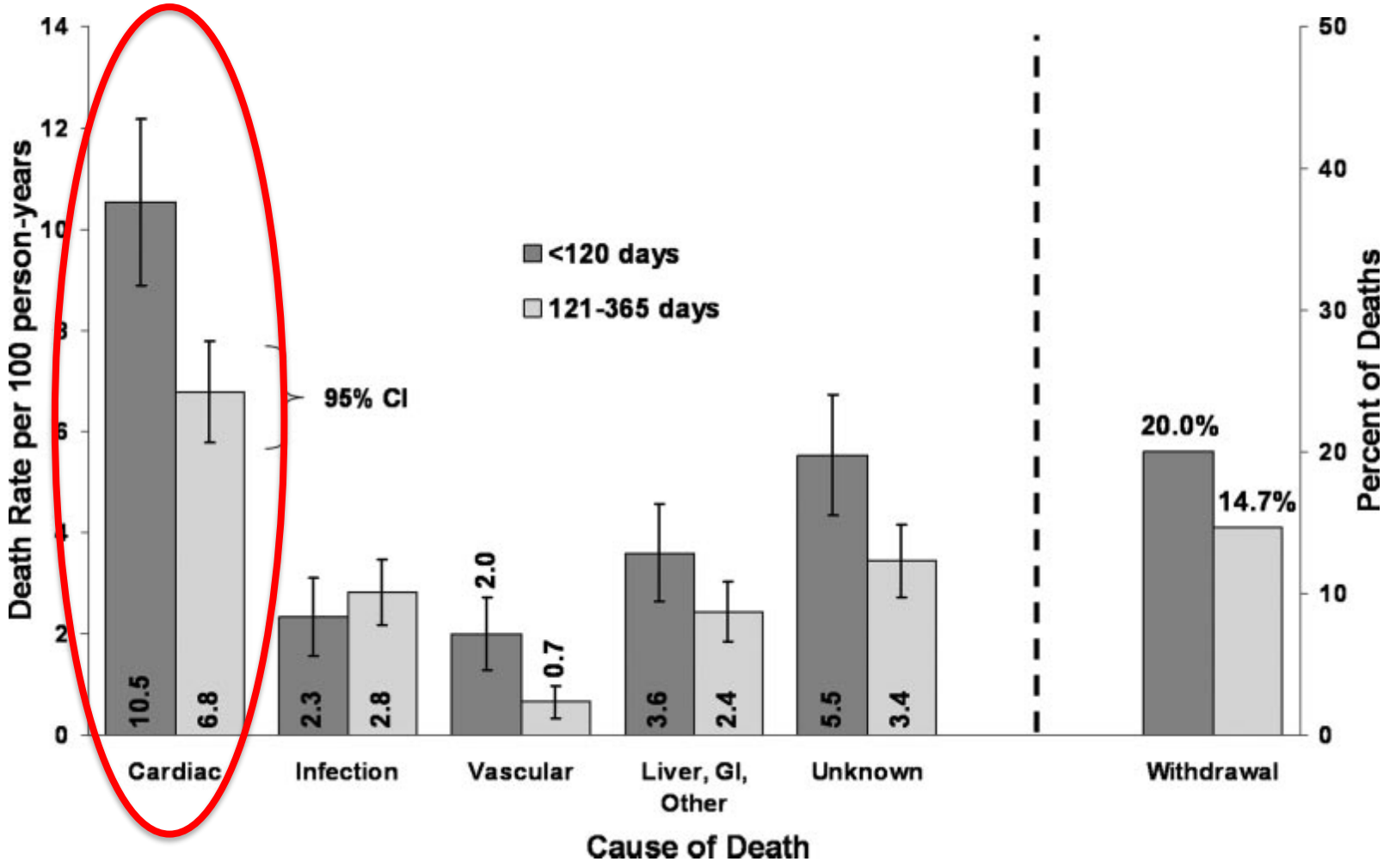
Cardiac Causes Primary Cause of Death in Dialysis



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Focusing Now On Acute Heart Failure

- When is a change in kidney function significant in acute heart failure?

What Change in Kidney Function Is Considered Significant? Worsening Renal Function (WRF)

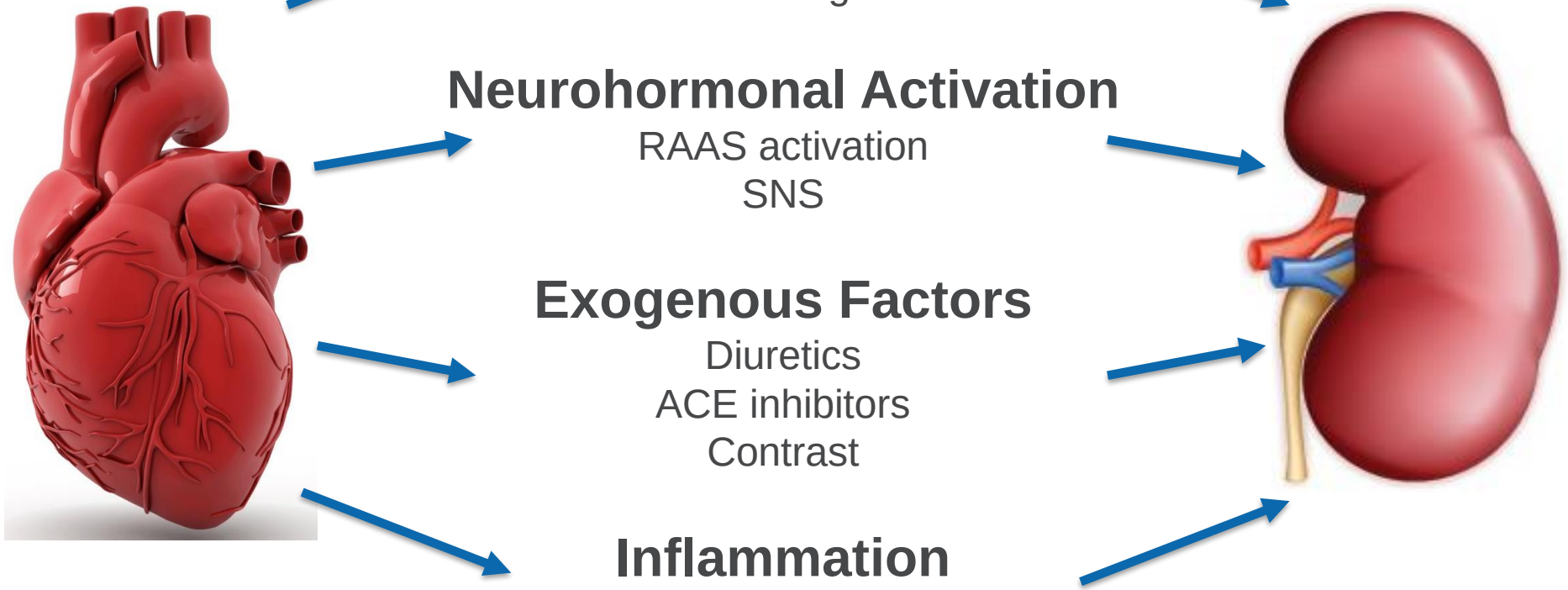
- Creatinine increase by 0.3 mg/dL
  - From admission?
  - From values prior to hospital presentation?
  - Over what time frame?
- Creatinine increase by 0.5 mg/dL
- Creatinine increase by 50%
- GFR decrease >20%
- Urine Output Decreases
- When You Need Dialysis

What Is Cardiorenal Syndrome?

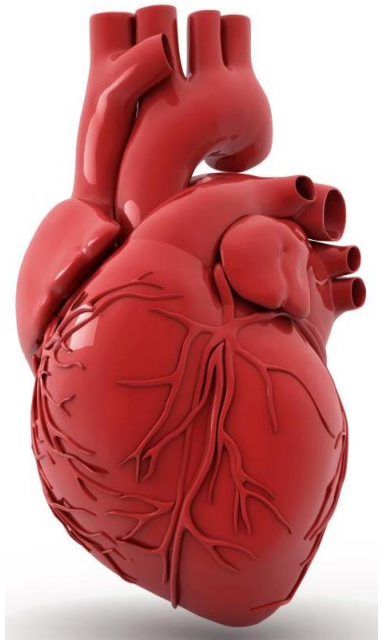
- Simply the heart and kidney interact closely and influence each other's health
- No defined change in renal (or cardiac) function to diagnose
- While a classification system exists, often cannot tell if kidney or heart is initial problem
- So 10 slides later and I really have not defined the syndrome well

Pathophysiology

What Drives Cardiorenal Syndrome



Similarly What Drives Renocardiac Syndrome



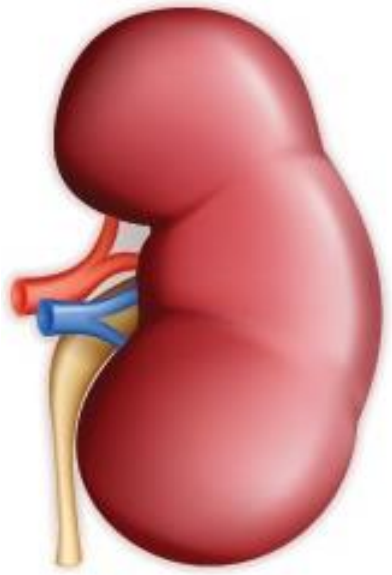
Hemodynamic Effects
Volume Retention/Expansion

Neurohormonal Activation
RAAS activation
SNS

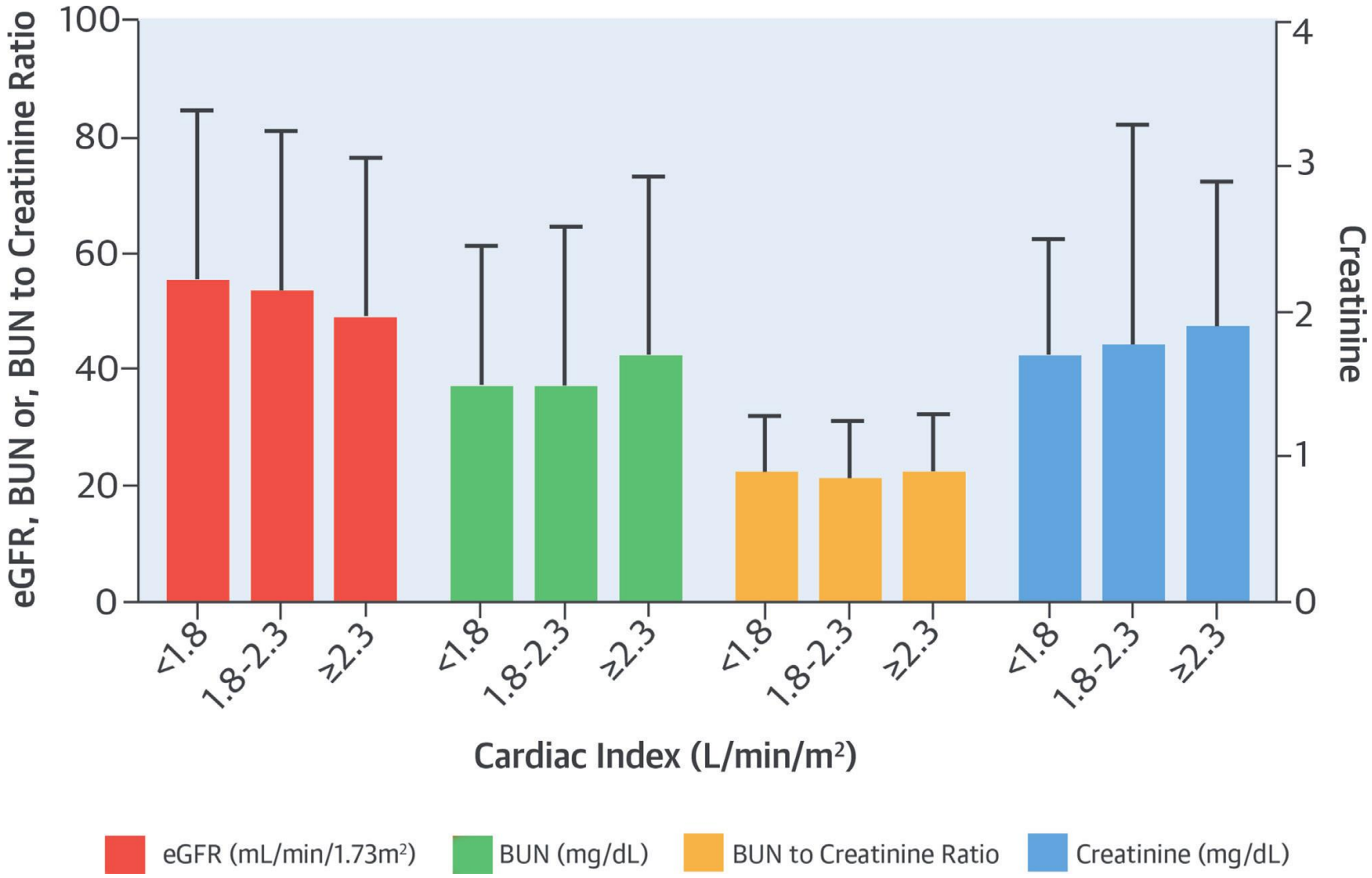
Electrolyte Imbalances

Acid Base Abnormalities

Inflammation
Immune mediated



Cardiac Output May Not be a Major Contributor to Changes in Renal Function



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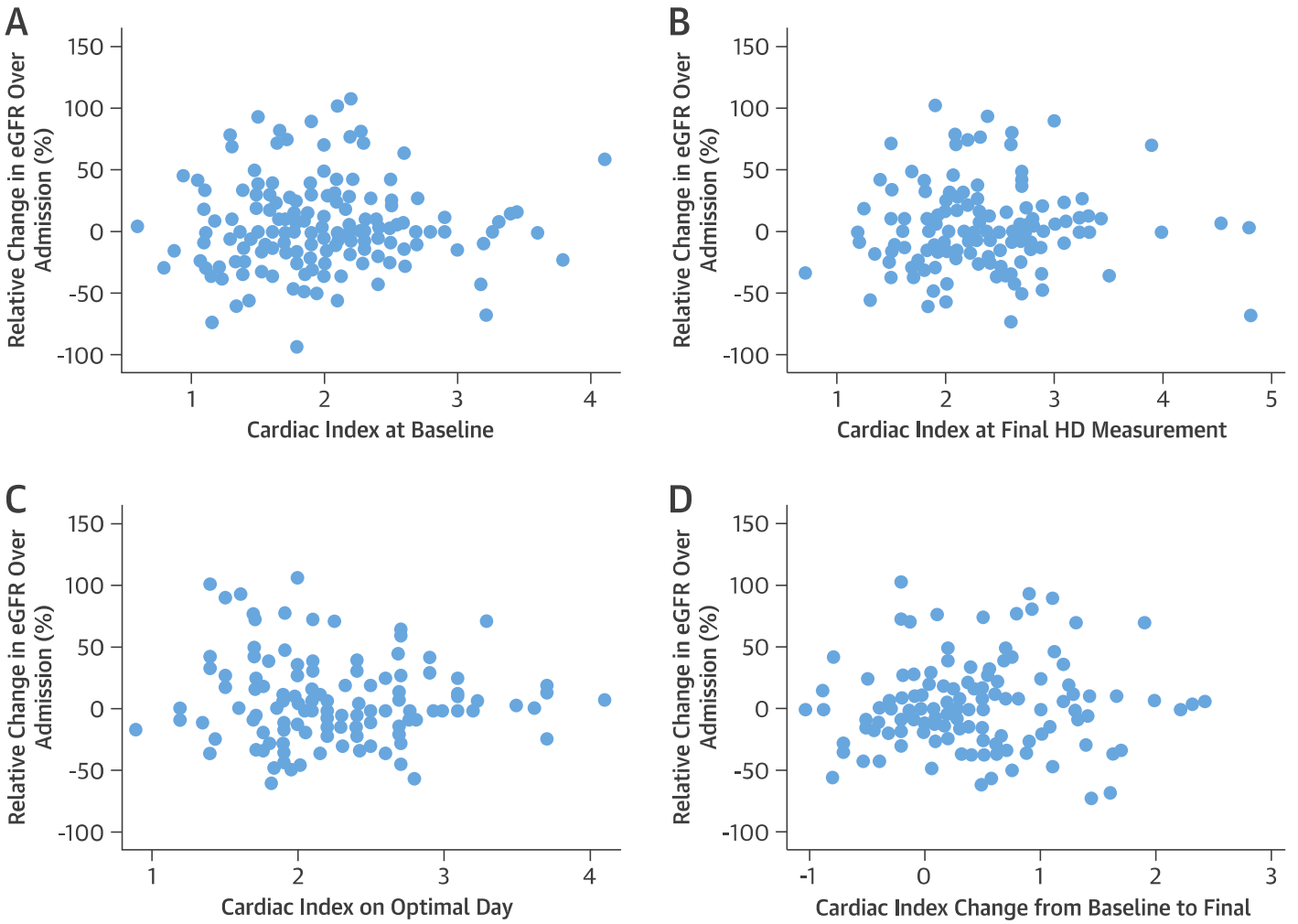
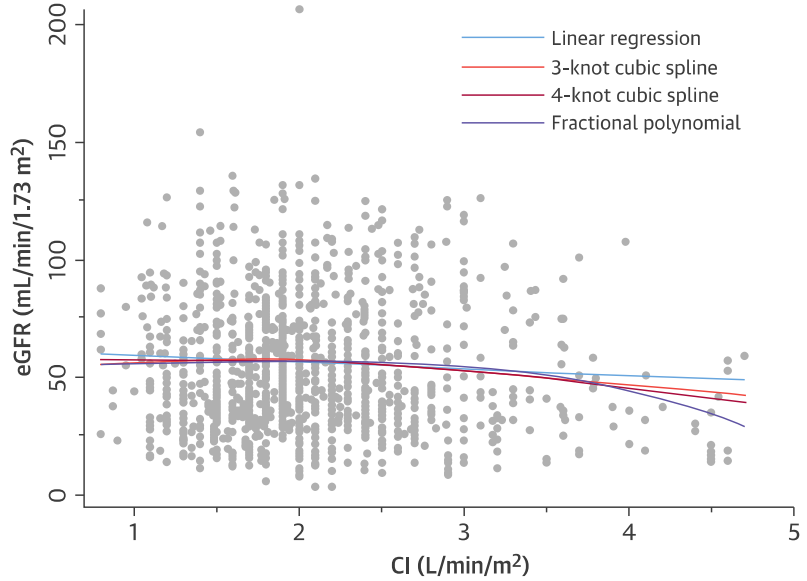
Hanberg, J Am Coll Cardiol. 2016 May 17;67(19):2199-208

Poor Correlation Between Cardiac Output and Renal Function





	Cardiac Index		
	Patients With WRF*	Patients Without WRF*	p Value
Static measurement of CI			
Baseline	1.9 ± 0.7	2.0 ± 0.6	0.43
Day 2	2.2 ± 0.7	2.1 ± 0.6	0.53
At PAC removal	2.3 ± 0.7	2.4 ± 0.6	0.28
Change in CI			
Baseline to day 2	0.4 ± 0.7	0.4 ± 0.7	0.51
Baseline to PAC removal	0.2 ± 0.6	0.1 ± 0.6	0.91

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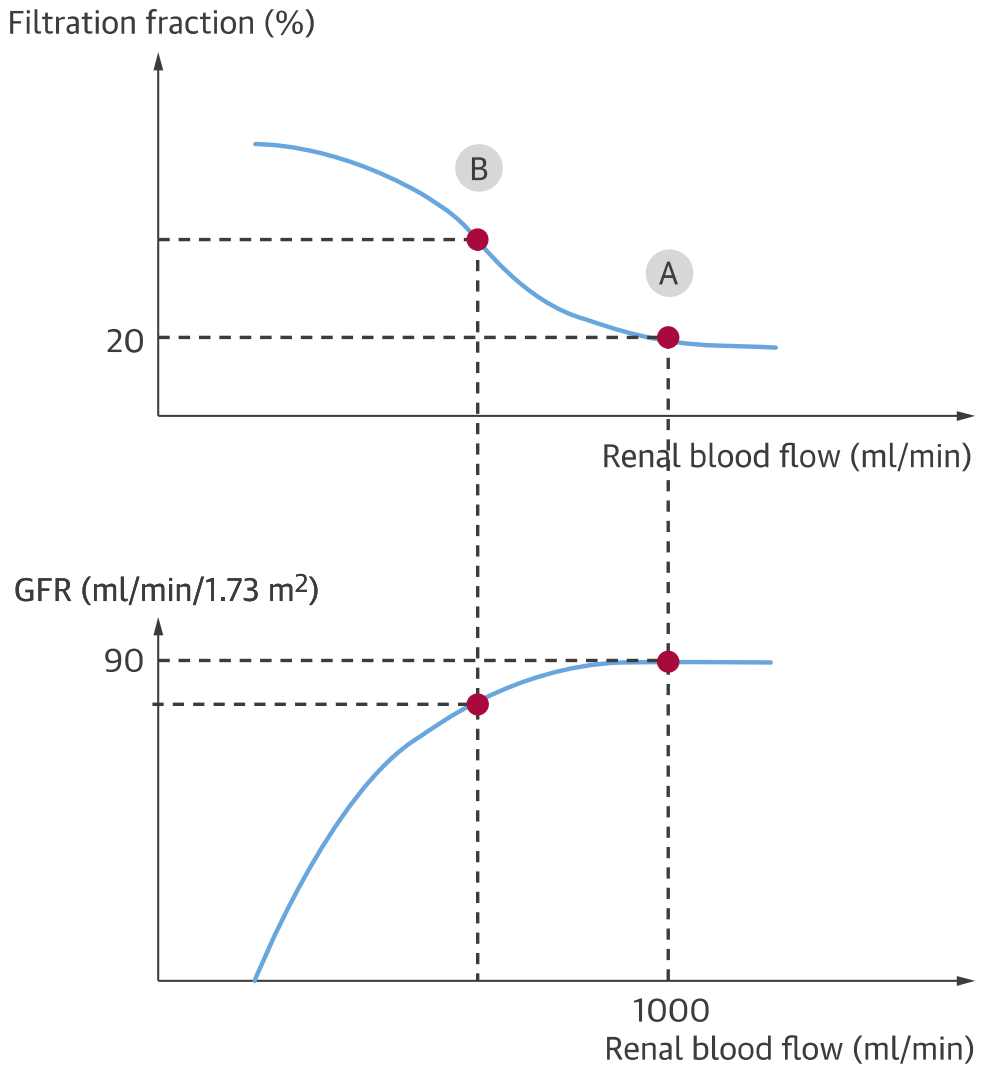
Hanberg, J Am Coll Cardiol. 2016 May 17;67(19):2199-208

Renal Autoregulation Preserves GFR May Protect From Reduced Cardiac Output



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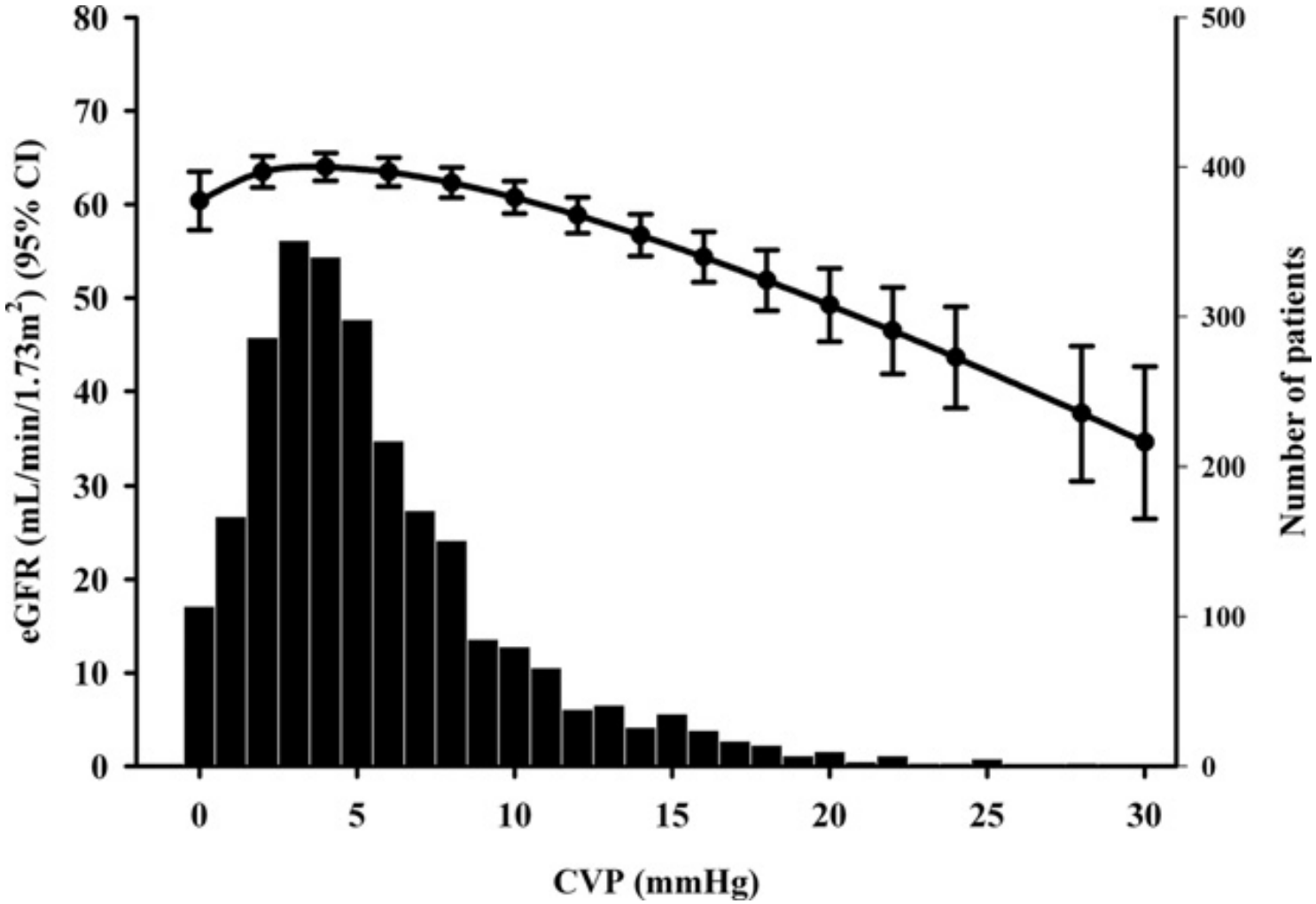
Mullens, J Am Coll Cardiol. 2016 May 17;67(19):2209-12

Elevated Right Sided Filling Pressures Drive Renal Dysfunction



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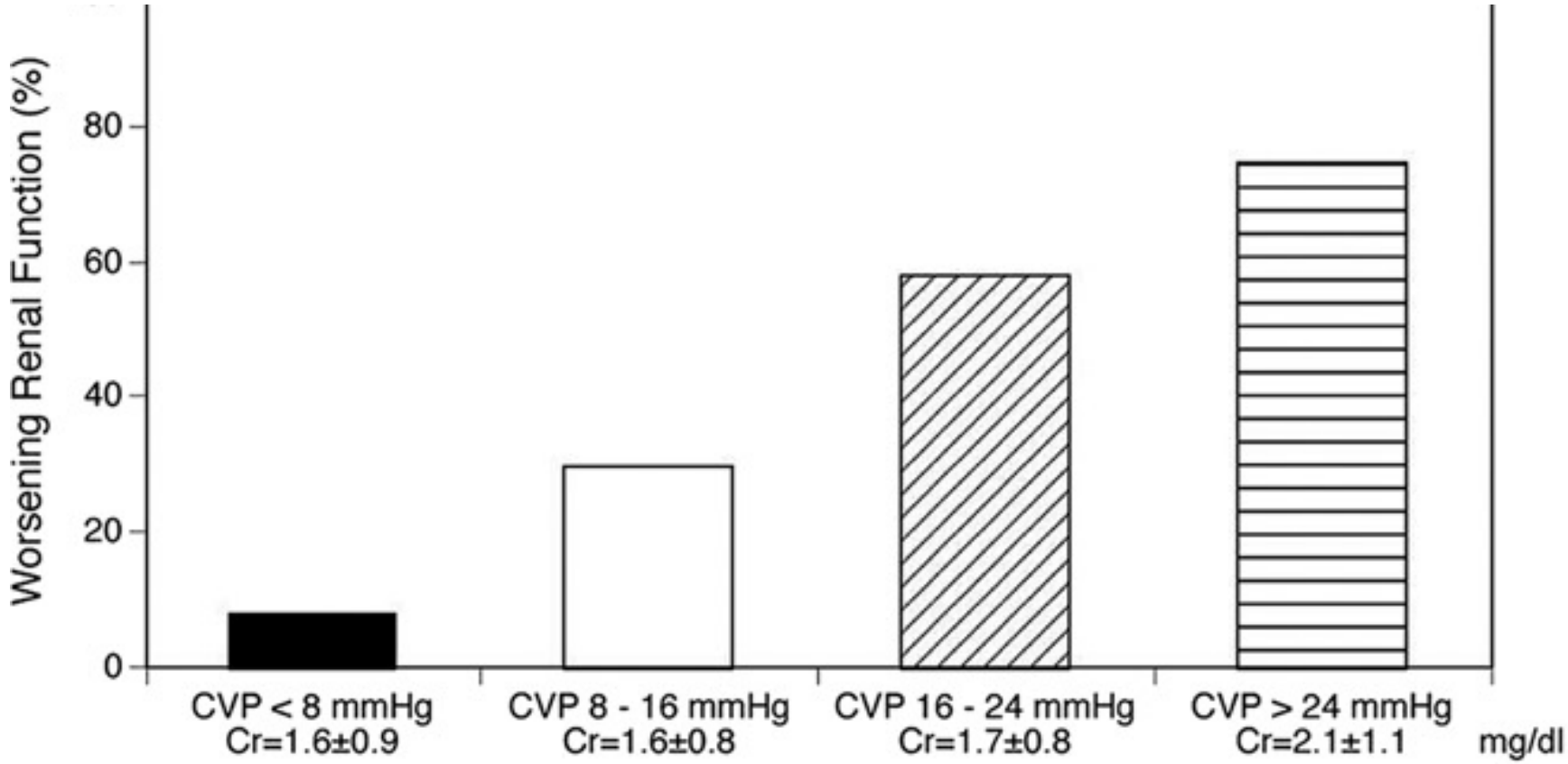
Damman, J Am Coll Cardiol. 2009 Feb 17;53(7):582-8

As CVP Rises so Does WRF



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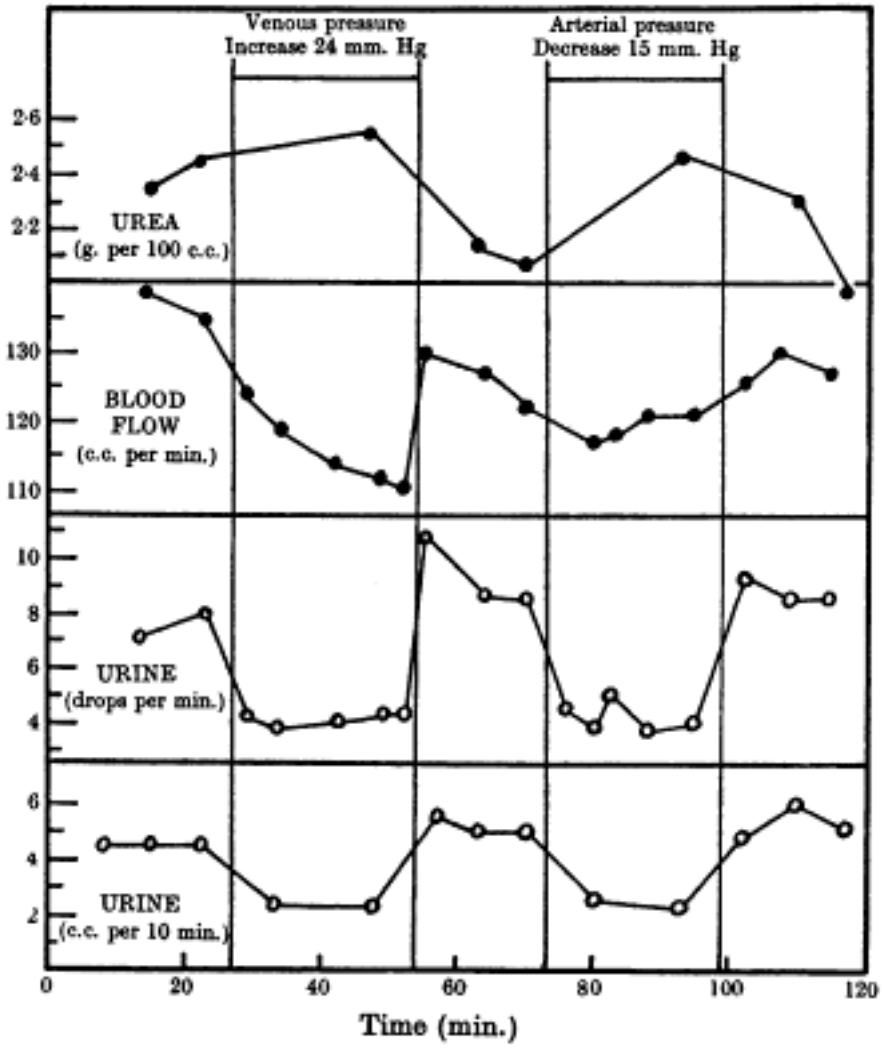
Mullens, J Am Coll Cardiol. 2009 Feb 17;53(7):589-96

This Phenomenon Recognized Almost 100 Years Prior



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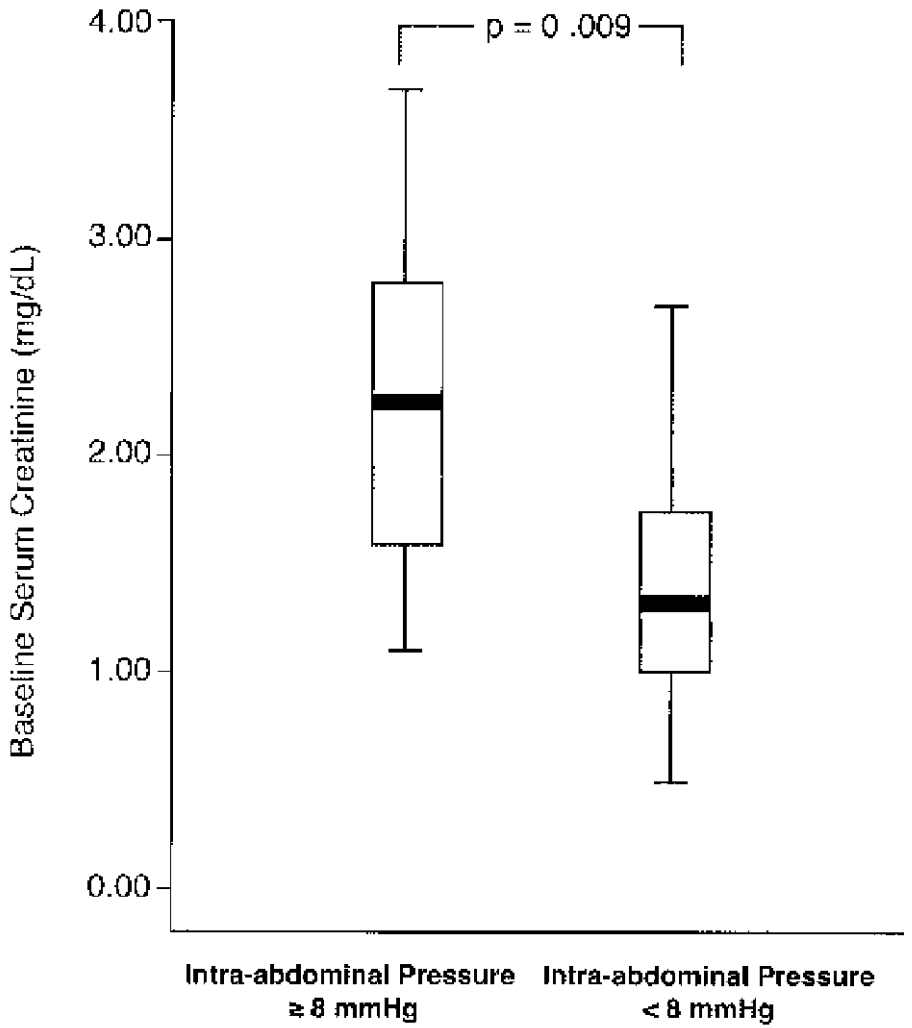
Winton, J Physiol. 1931 Jun 6; 72(1): 49–61

Why Does Elevated CVP Drive Renal Dysfunction

- Elevated venous pressure decreases arteriovenous pressure gradient
- Kidney Encapsulated
- Increased renal interstitial pressure
- Increased intratubular pressure
- Reduction in GFR
- Collapse of Renal Tubules
- Activation of RAAS, SNS, ROS, inflammation

Abdominal Compartment Syndrome



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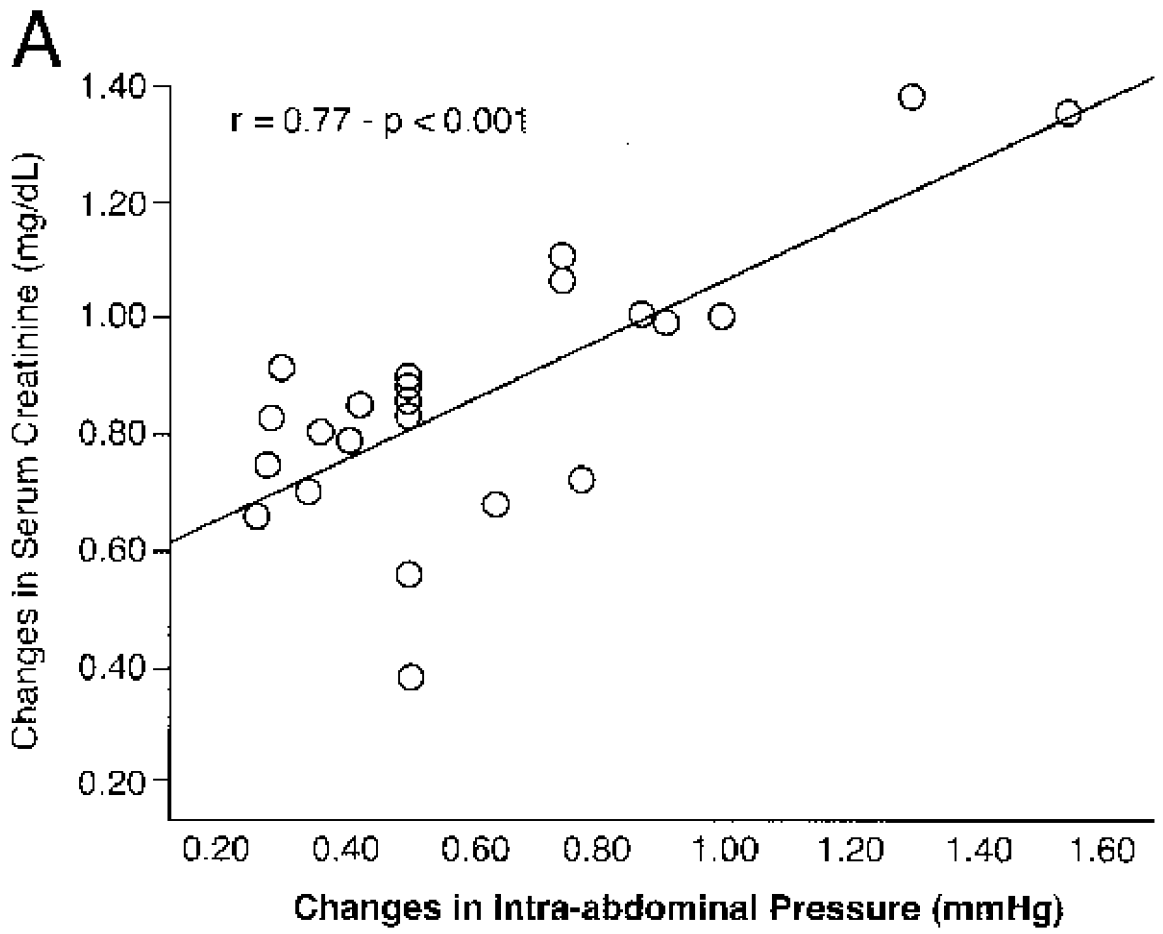
Mullens, J Am Coll Cardiol. 2008 Jan 22;51(3):300-6

Creatinine Changes with Abdominal Pressure



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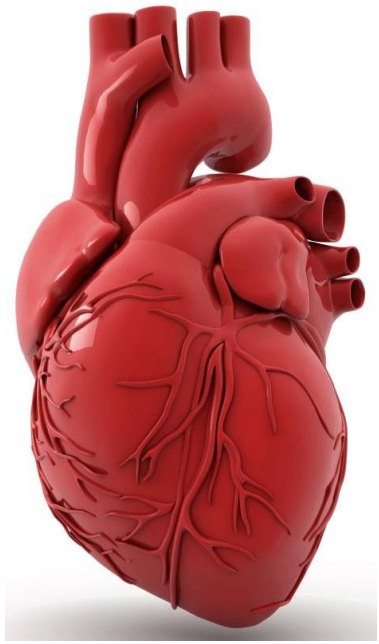
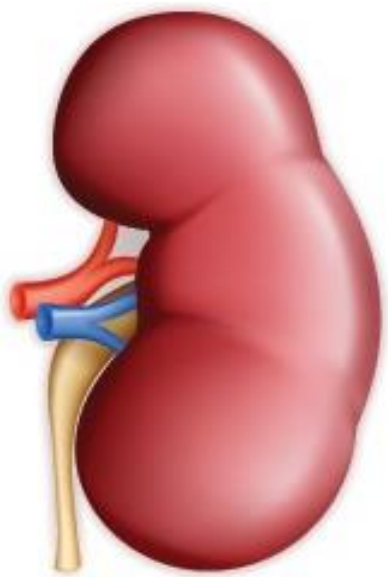
Mullens, J Am Coll Cardiol. 2008 Jan 22;51(3):300-6

Non-hemodynamic Factors Contributing to Changes in Renal Function

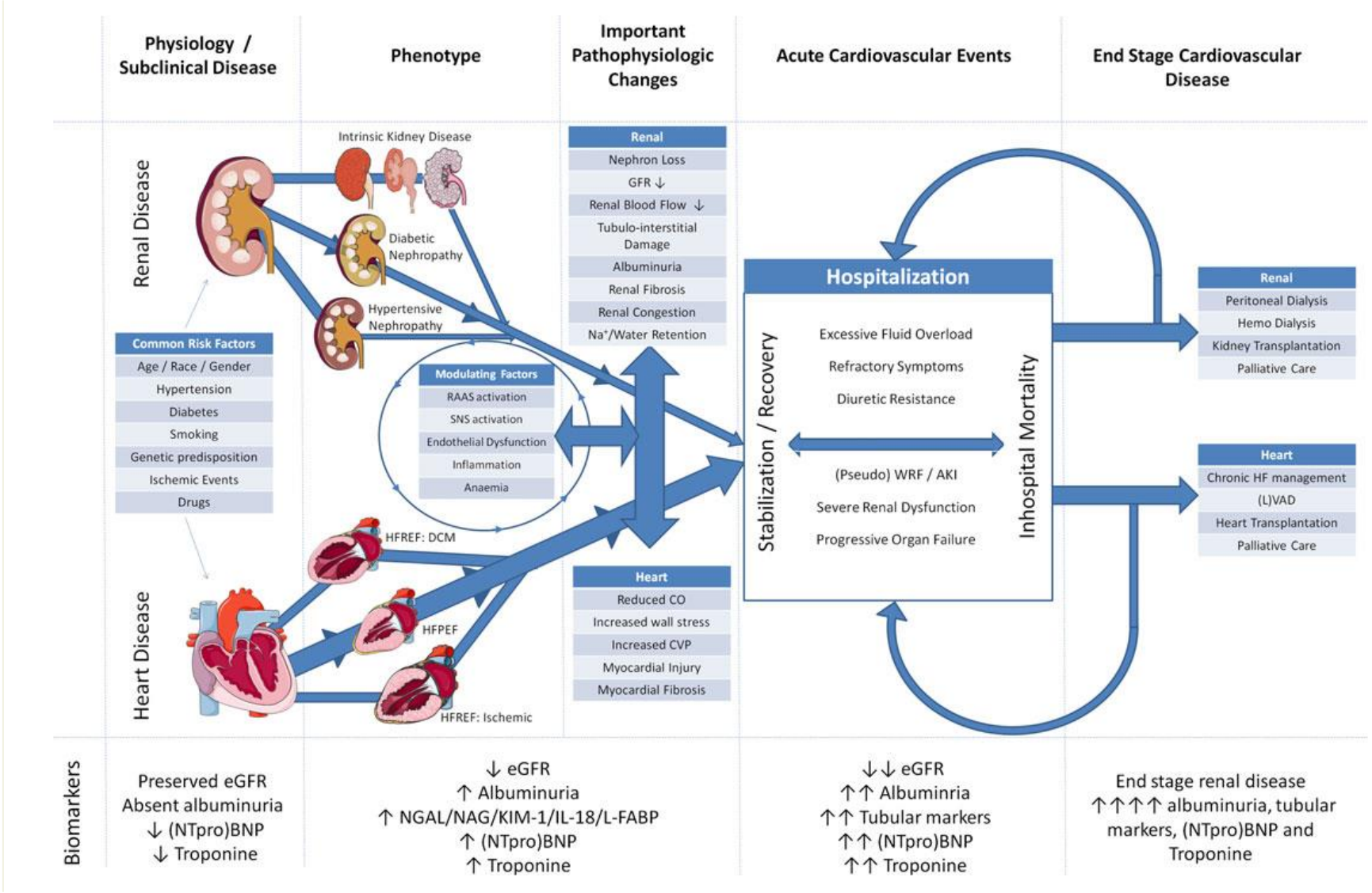
- Neurohormonal Activation
  - RAAS – renal fibrosis, alters GFR, sodium retention, hemodynamic alterations
  - SNS – salt retention, ROS, tubular injury
- Inflammation
  - Endotoxin
  - CRP, TNF-alpha, IL-1, IL-6
- Oxidative Stress
- Anemia
  - Erythropoietin has cardiotrophic effects




Relationship Status:
Interested in:
Looking for:
Single
In a Relationship
Engaged
Married
It's Complicated
In an Open Relationship
Widowed



More to the Relationship



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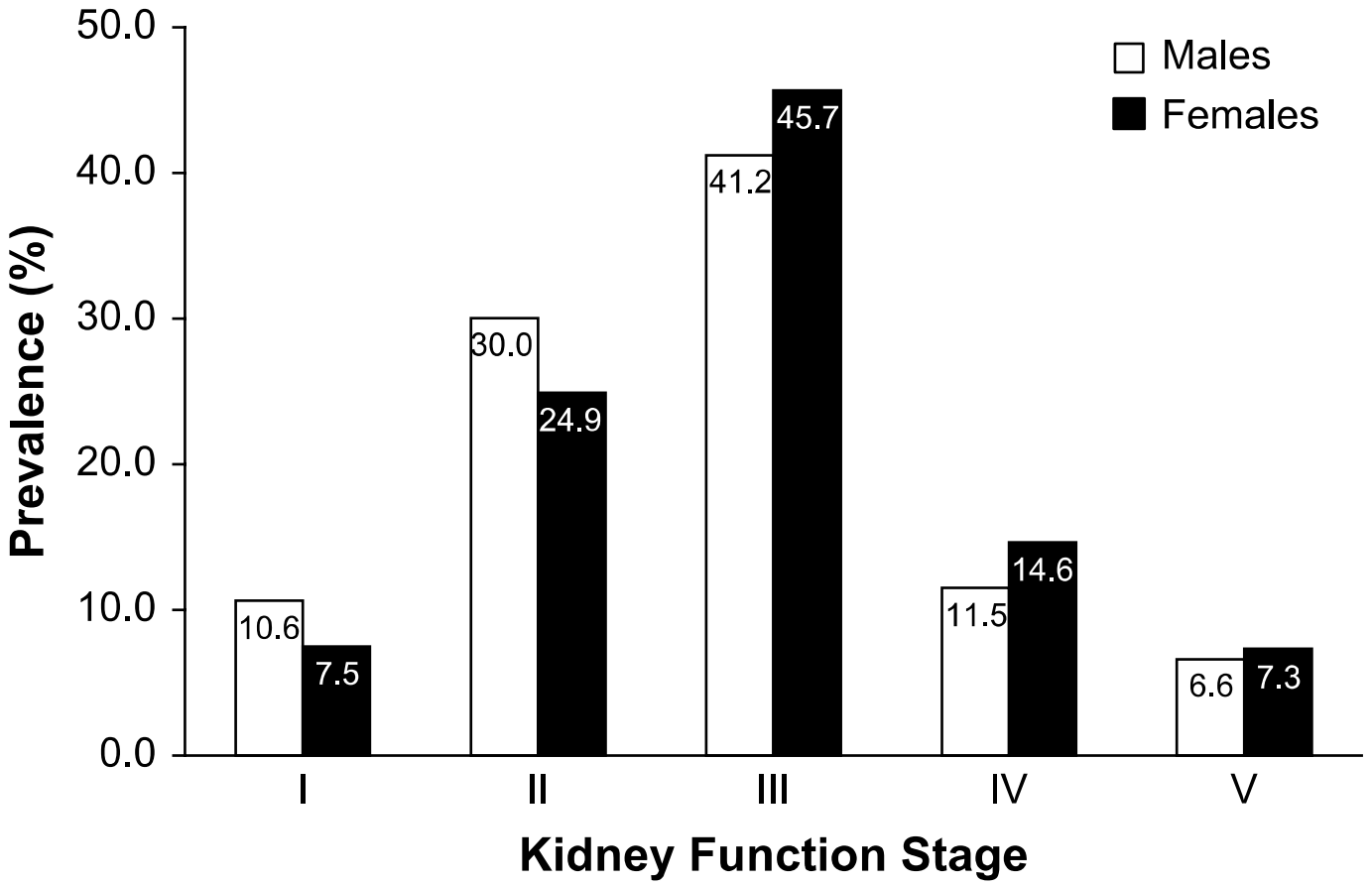
Damman, Eur Heart J. 2015 Jun 14;36(23):1437-44

Pathophysiology Summary

- Both hemodynamic and non-hemodynamic factors drive deterioration in both organs
- Elevated central venous pressure is the only hemodynamic pathophysiologic driver repeatedly shown to correlate with WRF
- Cardiac output likely plays some role, but not predominant driver in most heart failure patients
- Anemia, inflammation, oxidative stress and iatrogenic causes likely contribute but exact role not clear

Epidemiology and Outcomes

Most Heart Failure Patients Have Kidney Disease



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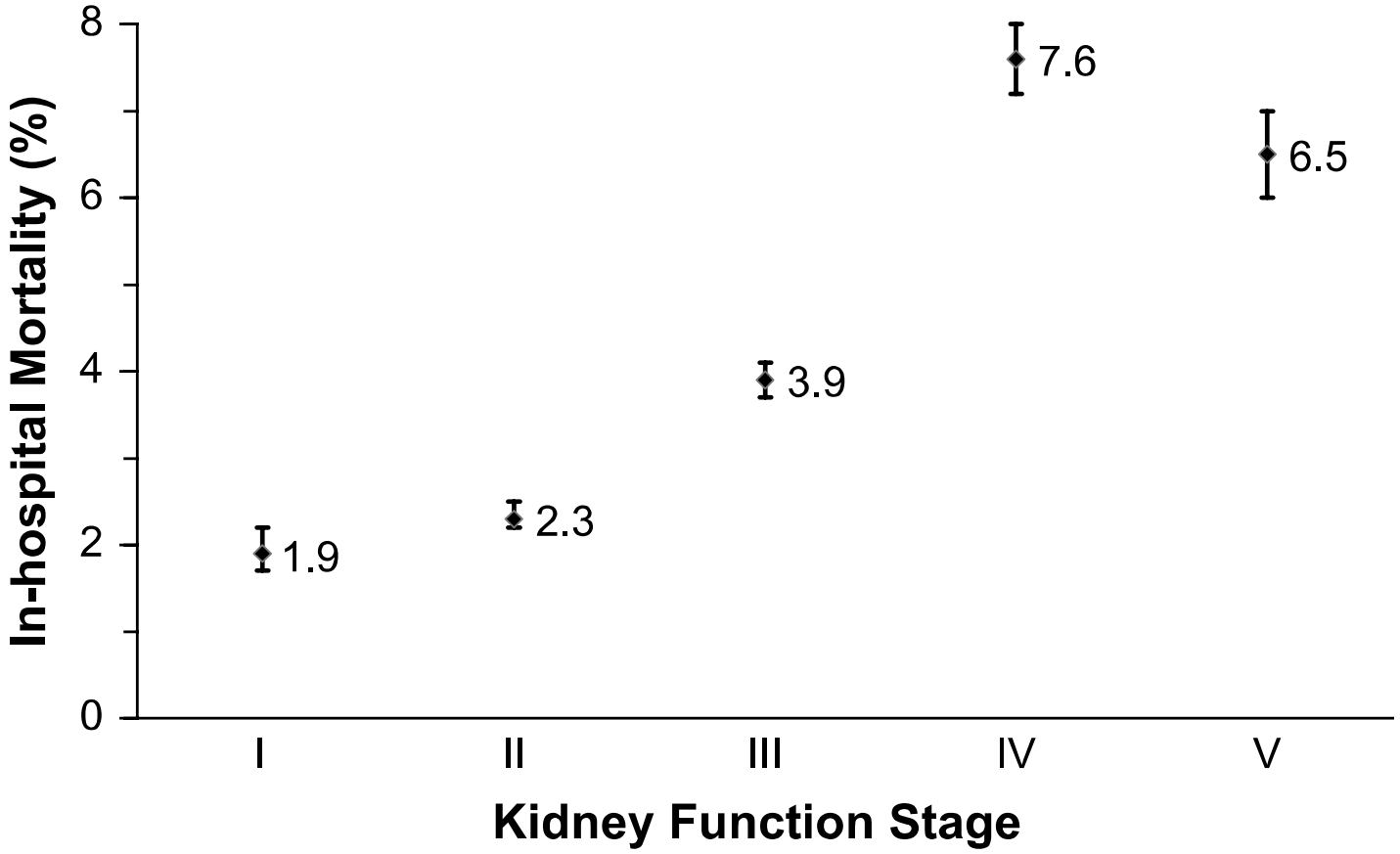
Heywood, J Card Fail. 2007 Aug;13(6):422-30

Chronic Kidney Disease Increases Heart Failure Mortality



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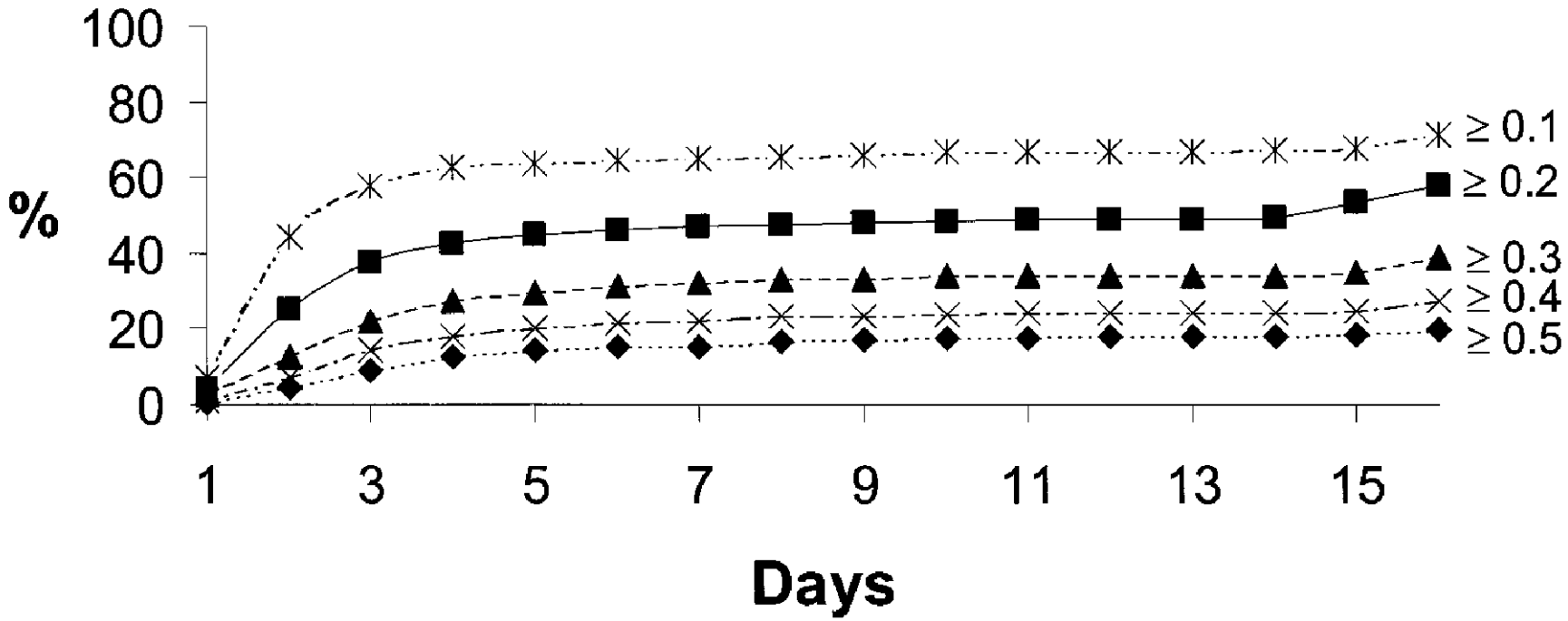
Heywood, J Card Fail. 2007 Aug;13(6):422-30

Rises in Creatinine Commonly Occur During Acute Heart Failure



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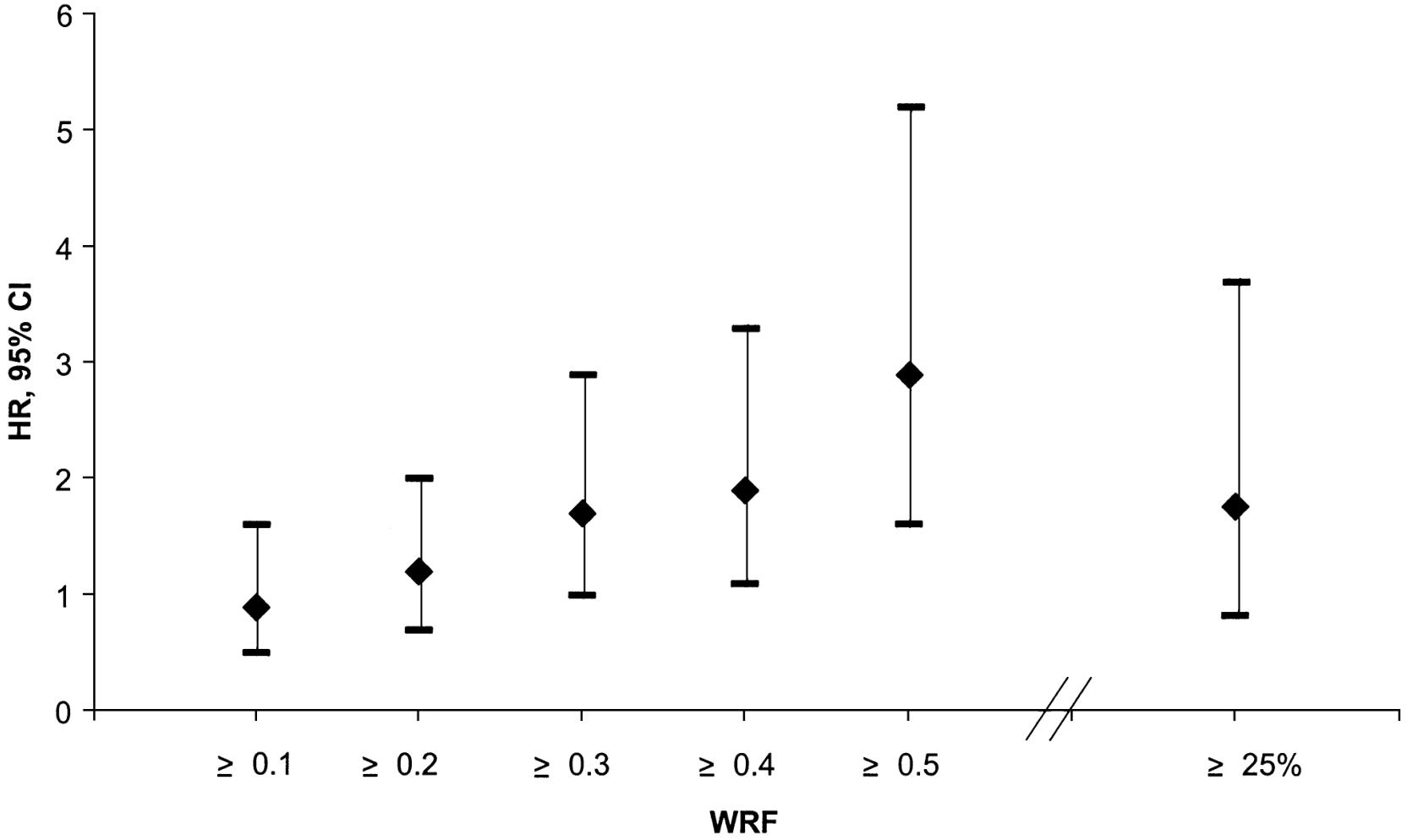
Gottlieb, J Card Fail. 2002 Jun;8(3):136-41.

Worsening Renal Function Increases Risk of In-Hospital Mortality



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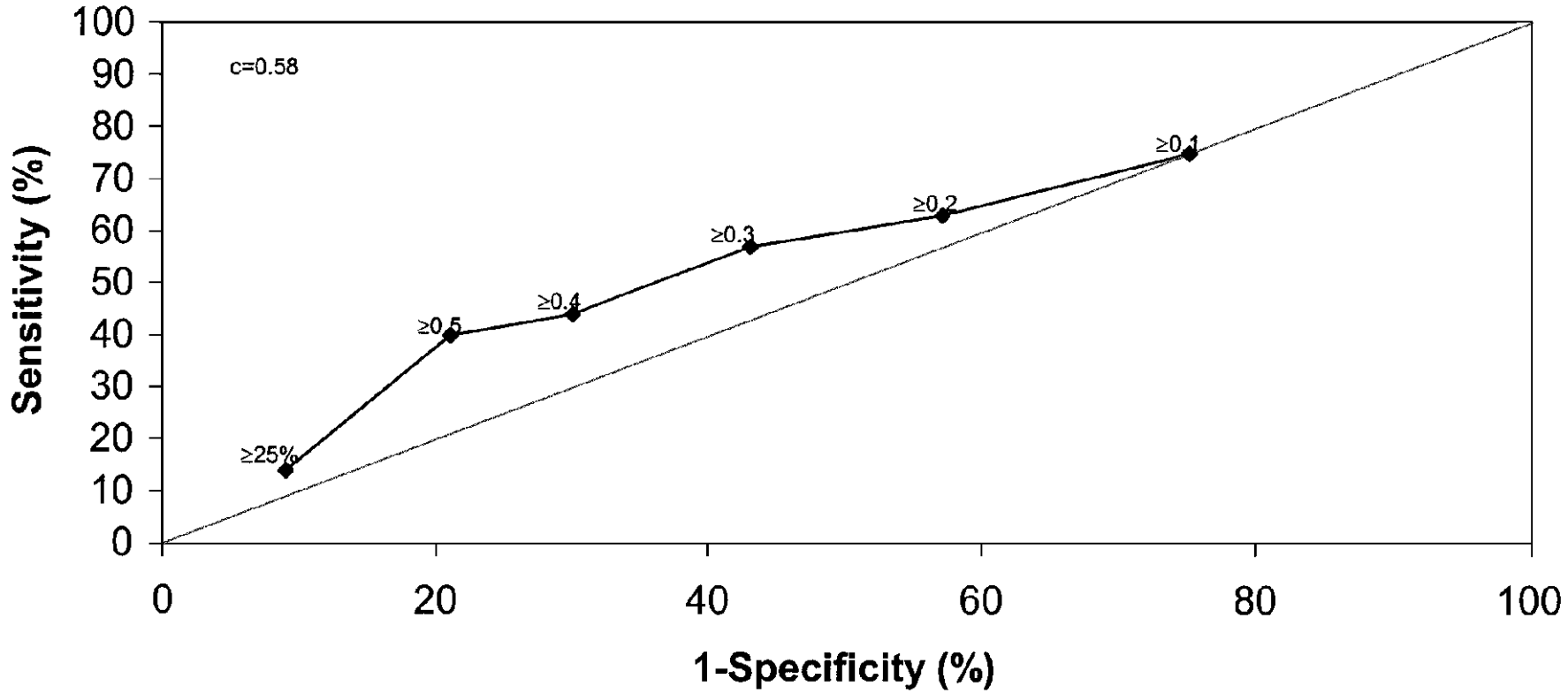
Smith, J Card Fail. 2003 Feb;9(1):13-25

Defining a Clinically Meaningful Cut-Off For WRF Difficult



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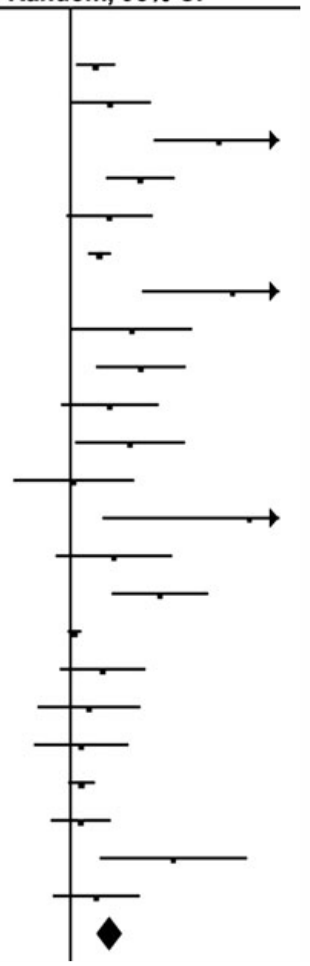
Smith, J Card Fail. 2003 Feb;9(1):13-25

The Majority of Prior Studies Associates Worsening Renal Function With Increased Mortality

Study or Subgroup	WRF Events	WRF Total	no WRF Events	no WRF Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Acute Heart Failure							
Krumholz	119	469	235	1212	5.4%	1.41 [1.10, 1.82]	2000
Smith	35	185	27	227	3.6%	1.73 [1.00, 2.98]	2003
Forman	19	273	7	731	2.1%	7.74 [3.21, 18.62]	2004
Akhter	45	119	68	361	4.1%	2.62 [1.66, 4.13]	2004
Cowie	26	98	35	201	3.4%	1.71 [0.96, 3.05]	2006
Owan	1095	1419	3215	4633	5.9%	1.49 [1.30, 1.71]	2006
Chittineni	11	16	12	63	1.3%	9.35 [2.73, 31.99]	2007
Cioffi	10	107	17	402	2.3%	2.33 [1.04, 5.26]	2007
Metra	28	107	25	211	3.3%	2.64 [1.45, 4.81]	2008
Lassus	18	46	67	246	3.0%	1.72 [0.89, 3.31]	2010
Testani (ESCAPE)	15	324	14	669	2.6%	2.27 [1.08, 4.76]	2010
Verdiani	8	43	63	351	2.3%	1.04 [0.46, 2.36]	2010
Hata	29	275	1	101	0.6%	11.79 [1.58, 87.72]	2010
Belziti	12	46	25	154	2.4%	1.82 [0.83, 3.99]	2010
Herout	25	252	16	515	3.0%	3.43 [1.80, 6.56]	2010
Kociol	1261	3581	5601	16482	6.1%	1.06 [0.98, 1.14]	2010
Testani	21	85	55	316	3.4%	1.56 [0.88, 2.76]	2010
Rusinaru	30	43	202	315	2.8%	1.29 [0.65, 2.57]	2011
Manzano-Fernandez	20	66	42	154	3.1%	1.16 [0.62, 2.18]	2011
Lanfear	467	887	771	1578	5.8%	1.16 [0.99, 1.37]	2011
Breidthardt	49	136	171	521	4.5%	1.15 [0.78, 1.71]	2011
Voors	11	68	7	157	1.8%	4.14 [1.53, 11.19]	2011
Ather	22	60	86	298	3.4%	1.43 [0.80, 2.55]	2012
Subtotal (95% CI)		**8705**		**29898**	**76.4%**	**1.75 [1.47, 2.08]**	



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Damman, Eur Heart J. 2014 Feb;35(7):455-69

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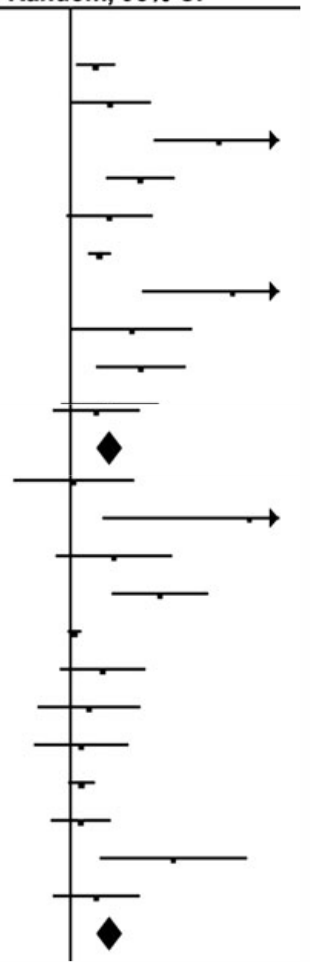

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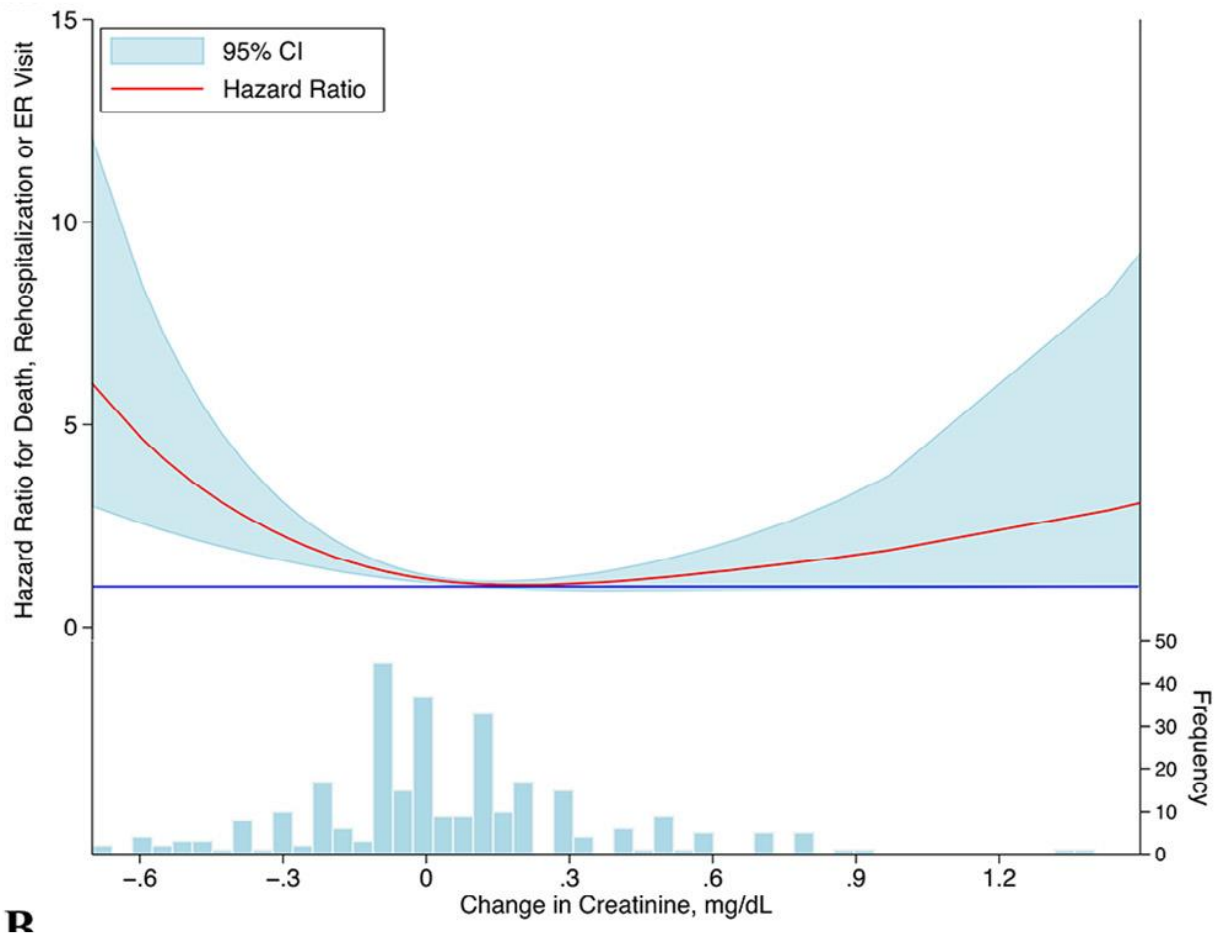
Summary of Meta-Analysis for Mortality

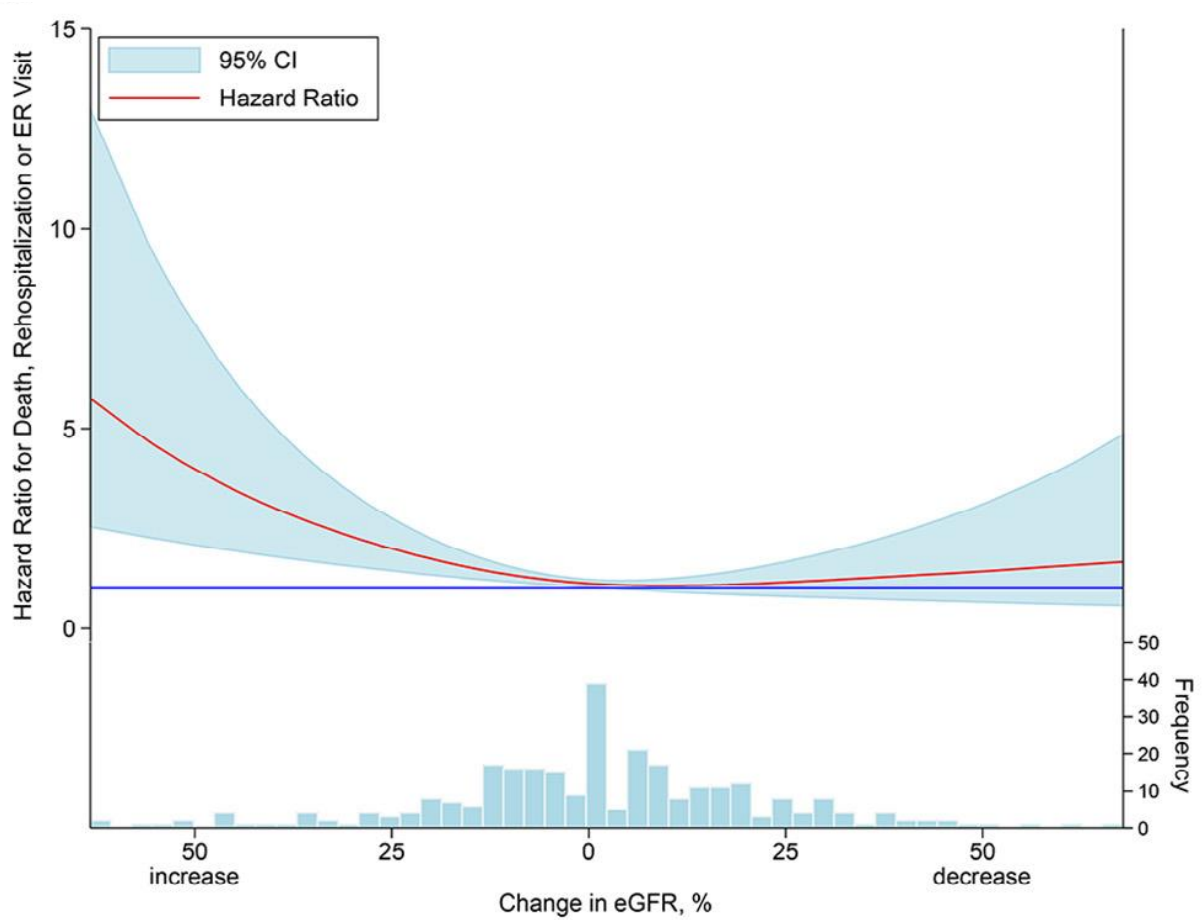
- WRF in acute HF
  - Odds Ratio 1.75 (1.47 - 2.08)
- WRF in chronic HF
  - Odds Ratio 1.96 (1.48 – 2.61)
- CKD in acute HF
  - Odds Ratio 2.39 (2.25 – 2.54)
- CKD in chronic HF
  - Odds Ratio 2.26 (2.08 – 2.47)

Damman, Eur Heart J. 2014 Feb;35(7):455-69

Paradoxes and Controversies

Improvements in Renal Function May Be More Prognostic of Outcomes Than WRF





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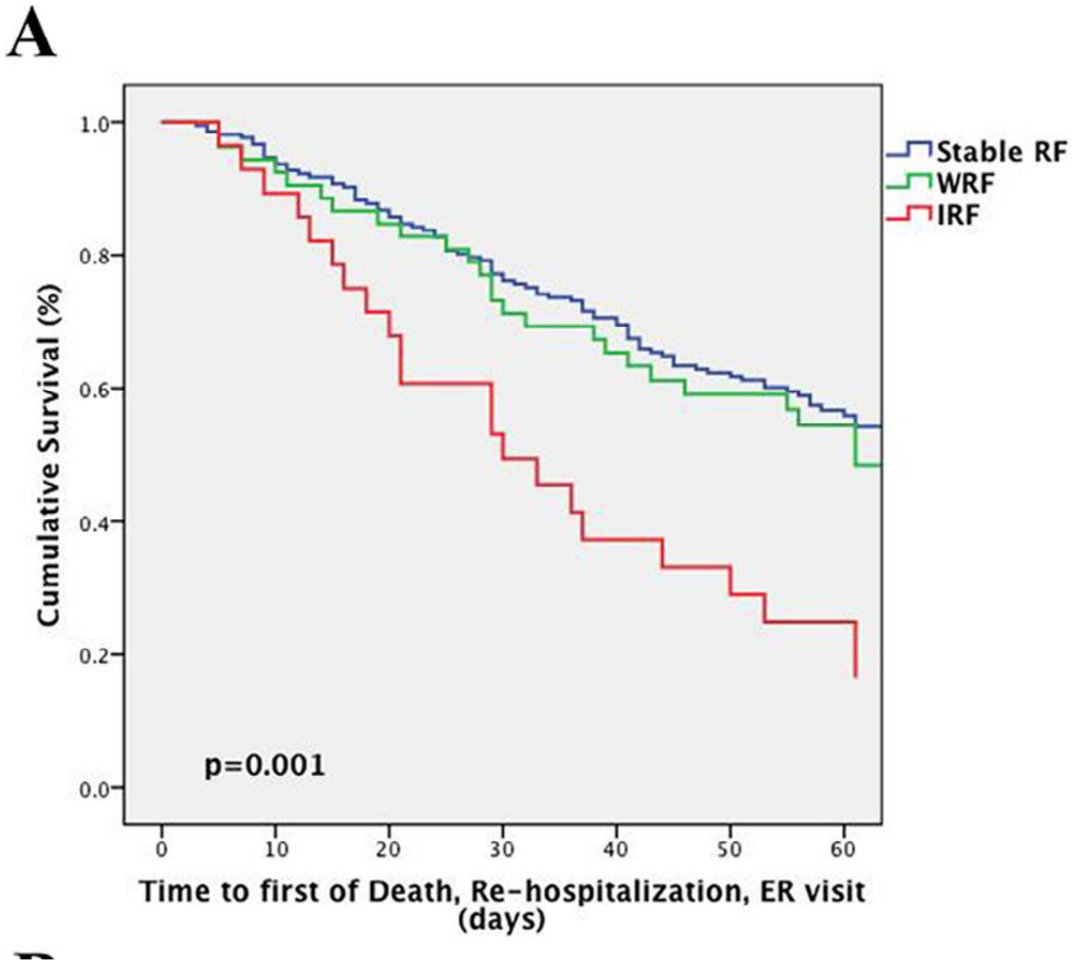
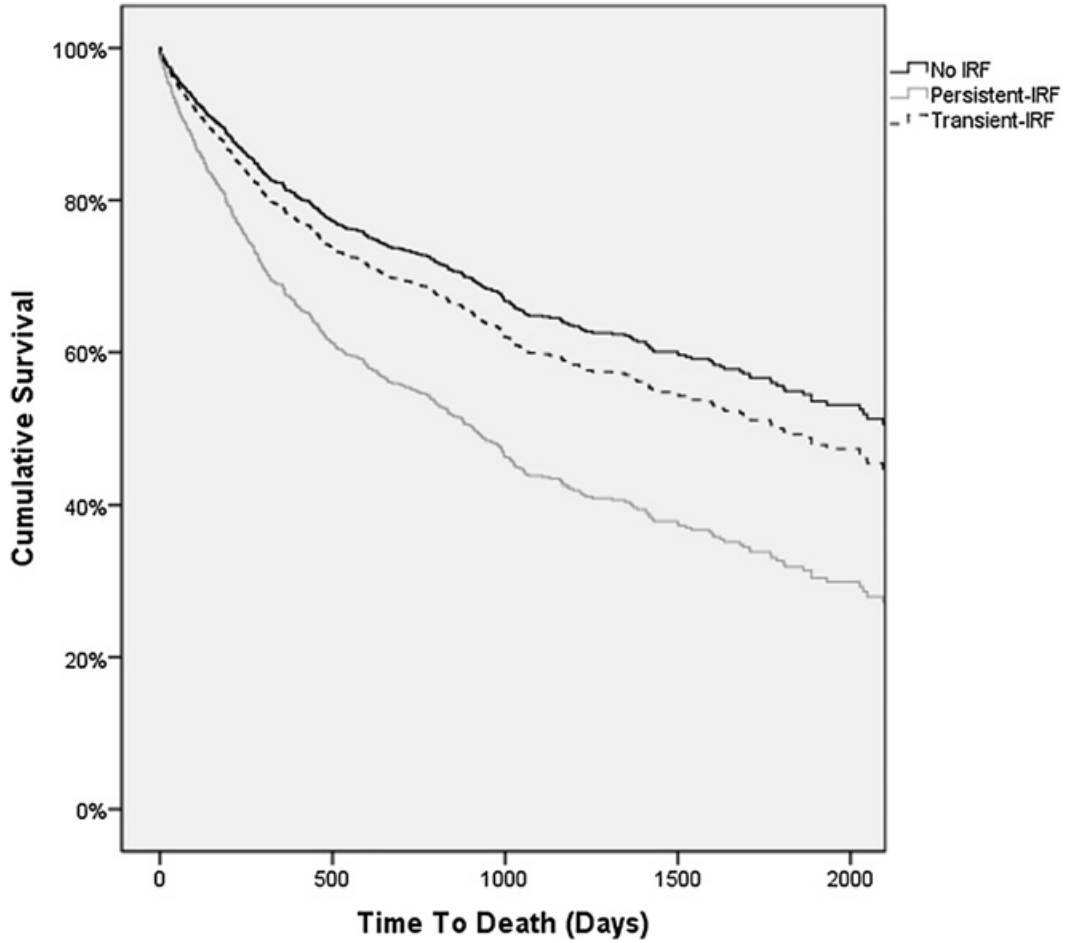
Brisco, J Card Fail. 2016 Oct;22(10):753-60

Improved Renal Function (IRF) Has Worse Outcomes Than WRF





Brisco, J Card Fail. 2016 Oct;22(10):753-60

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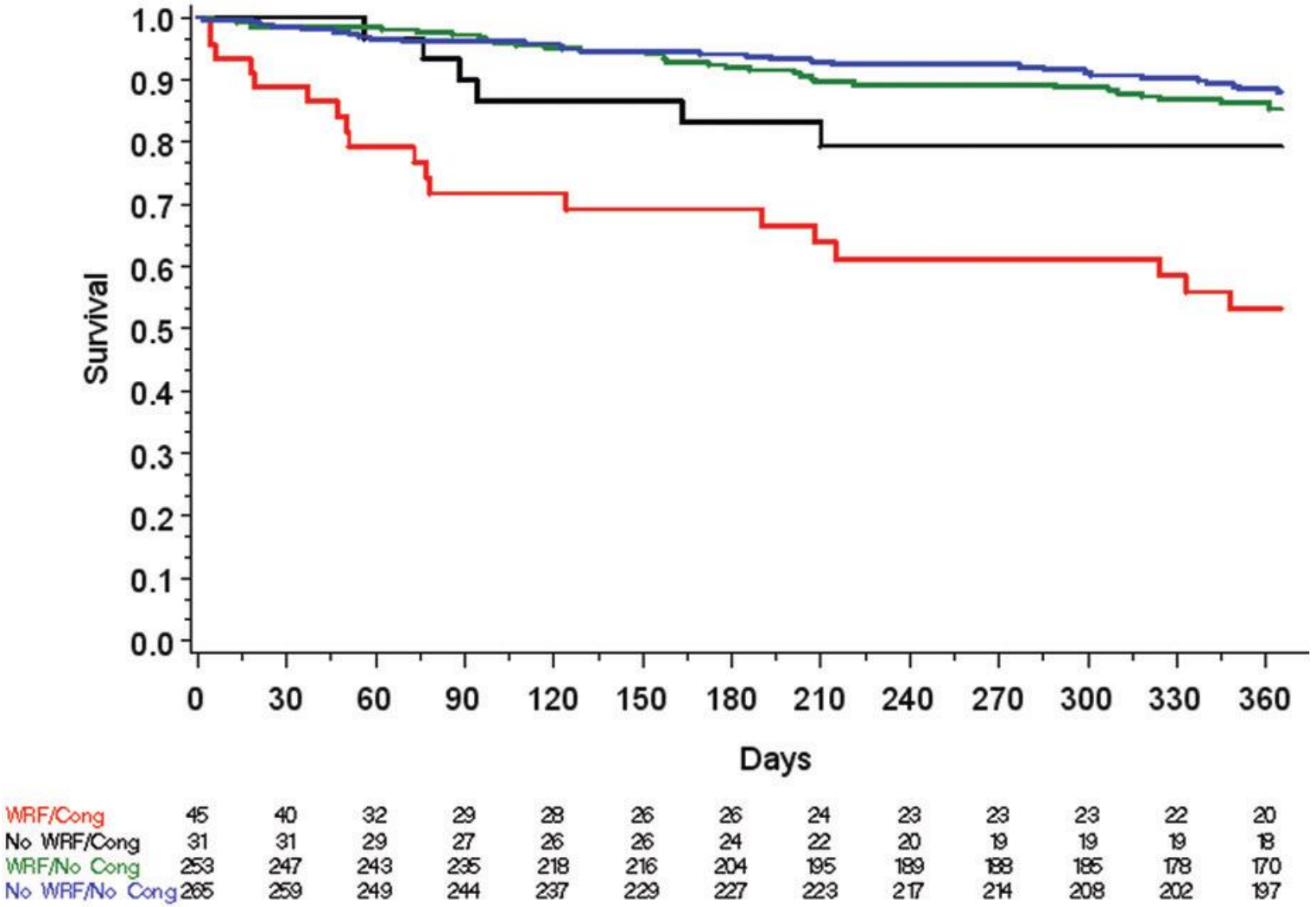
Testani, J Card Fail. 2011 Dec;17(12):993-1000

WRF Only Harmful If Congestion Not Relieved



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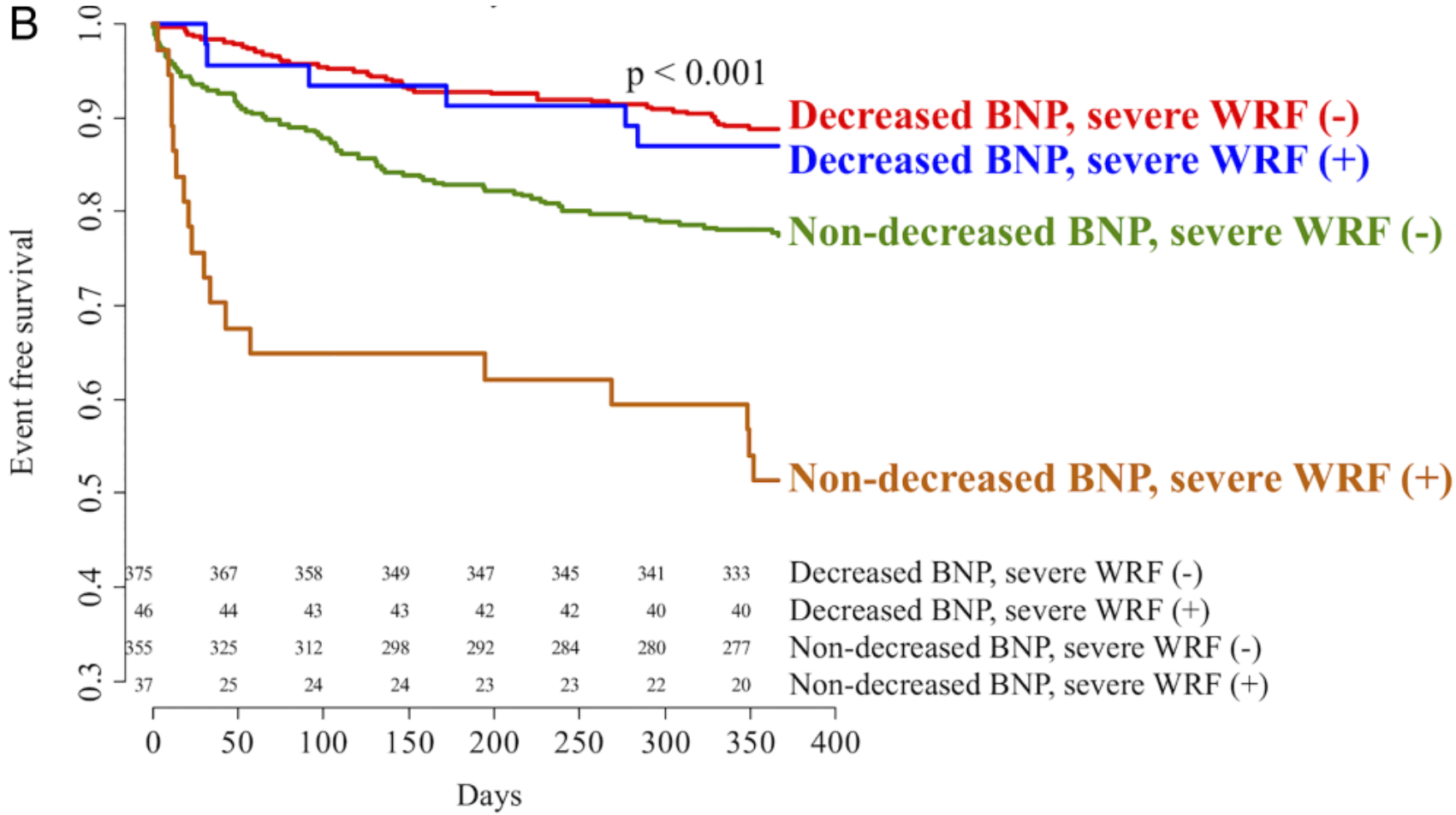
Metra, Circ Heart Fail. 2012 Jan;5(1):54-62

Short Divergence to Describe AKINESIS

- AKINESIS – Acute Kidney Injury N-gal Evaluation of Symptomatic heart fallure Study
- International, multicenter, prospective study focusing on cardiorenal syndrome
- Enrolled 930 patients presenting with signs and symptoms of acute heart failure and receiving intravenous diuretics
- Evaluated a novel kidney injury biomarker as primary analysis
- Other biomarkers collected and analyzed as well

Changes in BNP Discriminate Outcomes with WRF



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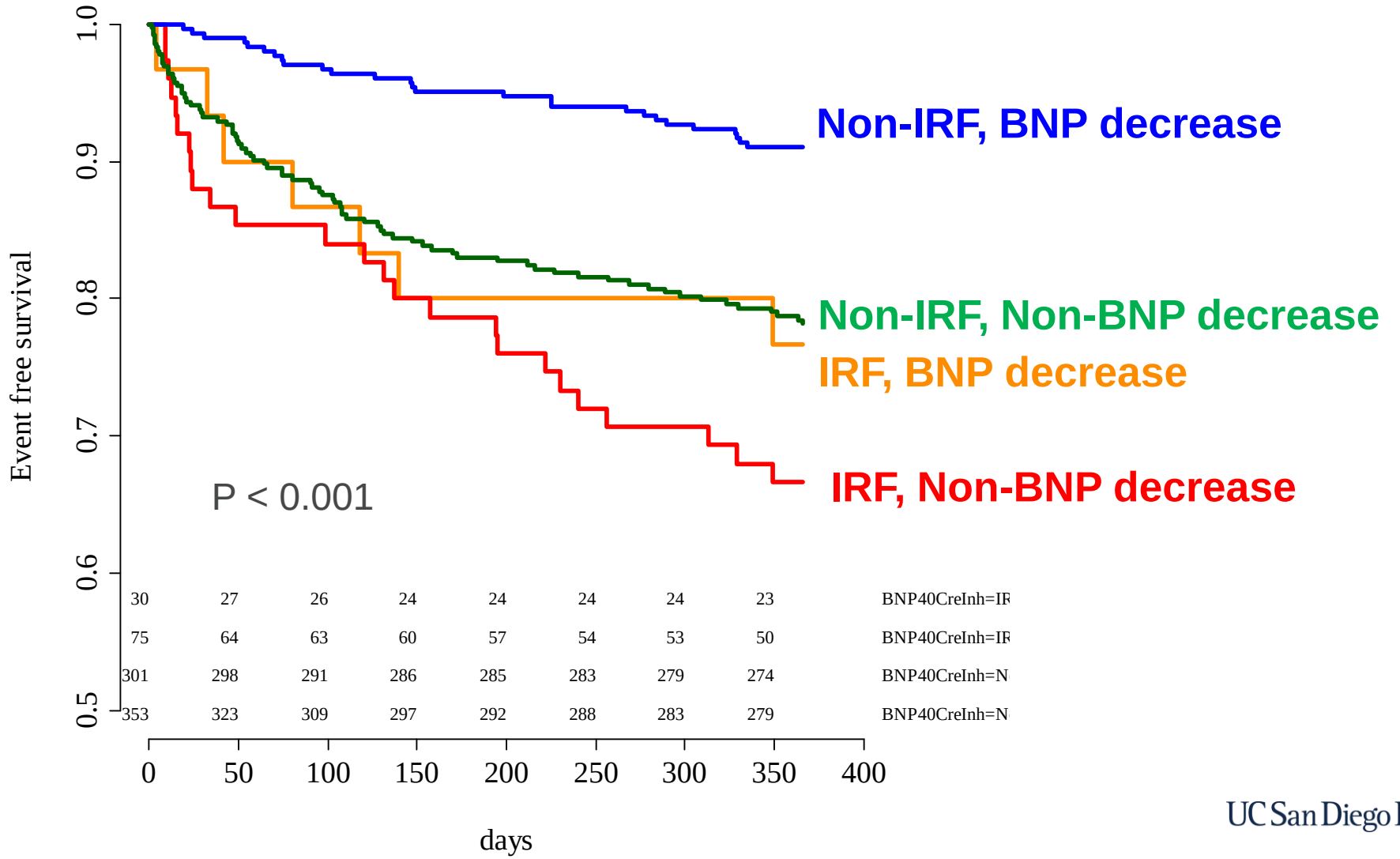
Wettersten, Eur J Heart Fail. 2019 Dec;21(12):1553-1560

Similarly, BNP Can Help Discriminate Outcomes with Improved Renal Function



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Changes in Renal Function Depend on The Context in Which They Occur

Table 4 Association of WRF with mortality up to 6 months after index hospitalization

Mortality, *n* (%)	WRF absent	WRF present	OR (95% CI)	*P*-value
For the 248 patients who did not develop a major in-hospital complication during the index admission[a]				
	$n = 176$	$n = 72$		
In-hospital	2 (1.1%)	3 (4.2%)	3.75 (0.62–23.1)	0.15
30 days	6 (3.4%)	3 (4.3%)	1.23 (0.30–5.1)	0.72
180 days	28 (16.5%)	12 (17.4%)	1.07 (0.51–2.24)	0.86
For the complete cohort of 299 patients hospitalized with worsening heart failure[b]				
	$n = 201$	$n = 98$		
In-hospital	3 (1.5%)	12 (12.3%)	9.2 (2.6–33.5)	0.002
30 days	9 (4.6%)	14 (14.6%)	3.5 (1.5–8.5)	0.003
180 days	35 (18.1%)	26 (28.0%)	1.8 (0.98–3.2)	0.08

[a]Follow-up by 30 days for mortality: 244/248 (98%) complete; follow-up by 180 days for mortality: 239/248 (96%) complete.
[b]Follow-up by 30 days for mortality: 291/299 (97%) complete; follow-up by 180 days for mortality: 285/299 (95%) complete.

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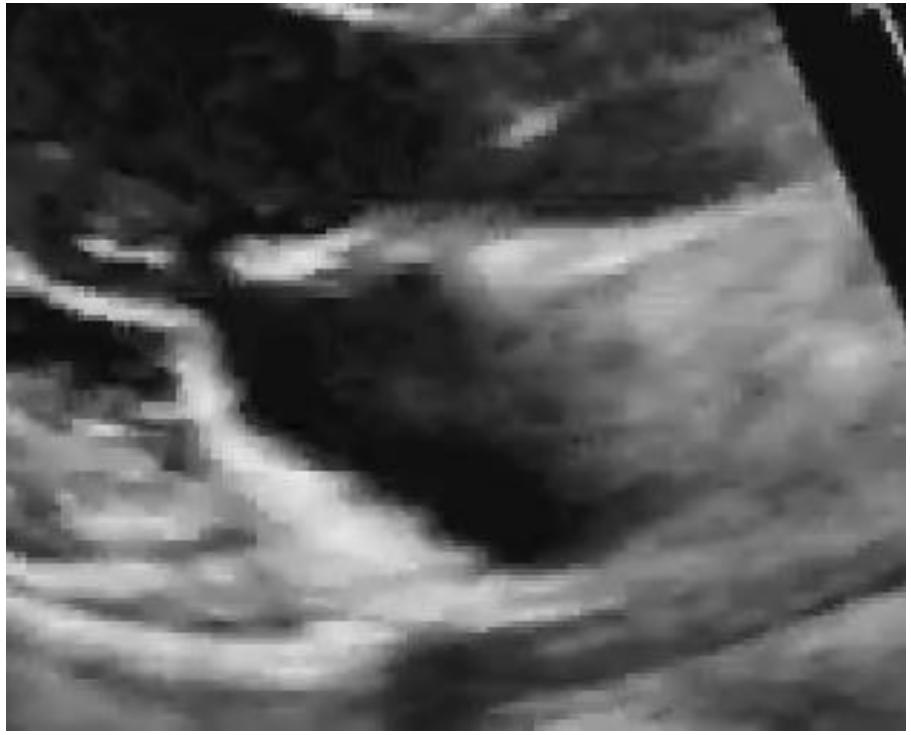
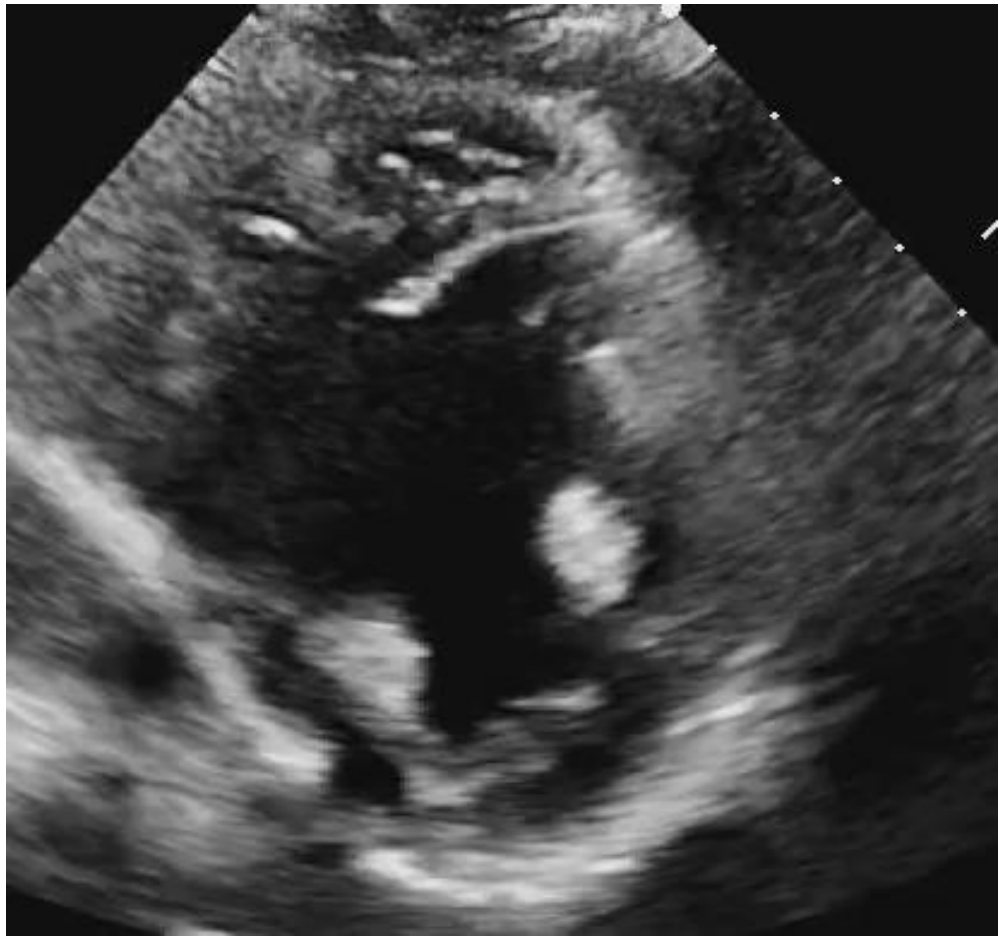
Cowie, Eur Heart J. 2006 May;27(10):1216-22

Paradoxes and Controversies Summary

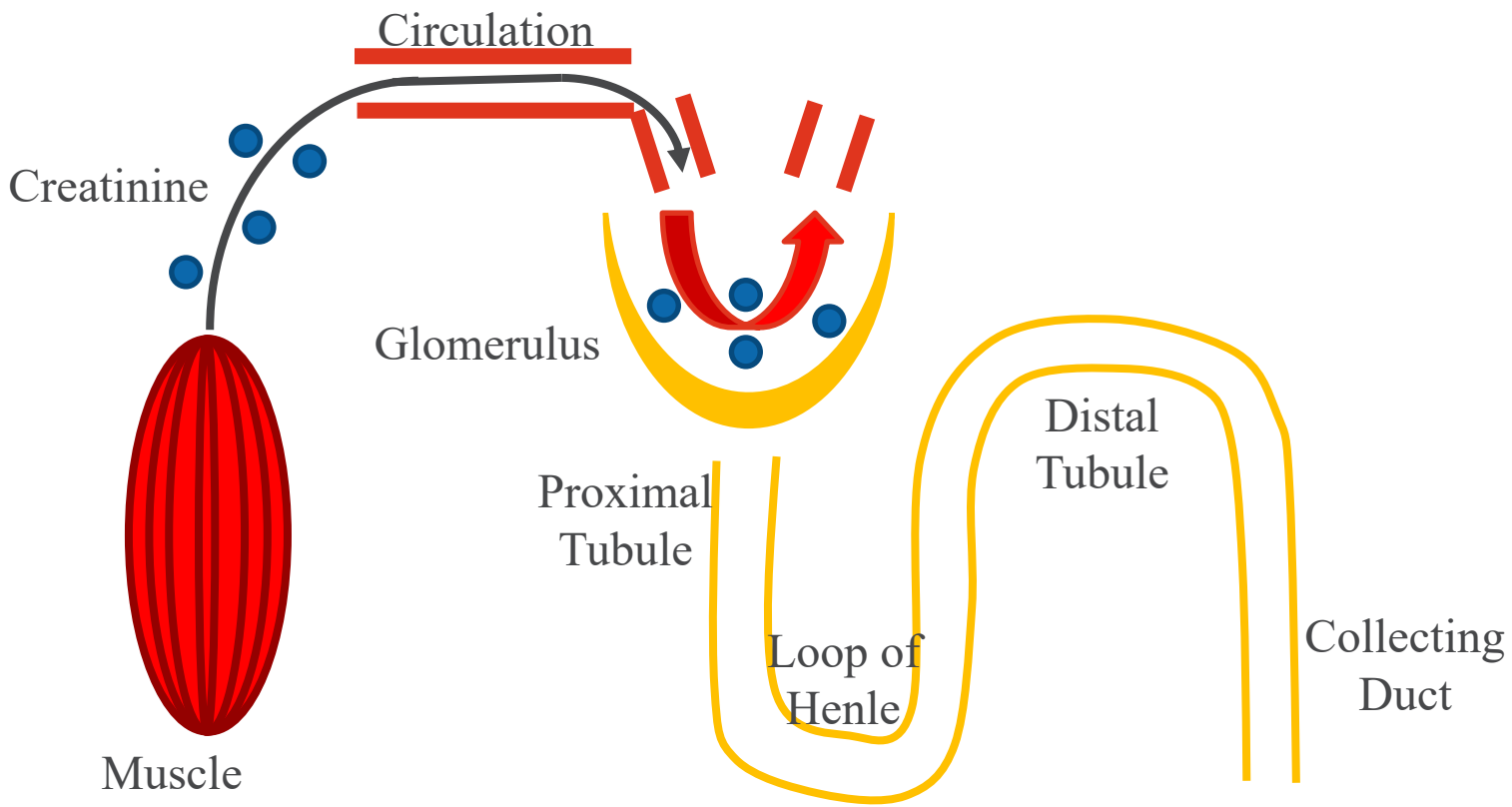
- Improved renal function also associated with worse outcomes
- WRF historically had worse outcomes, but when associated with appropriate diuresis/decongestion, may not be harmful
- Most WRF is ‘Pseudo-WRF’ or ‘Pseudo-AKI’
- IRF also not as bad outcomes with appropriate diuresis/decongestion; however, still worse than not having IRF at all

New Paradigms in Acute Kidney Injury





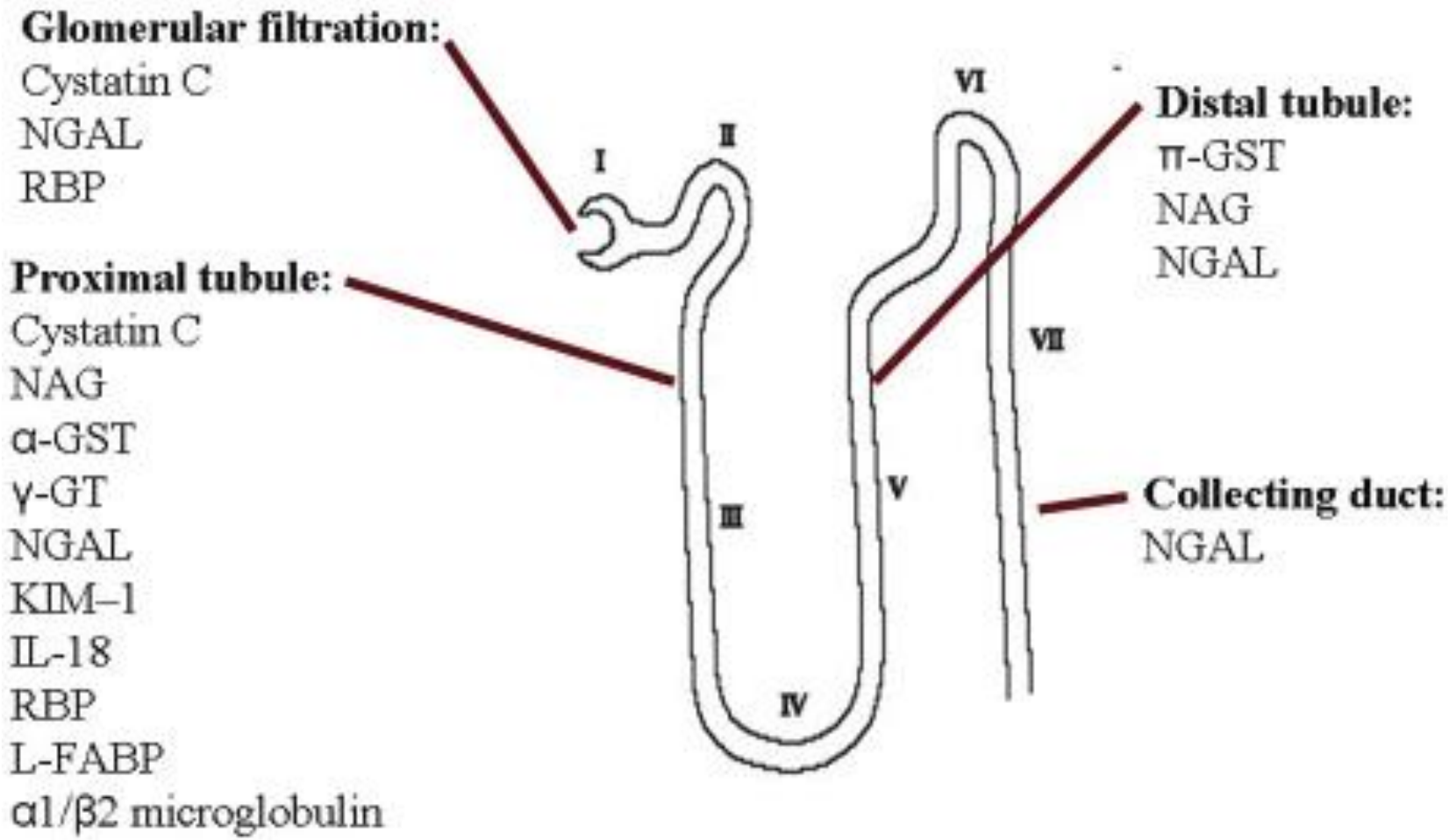
Creatinine Is Like Looking At One Valve to Assess the Whole Heart



New Paradigm in Acute Kidney Injury

Adapted from McCullough et al, Contrib Nephrol. 2013;182:13-29

Numerous Novel Biomarkers Are Being Evaluated



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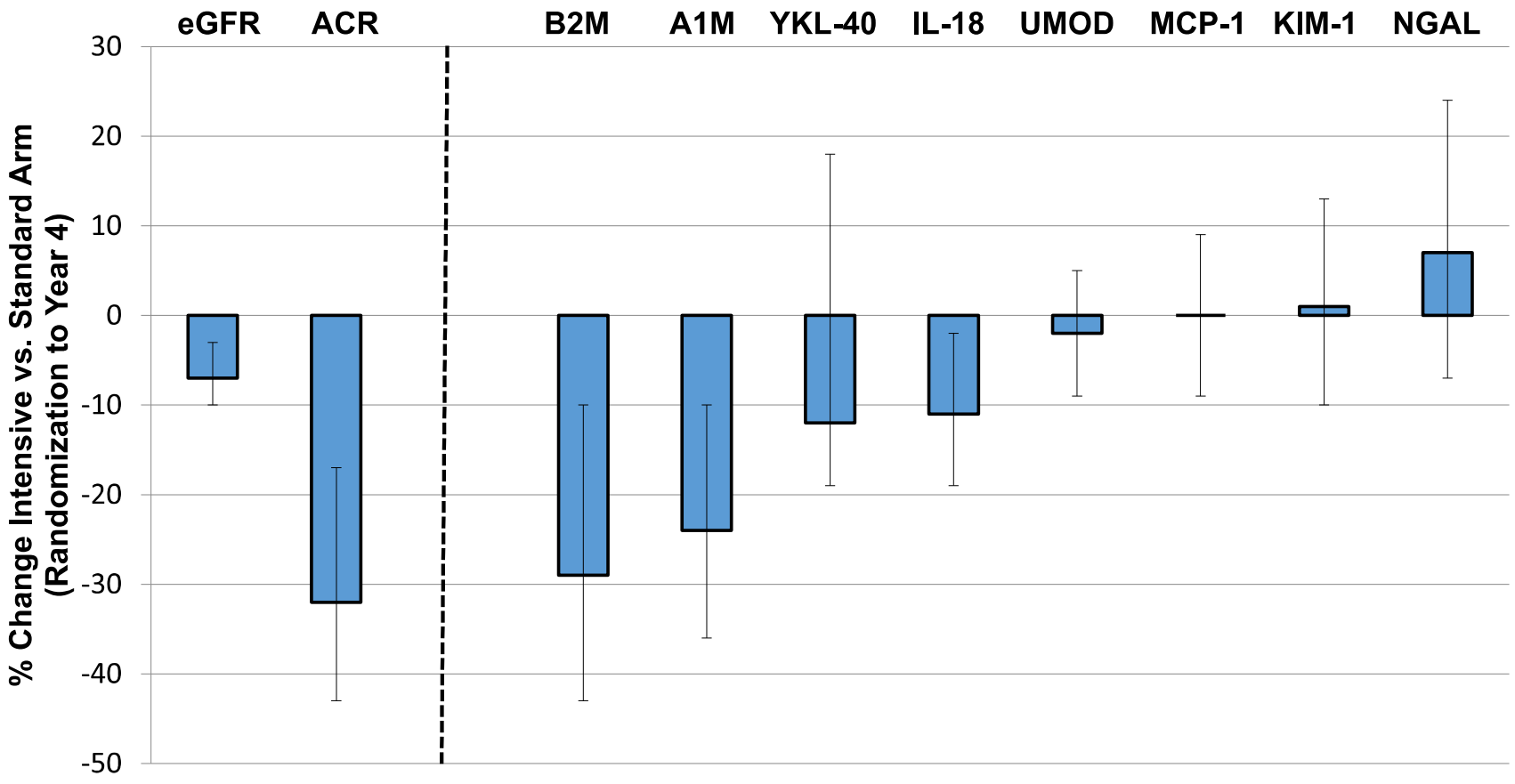
Ostermann, Crit Care. 2012 Sep 21;16(5):233

Biomarkers Are Defining Creatinine Changes in Hypertension



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Malhotra, Am J Kid Dis, 2018

Biomarkers in Acute Heart Failure for Cardiorenal Syndrome

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Neutrophil Gelatinase-Associated Lipocalin (NGAL)

- Small molecule of lipocalin found in neutrophils and renal tubular cells
- Released during acute phase of toxic or ischemic kidney injury
- Measurable in plasma and urine
- Predictive for AKI in cardiac surgery, contrast induced nephropathy, and critical illness
- Unknown if predictive of AKI in AHF

Bolignano et al., Am J Kidney Dis, 2008, 52:595-605
Zhou et al. Eur J Cardiothorac Surg, 2015
Haase et al., Am J Kidney Dis 2009;54:1012-24

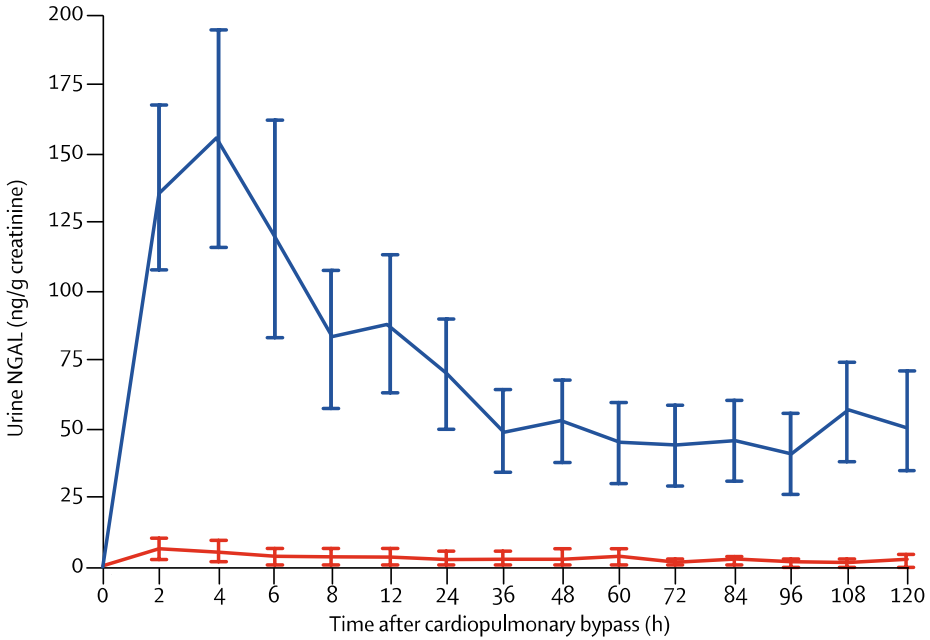
The Paper that Started NGAL Interest

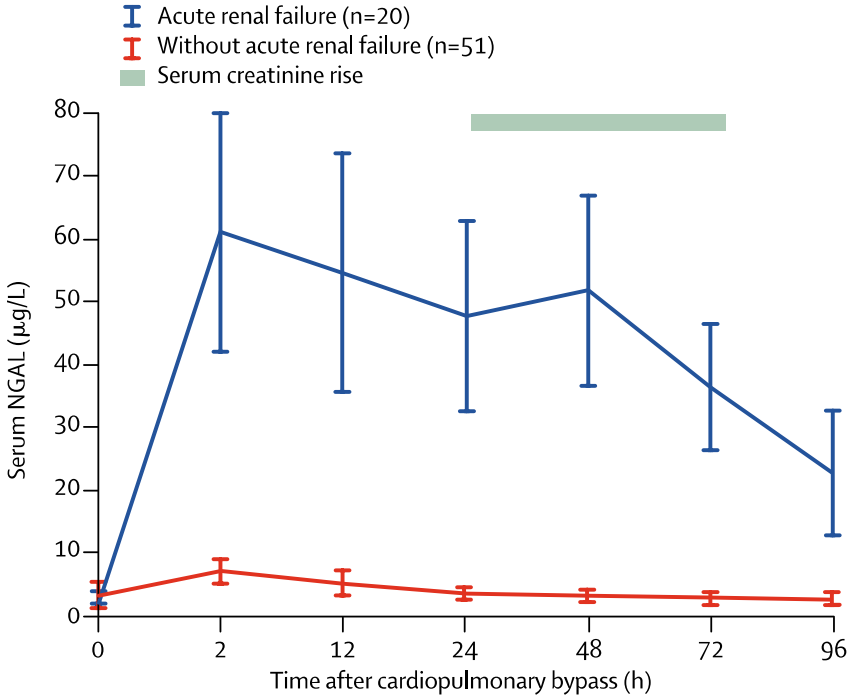
Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery

Jaya Mishra, Catherine Dent*, Ridwan Tarabishi*, Mark M Mitsnefes, Qing Ma, Caitlin Kelly, Stacey M Ruff, Kamyar Zahedi, Mingyuan Shao, Judy Bean, Kiyoshi Mori, Jonathan Barasch, Prasad Devarajan*

Lancet 2005; 365: 1231–38

See **Comment** page 1205





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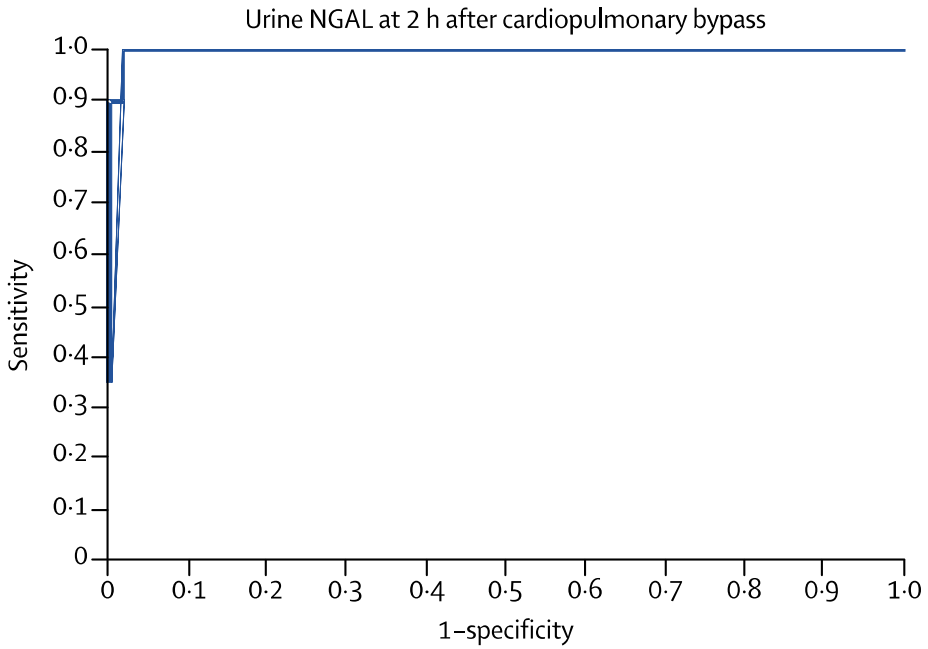
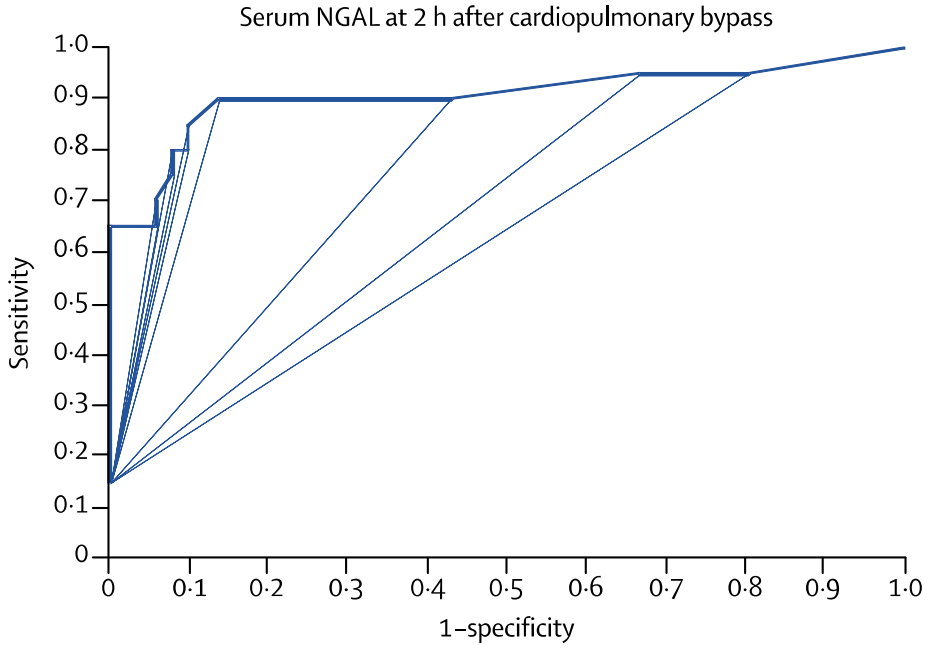
See **Comment** page 1205





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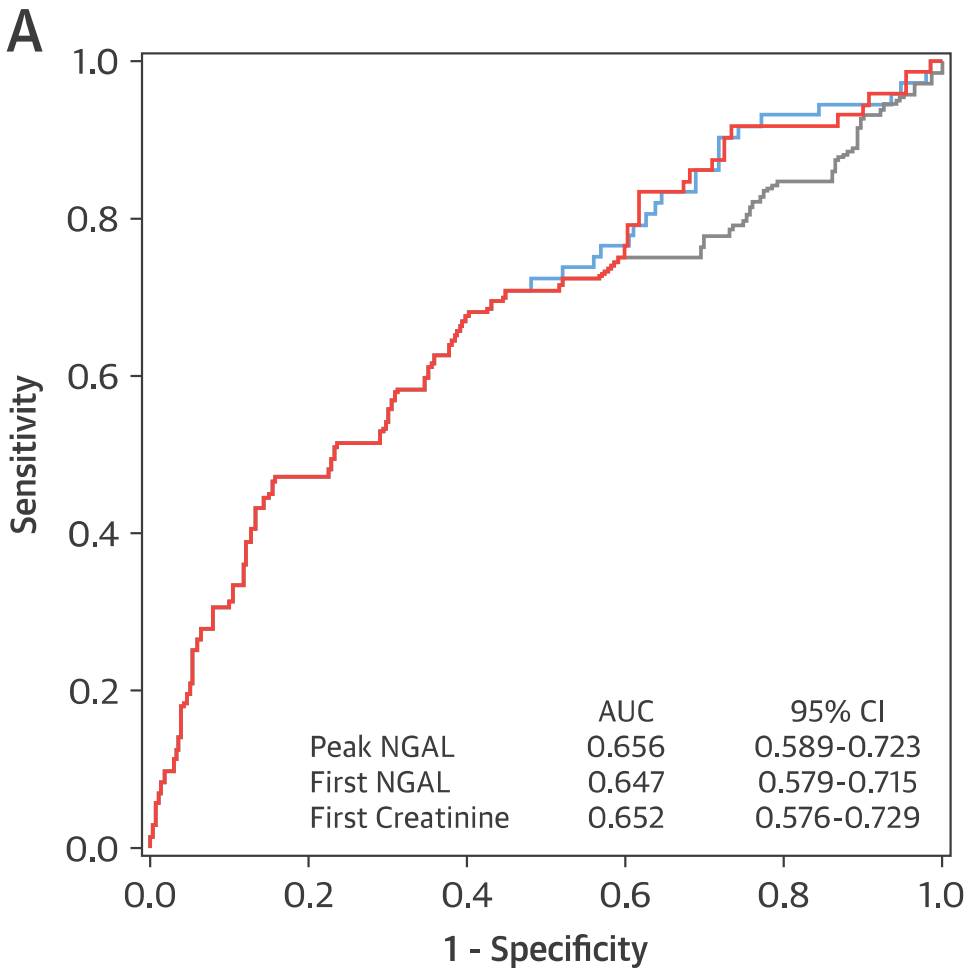
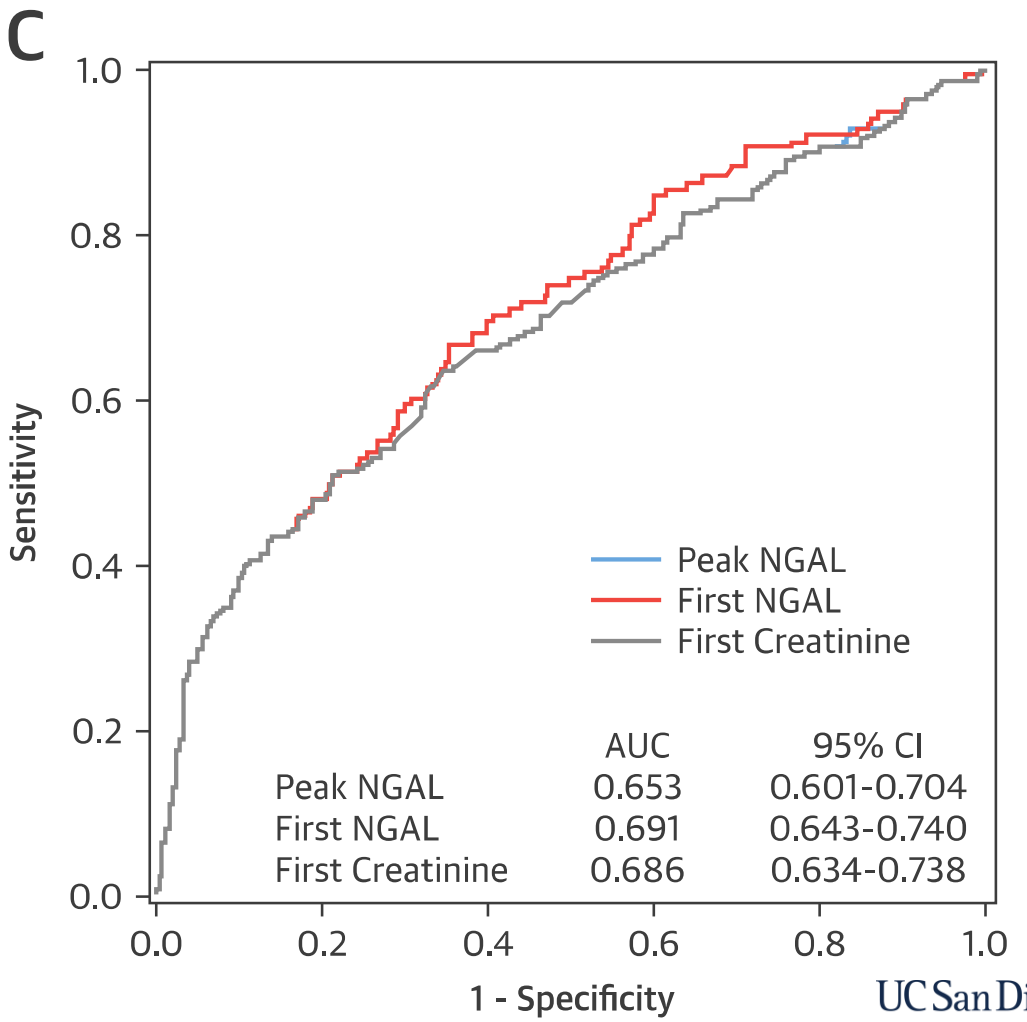
Serum NGAL Does Not Perform Well in Acute Heart Failure for WRF or Adverse Outcomes (AKINESIS)





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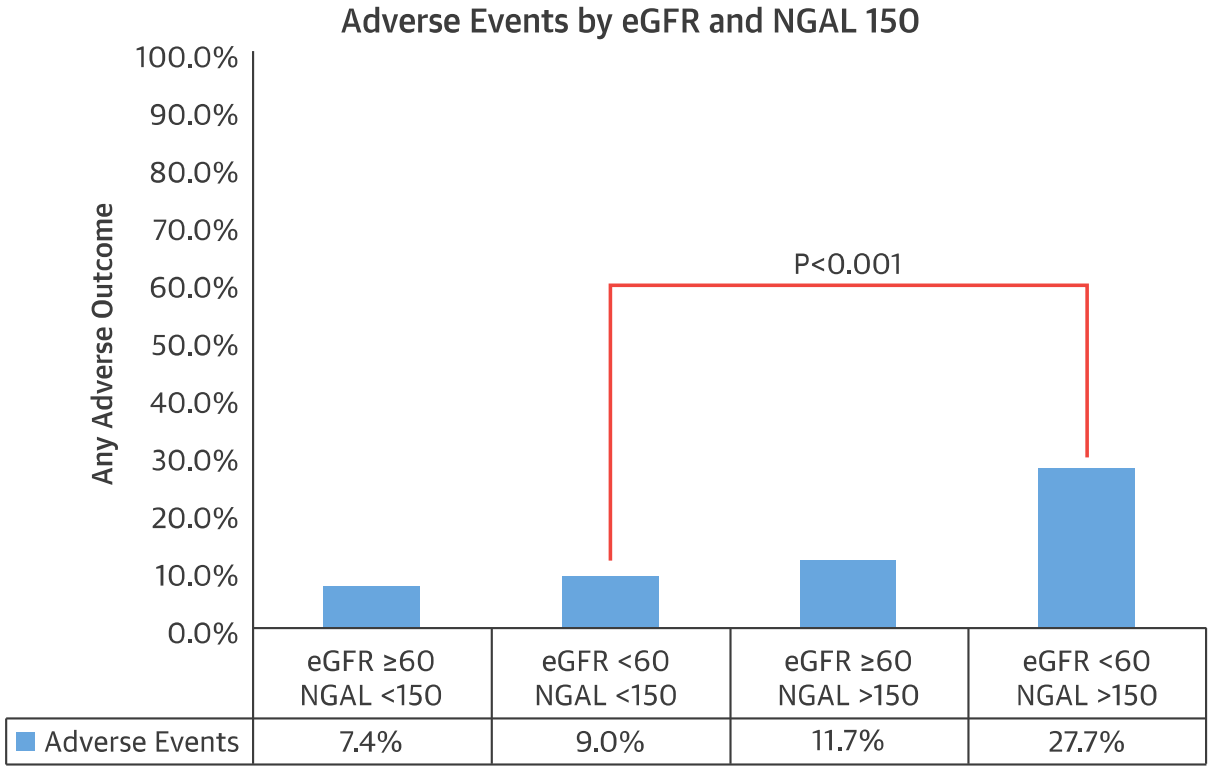
Maisel, J Am Coll Cardiol. 2016 Sep 27;68(13):1420-1431

Slight Signal May Help Rule Out Badness In Low eGFR

B



Predictive Performance eGFR<60 NGAL<150 mg/mL		
Sensitivity	84.5%	(CI 76.0%-90.5%)
Specificity	41.7%	(CI 36.8%-46.7%)
Positive Predictive Value	27.7%	(CI 23.0%-33.0%)
Negative Predictive Value	91.0%	(CI 85.8%-94.5%)

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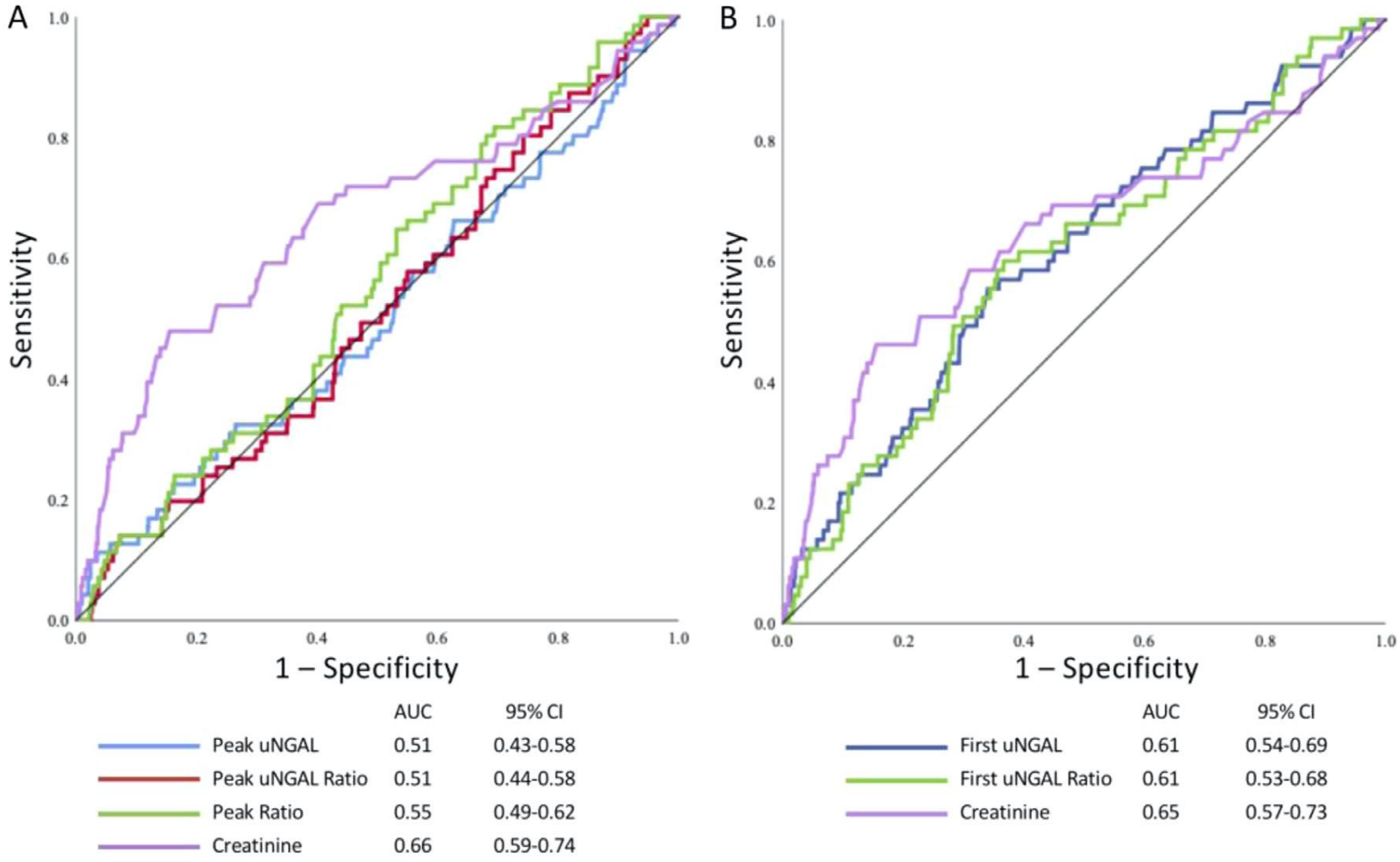
Maisel, J Am Coll Cardiol. 2016 Sep 27;68(13):1420-1431

Urine NGAL Also Does Not Perform Well



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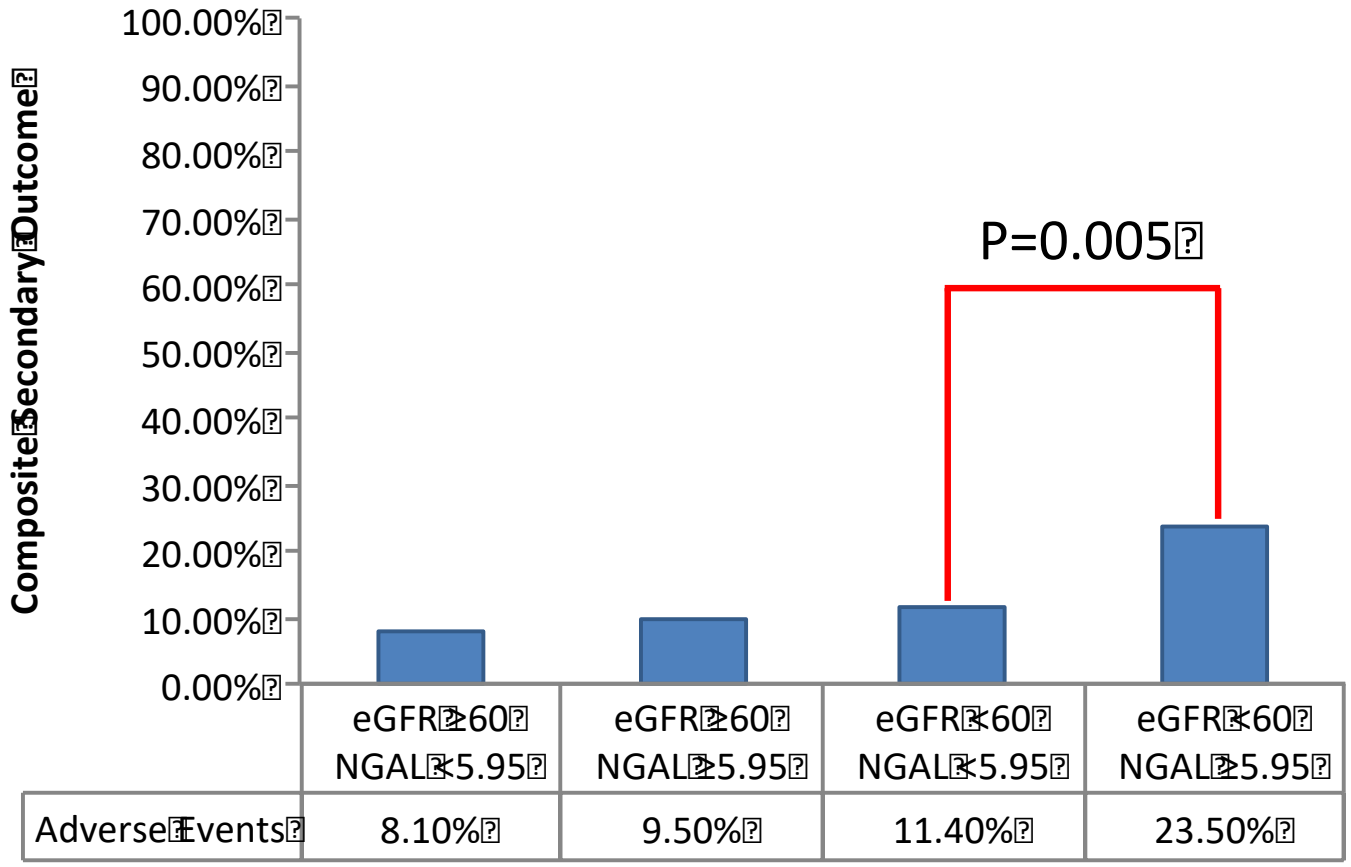
Murray, J Card Fail. 2019 Aug;25(8):654-665.

Again Some Signal for Low Urine NGAL and Low eGFR



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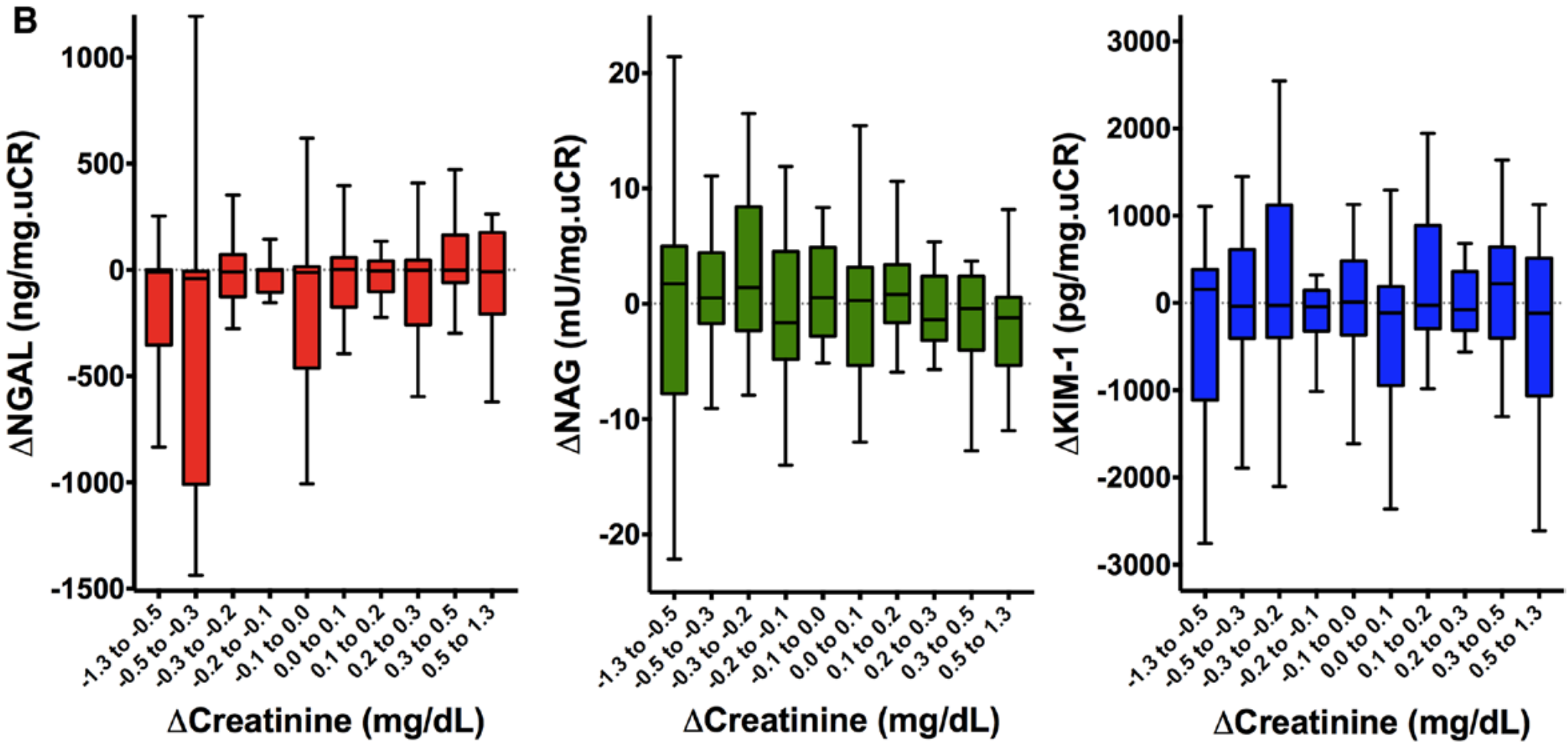
Murray, J Card Fail. 2019 Aug;25(8):654-665.

Others Have Similarly Shown Lack of Injury in Acute Heart Failure



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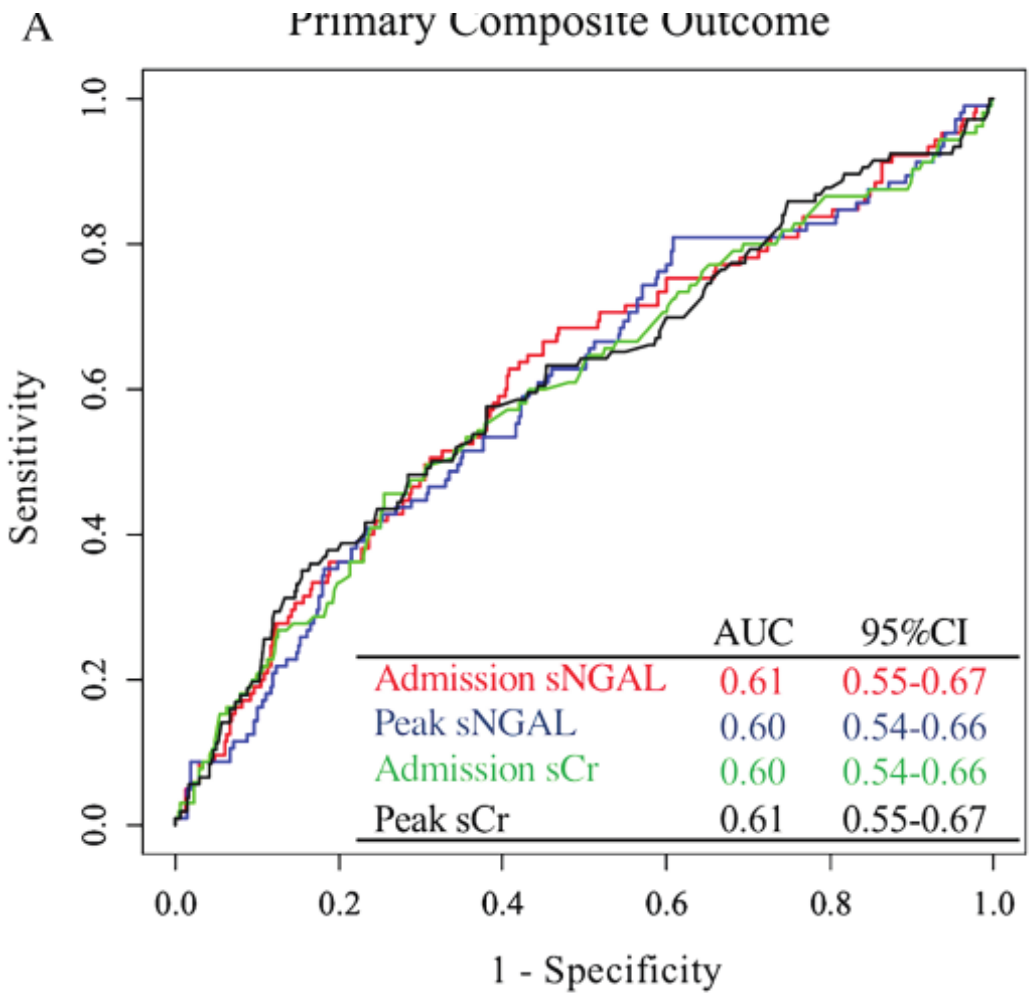
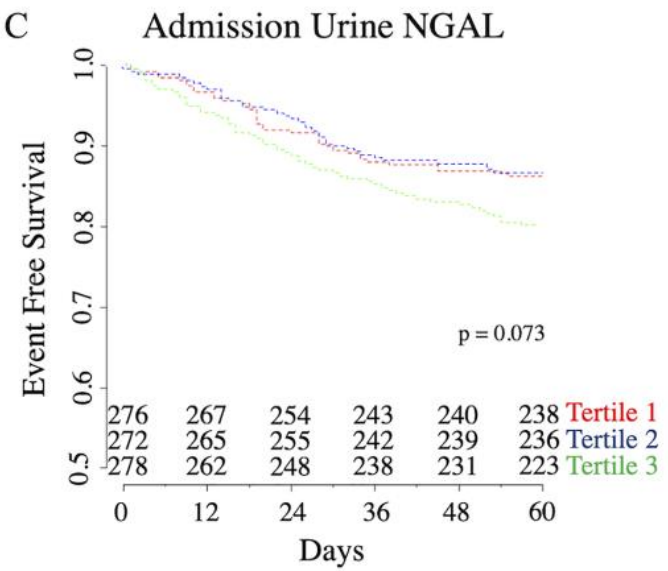
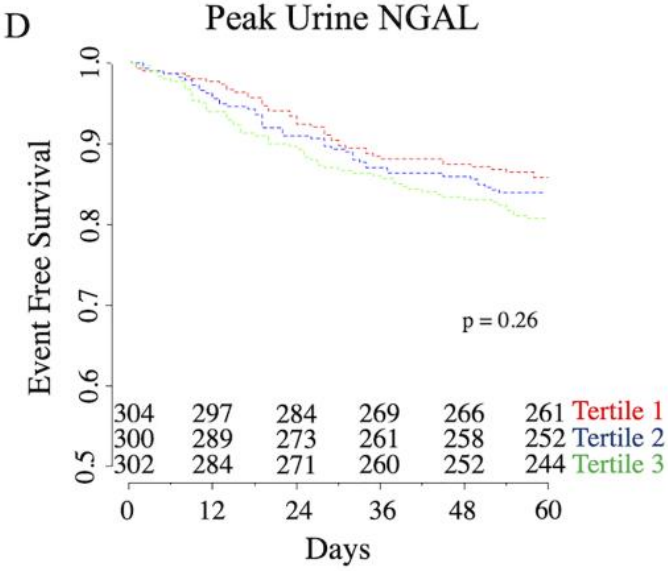
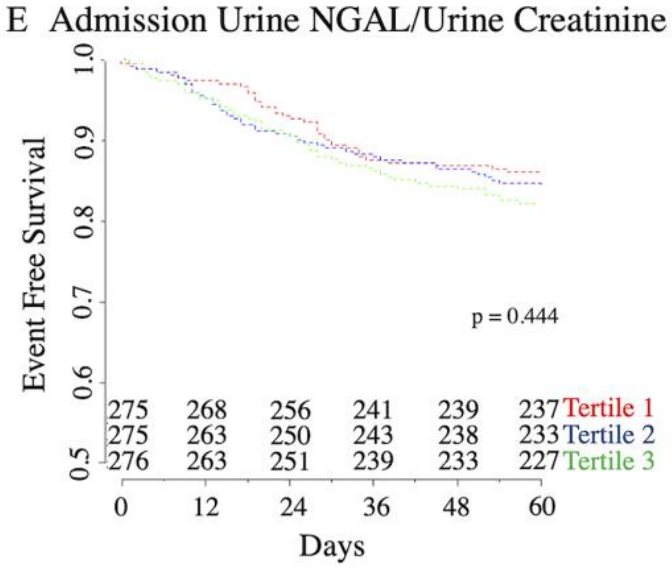
Ahmad, Circulation. 2018 May 8;137(19):2016-2028

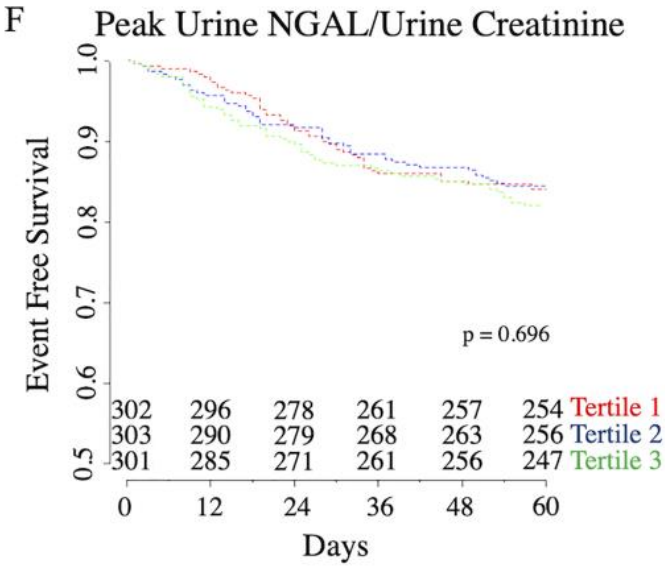
Plasma and Urine NGAL Do Not Predict Short-term Outcomes in Acute Heart Failure Either











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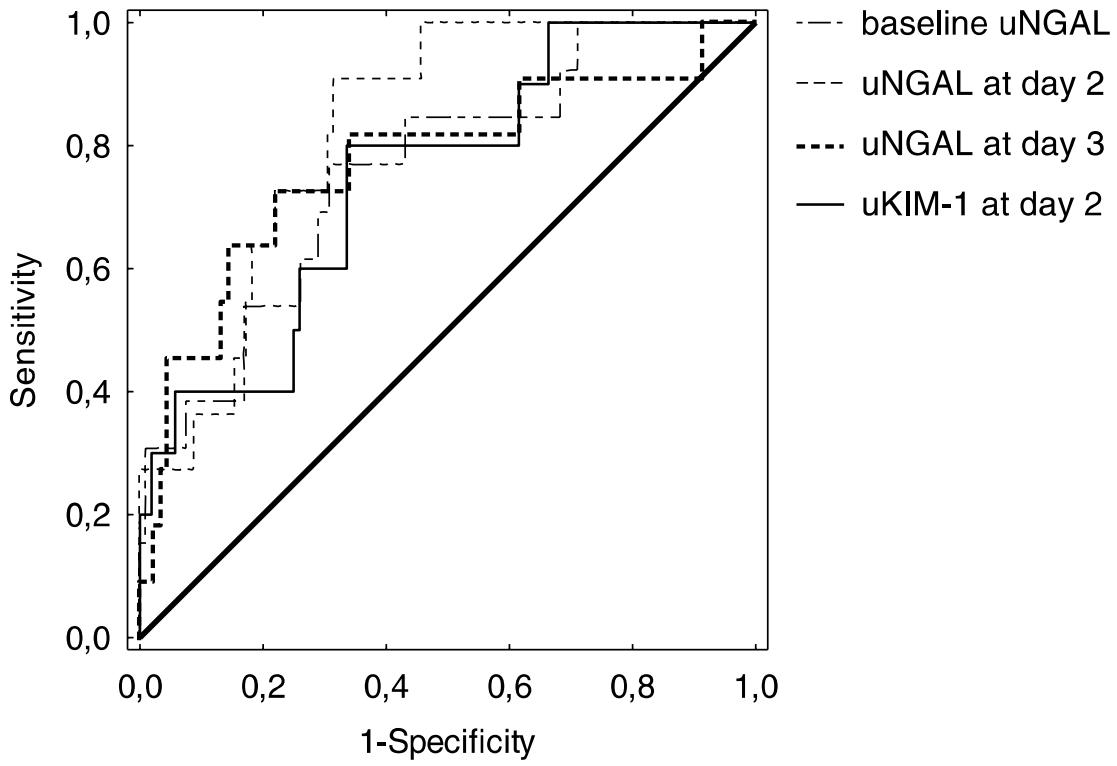
Wettersten, Eur J Heart Fail. 2020 Feb;22(2):251-263.

Why Do Novel Kidney Injury Biomarkers Not Work in Acute Heart Failure

- Not all rises in creatinine are bad
  - Concentration of creatinine in blood
  - Appropriate decongestion causes hemodynamic changes at glomerulus only
- Injury is rarely present in acute heart failure
- Biomarkers might detect ‘True-WRF’ and ‘pseudo-WRF’
- We have been evaluating wrong biomarkers

When Biomarkers Rise First then Bad Things Might Happen

Urinary levels of novel kidney biomarkers and risk of true worsening renal function and mortality in patients with acute heart failure



Biomarker	AUCs
Baseline uNGAL	0.76 (0.63-0.90)
uNGAL day 2	0.83 (0.73-0.93)
uNGAL day 3	0.77 (0.60-0.94)
uKIM-1 day 2	0.74 (0.59-0.90)

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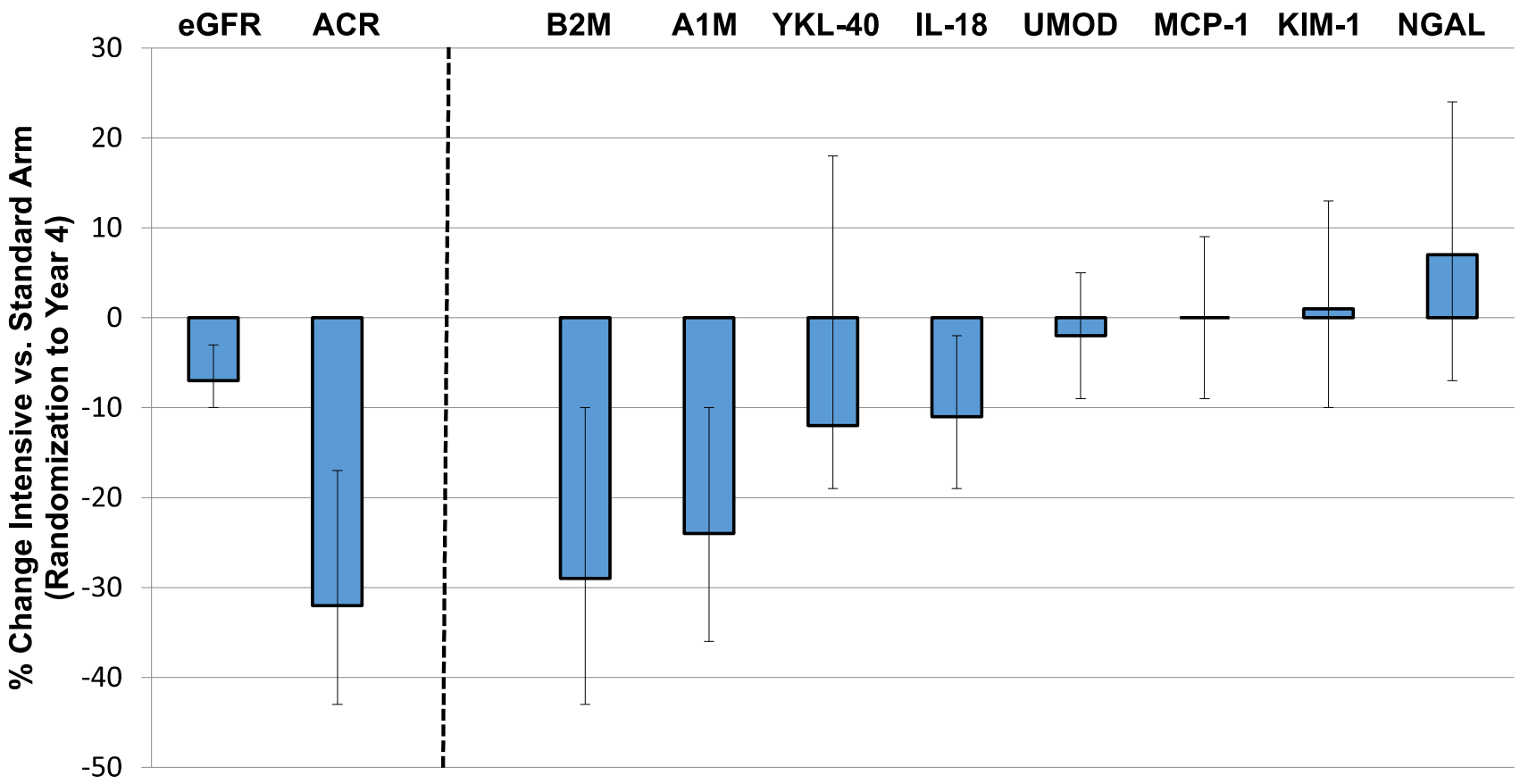
Sokolski, Eur J Heart Fail. 2017 Jun;19(6):760-767

New Urine Biomarkers Assess Injury AND Function



Summary of Biomarkers

- Multiple novel biomarkers for assessment of kidney injury and function have been discovered
- Studies have shown a general lack of kidney injury in acute heart failure
- Currently, there is limited to no role for these biomarkers in acute heart failure
- Future studies of different types of biomarkers or more selective roles for use may be discovered (i.e. discriminating true vs. pseudo WRF)

Take Away Points

- Cardiorenal syndrome is the dynamic pathophysiologic interaction between the heart and kidney throughout the spectrum of cardiovascular and kidney diseases
- In acute heart failure, both hemodynamic and non-hemodynamic processes influence kidney function with CVP being the hemodynamic factor most associated with kidney function
- Worsening of kidney function during treatment of acute heart failure does not impact prognosis if accompanied by adequate decongestion, but if inadequate decongestion, it portends a poor prognosis

Take Away Points

- Improvement in kidney function during treatment is associated with worse outcomes than stable or worsening kidney function
- Novel injury biomarkers show an overall lack of kidney injury in acute heart failure
  - But kidney injury likely impacts a subset of acute heart failure patients
- Novel kidney biomarkers, such as NGAL, currently do not have a role in acute heart failure management
  - But future studies may show specific uses

Take Away Points

- Sometimes it is the kidney's fault

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Thank You

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