

# Cardio-Renal Interactions and Renal Functional Reserve

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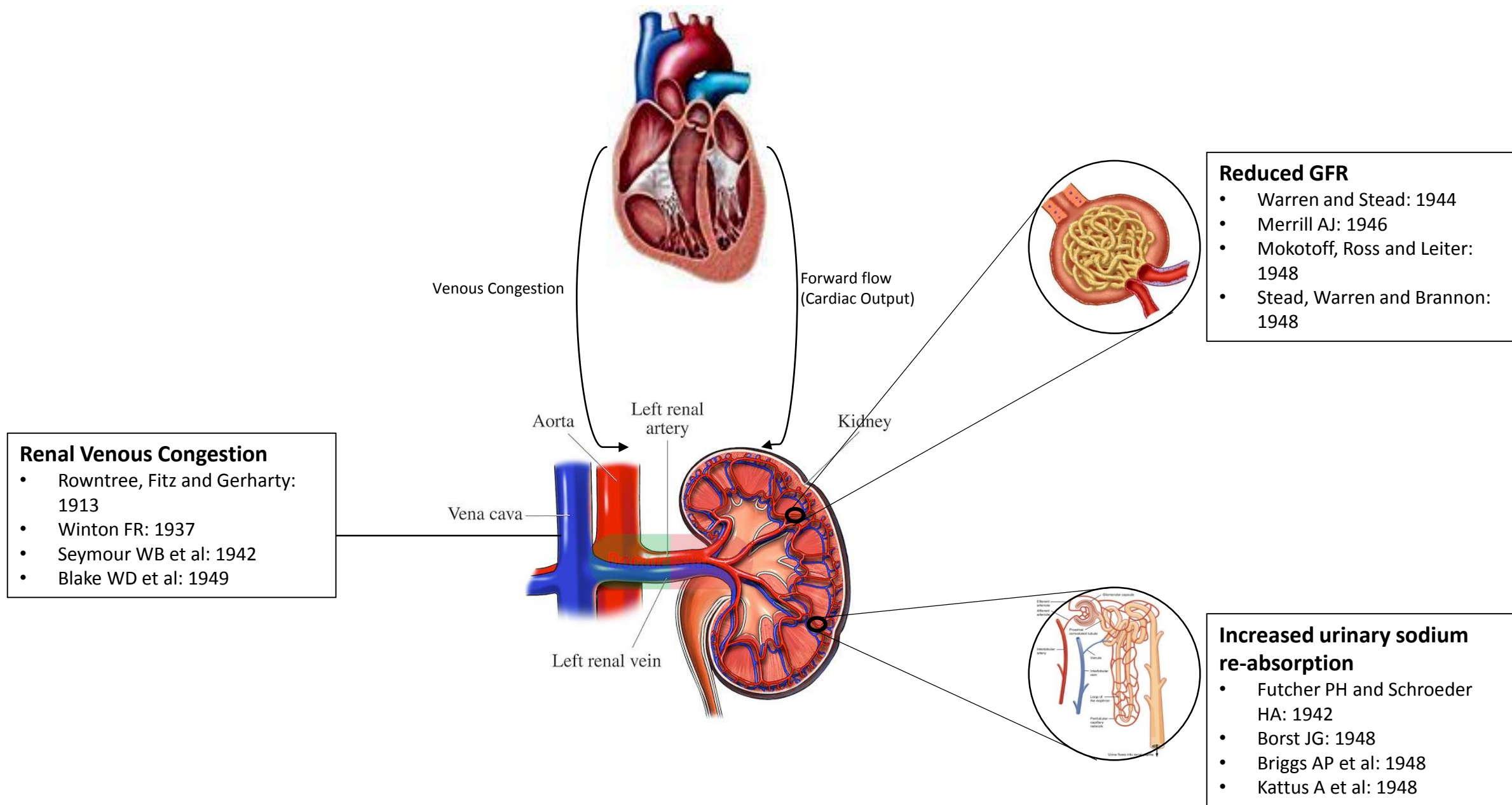
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# Talk outline

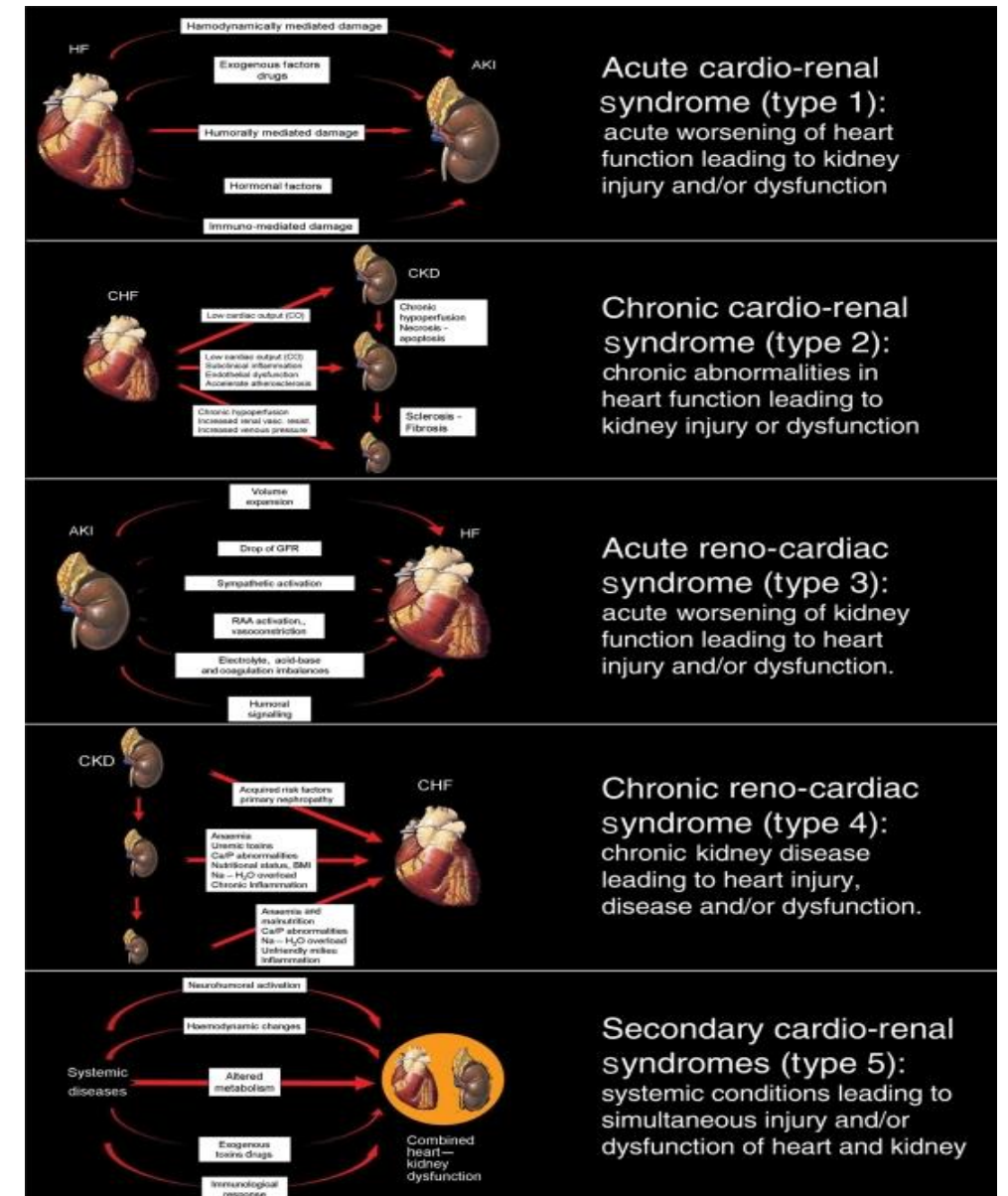
- Key landmarks in the history of cardiorenal interactions and RFR.
- Definition and concept of renal functional reserve (RFR).
- Physiology behind quantification of RFR.
- Peri-procedural acute kidney injury: RFR as a predictor
- RFR as a possible biomarker in type 2 cardiorenal syndrome
- Conclusions and future applications.





Ronco C , McCullough PA, Anker SD et al

Cardio-renal Syndromes: Report from the consensus conference of the Acute Dialysis Quality Initiative, European Heart Journal 2010



## 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 phenotypes. The mission of this scientific statement is to describe the epidemiology and pathogenesis of cardiorenal syndrome in the context of the continuously evolving nature of its clinicopathological description over the past decade. It also describes diagnostic and therapeutic strategies applicable to cardiorenal syndrome, summarizes cardiac-kidney interactions in special populations such as patients with diabetes mellitus and kidney transplant recipients, and emphasizes the role of palliative care in patients with cardiorenal syndrome. Finally, it outlines the need for a cardiorenal education track that will guide future cardiorenal trials and integrate the clinical and research needs of this important field in the future.

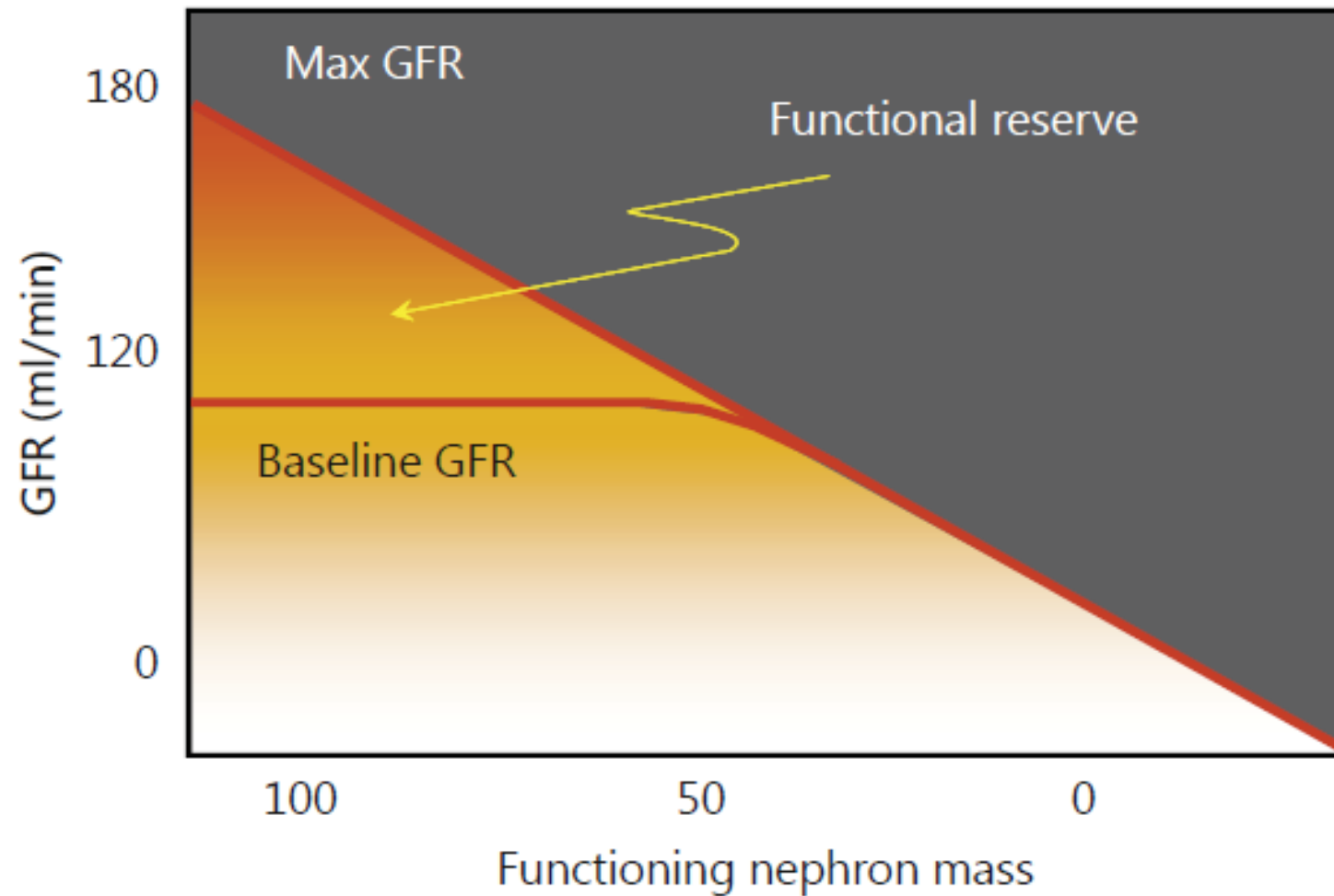
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MPH, FAHA, Chair  
On behalf of the American  
Heart Association  
Council on the Kidney in  
Cardiovascular Disease



# Renal functional reserve testing (RFR)

- RFR represents the capacity of the kidneys to increase glomerular filtration rate (GFR) in response to physiological or pathological stimuli
- It is calculated as the difference between baseline GFR and “stress” GFR
- In several conditions ( pregnancy , diabetic kidney disease, solitary kidney ), a large part of the RFR is used up to maintain baseline GFR.
- RFR is a technique that can be used for early detection of nephron loss and detection of frailty in the kidneys





Sharma A, Mucino MJ, Ronco C : Renal functional reserve and renal recovery after acute kidney injury: nephron  
Clinical Practice, 2014

# Determinants of baseline eGFR

- Birth weight
- Perinatal insults and epigenetic modifiers
- Age
- Sex
- Body size
- Dietary and hemodynamic conditions ( vegetarians/type 2CRS)
- Estimation of baseline eGFR alone is a poor method of detecting early kidney disease, or for follow up of kidney function



Addis and Drury: 1923/Pullman et al : 1954/ Bosch et al : 1983

Effects of high  
protein diet on  
eGFR

RFR=Stress GFR-  
Baseline GFR

Fliser et al : 1993

Differences in RFR  
between young and  
elderly healthy  
individuals

Ronco C et al : 1988

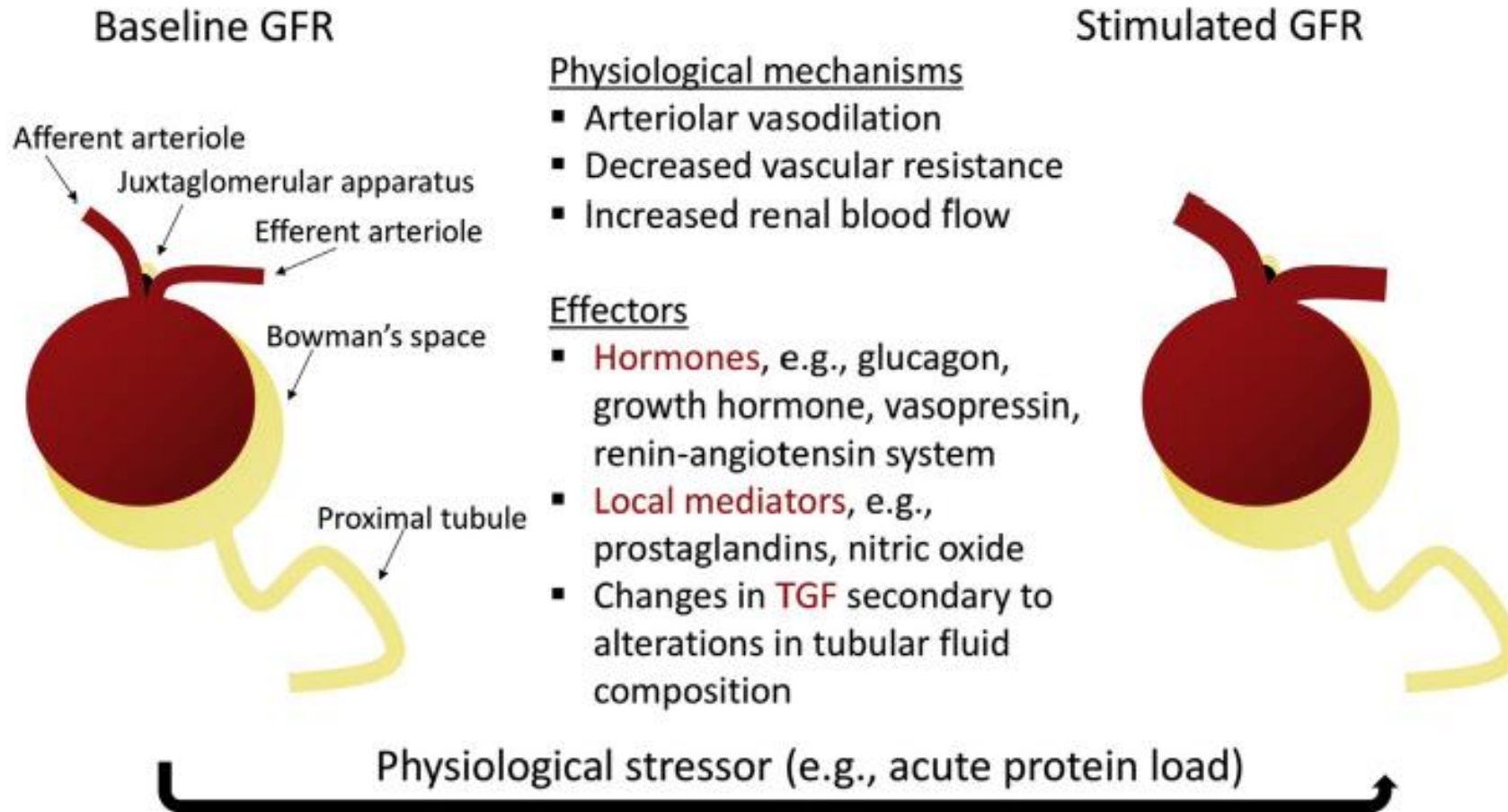
Assessment of  
baseline and stress  
GFR in normal and  
pregnant women



# Techniques used to assess RFR

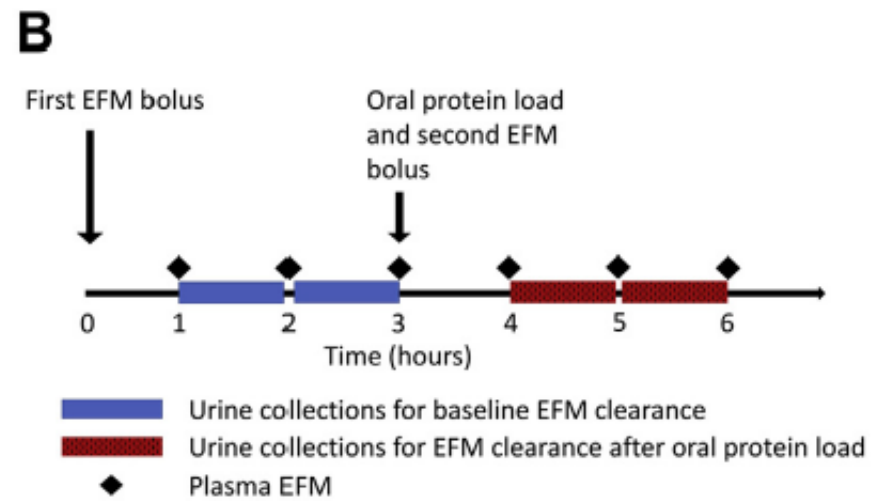
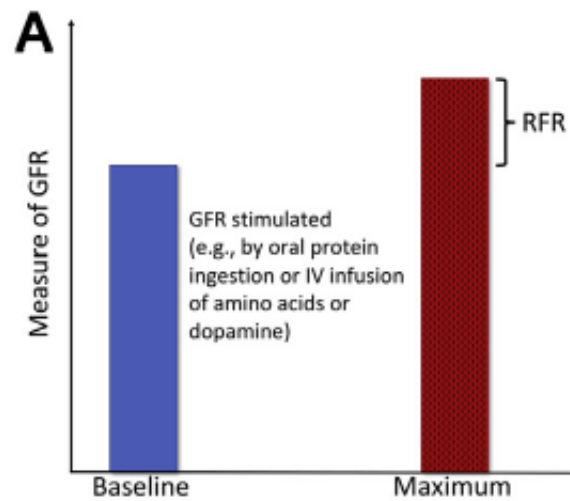
- Oral protein loading ( 1 gm/kg and 2 gram/kg)
- Intravenous protein loading ( arginine and glycine )
- Dopamine infusion
- Non invasive techniques : Measurement of renal resistive index variation with application of increased intra-abdominal pressure ( simulates same afferent arteriolar vasodilatory response )
- Radio-isotope tracer based GFR measurements

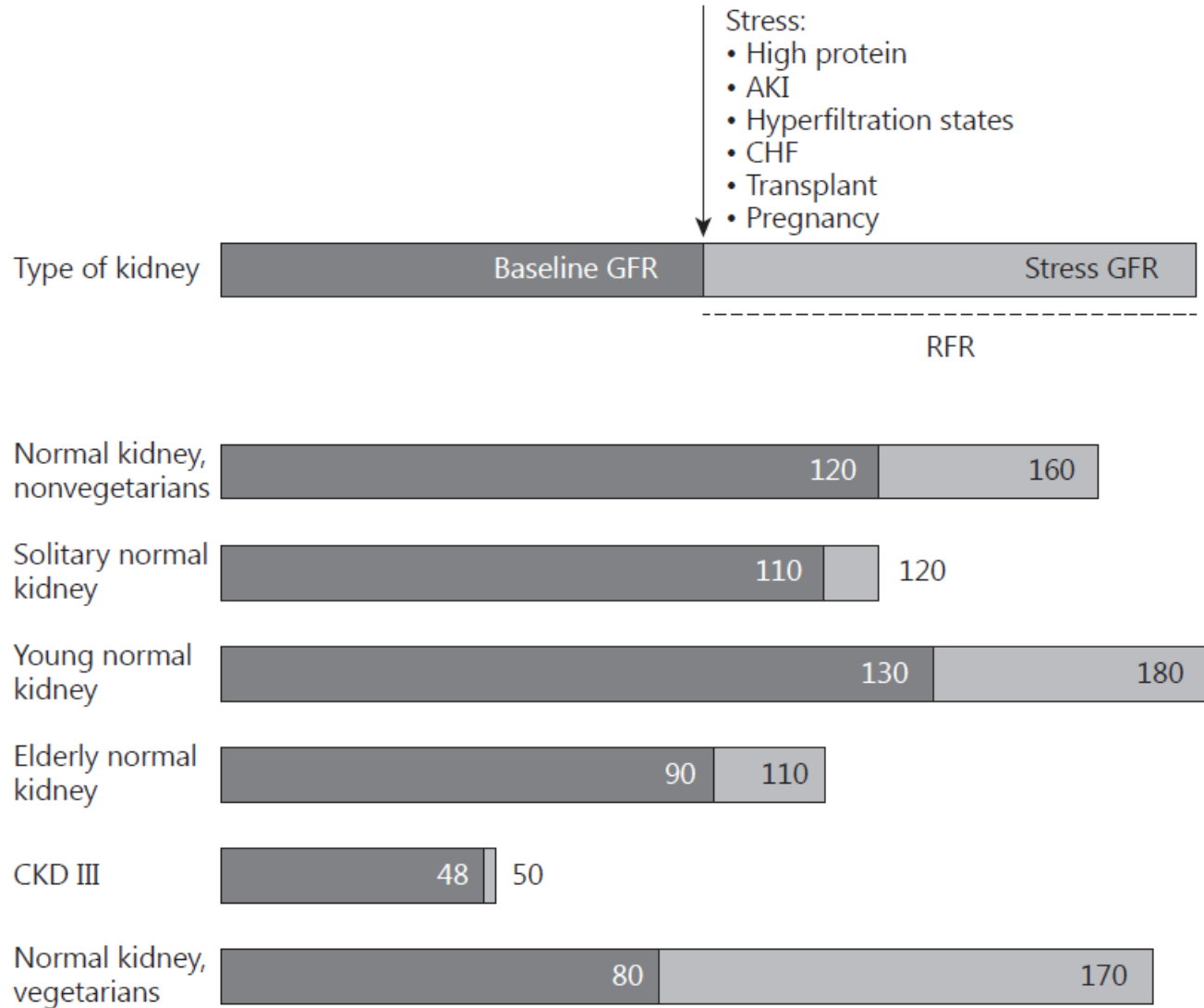




Palsson R and Waikar SS : Renal functional reserve revisited . Advances in Chronic Kidney disease, 2018







# RFR and Acute Kidney Injury : Future renal susceptibility

- eGFR estimates kidney function in a baseline and steady state
- It is not an accurate metric to quantify renal function in AKI
- After recovery from AKI , serum Cr is a poor marker to assess residual function and reserve given it can be intact despite > 50% nephron mass loss
- With cumulative episodes of AKI and loss of nephron mass , reserve function declines and increases risk of AKI with lesser degrees of renal insults .



# Potential Applications of Renal Functional Reserve Testing in Cardiorenal Medicine :

- Staged /complex percutaneous coronary interventions to achieve complete revascularization
- Before and after cardiac surgery
- To assist with prognostication in delivering goal directed therapies and decongestion after an episode of acute heart failure
- Biomarker of interest in prognostication of type 2 cardiorenal syndrome
- Predictor of reversibility of worsening renal function after LVAD implantation and predictor of post LVAD AKI occurrence
- Novel biomarker in patients with pre-eclampsia for long term prognostication.



# Effects of staged versus ad hoc percutaneous coronary interventions on renal function—Is there a benefit to staging?☆☆☆



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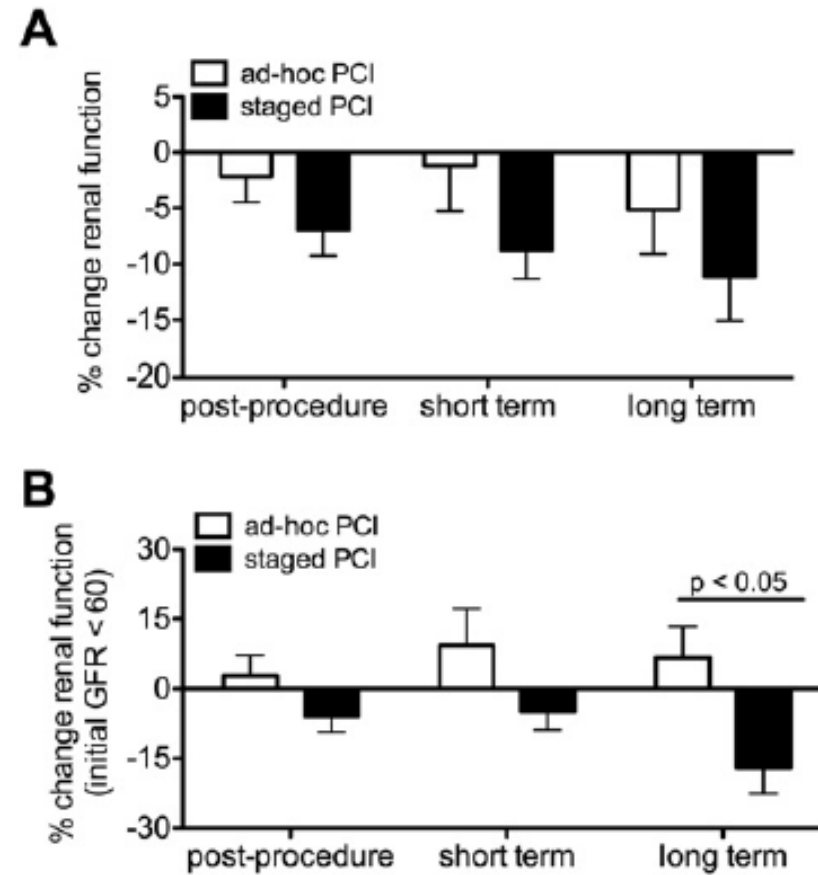
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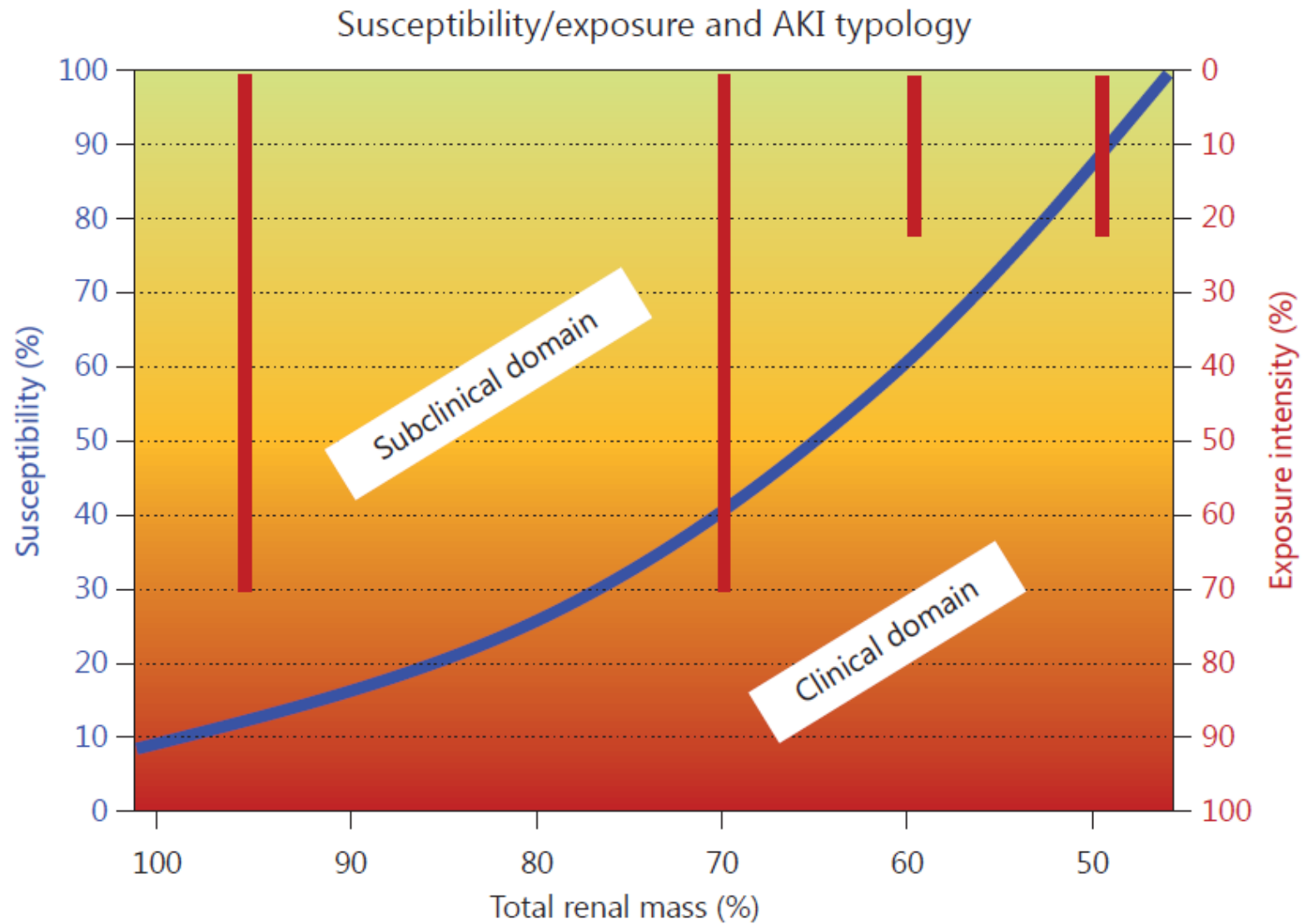
<sup>f</sup> Division of Cardiology, University of Illinois, Chicago, IL, United States





**Fig. 2.** Change in renal function after PCI. (A) There was a progressive decline in renal function following both ad hoc and staged PCI. (B) Patients with advanced chronic renal disease ( $GFR \leq 60 \text{ cm}^3/\text{min}$ ) undergoing staged PCI had significantly worse renal function at 4–12 weeks. (These data were adjusted for differences in baseline hypertension, diuretic and beta blocker use).





Sharma A, Mucino MJ, Ronco C : Renal functional reserve and renal recovery after acute kidney injury: nephron Clinical Practice, 2014

# Husein-Syed F et al : Renal Functional Reserve Predicts Risk of Acute Kidney Injury after Cardiac Operation: Annals of Thoracic Surgery, 2018

- Elective cardiac surgery in 110 patients with normal resting eGFR, and RFR was measured with protein loading
- Primary end point was to look at predictive value of pre operative RFR on AKI rates on day 7.
- Secondary end point : Predictor model integrating clinical data , RFR and cell cycle arrest markers to predict post op AKI

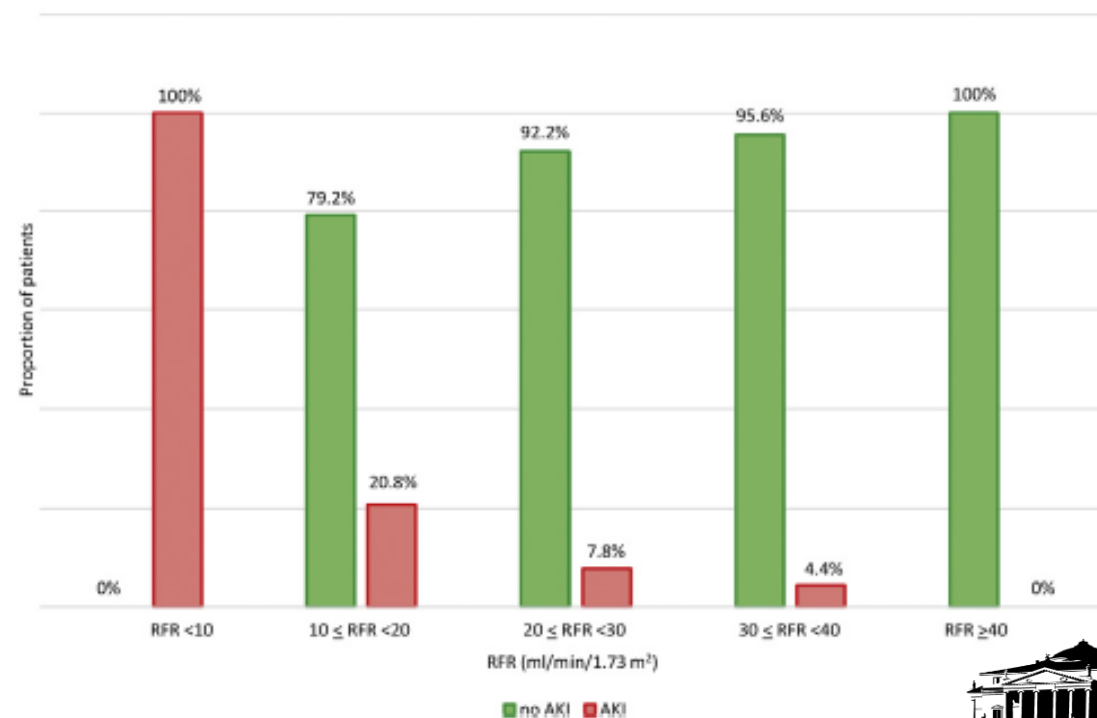
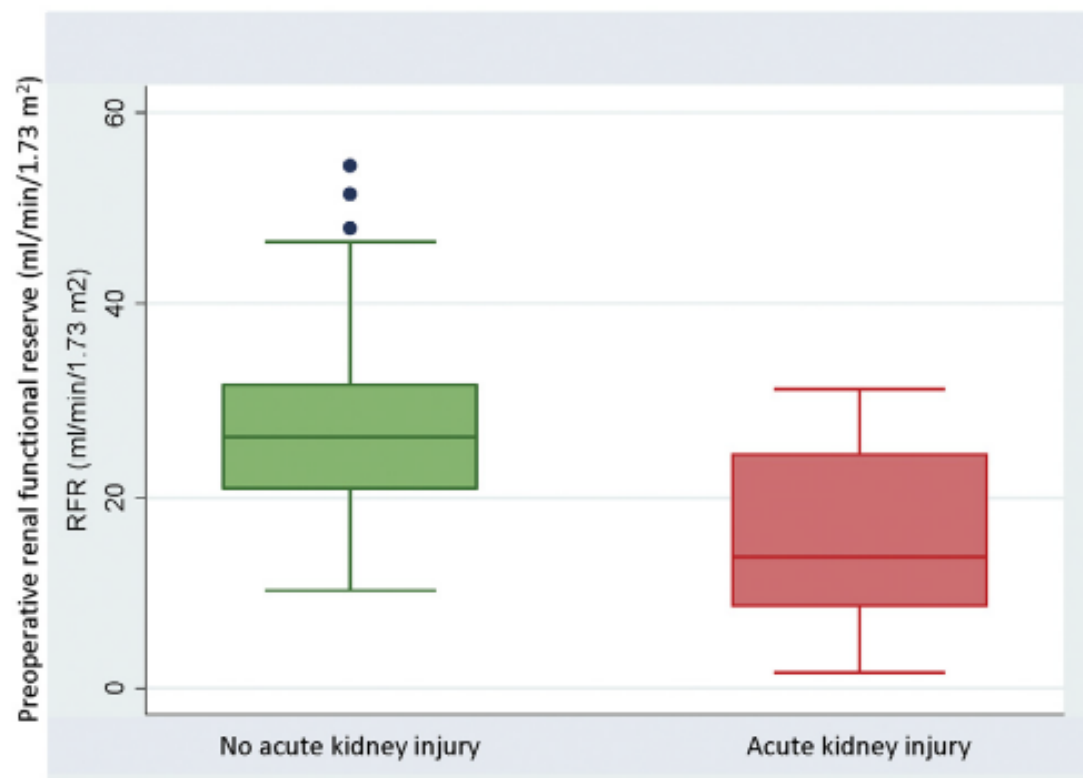


## Husein-Syed F et al : Renal Functional Reserve Predicts Risk of Acute Kidney Injury after Cardiac Operation: Annals of Thoracic Surgery, 2018

- AKI was seen in 13.6% patients .
- Pre op RFR was lower in subjects that experienced AKI ( $P < 0.001$ ) and predicted AKI with an AUC of 0.83 (95% CI= 0.70-0.97).
- Immediate post op cell cycle arrest markers (TIMP-2 and IGFBP7) also predicted AKI with an AUC of 0.87 ( 95% CI= 0.79-0.84).
- Subjects with pre op RFR  $< 15$  cc/min develop AKI with an OR of 11.8 (95 % CI= 4.62-29.89)



# Husein –Syed F et al : Preoperative Renal Functional Reserve Predicts Risk of Acute Kidney Injury after Cardiac Operation. Annals of Thoracic Surgery, 2018



Nephrol Dial Transplant (2019) 34: 308–317

doi: 10.1093/ndt/gfy227

Advance Access publication 19 July 2018

# Persistent decrease of renal functional reserve in patients after cardiac surgery-associated acute kidney injury despite clinical recovery

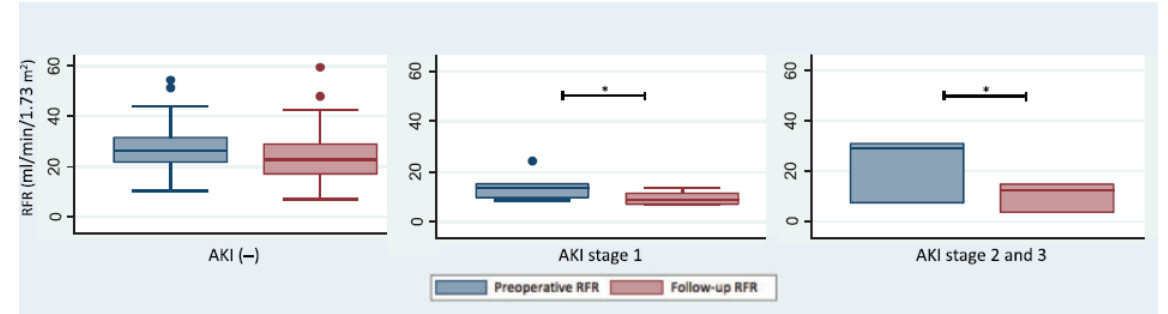
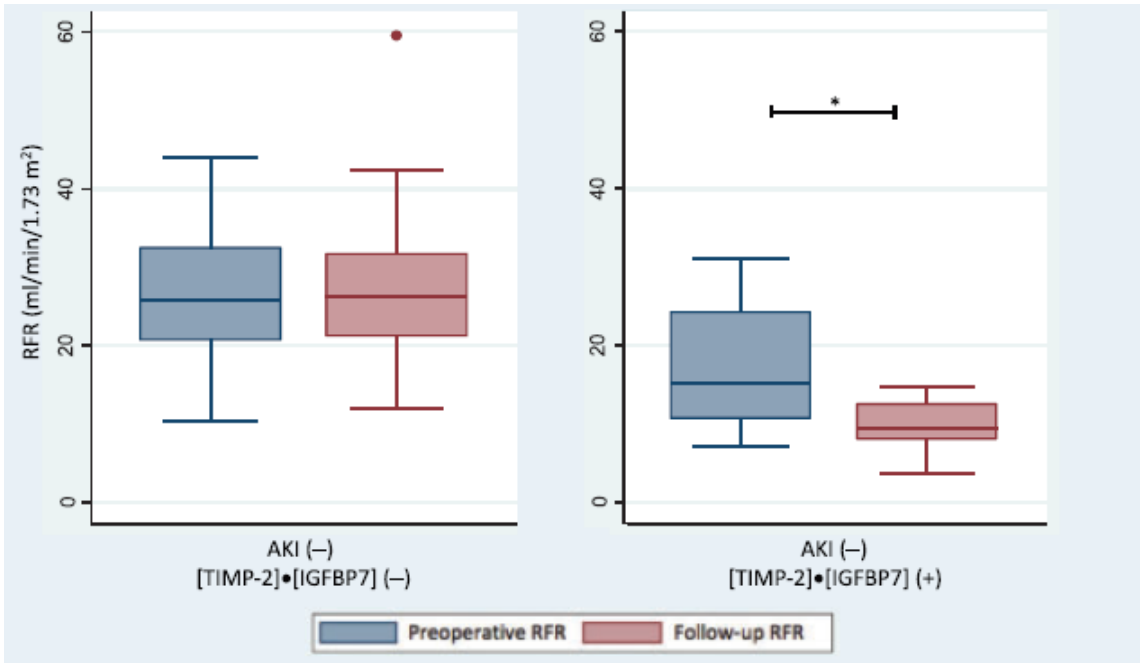
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# Changes in renal functional reserve after cardiac surgery

- At 3 months , 3 subjects developed de novo CKD . All other patients had normal resting GFR ( 93.3 cc/min +/- 15 cc/min)
- Subjects that were AKI(+) and CCA markers (+) showed reduction in post of RFR from **14.4 ml**/min/1.73m<sup>2</sup> [interquartile range (IQR) 9.5-24.3] to **9.1** (IQR 7.1-12.5) mL/min/1.73m<sup>2</sup>; P<0.001}
- Patients without AKI but CCA biomarkers (+) also experienced a similar decrease of RFR from **26.7** ml/min/1.73m<sup>2</sup> (IQR 22.9-31.5) to **19.7** (IQR 15.8-22.8) mL/min/1.73m<sup>2</sup>; P<0.001].
- Patients with neither clinical AKI nor positive biomarkers had no such decrease of RFR.
- Of the 3 patients who developed new CKD, two sustained AKI and 1 patient was CCA biomarker (+), but without AKI.





A. Renal functional reserve in groups without AKI stratified by CCA markers (-) and CCA markers (+)  
 B. Reduction in follow up RFR in subjects with stage 1 AKI and Stage 2 and 3 AKI post-cardiac surgery



Worsening Renal Function in Patients with Acute Heart Failure Undergoing Aggressive Diuresis is not associated with renal tubular injury.

Ahmad T et al: Circulation, May 2018.

- Platform : Renal Optimization Strategies Evaluation: Acute Heart Failure trial
- N: 283 patients with complete data
- Aim: To determine if renal tubular injury was a predominant cause of worsening renal function with aggressive diuresis in heart failure.
- Tubular injury biomarkers : Kidney injury molecule -1 ( KIM-1), Neutrophil gelatinase associated lipocalin ( NGAL), N –acetyl beta- glucosaminidase (NAG)
- Markers of glomerular filtration: Serum CysC, serum creatinine
- Co-primary end points : Cumulative urine output at 72 hours , changes in serum CysC.
- Tubular biomarkers were measured at baseline, 24/48/72 hours.



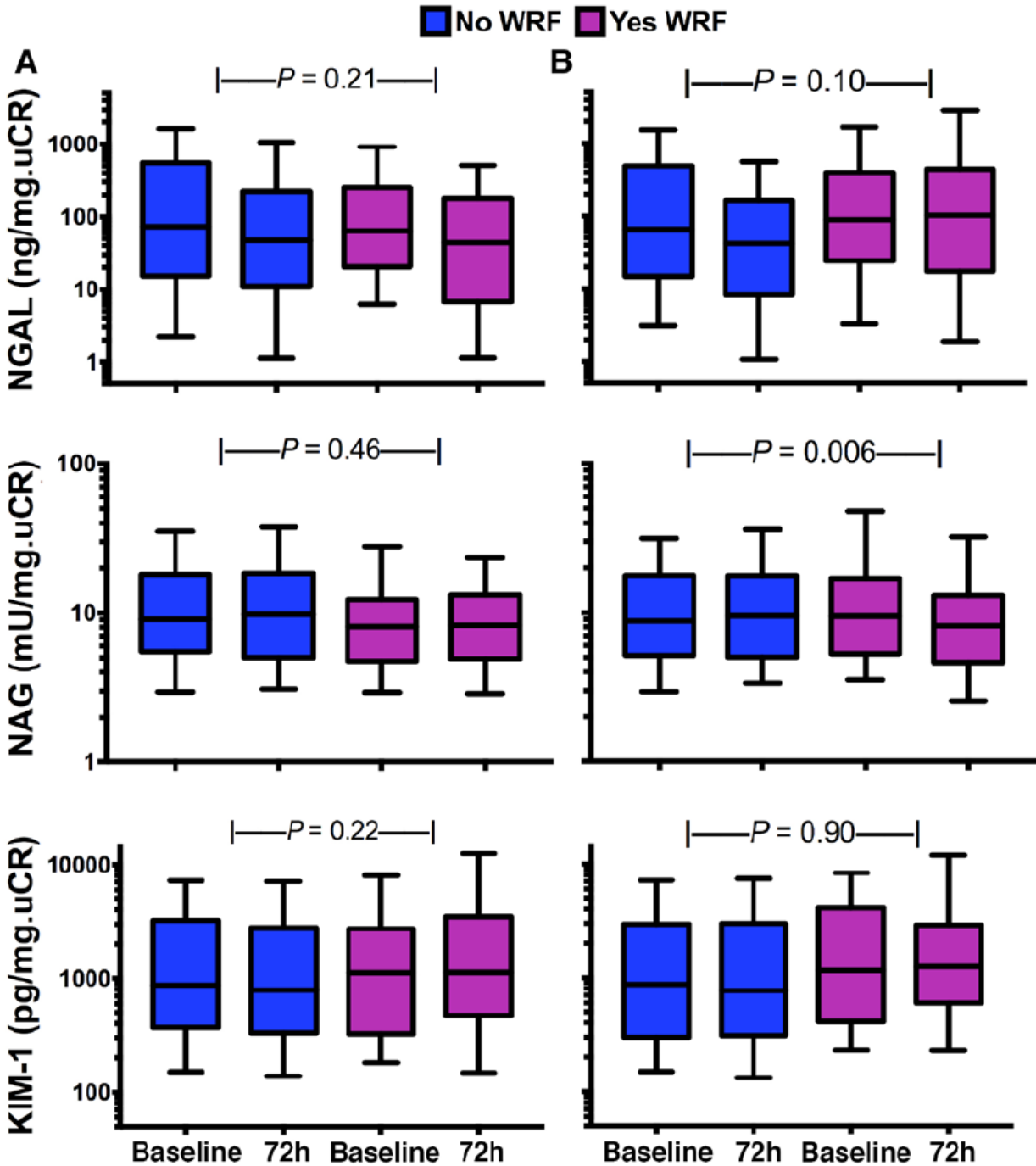
Worsening Renal Function in Patients with Acute Heart Failure Undergoing Aggressive Diuresis is not associated with renal tubular injury  
Ahmad T et al: Circulation, May 2018.

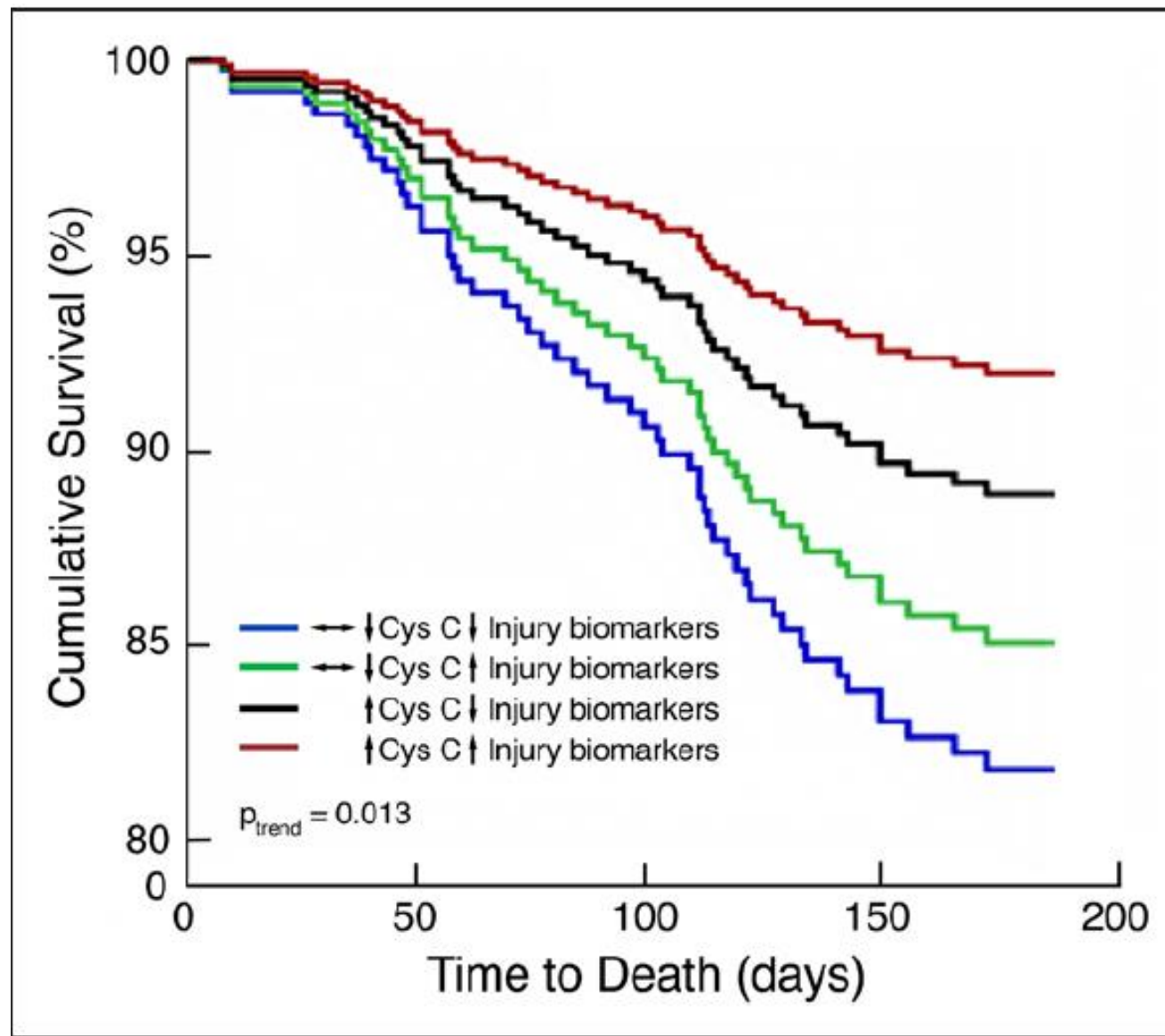
- Serial changes in the urine level of KIM-1, NAG and NGAL were not meaningfully associated with changes in serum CysC or serum Cr.
- Levels of tubular injury biomarkers were not different in those with and without worsening renal function.
- Worsening renal function ( 20% decline in GFR based on serum CysC) and increased tubular injury biomarkers were associated paradoxically with **better 180 day survival.**



Ahmad T, Jackson K, Rao V et al: Worsening Renal Function in Patients with Acute Heart failure Undergoing Aggressive Diuresis is not associated with renal tubular injury, Circulation, May 2018.

**Top to bottom:** A. Box plots ( 10-90<sup>th</sup> percentiles) in KIM-1, NAG and NGAL at baseline and 72 hours in subjects on high dose loop diuretics in ROSE-HF with and without WRF (serum CysC) B. Urine biomarker temporal changes as gauged by creatinine changes .





Ahmad et al , Circulation 2018: Association between kidney tubular injury biomarkers and renal dysfunction with survival.

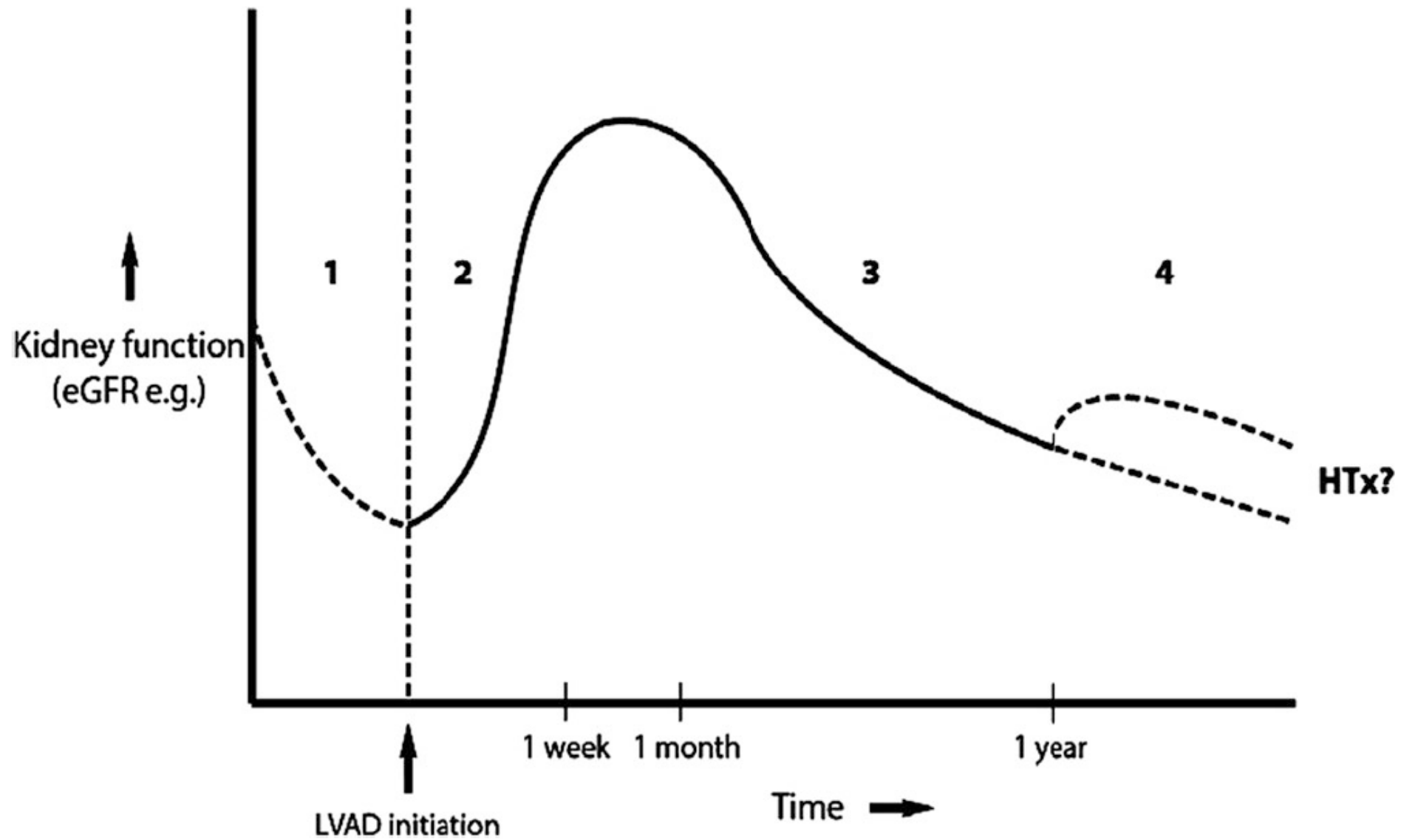


# Right Ventricular Free Wall Strain is Associated with Long Term Renal Function in Heart Failure with Preserved Ejection Fraction.

- Single center analysis of 70 subjects with acute heart failure with BNP > 100 pg/mL, PCWP > 15 mm Hg and EF > 50%.
- Strain echocardiography was performed on all subjects and pertinent clinical data points including eGFR at baseline and long term values ( 3-5 years )
- Of the echocardiographic metrics looking at RV function, RVFWS was significantly associated with long term eGFR ( beta co-efficient -1.422, P=0.022, CI=-2.635 to -0.208).
- Similar associations exist between invasive RHC based RV function measurements such as with RV stroke work index and pulmonary artery pulsatility index and long term kidney function in HF.

Lo KB, Ram P, Kanjanahattakij N, Gupta S, Pressman GS, Rangaswami J. Journal of Cardiac Failure, 2018





# Predictors of kidney injury reversibility after LVAD implantation.

Hasin T et al: Changes in renal function after left ventricular assist device implantation, JACC 2012.

- Younger age
- Preserved renal size on imaging
- Intra aortic balloon pump use pre LVAD implantation
- eGFR improvement with optimal goal directed medical therapy
- Elevated bilirubin levels
- Steady state measurement of RFR ?

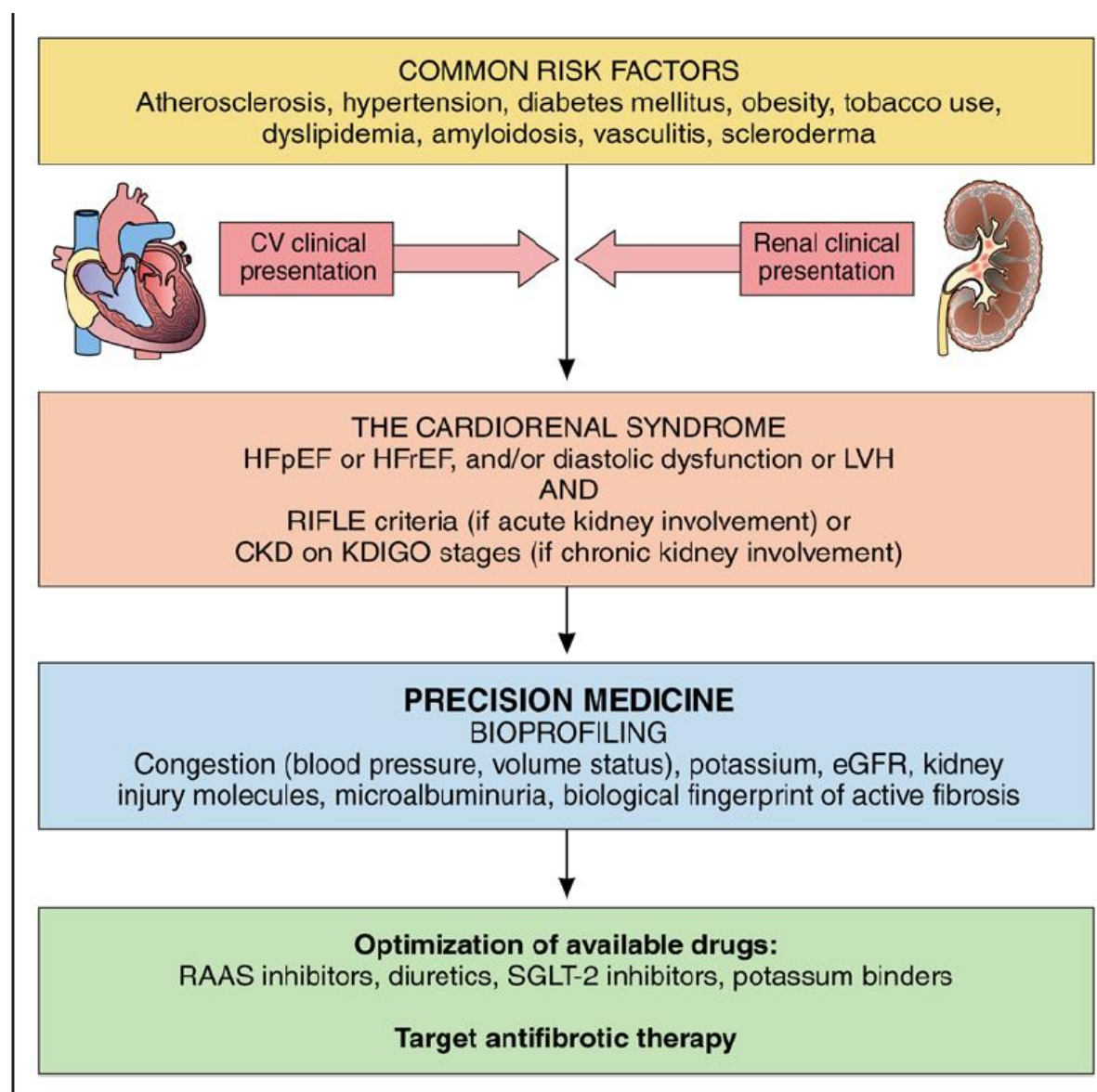


# Predictors of Acute Kidney Injury after LVAD placement

- Higher central venous pressures
- Prolonged cardiopulmonary bypass time
- Need for early re-exploration
- Higher intra-operative blood loss
- Higher pre-operative LVAD risk score
- Older age
- Baseline and stress RFR ??

Alba AC, Rao V, Ivanov J et al: Predictors of acute renal dysfunction after left ventricular assist device placement. Journal of Cardiac Failure, 2009.





Zannad F and Rossignol P: Proposed new paradigm in the diagnostic and therapeutic approach to cardiorenal syndrome, Circulation 2018

# Conclusions and Future Directions

- There is a long history to methods for assessing RFR as well as physiological relevance in cardio-renal interactions.
- The field of cardio-renal medicine lends itself across several clinical practice models to incorporate RFR into risk stratification, prognostication as well as guiding targeted therapies.
- There is a need to incorporate RFR testing into routine clinical practice in patients with different phenotypes of cardiorenal syndrome, as well as in future guidelines/position papers in this field .

