Barts Health NHS
NHS Trust

Barts and The London
School of Medicine and Dentistry

Biomarkers for Acute Kidney Injury – Application to Clinical Practice

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Queen Mary University of London

Outline - AKI

- What is the clinical problem
- Limitations of current diagnostics
- Novel AKI biomarkers
- Application of biomarkers to clinical practice
- Future approaches to research

Clinical Scenario #1

- 75 yr old lady is referred with community acquired pneumonia
- Type 2 Diabetes and Atrial Fibrillation
- BP 105/45 HR 105 T 37.9

  O2 Sats 94% on 28% O2, Resps 18,

  Creatinine 100

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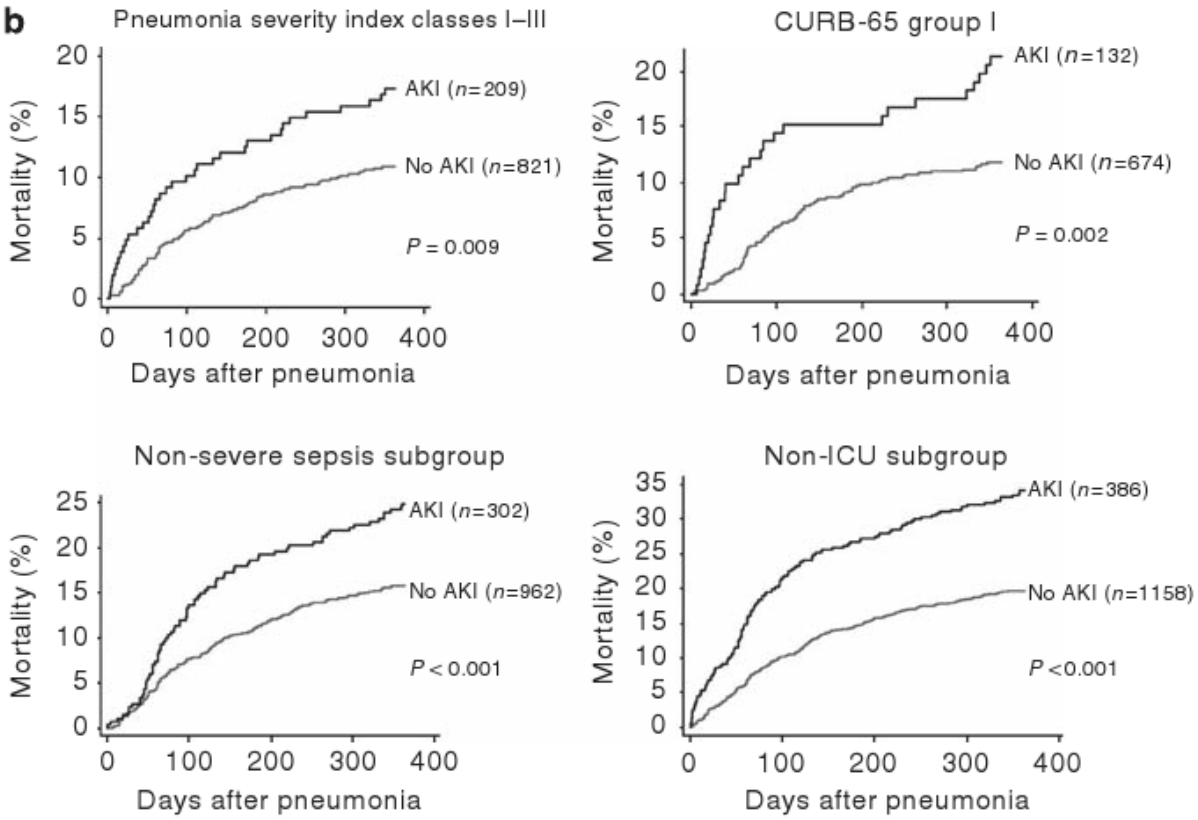
- Does she have or is she developing AKI?
- Where should she be managed?
- How should she be resuscitated?
- Will AKI affect outcome?

Published in final edited form as:
Kidney Int. 2010 March ; 77(6): 527–535. doi:10.1038/ki.2009.502.

Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival

Raghavan Murugan[1], **Vijay Karajala-Subramanyam**[1], **Minjae Lee**[1,2], **Sachin Yende**[1], **Lan Kong**[1,2], **Melinda Carter**[1], **Derek C. Angus**[1], and **John A. Kellum**[1] **on behalf of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Investigators**



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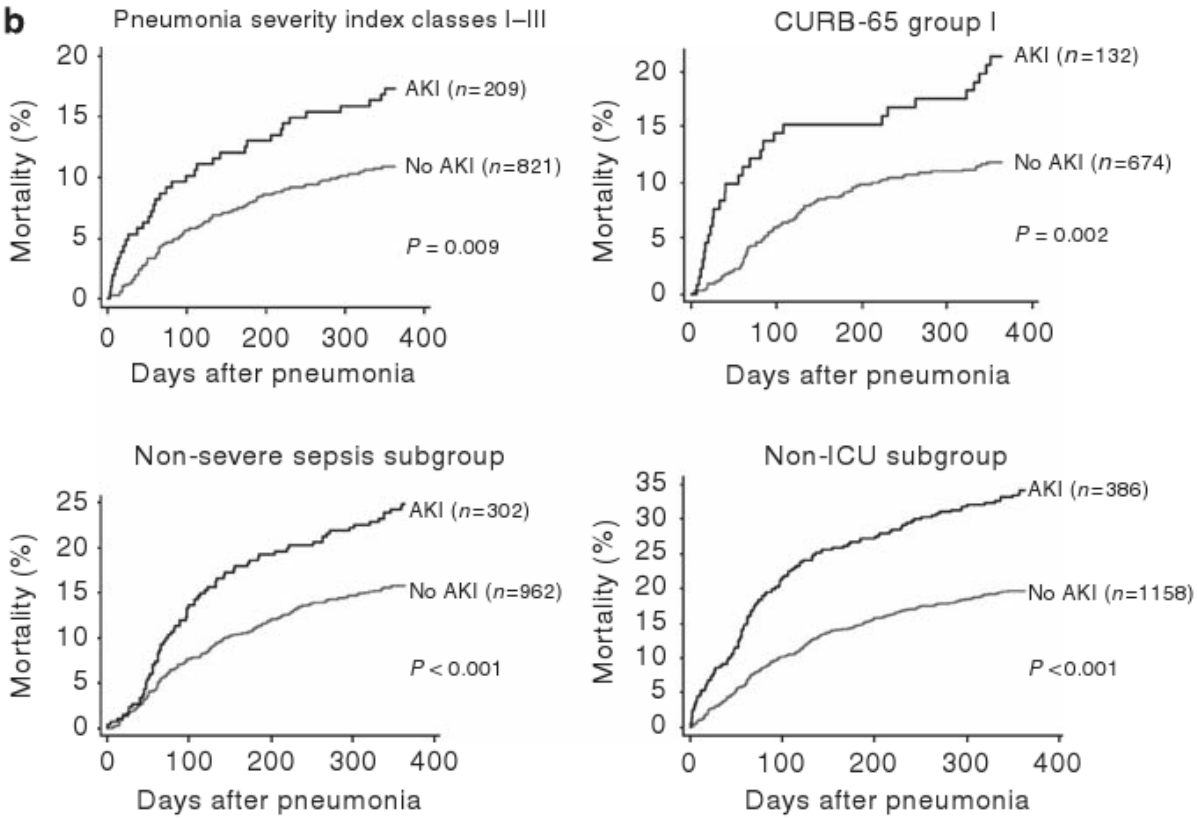

16–25% of the patients with non- severe pneumonia also developed acute kidney injury

Clinical Scenario #2

- 55 yr old man 12hr post open cholecystectomy
- High blood pressure, Moderate LV function
- poor analgesia
- BP 105/55 HR 110 BE -5 Lactate 1.8
- Fluid balance +4L in 12hr
- Urine 15ml/hr last 3hr

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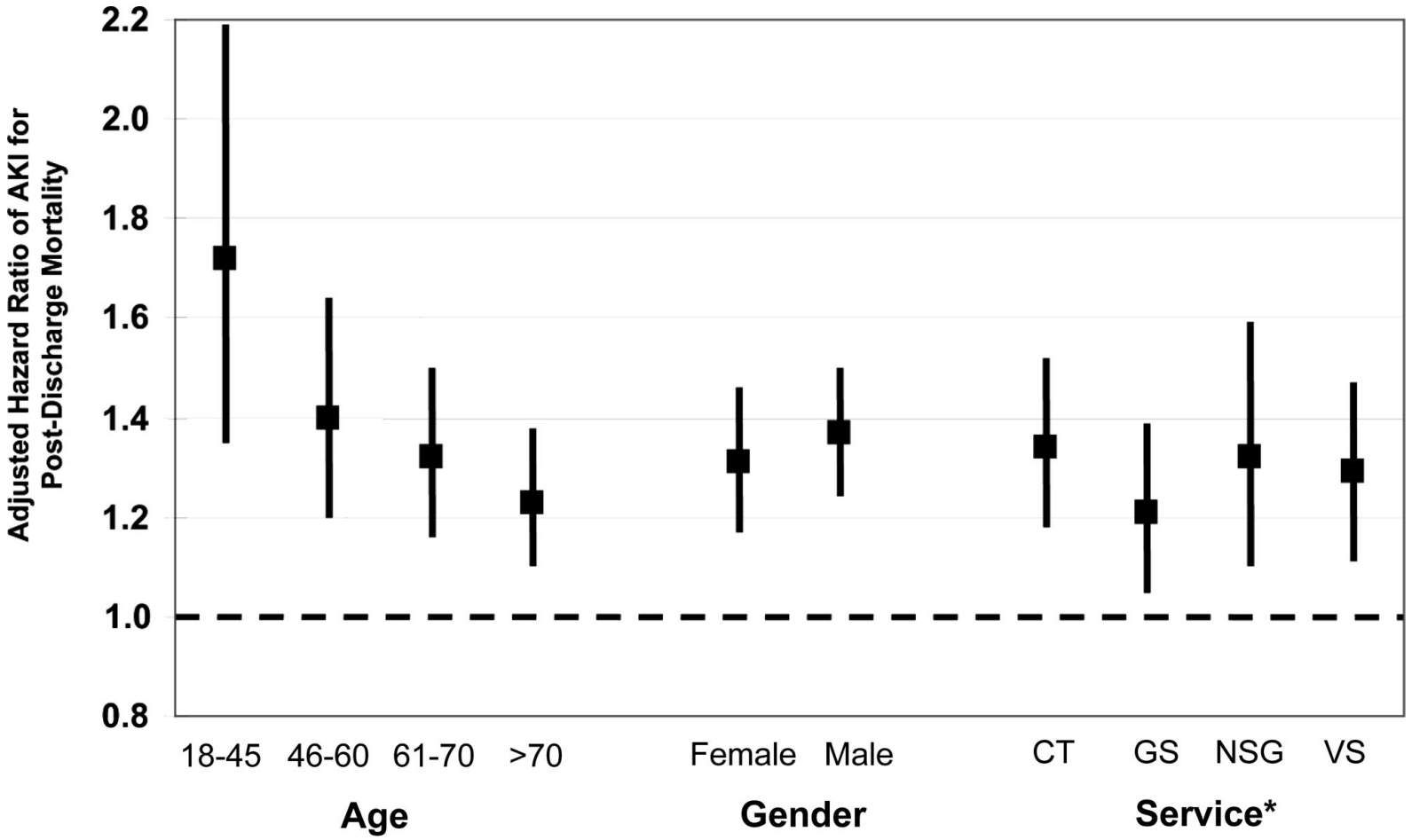
Long-Term Risk of Mortality and Acute Kidney Injury During Hospitalization After Major Surgery

Azra Bihorac, MD, Sinan Yavas, MD,* Sophie Subbiah, BA,* Charles E. Hobson, MD,†*
Jesse D. Schold, PhD,‡ Andrea Gabrielli, MD, A. Joseph Layon, MD,* and Mark S. Segal, MD, PhD‡*



(*Ann Surg* 2009;249: 851–858)

The Problem

- We are unable to risk stratify many patients early in the course of their illness
- Current diagnostics are inadequate to enable us to identify early AKI and intervene
- Late intervention may be of less benefit
- Avoidance of harm in established AKI

We need to identify who benefit from:

- Specific intervention
- Concentration on supportive care and avoidance of secondary injury

Conventional diagnosis of AKI

- Serum Creatinine
- Urine output

KDIGO AKI definitions

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (≥26.5 mmol/l) increase within 48hr	≤0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	≤0.5 ml/kg/h for X12 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 X24 hours OR Anuria for X12 hours

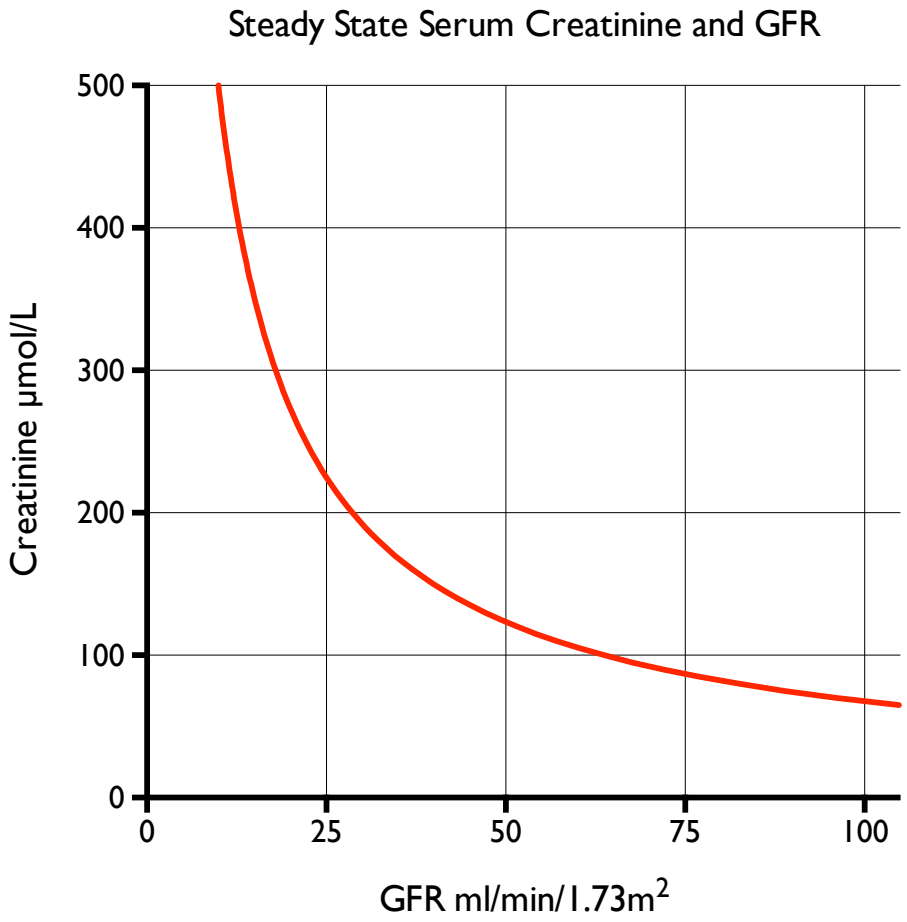
Creatinine:
At Steady State: *In = Out*

$$Production = GFR.[Cr]$$

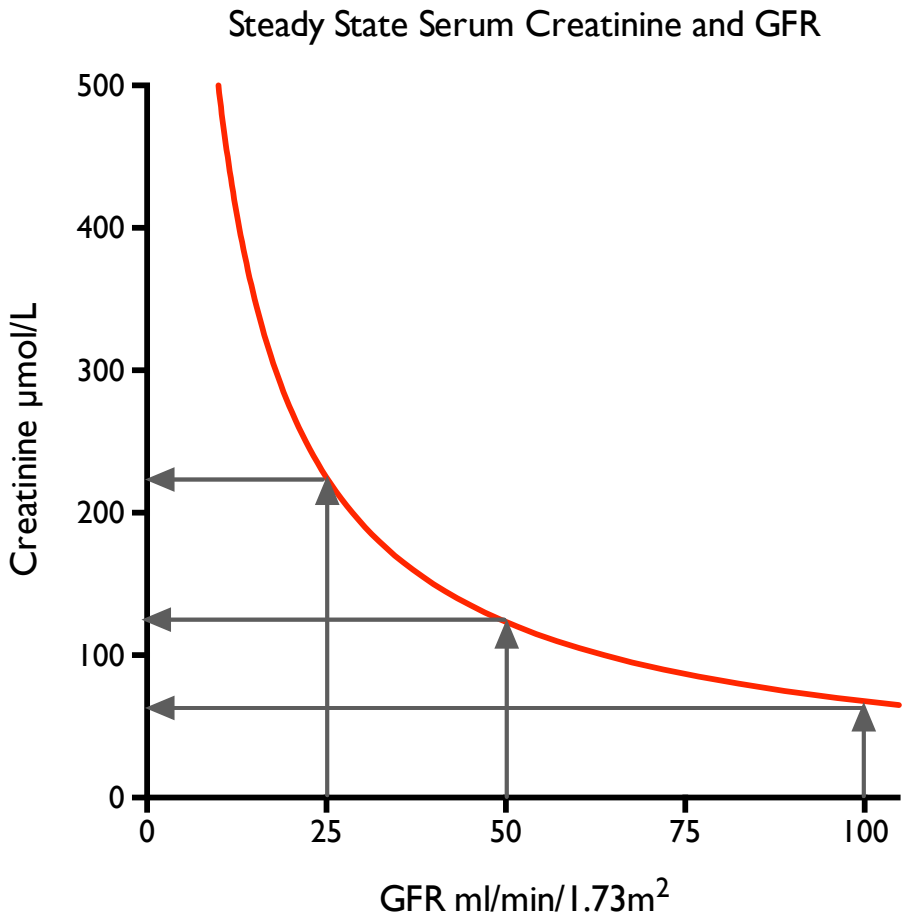
$$GFR = \frac{P}{[Cr]}$$

Double Creatinine = Half GFR

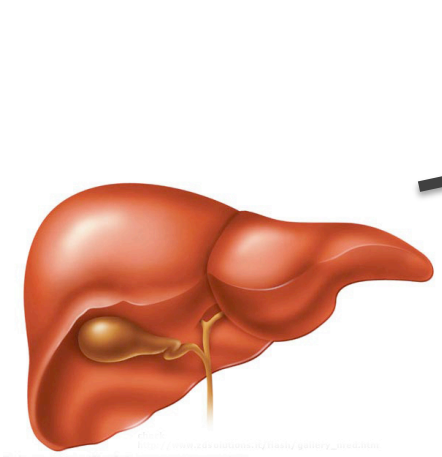
Plasma Creatinine and GFR at Steady State

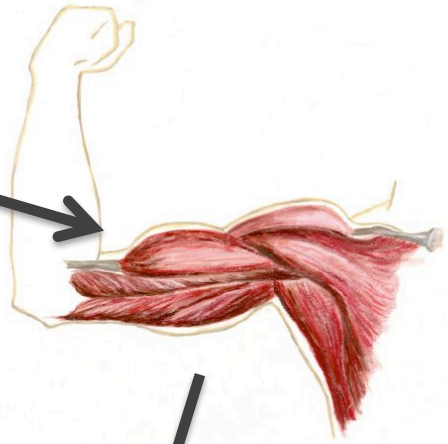


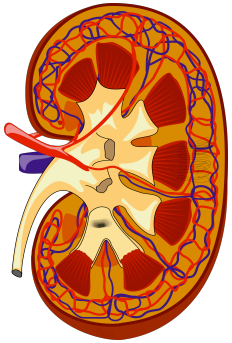
Plasma Creatinine and GFR at Steady State

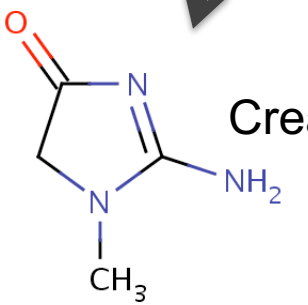


Creatinine Production





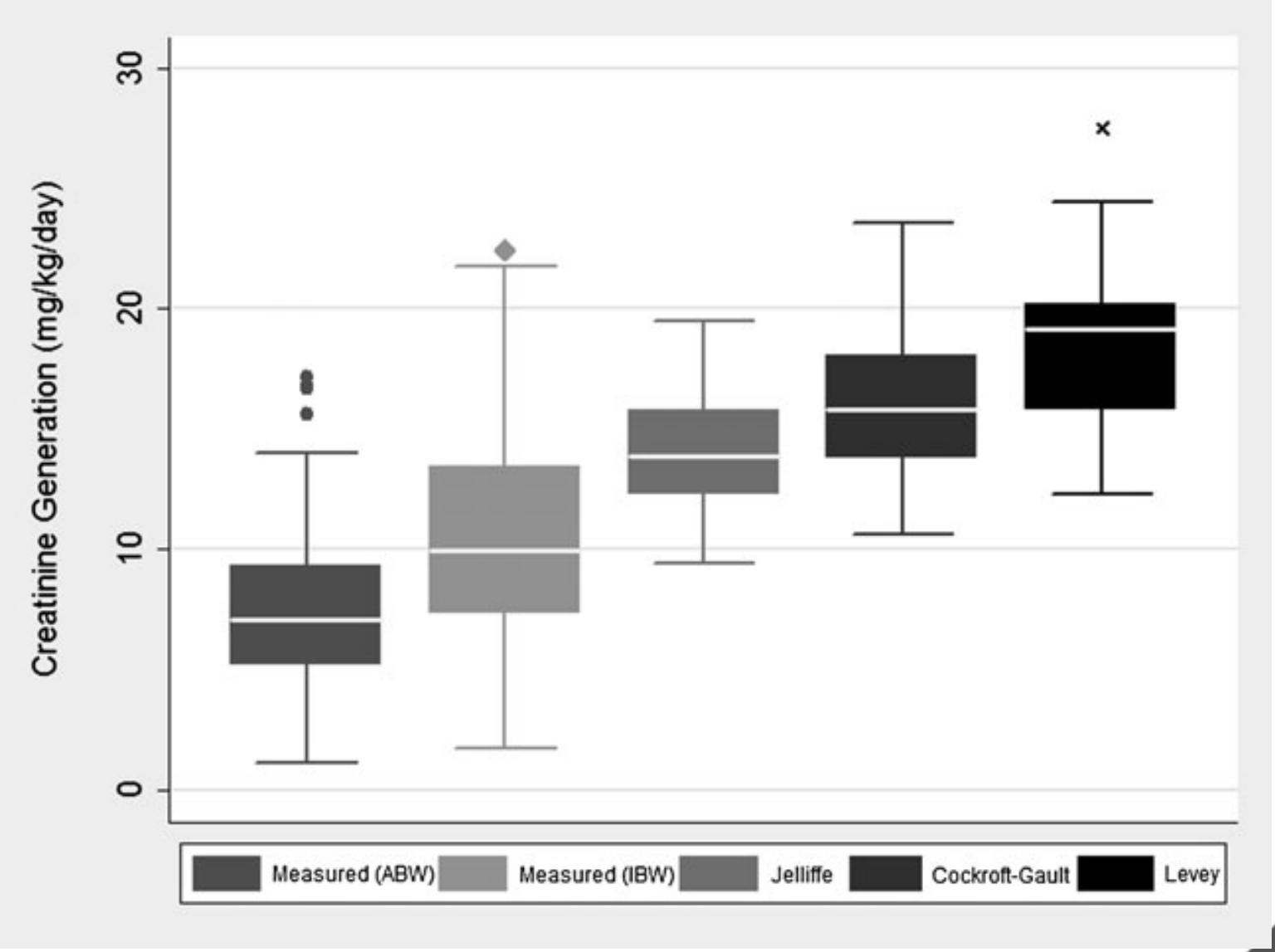


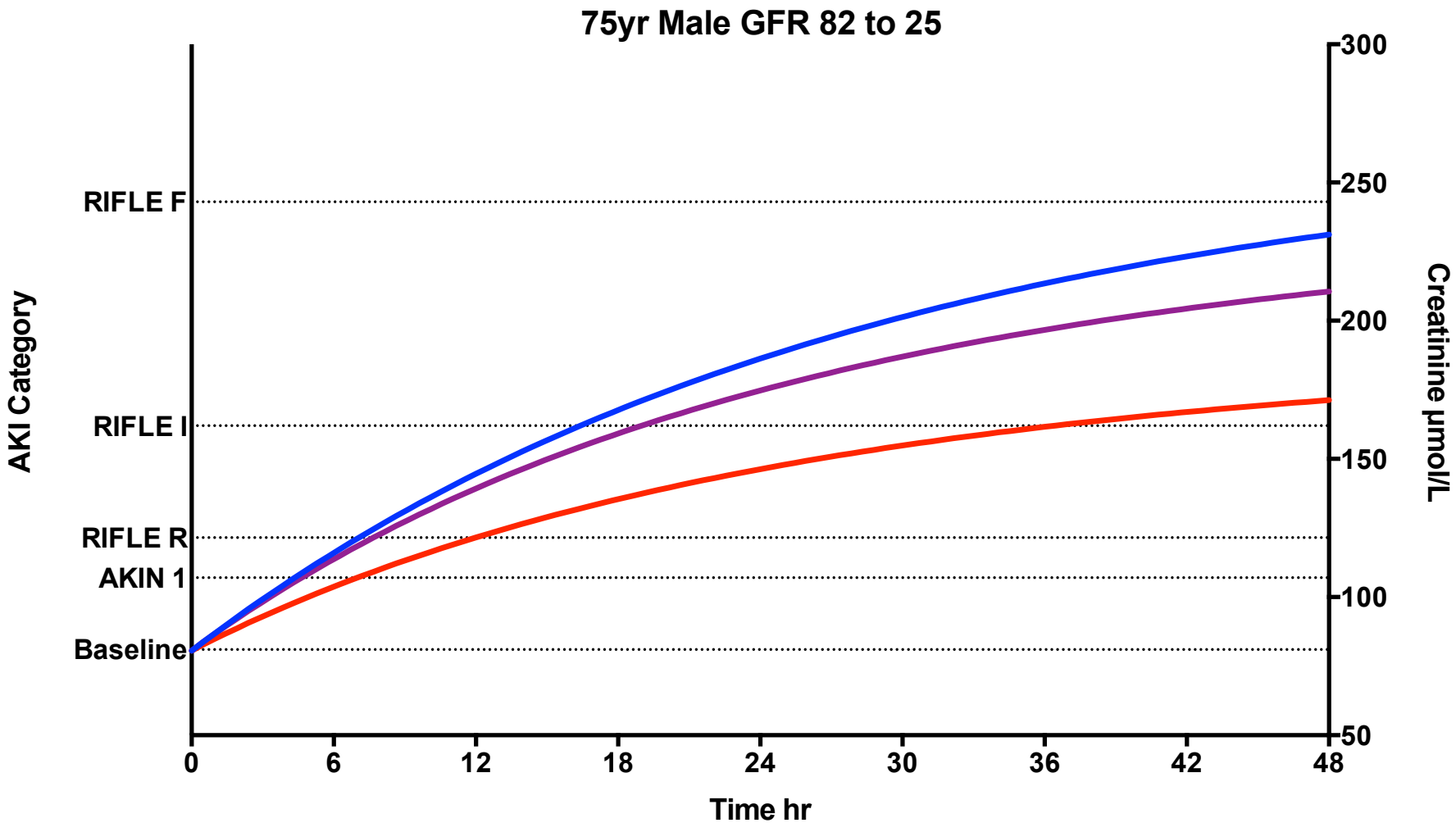


Creatinine

Creatinine generation is reduced in patients requiring continuous venovenous hemodialysis and independently predicts mortality

Nephrol Dial Transplant (2012) 0: 1–7
doi: 10.1093/ndt/gfr809




75yr Male GFR 82 to 25
AKI Category
RIFLE F
RIFLE I
RIFLE R
AKIN 1
Baseline
0
6
12
18
24
30
36
42
48
Time hr
300
250
200
150
100
50
Creatinine µmol/L
Creatinine even FB
Creatinine modeled with +ve FB 8L over 48hr
Creatinine modeled with +ve FB 8L over 48hr and 20% fall in G

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- Oliguria has poor sensitivity and specificity
- Many specific interventions for AKI have been promising experimentally but failed in clinical practice
- Delayed and imprecise diagnosis prevents effective intervention and risk stratification

Biomarkers to the rescue?

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What is a Biomarker?

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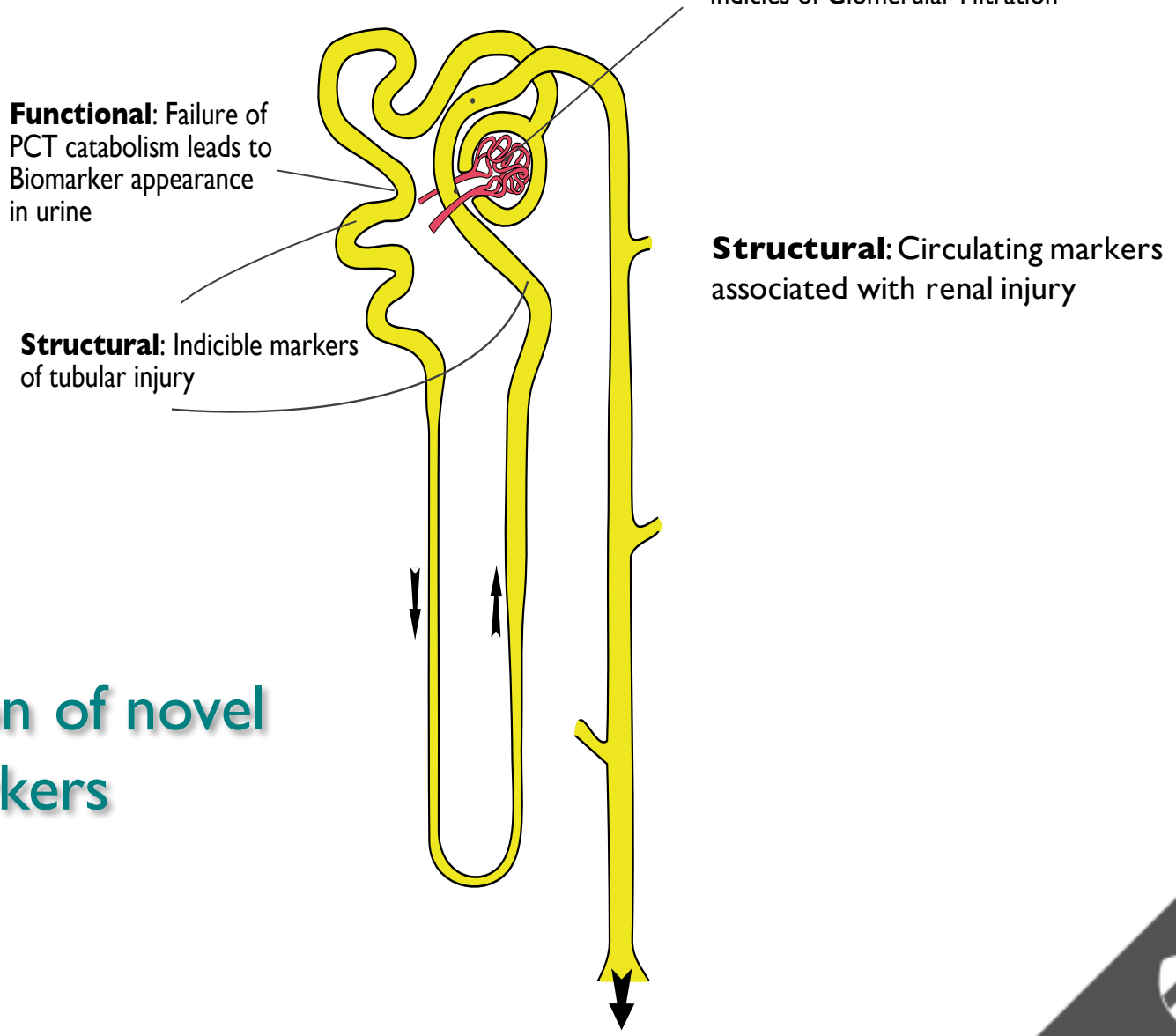
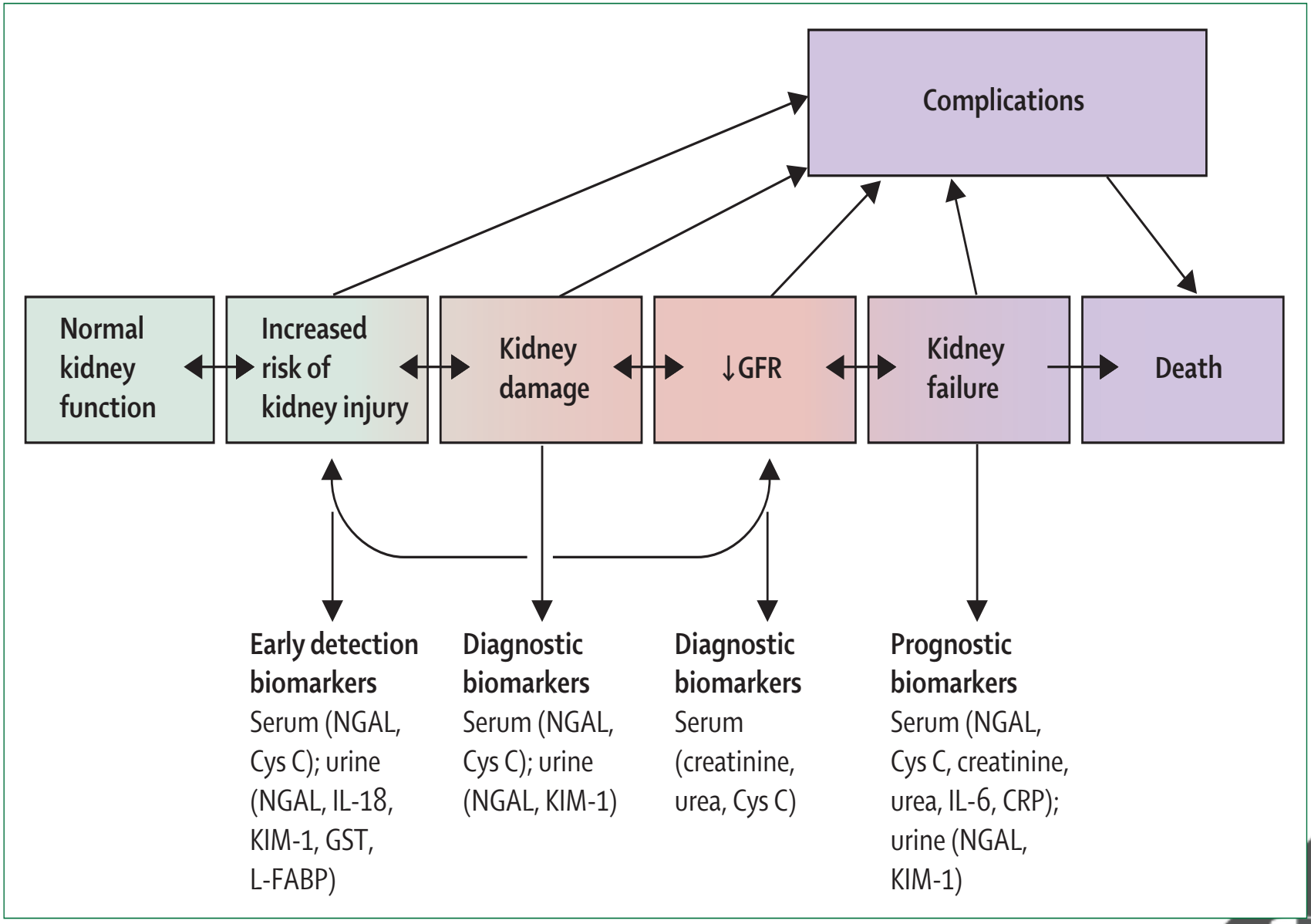
  - Better connected with pathology of interest
- Do we have them?
- Will they alter outcomes?

Classification of novel AKI biomarkers

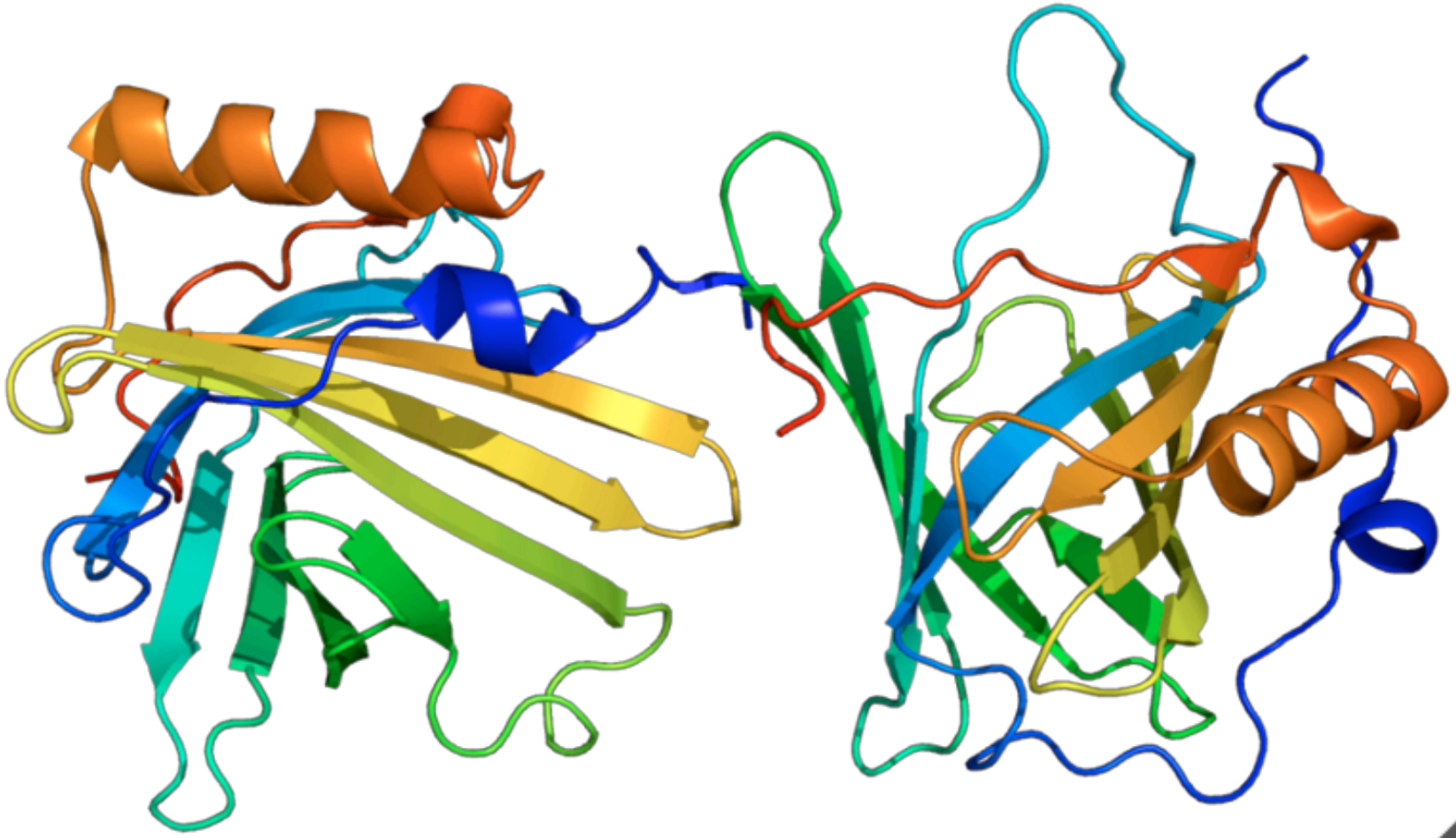
Urine

Blood




Complications
Normal kidney function
Increased risk of kidney injury
Kidney damage
↓GFR
Kidney failure
Death
Early detection biomarkers
Serum (NGAL, Cys C); urine (NGAL, IL-18, KIM-1, GST, L-FABP)
Diagnostic biomarkers
Serum (NGAL, Cys C); urine (NGAL, KIM-1)
Diagnostic biomarkers
Serum (creatinine, urea, Cys C)
Prognostic biomarkers
Serum (NGAL, Cys C, creatinine, urea, IL-6, CRP); urine (NGAL, KIM-1)

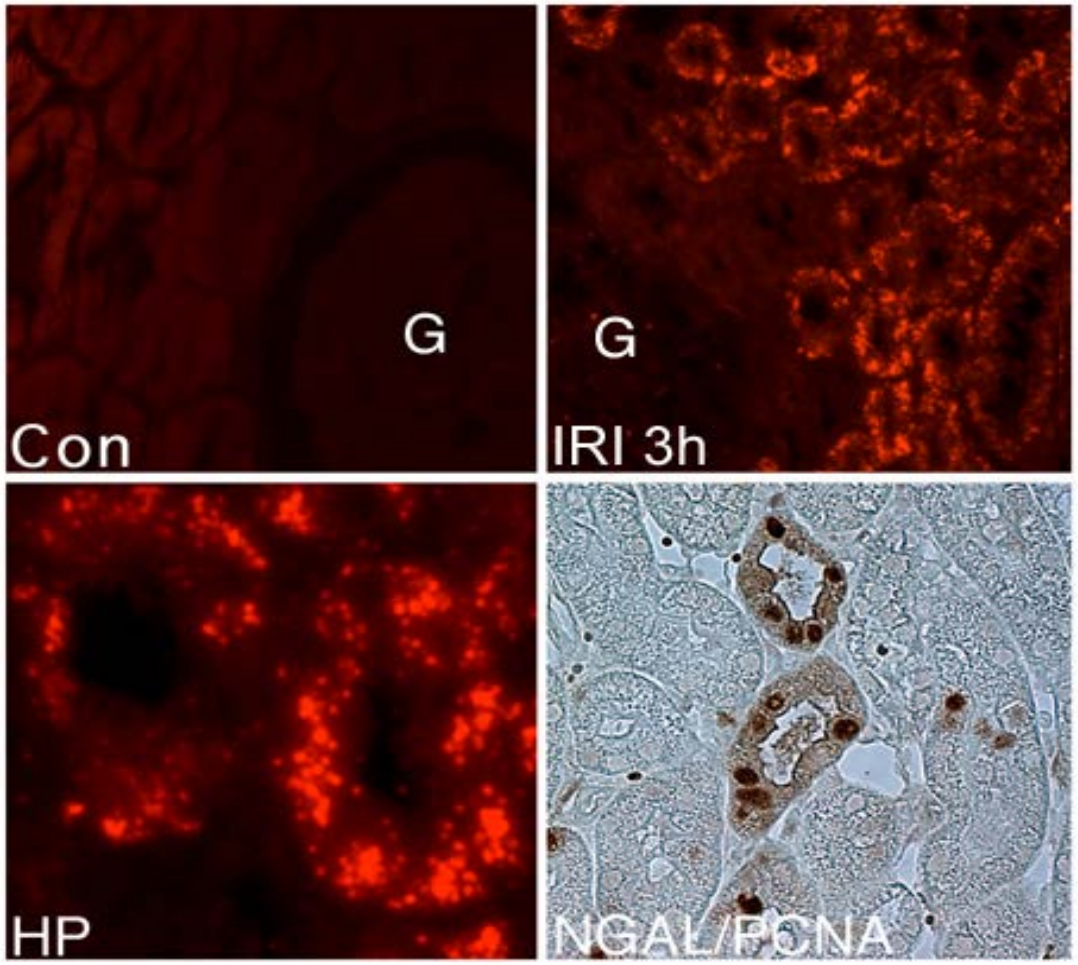
Neutrophil Gelatinase-Associated Lipocalin (NGAL)



J Am Soc Nephrol 14: 2534–2543, 2003

Identification of Neutrophil Gelatinase-Associated Lipocalin as a Novel Early Urinary Biomarker for Ischemic Renal Injury

JAYA MISHRA,* QING MA,* ANNE PRADA,* MARK MITSNEFES,* KAMYAR ZAHEDI,* JUN YANG,† JONATHAN BARASCH,† and PRASAD DEVARAJAN*



- Mouse Ischemia
- 30 min ischemia
- S creat ↑ 24 h
- Kidney NGAL ↑ 3 h
- NGAL in tubule lumen

Neutrophil gelatinase-assoiated lipocalin (NGAL)

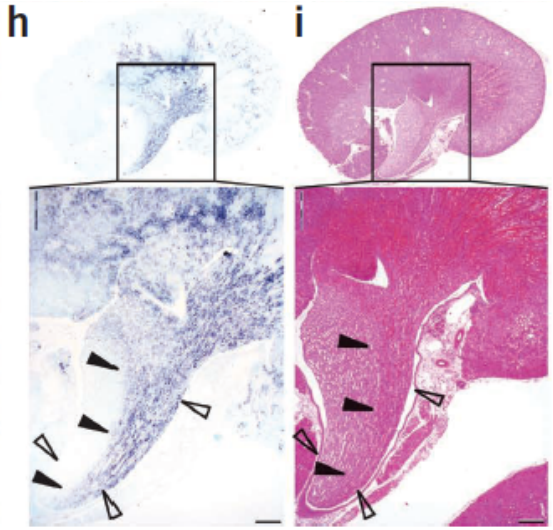
- 25kDa protein
- Binds siderophores
- Bacteriostatic iron chelating activity
- Inducible in neutrophils
- Up-regulated in injured epithelia including kidney via NF-KB

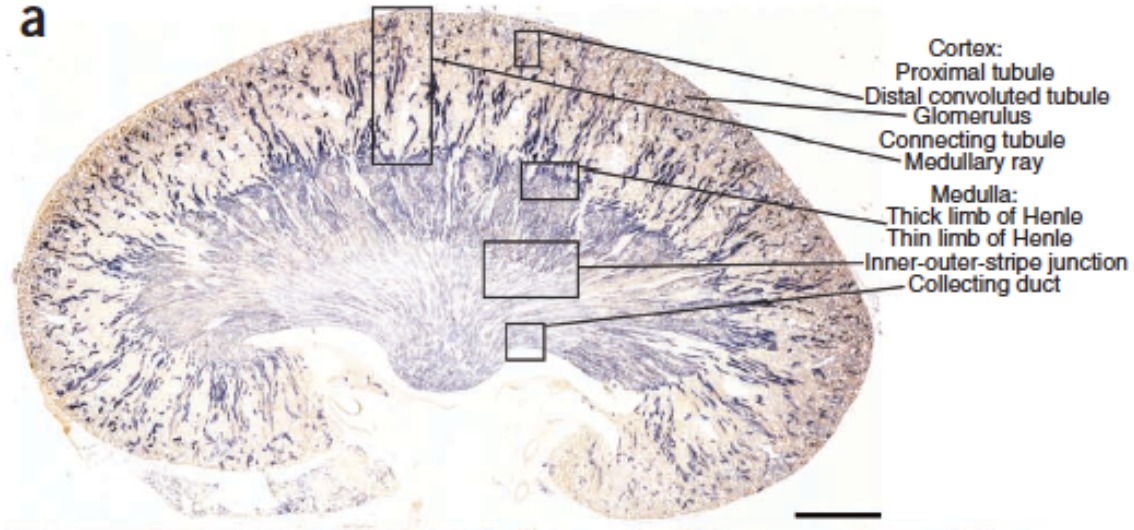
TECHNICAL REPORTS

nature medicine

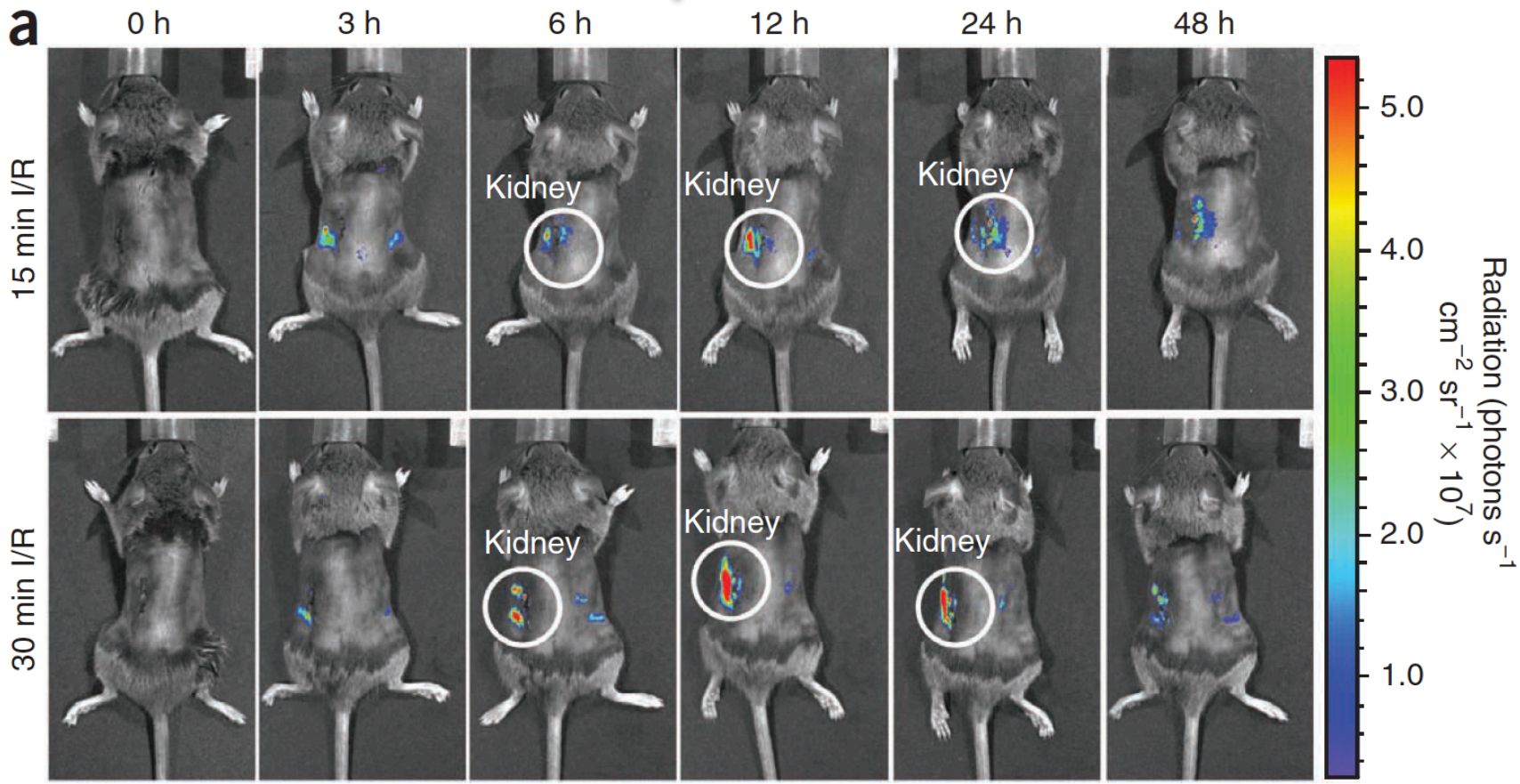
The Ngal reporter mouse detects the response of the kidney to injury in real time

Neal Paragas[1,5], Andong Qiu[1,5], Qingyin Zhang[1], Benjamin Samstein[1], Shi-Xian Deng[1], Kai M Schmidt-Ott[2], Melanie Viltard[1], Wenqiang Yu[1], Catherine S Forster[1], Gangli Gong[1], Yidong Liu[1], Ritwij Kulkarni[1], Kiyoshi Mori[3], Avtandil Kalandadze[1], Adam J Ratner[1], Prasad Devarajan[4], Donald W Landry[1], Vivette D'Agati[1], Chyuan-Sheng Lin[1] & Jonathan Barasch[1]





Unilateral ischaemia-perfusion



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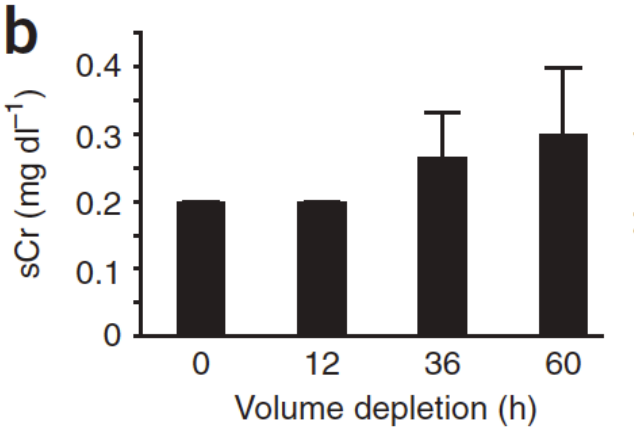
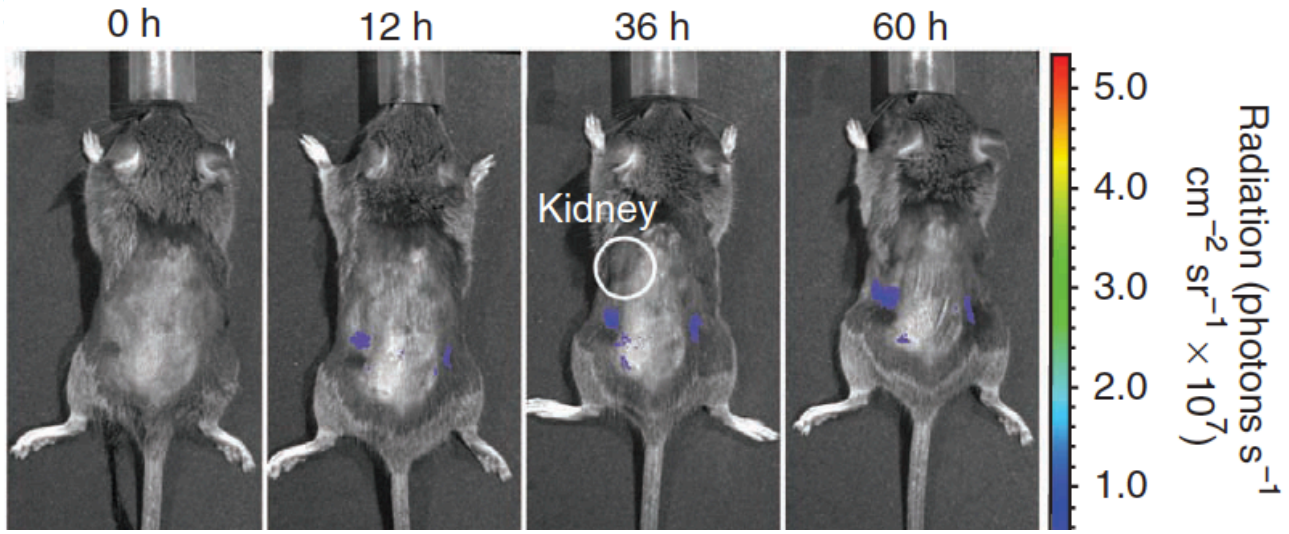
Volume Depletion





How does NGAL perform clinically?

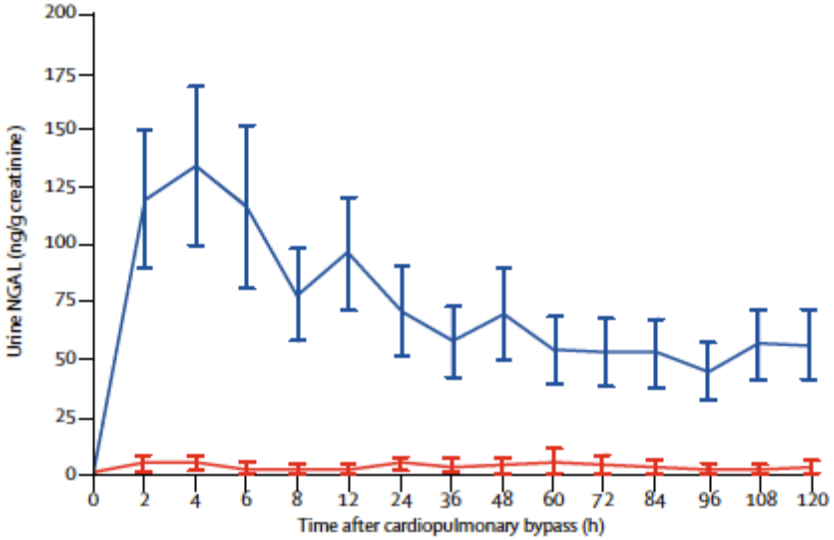
Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery

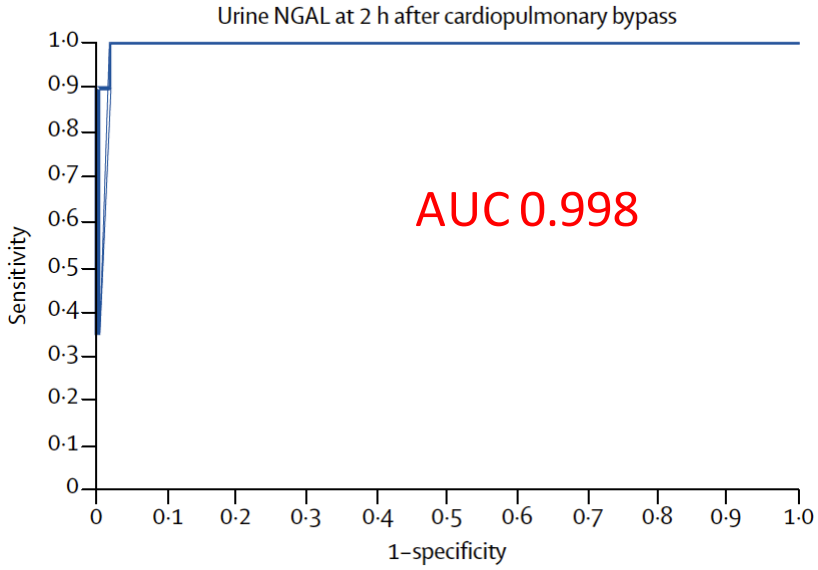
Jaya Mishra, Catherine Dent*, Ridwan Tarabishi*, Mark M Mitsnefes, Qing Ma, Caitlin Kelly, Stacey M Ruff, Kamyar Zahedi, Mingyuan Shao, Judy Bean, Kiyoshi Mori, Jonathan Barasch, Prasad Devarajan*

Lancet 2005; 365: 1231–38

See Comment page 1205

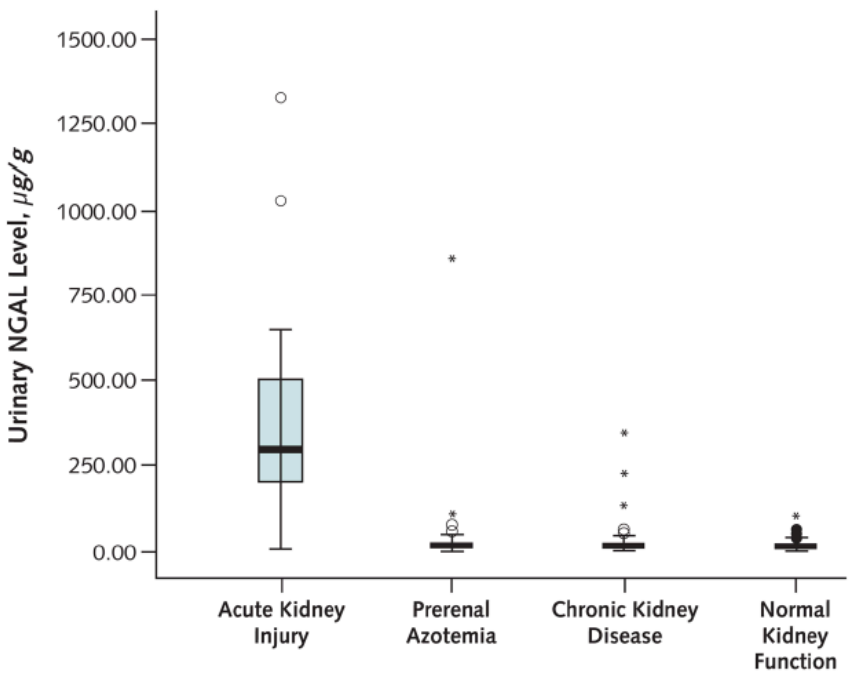
71 children undergoing cardiopulmonary bypass.

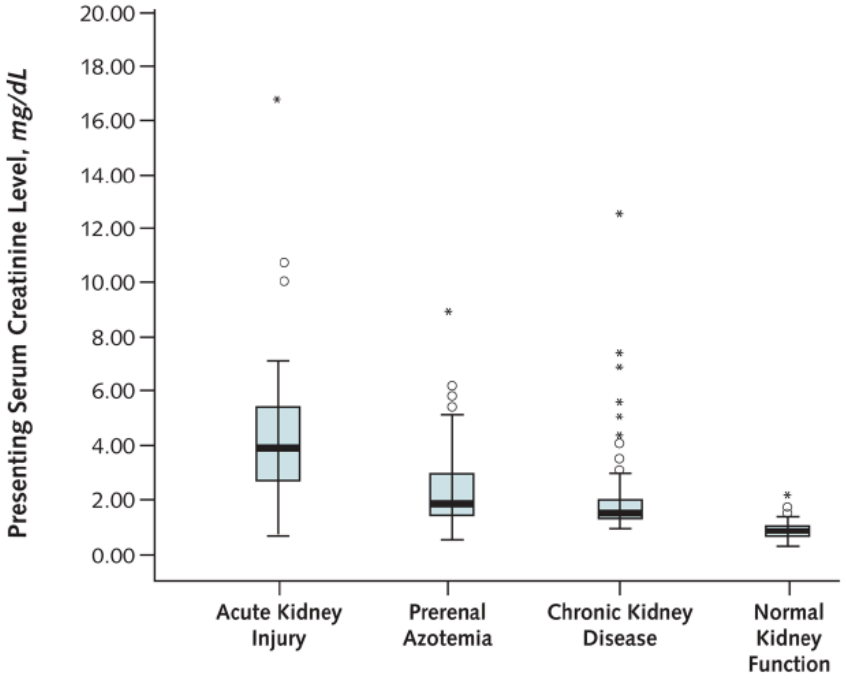




AUC 0.998

ER Presentations NGAL & subsequent AKI





Ann Intern Med. 2008 June 3; 148(11): 810–819.

Sensitivity and Specificity of a Single Emergency Department Measurement of Urinary Neutrophil Gelatinase–Associated Lipocalin for Diagnosing Acute Kidney Injury

Dr Thomas L. Nickolas, MD, MS, Mr Matthew J. O'Rourke, BS, Dr Jun Yang, MD, PhD, Ms Meghan E. Sise, BS, Dr Pietro A. Canetta, MD, Mr Nicholas Barasch, BS, Mr Charles Buchen, Dr Faris Khan, MD, Dr Kiyoshi Mori, MD, PhD, Dr James Giglio, MD, Dr Prasad Devarajan, MD, and **Dr Jonathan Barasch, MD, PhD**
Columbia University, New York, New York; Kyoto University Graduate School of Medicine, Kyoto, Japan; and Cincinnati Children's Hospital, University of Cincinnati, Cincinnati, Ohio

NGAL>130 = 25 fold odds of composite clinical outcome (nephrology consultation, intensive care admission, dialysis initiation, mortality)

NGAL Meta-analysis

Biomarkers for AKI – Where now?

Table 5. Pooled Diagnostic and Prognostic Accuracy of NGAL

Setting (no. of events/total patients; no. of studies [data sets])	Sensitivity[a] (95% CI)	Specificity[a] (95% CI)	DOR[a] (95% CI)	AUC-ROC[a] (95% CI)	I^2 (%)	NGAL Cutoff[a] (ng/mL)
AKI across settings (487/2,538; 19 [23])	76.4 (70.4-81.6)	85.1 (76.6-90.9)	18.6 (9.0-38.1)	0.815 (0.732-0.892)	43.5	190.2 (122.8-257.2)
AKI after cardiac surgery (307/1,204; 10 [13])	75.5 (70.2-82.4)	75.1 (65.2-86.3)	13.1 (5.7-34.8)	0.775 (0.669-0.867)	27.8	273.6 (145.0-289.2)
AKI in critically ill patients (123/602; 5 [5])	76.4 (59.9-87.5)	75.5 (52.2-89.7)	10.0 (3.0-33.1)	0.728 (0.615-0.834)	17.5	155.0 (150.8-169.0)
AKI after contrast infusion (34/191; 3 [4])	77.8 (62.8-88.0)	96.3 (74.4-99.6)	92.0 (10.7-794.1)	0.894 (0.826-0.950)	3.2	100.0 (80.0-100.0)
AKI in children across settings (213/663; 6 [8])	77.6 (69.7-83.9)	88.0 (75.8-94.5)	25.4 (8.9-72.2)	0.930 (0.883-0.968)	3.5	135.0 (50.0-150.0)
AKI in adults across settings (271/1,842; 12 [14])	72.5 (62.9-80.4)	80.1 (71.2-86.2)	10.6 (4.8-23.4)	0.782 (0.689-0.872)	27.5	175.0 (150.0-271.5)
AKI prediction using plasma/serum NGAL (226/1,039; 9 [9])	73.4 (62.3-82.2)	86.6 (72.0-94.3)	17.9 (6.0-53.7)	0.775 (0.679-0.869)	20.2	179.2 (153.9-199.3)
AKI prediction using urine NGAL (319/1,783; 14 [14])	77.8 (70.9-83.5)	84.3 (72.8-91.3)	18.6 (7.2-48.4)	0.837 (0.762-0.906)	21.9	193.2 (123.7-405.7)
AKI prediction using research-based assays (242/1,730; 14 [18])	76.9 (69.4-83.1)	83.4 (72.0-90.8)	16.7 (7.1-39.7)	0.732 (0.656-0.830)	31.6	246.4 (88.5-277.2)
AKI prediction using standardized platforms (245/808; 5 [5])	75.4 (63.8-84.2)	89.3 (81.9-93.9)	25.5 (8.9-72.8)	0.830 (0.741-0.918)	7.0	150.6 (145.0-155.0)
Initiation of RRT across AKI settings (84/1,948; 9 [10])	76.0 (65.1-84.4)	80.3 (59.5-91.9)	12.9 (4.9-33.9)	0.782 (0.648-0.917)	9.5	278.3 (141.9-381.6)
In-hospital mortality across AKI settings (88/1,617; 6 [7])	65.0 (51.2-80.8)	82.6 (51.8-95.5)	8.8 (1.9-40.8)	0.706 (0.530-0.747)	10.3	212.0 (121.8-506.7)

American Journal of Kidney Diseases, Vol 54, No 6 (December), 2009: pp 1012-1024

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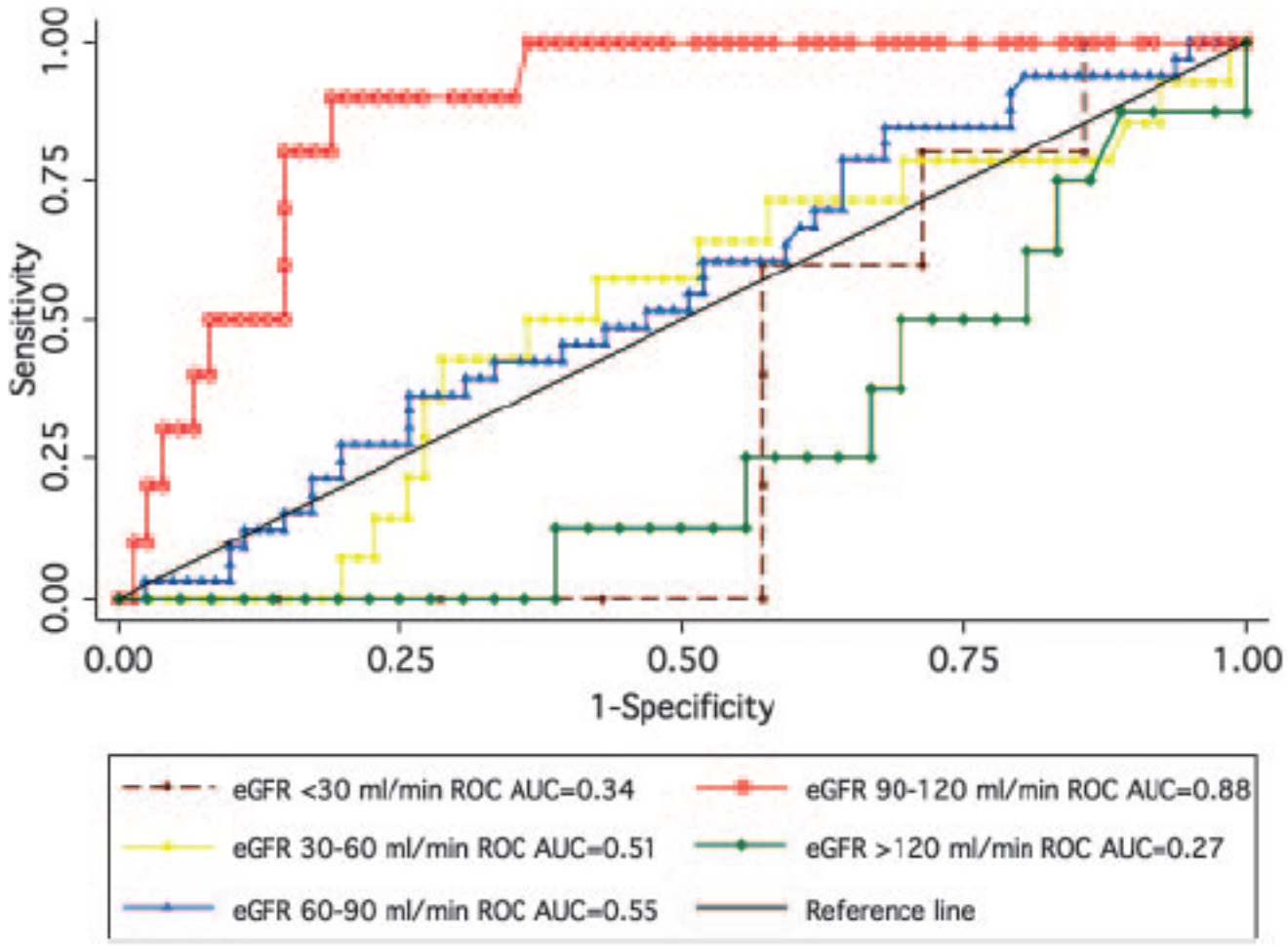
AKI after contrast infusion (34/191; 3 [4])	77.8 (62.8-88.0)	96.3 (74.4-99.6)	92.0 (10.7-794.1)	0.894 (0.826-0.950)	3.2	100.0 (80.0-100.0)
AKI in children across settings (213/663; 6 [8])	77.6 (69.7-83.9)	88.0 (75.8-94.5)	25.4 (8.9-72.2)	0.930 (0.883-0.968)	3.5	135.0 (50.0-150.0)
AKI in adults across settings (271/1,842; 12 [14])	72.5 (62.9-80.4)	80.1 (71.2-86.2)	10.6 (4.8-23.4)	0.782 (0.689-0.872)	27.5	175.0 (150.0-271.5)
AKI prediction using plasma/serum NGAL (226/1,039; 9 [9])	73.4 (62.3-82.2)	86.6 (72.0-94.3)	17.9 (6.0-53.7)	0.775 (0.679-0.869)	20.2	179.2 (153.9-199.3)
AKI prediction using urine NGAL (319/1,783; 14 [14])	77.8 (70.9-83.5)	84.3 (72.8-91.3)	18.6 (7.2-48.4)	0.837 (0.762-0.906)	21.9	193.2 (123.7-405.7)
AKI prediction using research-based assays (242/1,730; 14 [18])	76.9 (69.4-83.1)	83.4 (72.0-90.8)	16.7 (7.1-39.7)	0.732 (0.656-0.830)	31.6	246.4 (88.5-277.2)
AKI prediction using standardized platforms (245/808; 5 [5])	75.4 (63.8-84.2)	89.3 (81.9-93.9)	25.5 (8.9-72.8)	0.830 (0.741-0.918)	7.0	150.6 (145.0-155.0)
Initiation of RRT across AKI settings (84/1,948; 9 [10])	76.0 (65.1-84.4)	80.3 (59.5-91.9)	12.9 (4.9-33.9)	0.782 (0.648-0.917)	9.5	278.3 (141.9-381.6)
In-hospital mortality across AKI settings (88/1,617; 6 [7])	65.0 (51.2-80.8)	82.6 (51.8-95.5)	8.8 (1.9-40.8)	0.706 (0.530-0.747)	10.3	212.0 (121.8-506.7)

American Journal of Kidney Diseases, Vol 54, No 6 (December), 2009: pp 1012-1024

NGAL poor in Context of CKD



Clin J Am Soc Nephrol 5: 211–219, 2010

NGAL Performance - Summary

- Children > Adults
- Cardiac Surgery > Critical Illness (Sepsis)
- Normal Baseline Function > CKD
- Urine > Plasma

The Local and Systemic Inflammatory Transcriptome after Acute Kidney Injury

Dmitry N. Grigoryev,* Manchang Liu,* Heitham T. Hassoun,† Chris Cheadle,*
Kathleen C. Barnes,* and Hamid Rabb*

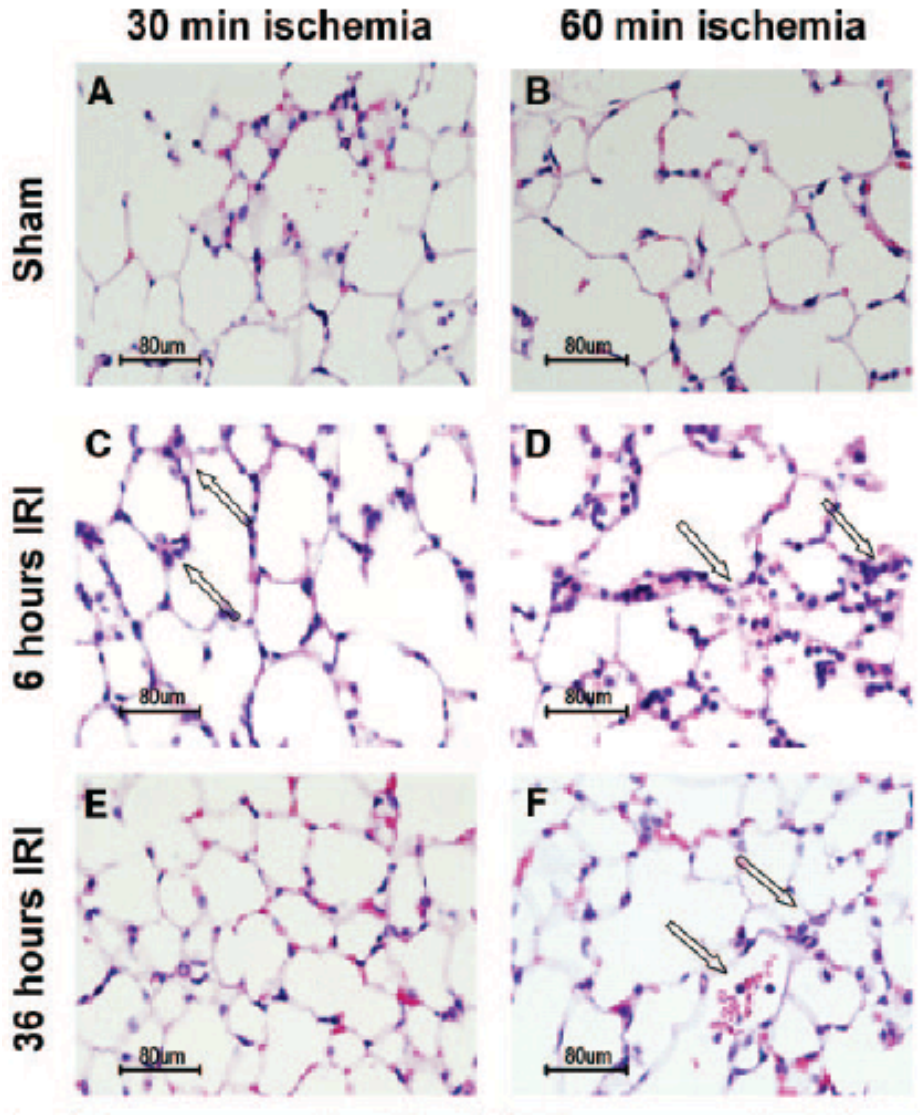
Kidney Injury

↓

Lung Injury

↓

Plasma NGAL



Predictive power of biomarkers vs Creatinine

- +ve NGAL but no Creatinine diagnosis of AKI?
  - Is this really a false positive?

The Outcome of Neutrophil Gelatinase-Associated Lipocalin-Positive Subclinical Acute Kidney Injury

A Multicenter Pooled Analysis of Prospective Studies

JACC Vol. 57, No. 17, 2011
April 26, 2011:1752–61

Michael Haase, MD,*† Prasad Devarajan, MD,‡ Anja Haase-Fielitz,
Rinaldo Bellomo, MD,§ Dinna N. Cruz, MD, MPH,‖ Gebhard Wag
Catherine D. Krawczeski, MD,‡ Jay L. Koyner, MD,# Patrick Murra
Michael Zappitelli, MD, MSc,†† Stuart L. Goldstein, MD,‡‡ Konst
Claudio Ronco, MD,‖ Johan Martensson, MD,‖‖ Claes-Roland Martl
Edward Siew, MD,¶¶ Lorraine B. Ware, MD,¶¶ T. Alp Ikizler, MI

Sub-clinical AKI?

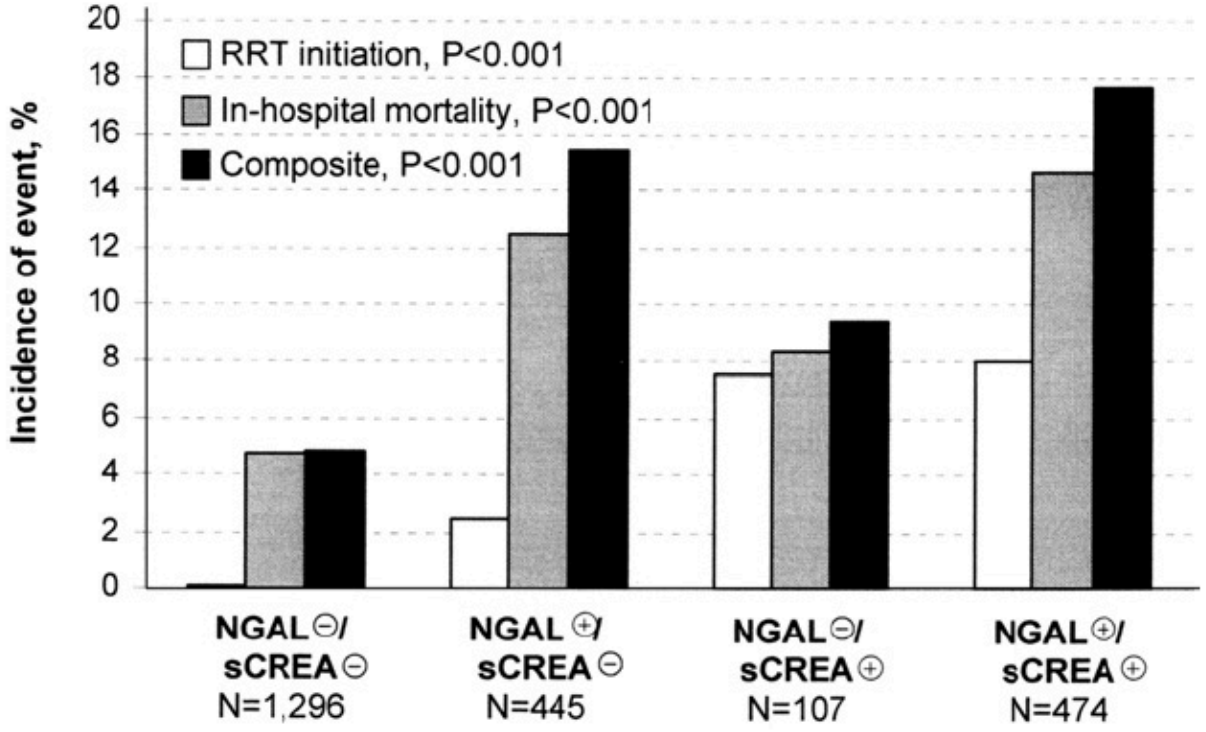


Figure 3 Incidence of Events

Incidence of RRT initiation, in-hospital morality, and a combination of both according to NGAL and sCREA. There was a stepwise increase in all outcomes. Abbreviations as in Figures 1 and 2.

Journal of the American College of Cardiology
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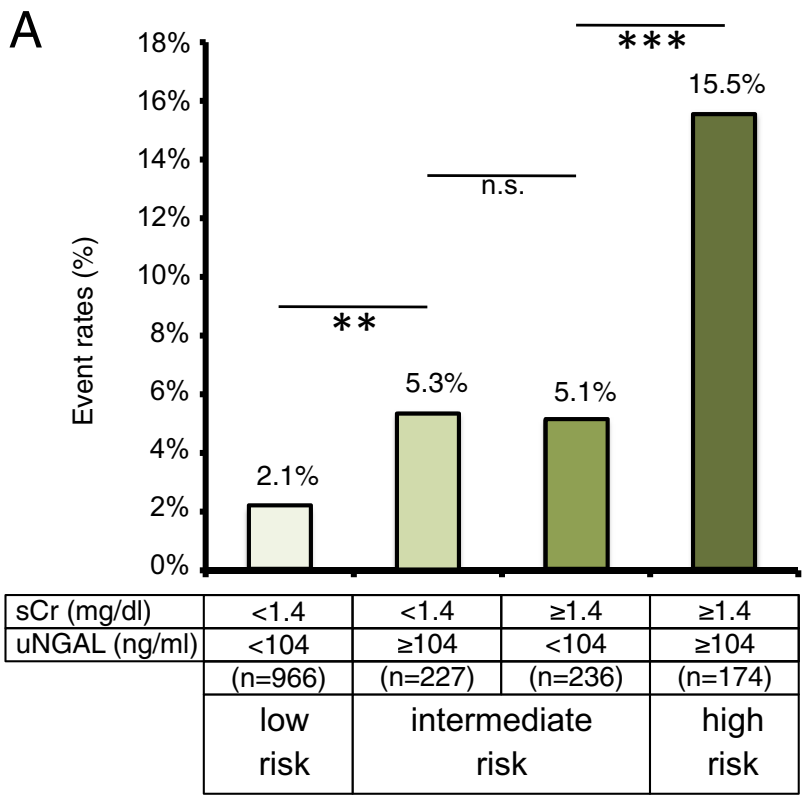
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.10.854

Diagnostic and Prognostic Stratification in the Emergency Department Using Urinary Biomarkers of Nephron Damage

A Multicenter Prospective Cohort Study

Biomarkers for AKI – Where now?

Synergistic information



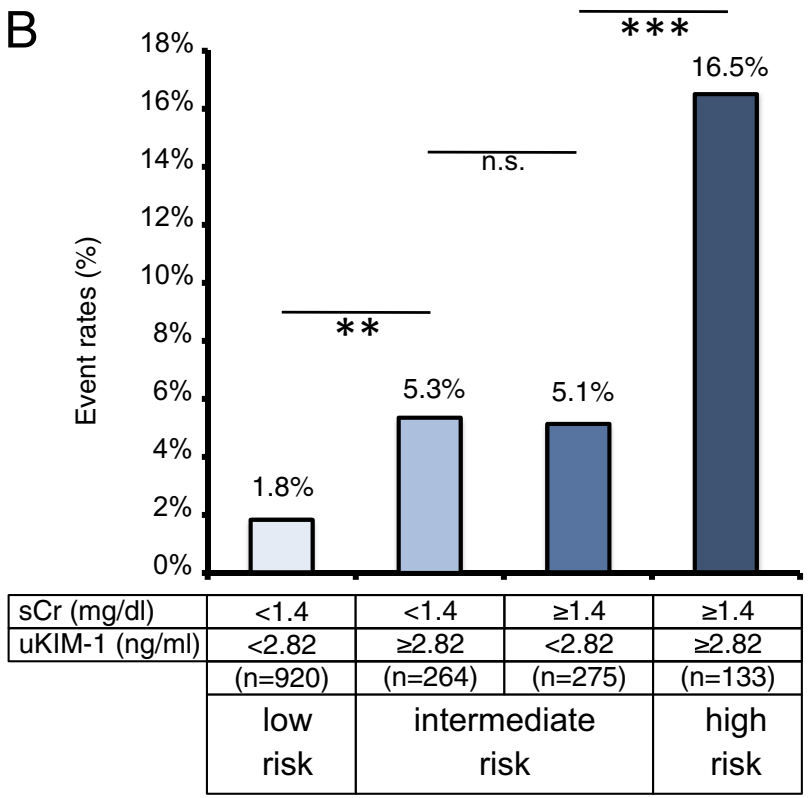
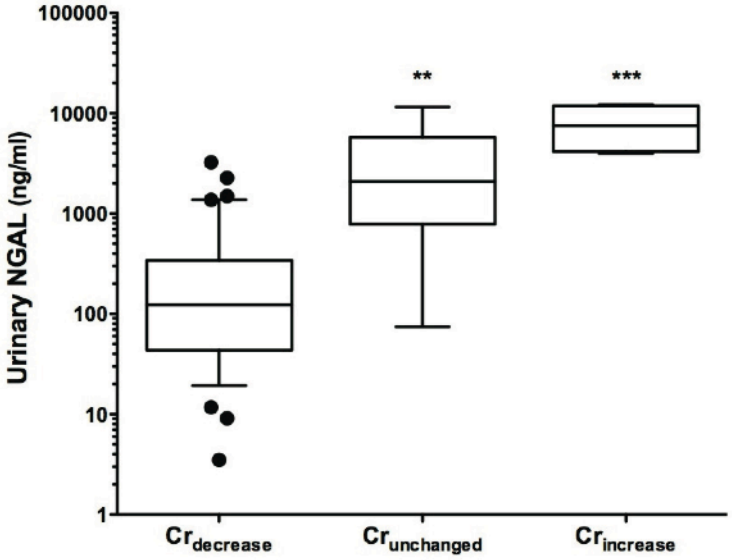


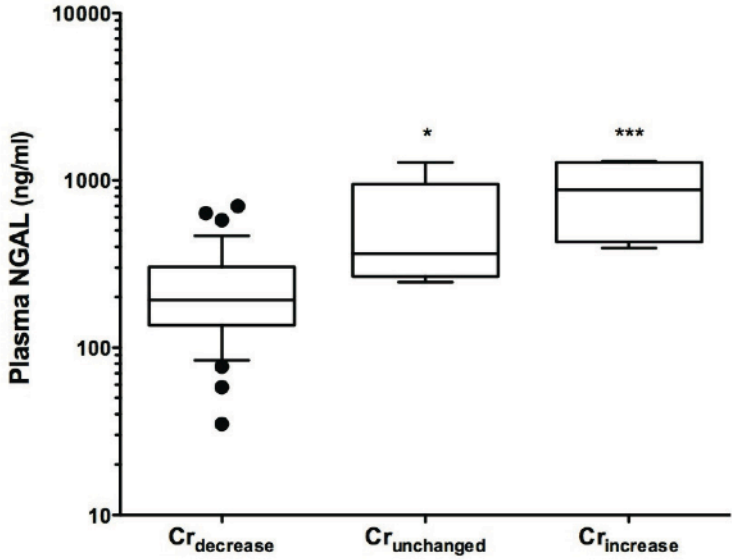
Figure 3 **Risk Stratification by Serum Creatinine and Urinary Biomarkers**

Rates of clinical events (initiation of dialysis or in-hospital mortality) in patients stratified by admission sCr and uNGAL **(A)** or sCr and uKIM-1 **(B)**. Cutoffs were applied at the 75th percentile for each biomarker (sCr, 1.4 mg/dl; uNGAL, 104 ng/ml; uKIM-1, 2.82 ng/ml). Significance level was determined by Pearson's chi-square test. ***$p < 0.001$, **$p < 0.01$. Abbreviations as in Figures 1 and 2.

NGAL reflects sub-clinical AKI after cardiac arrest

Pickering *et al*. *Critical Care* 2013, **17**:R7
http://ccforum.com/content/17/1/R7





Pickering *et al. Critical Care* 2013, **17**:R7
http://ccforum.com/content/17/1/R7

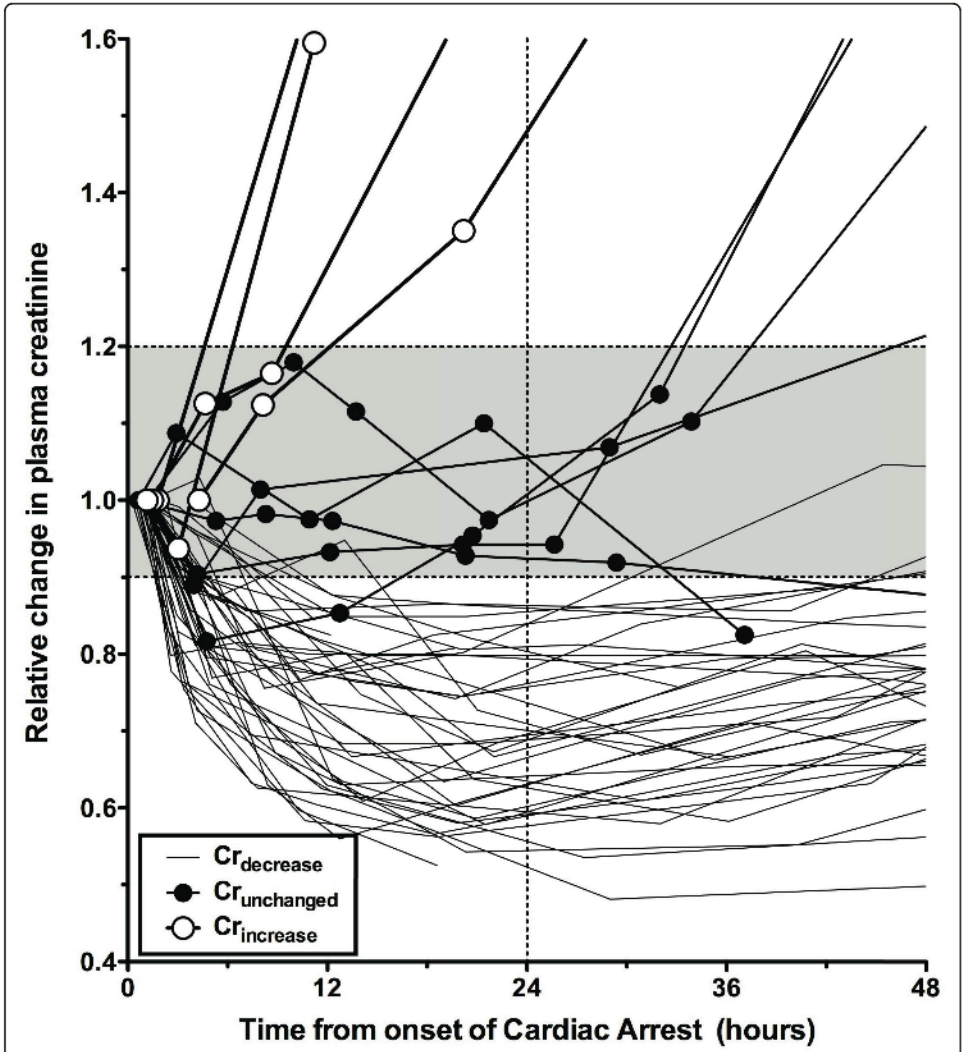
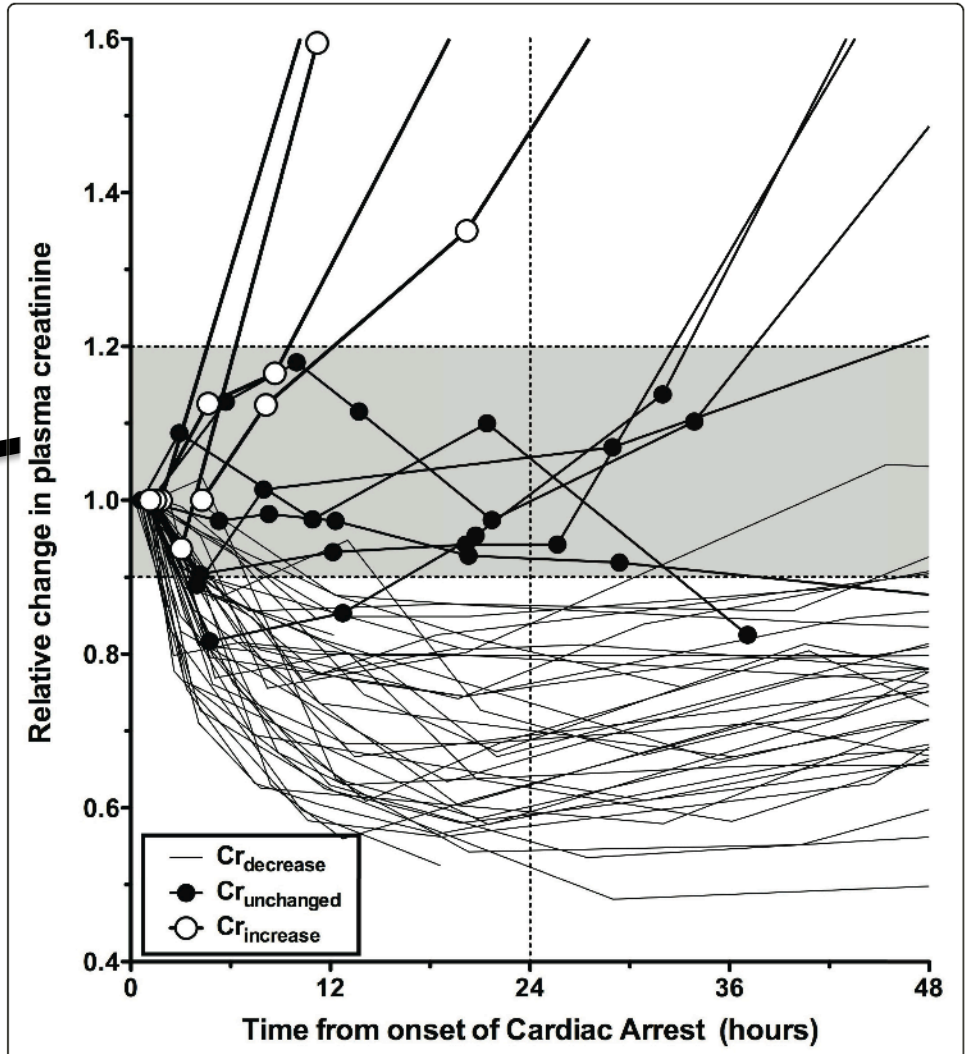


Figure 4 Changes in plasma creatinine concentration relative to the first creatinine measured in the emergency department followed one of three patterns. These patterns are $Cr_{increase}$ (open white circles), in which the increase in plasma creatinine was greater than 20% at 24 hours after cardiac arrest; $Cr_{unchanged}$ (closed solid circles), in which plasma creatinine increased no more than 20% or decreased no more than 10% at 24 hours after cardiac arrest, and $Cr_{decrease}$, in which plasma creatinine decreased exponentially by more than 10% by 24 hours after cardiac arrest.

Pickering *et al. Critical Care* 2013, **17**:R7
http://ccforum.com/content/17/1/R7

A mean 52% decrease in GFR was required to account for the lack of reduction in plasma creatinine



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Problem

- The potential for sub-clinical AKI poses significant difficulties in the use of serum creatinine a gold standard for AKI diagnosis.

Better Biomarkers?

Kashani *et al. Critical Care* 2013, **17**:R25
http://ccforum.com/content/17/1/R25

RESEARCH Open Access

Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury

Kianoush Kashani[1], Ali Al-Khafaji[2], Thomas Ardiles[3], Antonio Artigas[4], Sean M Bagshaw[5], Max Bell[6], Azra Bihorac[7], Robert Birkhahn[8], Cynthia M Cely[9], Lakhmir S Chawla[10], Danielle L Davison[10], Thorsten Feldkamp[11], Lui G Forni[12], Michelle Ng Gong[13], Kyle J Gunnerson[14], Michael Haase[15], James Hackett[16], Patrick M Honore[17], Eric AJ Hoste[18], Olivier Joannes-Boyau[19], Michael Joannidis[20], Patrick Kim[21], Jay L Koyner[22], Daniel T Laskowitz[23], Matthew E Lissauer[24], Gernot Marx[25], Peter A McCullough[26], Scott Mullaney[27], Marlies Ostermann[28], Thomas Rimmelé[29], Nathan I Shapiro[30], Andrew D Shaw[31], Jing Shi[32], Amy M Sprague[33], Jean-Louis Vincent[34], Christophe Vinsonneau[35], Ludwig Wagner[36], Michael G Walker[32], R Gentry Wilkerson[37], Kai Zacharowski[38] and John A Kellum[39*]

Discovery-Validation Pathway

Discovery Study
340 proteins analyzed (including KIM-1, urine NGAL, plasma NGAL, Cystatin-C, IL-18, pi-GST, and L-FABP)

Vienna Cohort
Age ≥ 18,
in ICU + Sepsis
N = 134

Duke Cohort
Age ≥ 18,
At least 1 risk factor[1]
N = 123

Mayo Cohort
Age ≥ 18,
At least 1 risk factor[2]
N = 265

Best Two Markers

Validation Study
Primary Endpoint: moderate to severe AKI (KDIGO stage 2-3) within 12 hours of sample collection (based on serum creatinine and hourly urine output)

Sapphire Study
35 sites
(20 North America, 15 Europe)
Age > 21, Critically Ill[3],
no AKI (Stage 2 or 3)[4]
N = 744

16 patients excluded
(2 withdrew consent, 7 lost to follow-up, 7 with invalid or missing test results)

N = 728[5]

No AKI
N = 416

AKI Stage 1
N = 211

AKI Stage 2
N = 83

AKI Stage 3
N = 18

Within 12 hrs

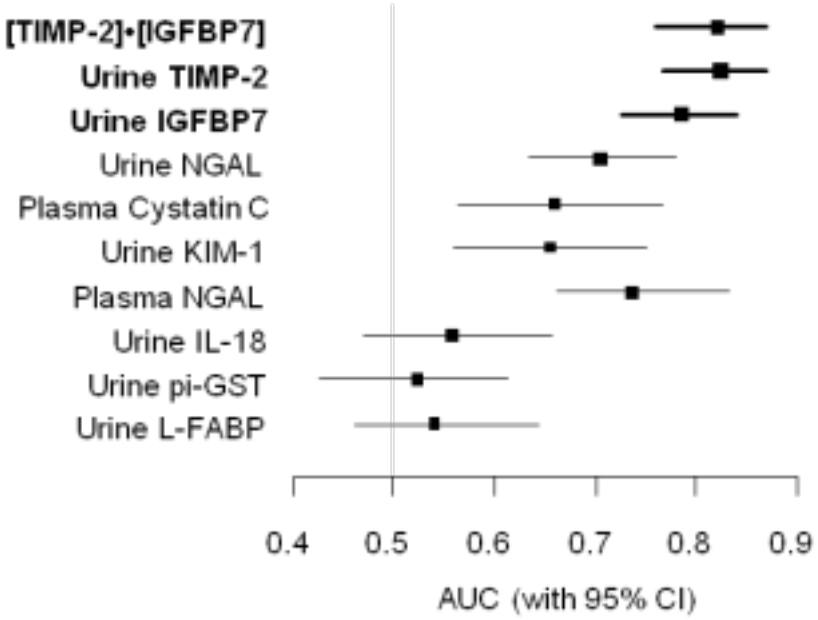
Kashani et al. Critical Care 2013, 17:R25

Novel Biomarkers Were Identified

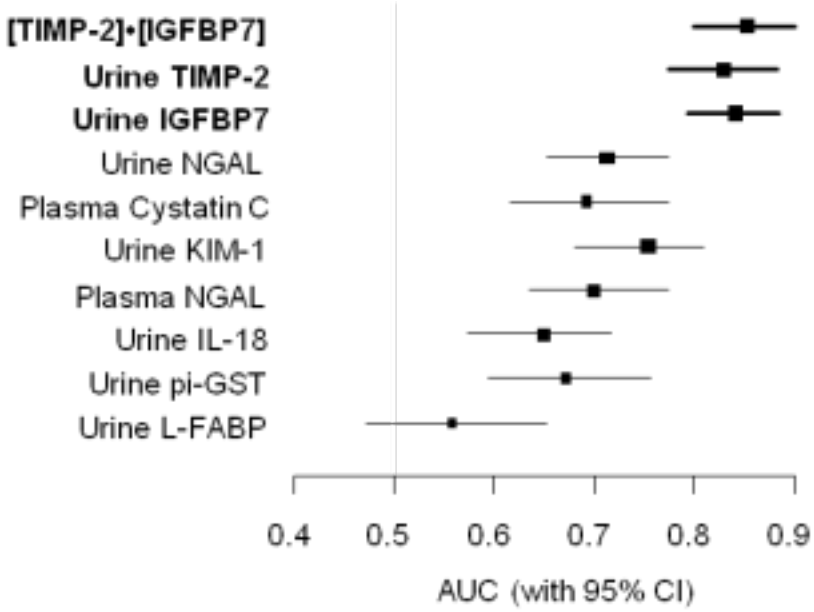
- Biomarkers ranked by ability to predict development of AKI RIFLE I or F within 12 to 36 hours
- Of 340 candidates the top performing biomarkers were:
  - Tissue Inhibitor of Metalloproteinases-2 (TIMP-2)
  - Insulin-like Growth Factor Binding-Protein 7 (IGFBP7)

TIMP-2 and IGFBP7 Work Well In Important Subgroups

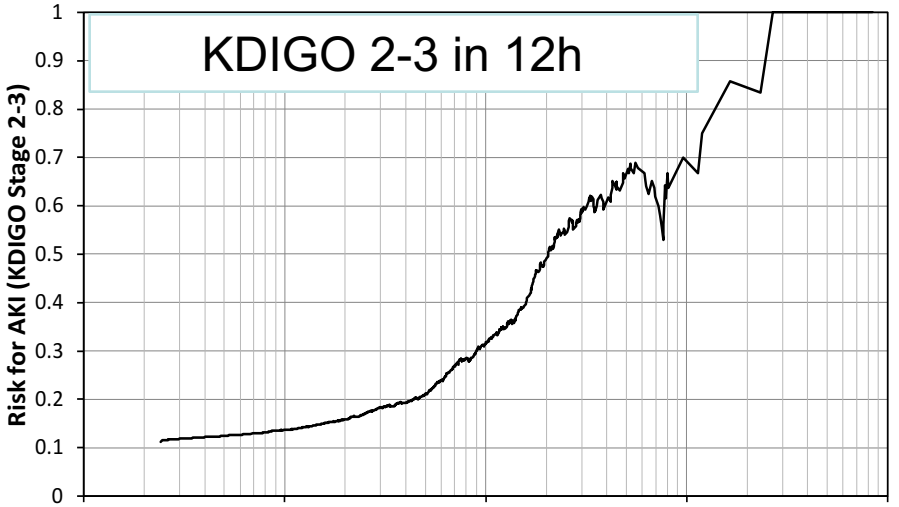
Sepsis

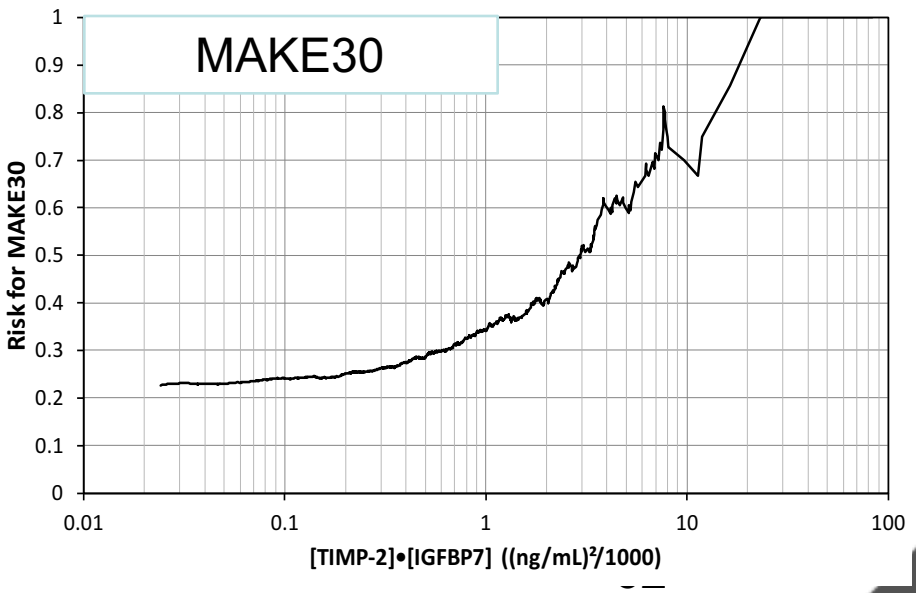


Surgery



TIMP-2 and IGFBP7 are related to clinically meaningful outcomes

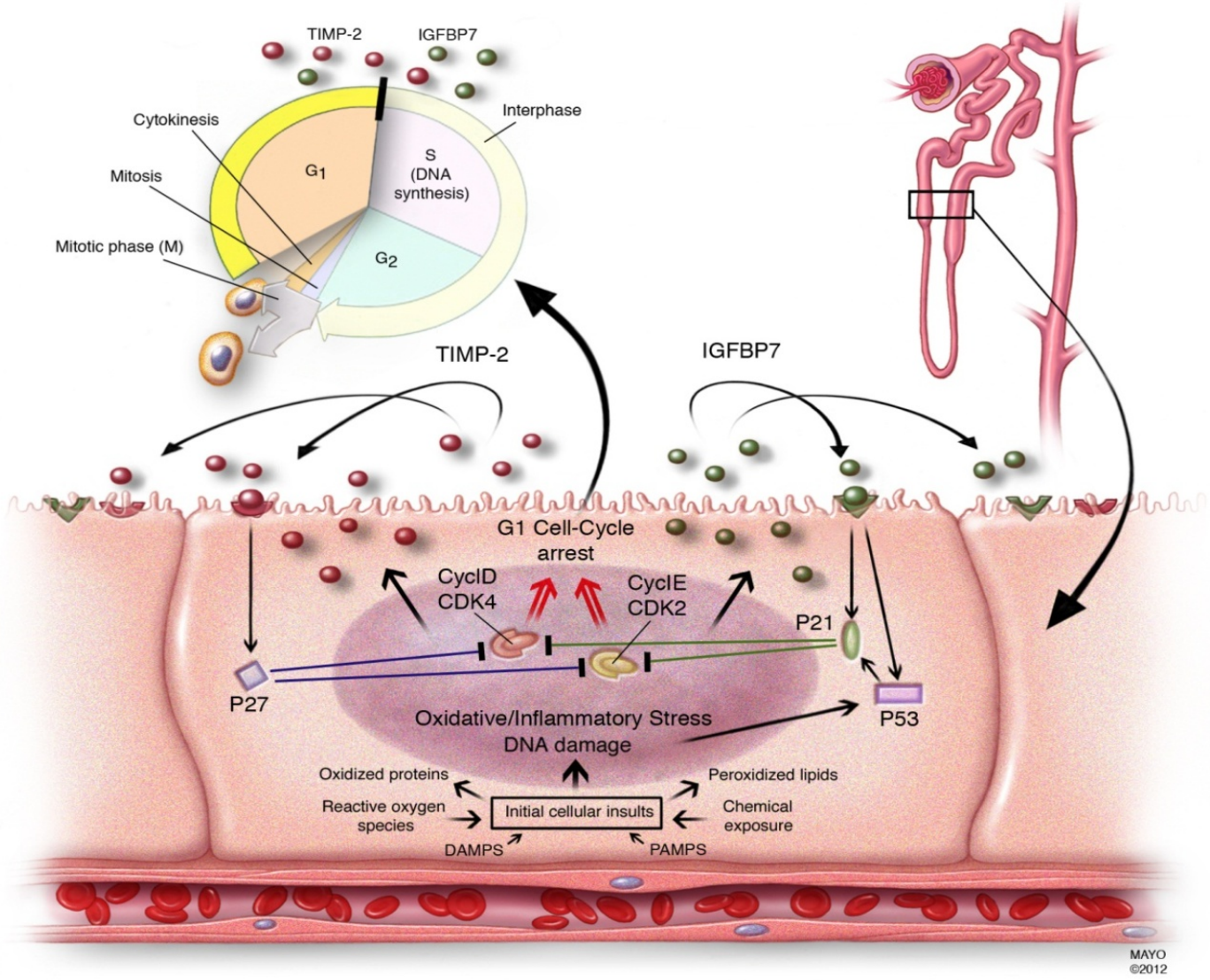




MAKE30 (30 days)

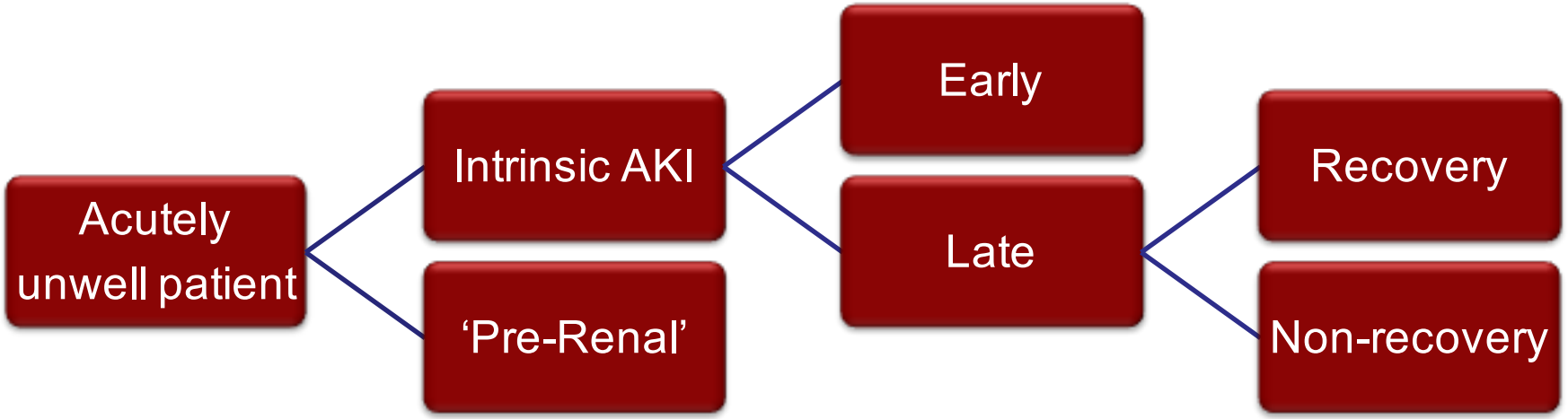
- Death
- RRT
- Persistently elevated sCr (2x over baseline)

TIMP-2 and IGFBP7 Have Mechanistic Origins in Early Cellular Injury



- AUC is still only 0.8 in a real-world clinical population
  - Compared against creatinine
- Renal biomarkers could be very good, but we are unable to prove it
- How should we move forward?

Staging AKI:
Different interventions in different groups



What to do with Biomarker results?

- Nothing
- Stratify care
- Give intervention
- Stratify discharge and follow-up
- I don't have enough evidence to guide my therapy

How does early AKI diagnosis help me in the ICU?

How does early AKI diagnosis help me in the ICU?

- What are the interventions for AKI?

How does early AKI diagnosis help me in the ICU?

- What are the interventions for AKI?
  - Best supportive care

How does early AKI diagnosis help me in the ICU?

- What are the interventions for AKI?
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  - Avoid secondary injury

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  - Timely CRRT to clinical indications

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- What is good ICU care?

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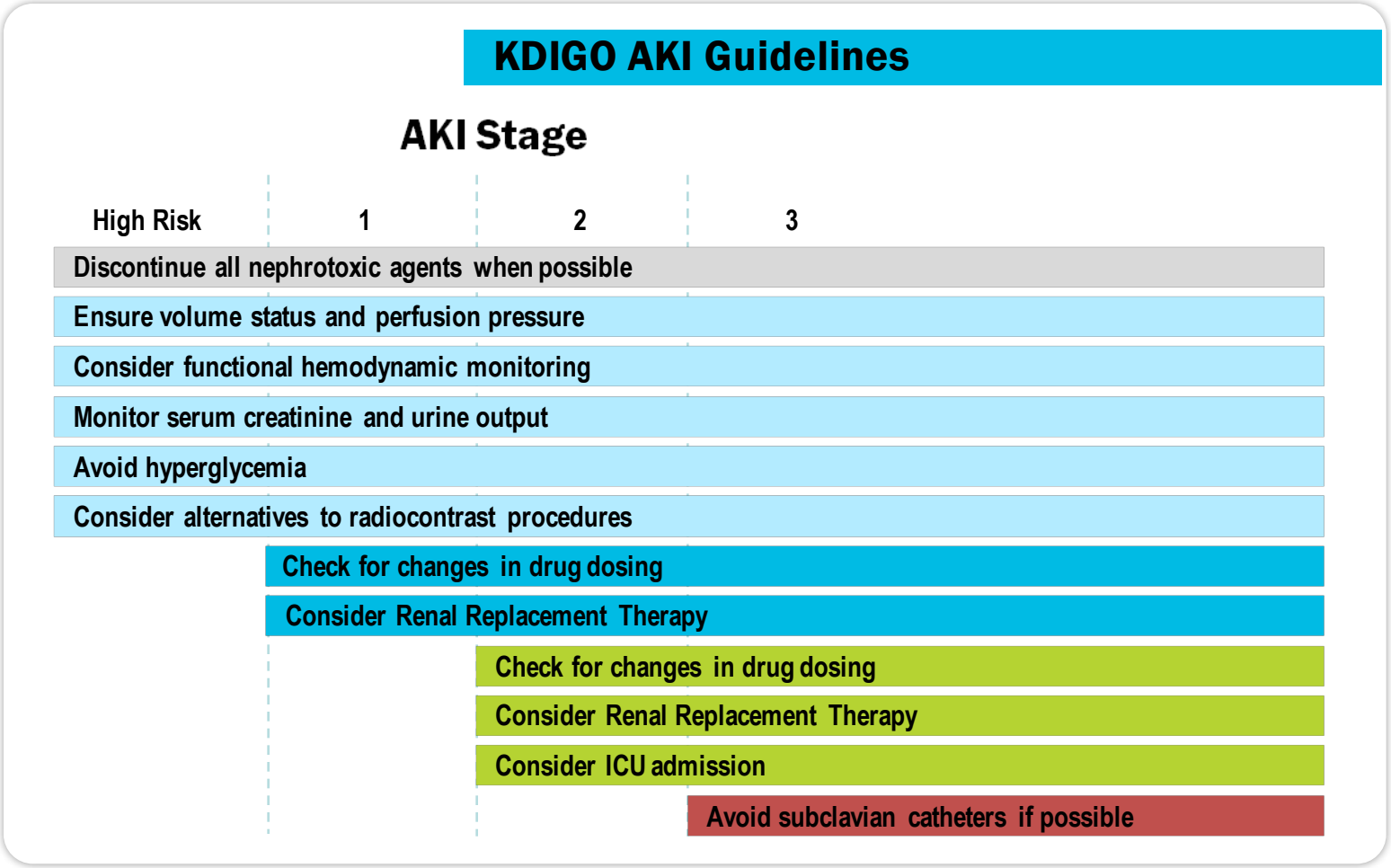
How does early AKI diagnosis help me in the ICU?

- What are the interventions for AKI?
  - Best supportive care
  - Avoid secondary injury
  - Timely CRRT to clinical indications
- What is good ICU care?
  - Best support care
  - Avoid secondary injury
  - Timely organ support to clinical indications

Recommended action after early assessment of AKI



Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2012; Volume 2, Issue 1:1–126.

Where to study patients

- Ward
- ED
- Community
- ICU ?
  - ICU as a biomarker driven treatment not a patient group
  - Admission & Discharge
- Exclusion of AKI

Relevant biomarker outcomes

- GFR rather than creatinine
- Development Chronic Kidney Disease rather than AKI
- Interventional studies

So am I interested in AKI biomarkers in ICU?

So am I interested in AKI biomarkers in ICU?

- What about Intervention X?
  - ie RRT, Any number of drugs

So am I interested in AKI biomarkers in ICU?

- What about Intervention X?
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- I don't know is this is effective in early AKI
  - OK lets test it!

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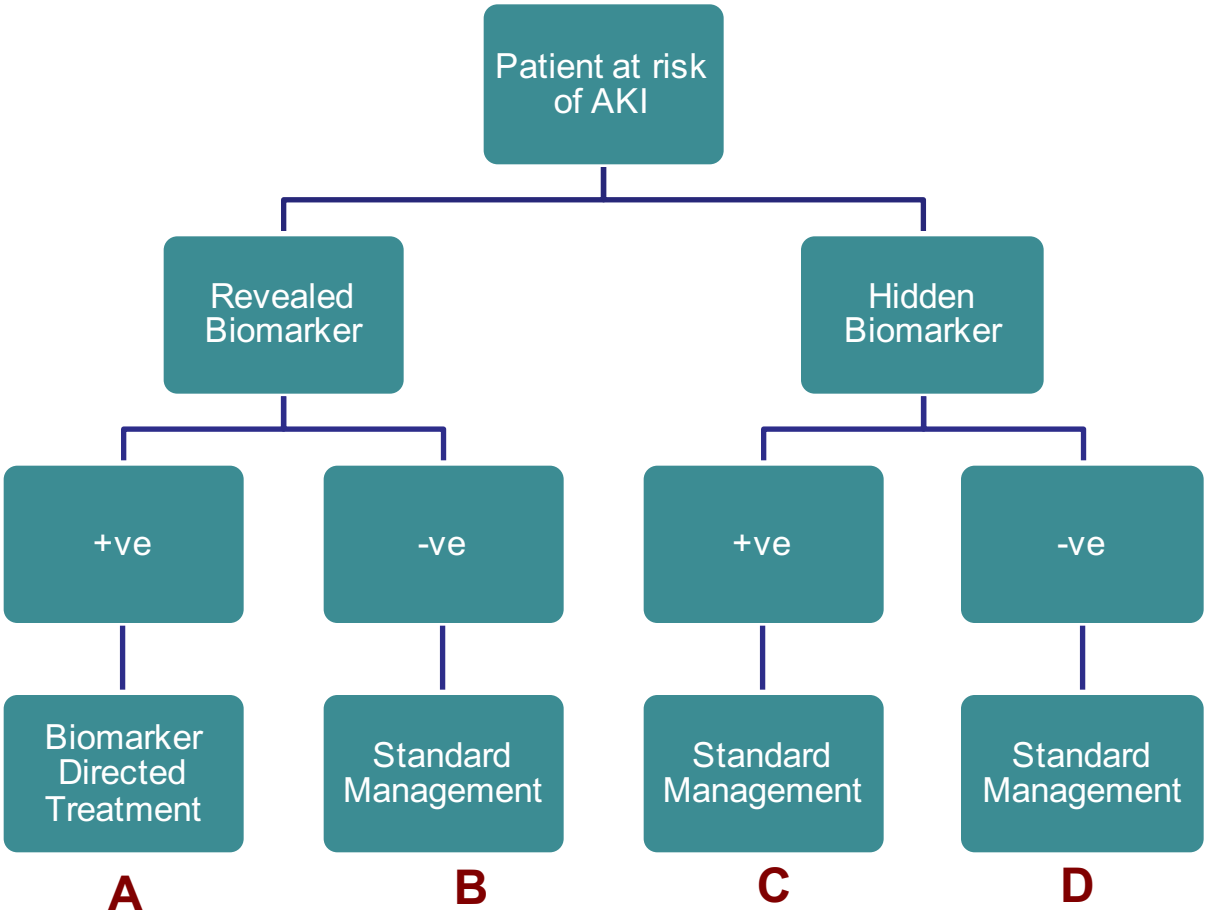
  - OK lets test it!
- I don't know if biomarker Y reliably diagnoses early AKI
  - The gold standard is inadequate

So am I interested in AKI biomarkers in ICU?

- What about Intervention X?
  - ie RRT, Any number of drugs
- I don't know is this is effective in early AKI
  - OK lets test it!
- I don't know if biomarker Y reliably diagnoses early AKI
  - The gold standard is inadequate
- Can we test both these things in a pragmatic study?

Approach #1
Validating Biomarker Directed Therapy

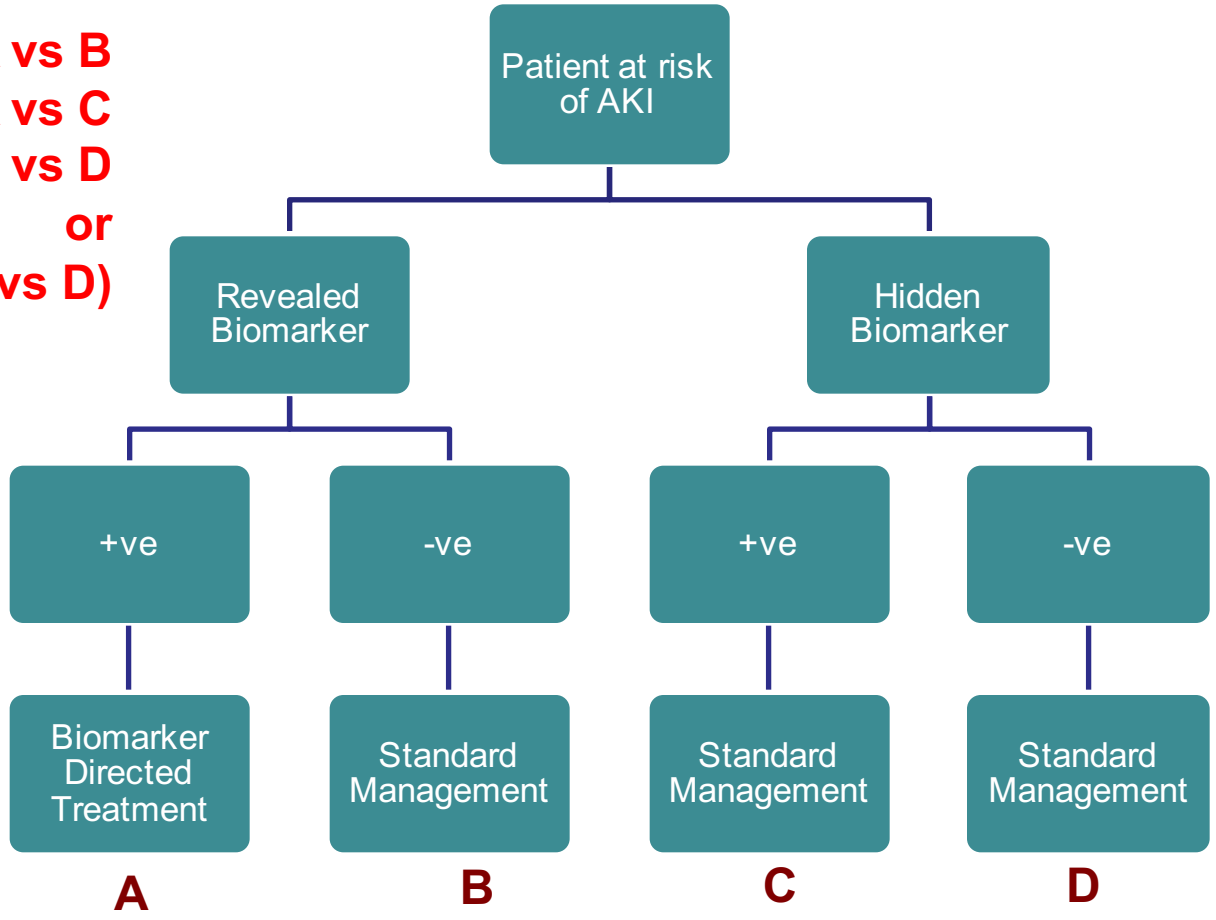


Measure a patient-centred endpoint such as mortality or new CKD

Approach #1
Validating Biomarker Directed Therapy

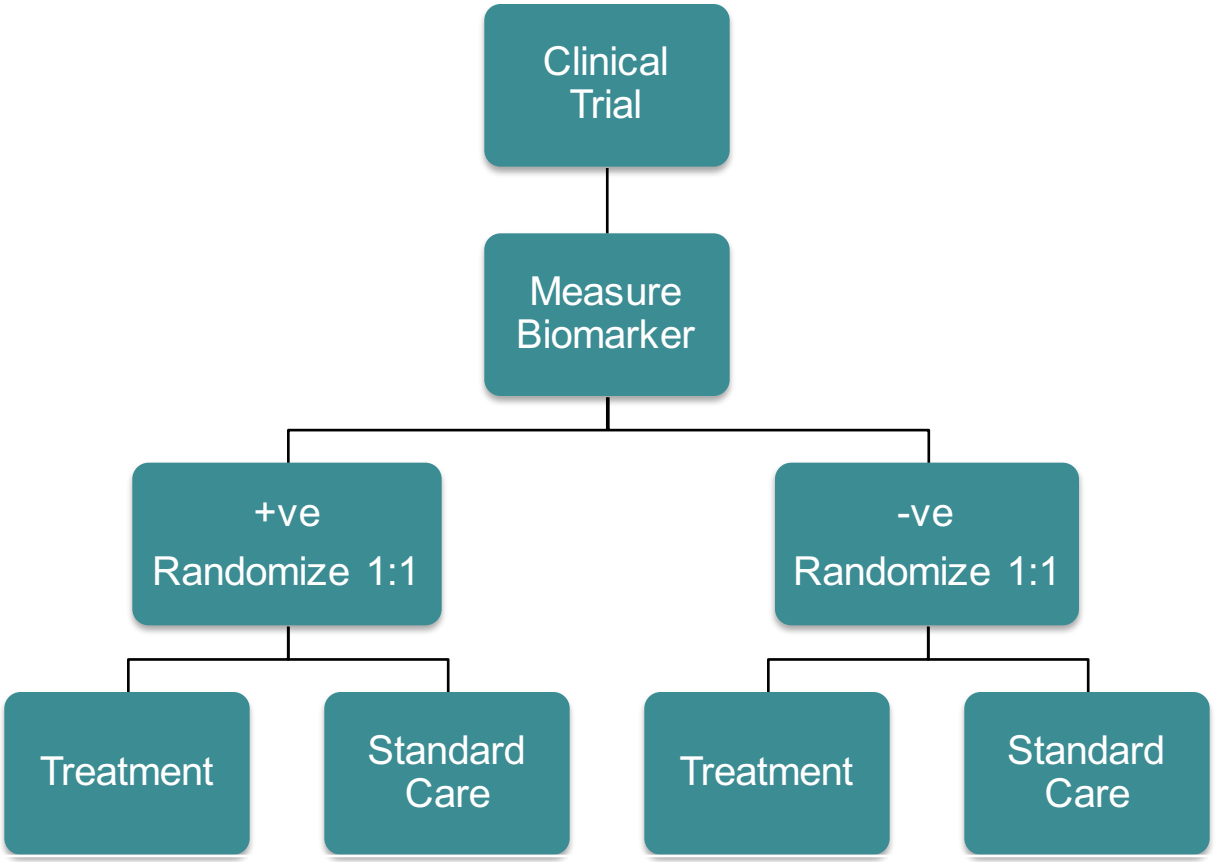
Comparisons:

A vs B
A vs C
C vs D
or
(A vs B) vs (C vs D)



Measure a patient-centred endpoint such as mortality or new CKD

Approach #2
Stratified Randomization for Biomarker – Biomarker specific treatment effect?



Do AKI biomarkers have a role in clinical practice now?

Do AKI biomarkers have a role in clinical practice now?

- Need validation by proving clinical- and cost-effectiveness of biomarker directed management

Do AKI biomarkers have a role in clinical practice now?

- Need validation by proving clinical- and cost-effectiveness of biomarker directed management
- What therapies?
  - AKI care bundle
  - Critical Care admission
  - Pharmacotherapy
  - RRT
  - CRRT/IHD
  - Follow-up


Thank you for you kind attention
THE ROYAL LONDON HOSPITAL