Guidelines for Acute Kidney Injury Diagnosis,Prognosis & Treatment

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- **KDIGO – John Kellum, MD**
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- **Ayumi Shintani, PhD,MPH**

Outline

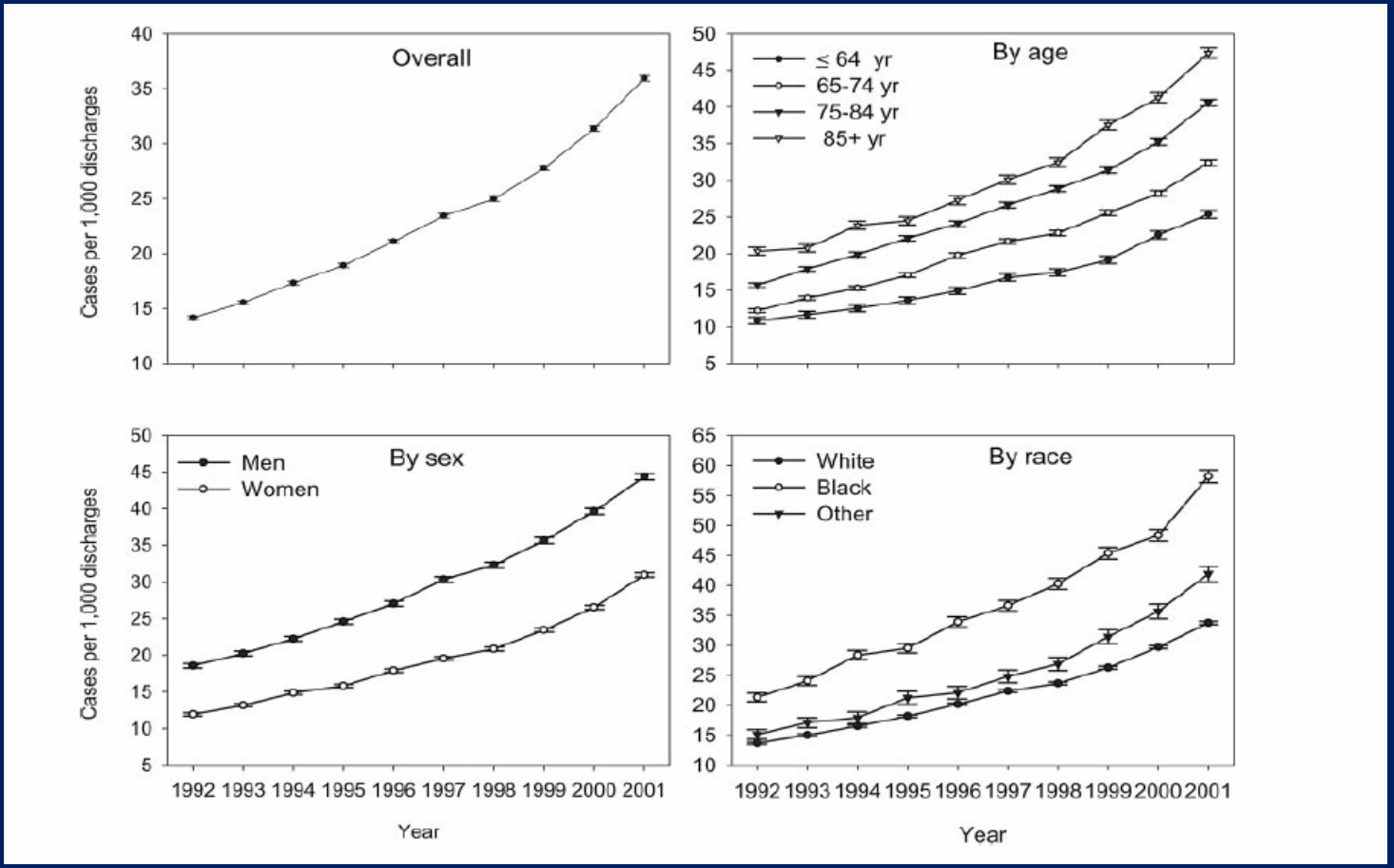
- Epidemiology of AKI
- The Diagnostic/Phenotyping/Prognostic Ability
- Biomarkers of AKI – The “Early” Experience
- Treatment of AKI

AKI – The Problem

- 1.9-7.2% (3-30% ICU) hospitalized patients
  - 17 million admissions annually
  - Estimated $10 billion annual costs
- Mortality up to 60% in those requiring dialysis
- **Independent** predictor of morbidity and mortality

Shusterman, et al. Am J Med 1987;83:65-71
Nash et al, AJKD 2002; 39(5): 930-936
Joannidis, et al. Crit Care Clin 2005;21: 239-249

AKI Incidence is Increasing



Xue, JL JASN 2006; 17:1135-1142

BEST Kidney Investigators

- Multi-Center, Multi-Country ICU Cohort (N=29,269)
  - 5.7% with Severe AKI (30% with CKD)
    - RRT, UO <200 ml/12 hours, BUN>84 mg/dl
  - Risk Factors/Causes
    - Septic shock 48%
    - Major surgery 34%,
    - Cardiogenic shock 27%,
    - Hypovolemia 26%
    - Nephrotoxins 19%

BEST Kidney Investigators *JAMA* 2005; 294(7): 813-818

CKD as a Risk Factor for AKI

Risk-factor	Adjusted Odds Ratio† for Dialysis-Requiring AKI (95% Confidence Interval)
Baseline eGFR (ml/min/1.73m^2)	
≥ 60	Reference
45-59	1.66 (1.40-1.97)
30-44	4.75 (4.01-5.63)
15-29	20.42 (17.40-23.96)
< 15	47.17 (39.22-56.74)
Diabetes mellitus	1.99 (1.78-2.23)
Diagnosed hypertension	1.55 (1.37-1.76)
Documented proteinuria	2.84 (2.52-3.19)

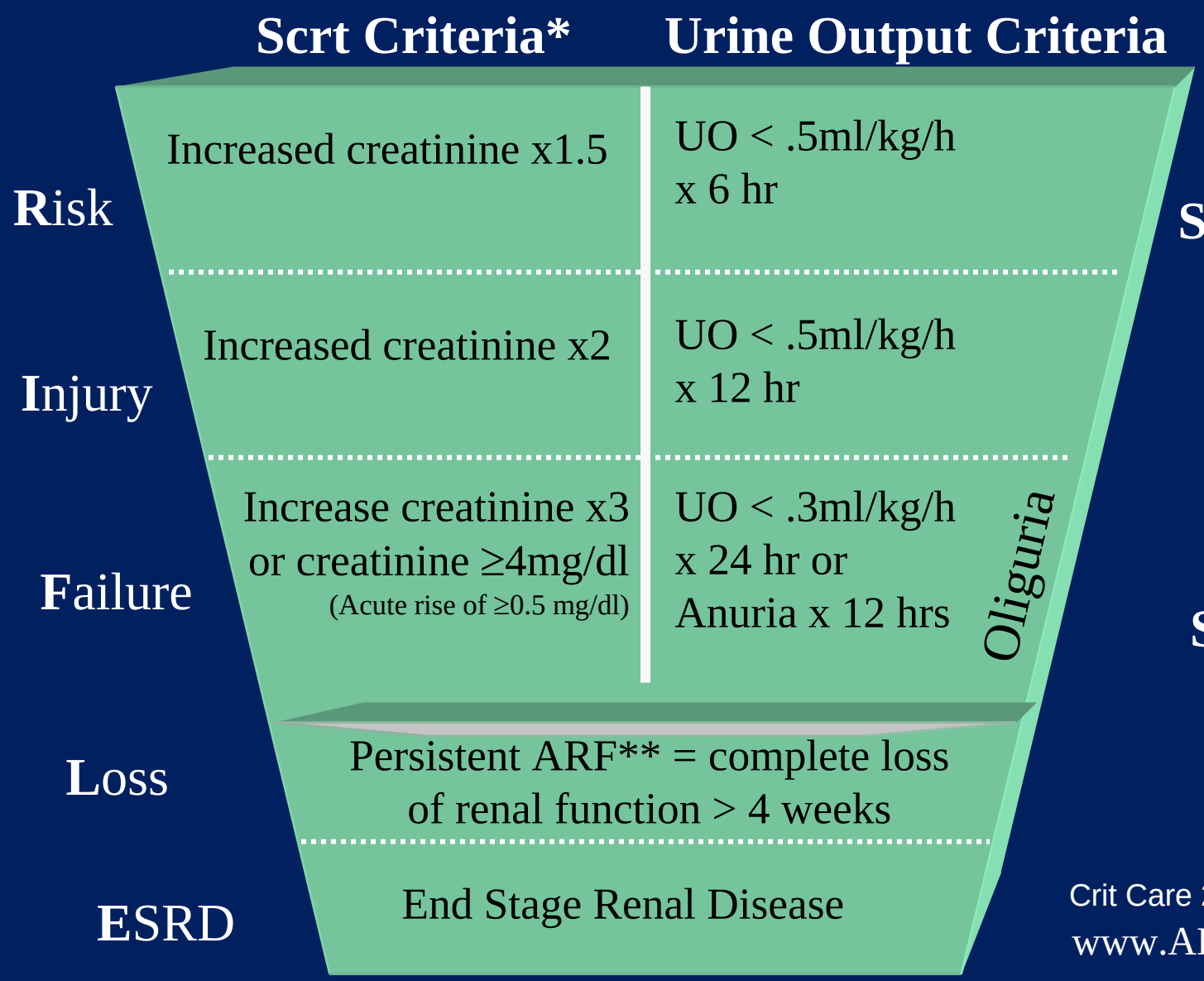
† Adjusted for age, sex, ethnicity, hyperbilirubinemia, ICU stay, mech ventilation, CABG, cardiac surgery, PCI, and cardiac catheterization

Adapted from: Hsu KI 2008; 74:101-107

The Problem: Varied Definitions of AKI

Author	Setting	Definition	Incidence
Rangel-Fraustro 1995	ICU w/sepsis	Increase >2 mg/dl, need for RRT, doubling of SCr	9%
Hoste 2003	Surgical ICU w/sepsis	Increase from ≤1.0 to ≥ 2.0 mg/dl SCr	30%
Chwala 2005	Sepsis	Increase >75% if baseline ≤ 2.0 or > 50% if baseline >2.0	18%
Chertow 1997	CABG/Valvular Surgery	Need for Dialysis	1.1%
Marenzi 2004	PCI	Increase > 0.5 mg/dl	19%
Prinsen 2004	AAA Repair	Increase Scr ≥20%	13%

RIFLE Criteria for Acute Kidney Injury



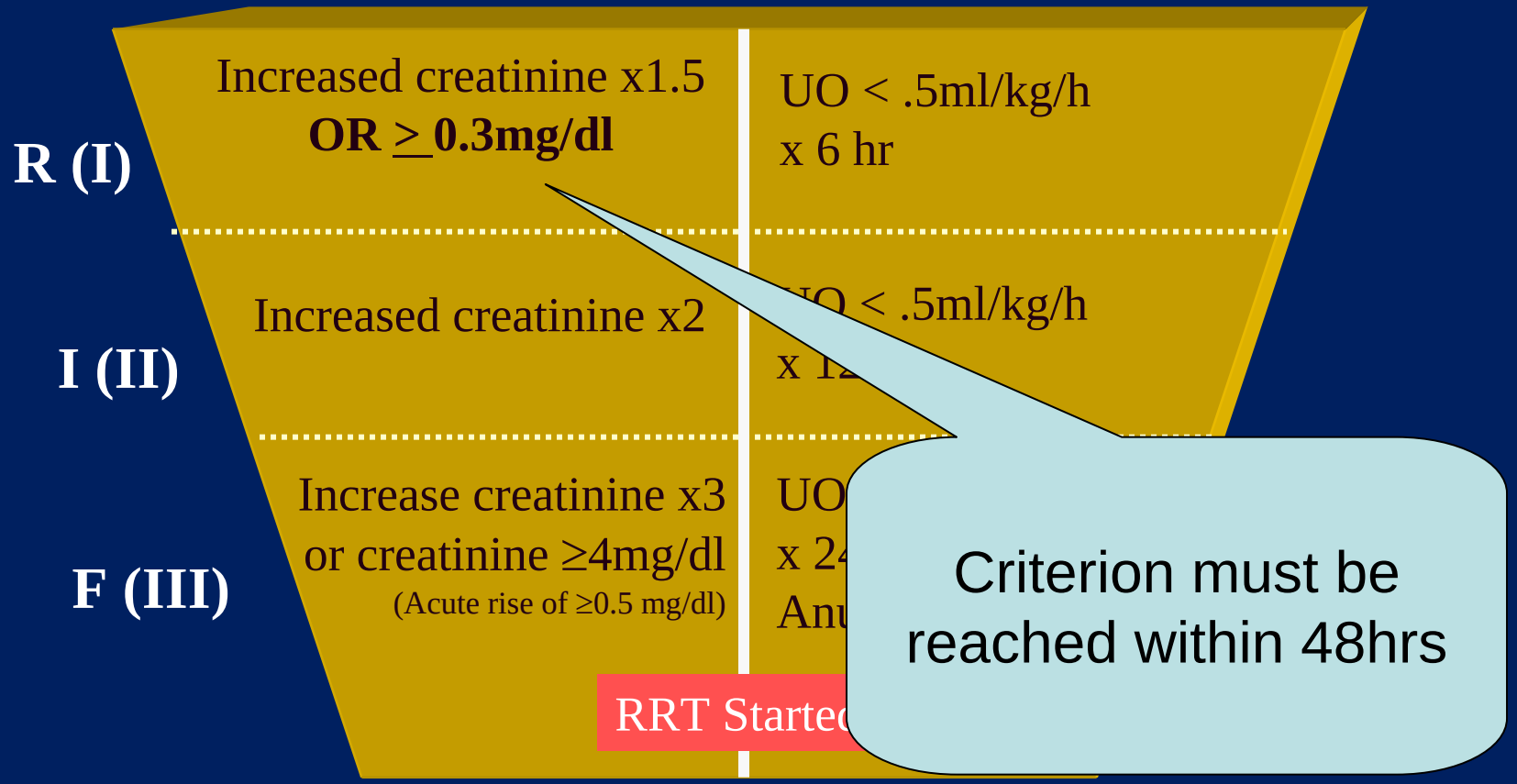
Crit Care 2004, 8:R204-12

www.ADQI.net

RIFLE has been validated in >200,000 pts

- Hospital and ICU based studies
  - Recent studies
    - 120,123 patients in 57 ICUs in Australia (Bagshaw et al)
      - 36.1% developed AKI
      - Hosp Mortality: R:17.9%, I:27.7%, F:33.2%
    - 41,972 patients in 22 ICUs in Europe (Ostermann et al.)
      - 35.8% developed AKI
      - Hosp Mortality: R:20.9%, I:45.6%, F:56.8%
- Population based studies
  - Northern Scotland (pop 523,390) (Ali et al.)
    - AKI incidence 2147 pmp (16% CKD)
    - By comparison the incidence of acute MI in US is approximately 2667 pmp

Modified RIFLE as Proposed by AKIN



CHAPTER 2.1: DEFINITION AND CLASSIFICATION OF AKI

- **2.1.1: Acute kidney injury (AKI) is defined as any of the following (*Not Graded*):**
  - **Increase in SCr by ≥ 0.3 mg/dl within 48 hours; or**
  - **Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within prior 7 days; or**
  - **Urine volume <0.5 ml/kg/h for 6 hours.**

CHAPTER 2.1: DEFINITION AND CLASSIFICATION OF AKI

- **2.1.2: AKI is staged for severity according to the following criteria (*Not Graded*):**

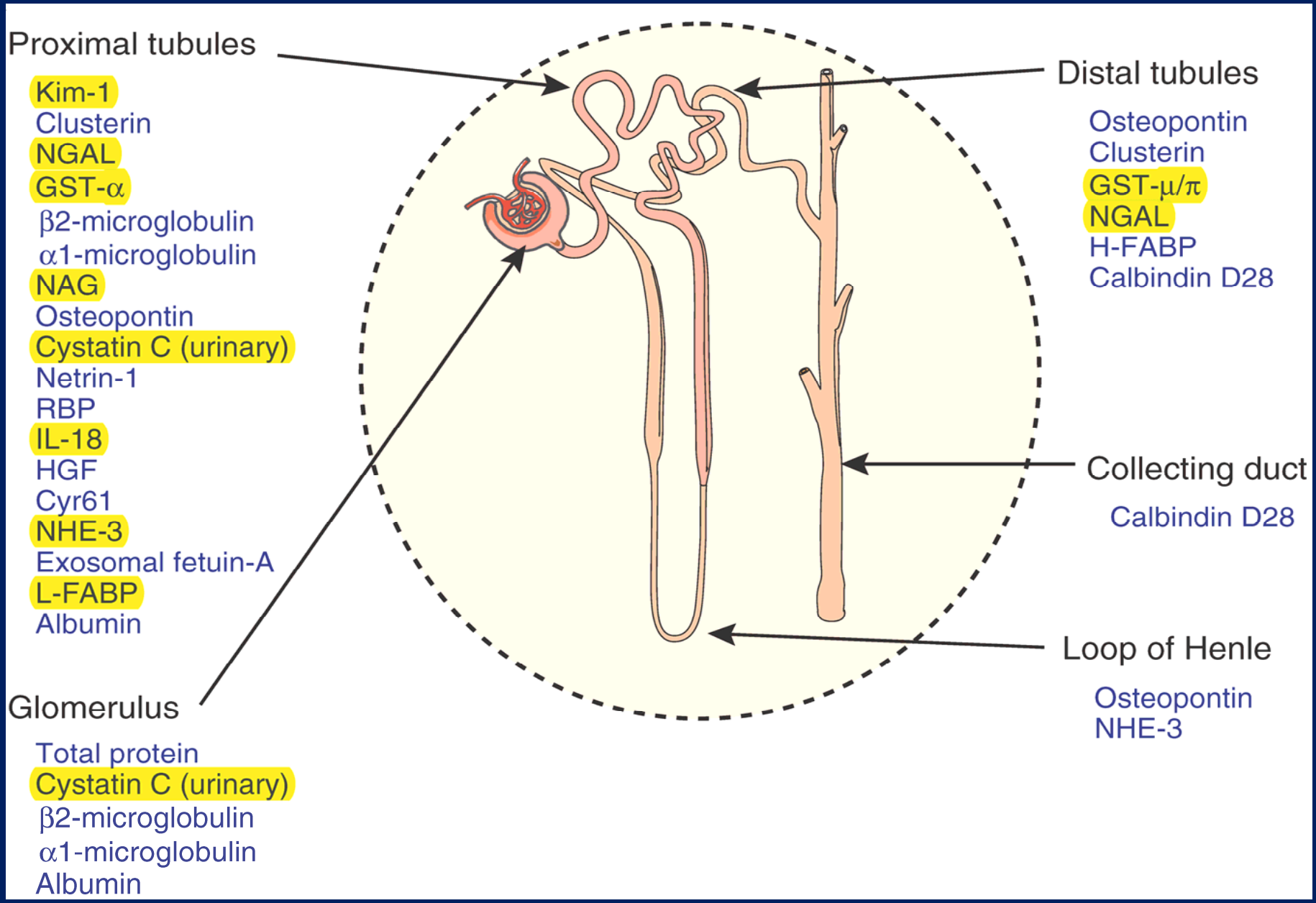
Stage	Serum Creatinine	Urine output
1	1.5-1.9 times baseline OR ≥0.3 mg/dl increase	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl OR Initiation of renal replacement therapy *OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m²*	<0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

KDIGO - AKI

AKIN: Remaining Questions

- Validity/Utility of Urine Output Criteria
- Dynamics of Creatinine Change
- Use in specific subgroups (CKD, DM?)
- Which baseline?
- Impact of emerging biomarkers

Disease	Injury Markers	Functional Markers	Available Therapies
Myocardial Infarction	EKG, AST→CKMB→ Troponin	Ejection Fraction, CO/CI	ASA, Heparin, β -blockers, IIB-IIIA, thrombolytics, PTCA, statins, ACE/ARB
ALI/ARDS	Acute Bilateral Infiltrates on CXR	Oxygenation (P/F Ratio)	Low Tidal Volume Ventilation
Sepsis	Tissue Gram Stain, WBC count	SIRS Criteria	Activated Protein C, EGDT, steroids
Nephrology	**…..** ←	**Serum Creatinine, Urine Output,**	***"renal bed rest"***



Bonventre *Nature Biot 28(5), 2010*

Proposed Stages of Human Biomarker Validation

Phases	#1	#2	#3	#4	#5	#6
	Proof of Concept (AKI vs. no AKI)	Prospective Validation (Hard Outcomes)	Incremental Value to Known Predictors	Does it Change Management (clinical utility)?	Improve Clinical Outcomes?	Cost-Effective?
Potential Study Designs	Cross Sectional/ Case Control/ Prospective Cohort	Nested Case Control/ Prospective Cohort	Prospective Cohort (discrimination, calibration, reclassification	Prospective/ Randomized Clinical Trial		
STUDIES						

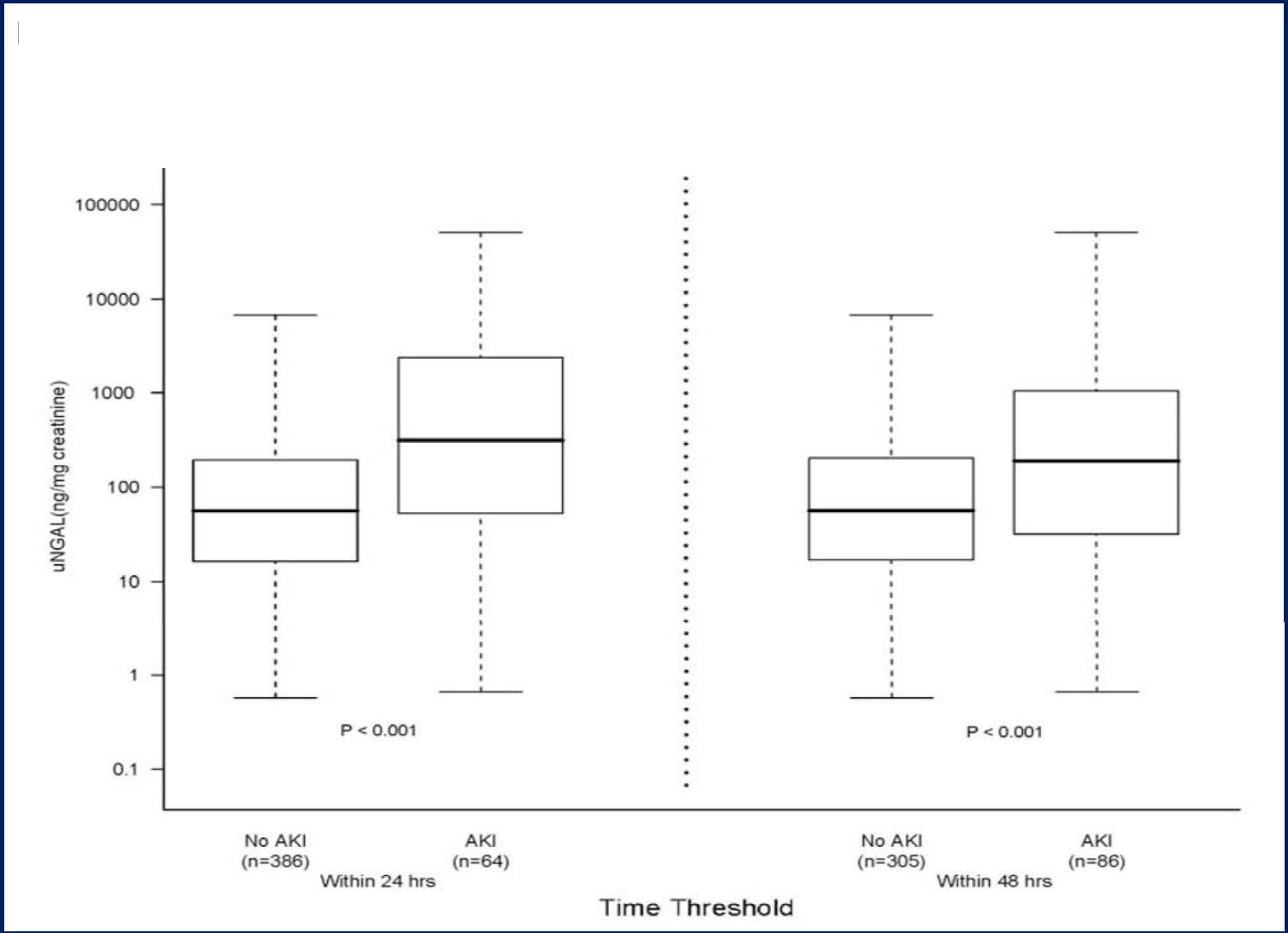
Siew, Ware, Ikizler *JASN 22(5): 810-20, 2011*
Adapted for AKI from Hlatkey et al. *Circulation 119:2408,*

Most Candidate Markers Being Tested Perform Well in Established AKI

Biomarker	AUC-ROC (95% CI)	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)
L-FABP (ng/mg)	0.93 (0.88–0.97)	47.1	83% (73–90%)	90% (77–97%)
NGAL (ng/mg)	0.92 (0.86–0.96)	186.8	81% (71–89%)	100% (92–100%)
KIM-1 (ng/mg)	0.89 (0.82–0.94)	1.7	77% (67–85%)	100% (92–100%)
NAG (U/mg)	0.89 (0.82–0.94)	0.007	99% (94–100%)	64% (48–78%)
IL-18 (pg/mg)	0.83* (0.76–0.89)	2.2	71% (60–80%)	90% (77–93%)

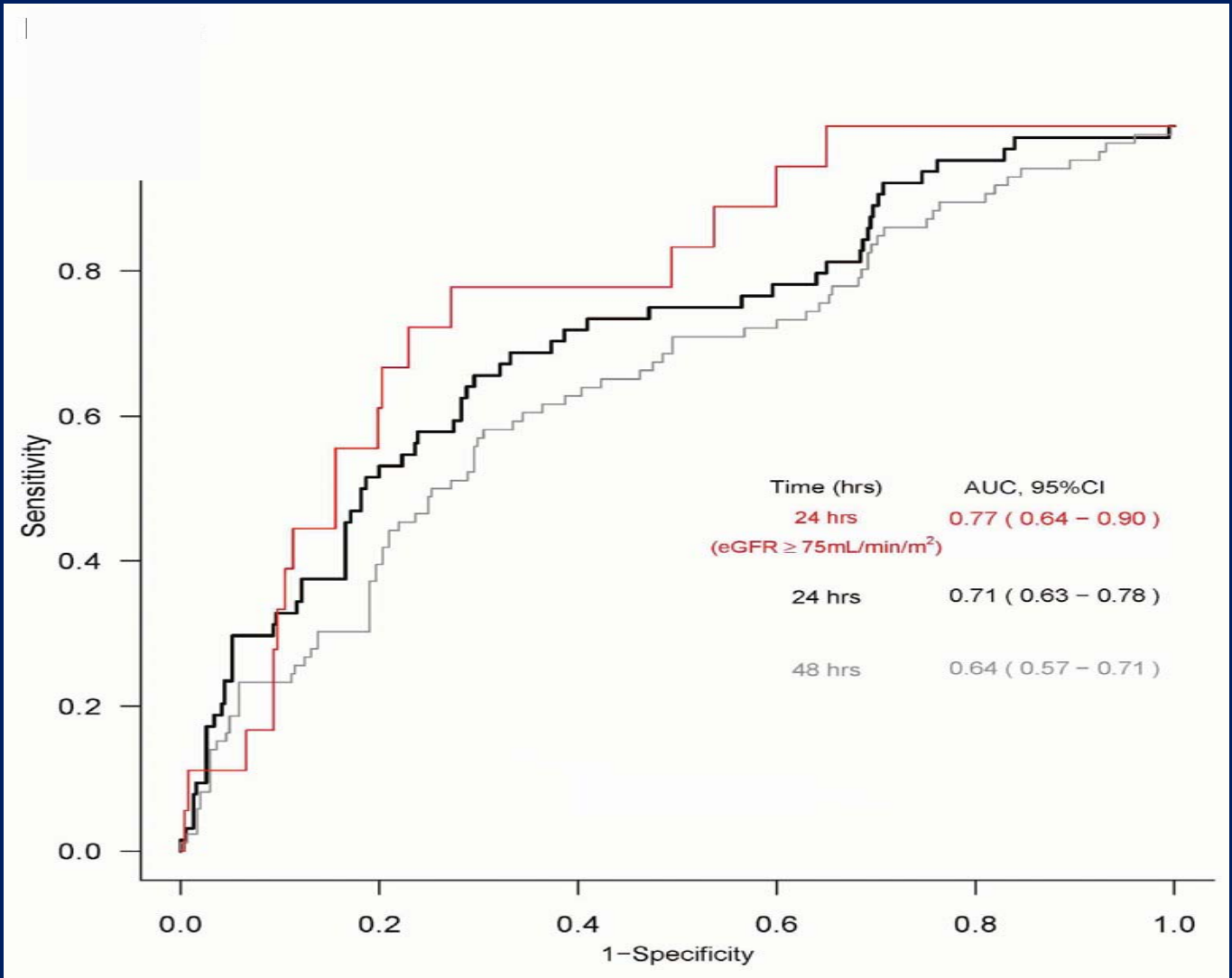
Adapted from Ferguson *Kid Intern* 77, 2010

Urine NGAL for Prediction of AKI in a Mixed Adult ICU Population



Siew, Ware, Ikizler et al. *JASN* 2009

Prediction of AKI by Urine NGAL in a Mixed Adult ICU



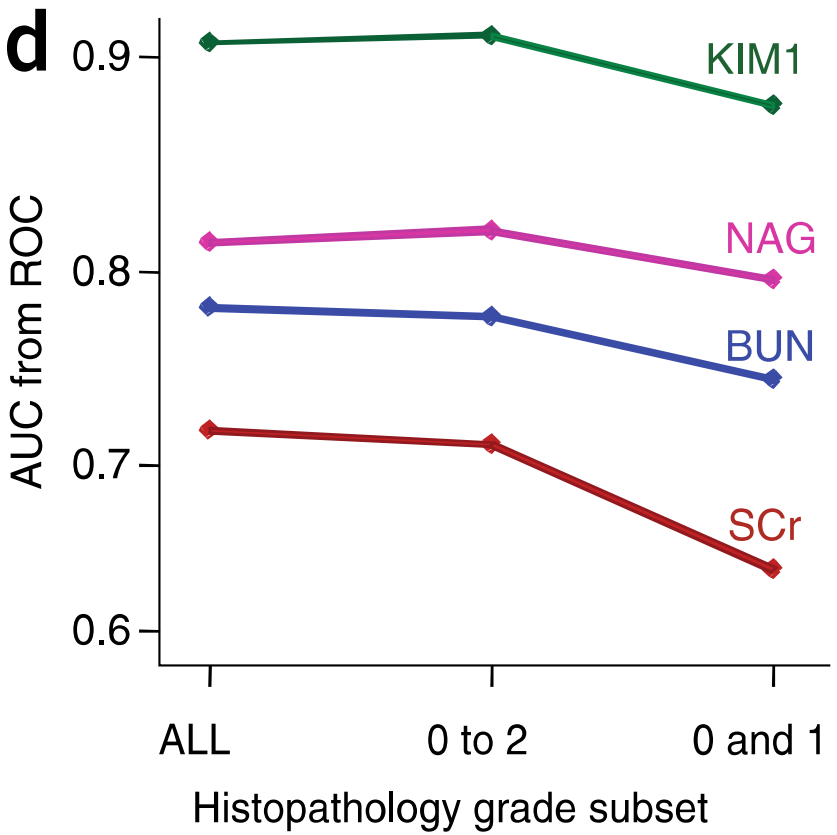
Siew, Ware, Ikizler et al. *JASN* 2009

Reference	Setting	Source	Total N	AKI N	AUC-ROC
Wheeler *Crit Care Med 2008*	**Pediatric ICU with SIRS/Septic Shock**	**Serum**	**143**	**22**	**0.68**
Siew *JASN 2009*	**Mixed Adult ICU**	**Urine**	**451**	**86**	**0.64-0.77**
Cruz *Intens Care Med 2010*	**Med-Surg ICU**	**Plasma**	**301**	**133**	**0.67-0.78**
De Geus *AJRCCM 2010*	**Adult ICU**	**Both**	**632**	**171**	**P 0.75 U 0.79**
Zappitelli *Crit Care 2007*	**Pediatric ICU**	**Urine**	**140**	**21**	**0.78-0.79**
Martensson *Intens Care Med 2010*	**Adult General ICU**	**Both**	**45**	**18**	**P 0.85 U 0.86**
Constantin *J Crit Care 2010*	**Adult ICUs**	**Plasma**	**88**	**36**	**0.92**
Makris *Clin Chem Lab Med 2010*	**Trauma ICU**	**Urine**	**31**	**11**	**0.98**

Potential Challenges to Diagnostic Biomarker Performance in the ICU

- ? Kinetics of biomarker expression
- ? Effects of systemic expression
- ? Which baseline
- ? Creatinine as a reference standard

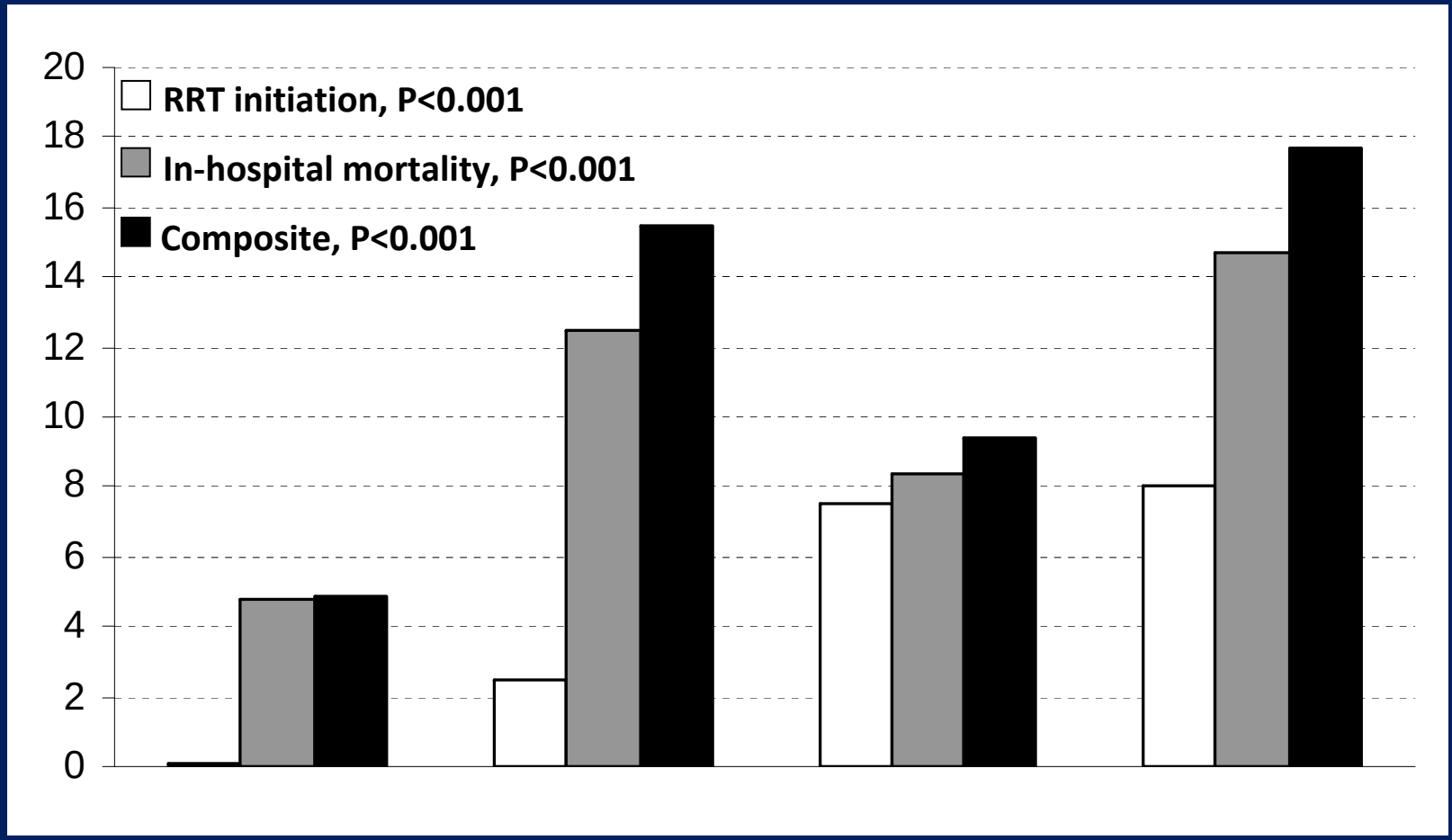
KIM-1 and NAG May Correlate Better with Histologic Injury than Creatinine



Vaidya *Nat Biotech* 28(5), 2010

	Biomarker (+)	Biomarker (-)
Serum Creatinine (+)	Verify correlation between higher biomarker levels and increased risk for AKI and related outcomes	?"False Positive" volume depletion meds rhabdo increased production absence of tubular dysfunction lower risk for outcomes
Serum Creatinine (-)	?"False Negative" Increase risk for future AKI, CKD, mortality. Other Evidence of tubular dysfunction present?	Verify correlation between lower biomarker levels and decreased risk for AKI and related outcomes

Siew, Ware, Ikizler *JASN 22(5): 810-20, 2011*



Haase, et al. (*JACC 2011*)

Steps to Avoid Becoming "Lost in Translation"

- Improved understanding of:
  - Kinetics/pattern of expression in different settings
  - Tissue origin (e.g. exosomes, histones)
- Extension beyond creatinine
- Leveraging of larger cohorts to sufficiently examine clinical endpoints, determine incremental value, and provide opportunities for cross-validation.

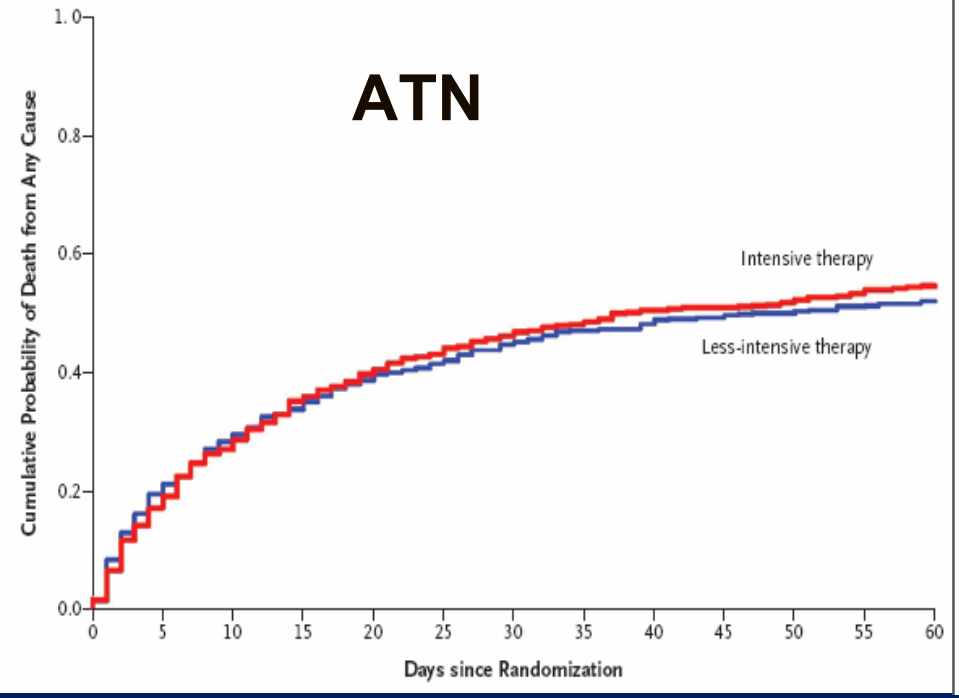
Prevention and Treatment of AKI

Prevention/Treatment of AKI

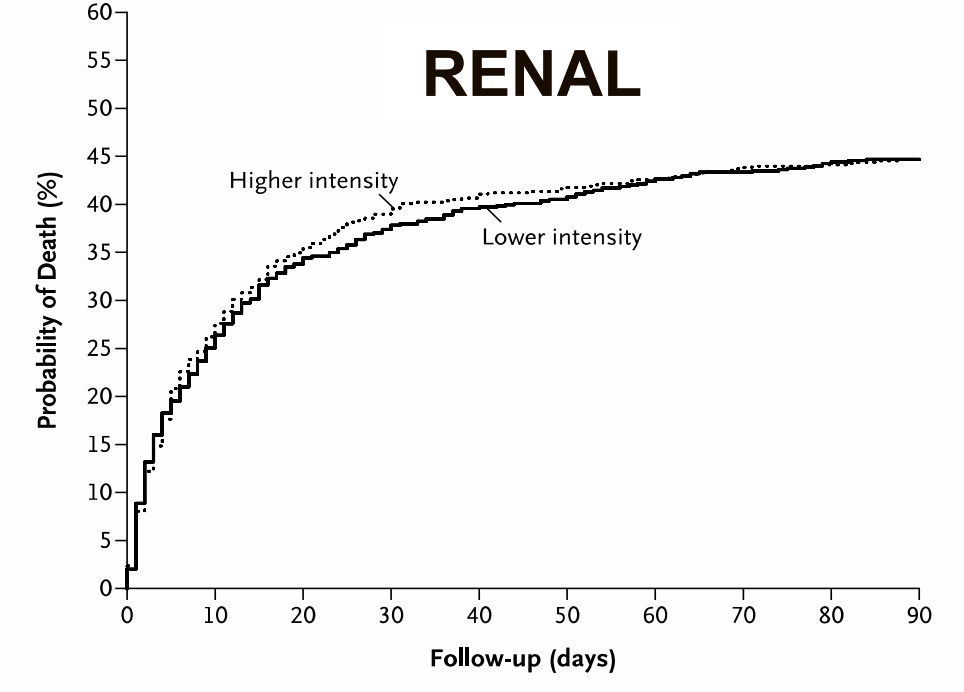
- Renal-dose dopamine
- Fenoldopam
- Diuretics
- Atrial Natriuretic Peptide
- Endothelin receptor antagonists
- Growth Factors

FAILED

Therapeutic Ceiling in Conventional RRT?



NEJM 2008;10.1056



NEJM 361:17 2009

CHAPTER 3.1: HEMODYNAMIC MONITORING AND SUPPORT FOR PREVENTION & MANAGEMENT OF AKI

- **3.1.1: In the absence of hemorrhagic shock, we suggest using isotonic crystalloids rather than colloids (albumin or starches) as initial management for expansion of intravascular volume in patients at risk for AKI or with AKI. (*2B*)**

CHAPTER 3.4: THE USE OF DIURETICS IN AKI

- **3.4.1: We recommend not using diuretics to prevent AKI. (*1B*)**

- **3.4.2: We suggest not using diuretics to treat AKI, except in the management of volume overload. (*2C*)**

Contrast-Induced AKI

CHAPTER 4.3: NON-PHARMACOLOGICAL PREVENTION STRATEGIES OF CI-AKI

- **4.3.1: Use the lowest possible dose of contrast medium in patients at risk for CI-AKI. *(Not Graded)***

- **4.3.2: We recommend using either iso-osmolar or low-osmolar iodine contrast media, rather than high osmolar iodine contrast media in patients at increased risk of CI-AKI. *(1B)***

CHAPTER 4.4: PHARMACOLOGICAL PREVENTION STRATEGIES OF CI-AKI

- **4.4.1: We recommend intravenous volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no intravenous volume expansion, in patients at increased risk for CI-AKI. (*1A*)**

- **4.4.2: We recommend not using oral fluids alone in patients at increased risk of CI-AKI. (*1C*)**

CHAPTER 4.4: PHARMACOLOGICAL PREVENTION STRATEGIES OF CI-AKI

- **4.4.3: We suggest using oral N-acetylcysteine (NAC), together with IV isotonic crystalloids, in patients at increased risk of CI-AKI. (*2D*)**

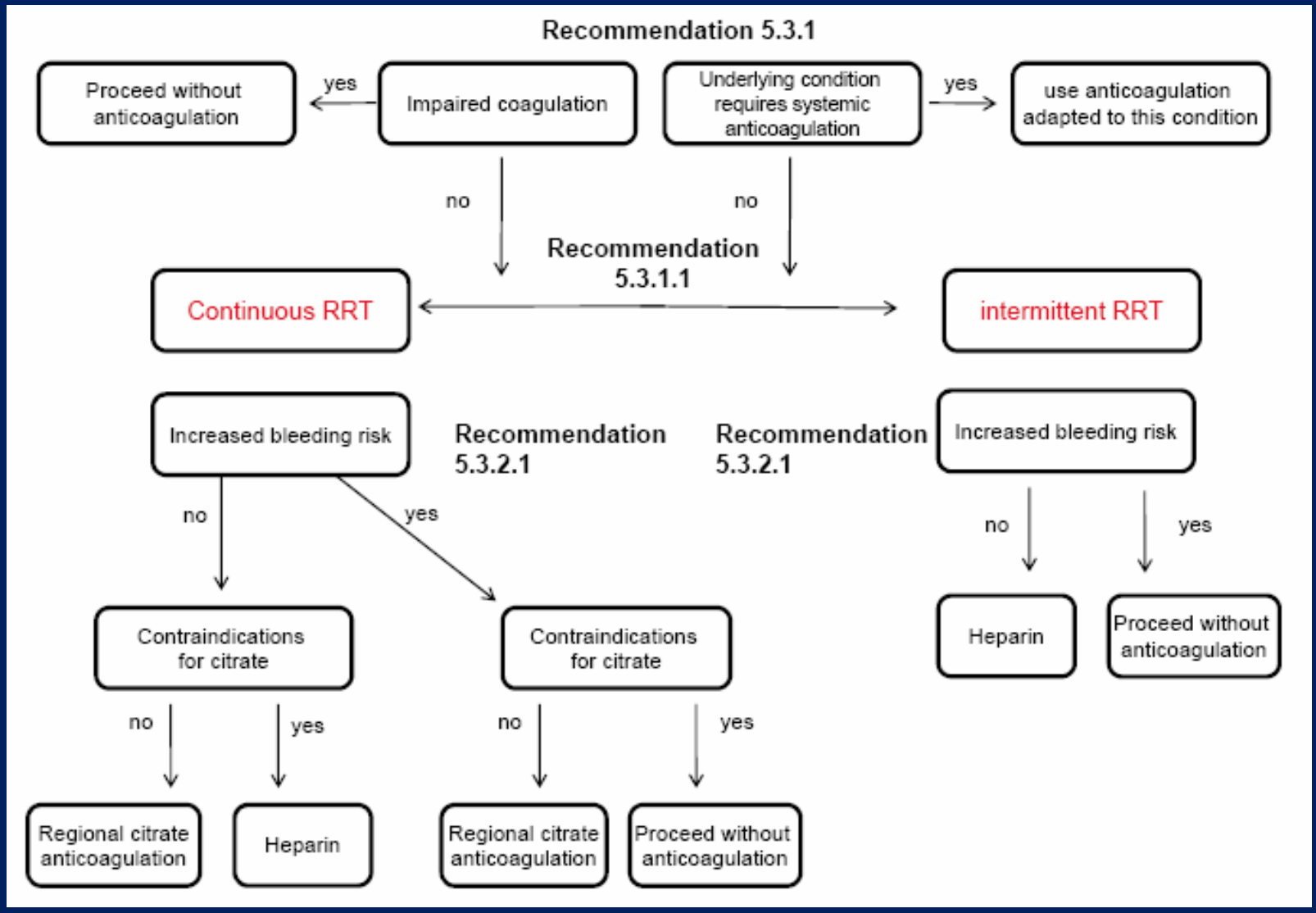
- **4.4.4: We suggest not using theophylline to prevent CI-AKI. (*2C*)**

- **4.4.5: We recommend not using fenoldopam to prevent CI-AKI. (*1B*)**

CHAPTER 4.5: EFFECTS OF HEMODIALYSIS OR HEMOFILTRATION

- **4.5.1: We suggest not using prophylactic hemodialysis or hemofiltration for contrast-media removal in patients at increased risk for CI-AKI. (*2C*)**

Dialysis Interventions for Treatment of AKI


Recommendation 5.3.1
Proceed without anticoagulation
yes
Impaired coagulation
Underlying condition requires systemic anticoagulation
yes
use anticoagulation adapted to this condition
no
no
Recommendation 5.3.1.1
Continuous RRT
intermittent RRT
Increased bleeding risk
Recommendation 5.3.2.1
Recommendation 5.3.2.1
Increased bleeding risk
no
yes
no
yes
Contraindications for citrate
Contraindications for citrate
Heparin
Proceed without anticoagulation
no
yes
no
yes
Regional citrate anticoagulation
Heparin
Regional citrate anticoagulation
Proceed without anticoagulation

CHAPTER 5.6:
MODALITY OF RRT FOR PATIENTS WITH AKI

- **5.6.1: Use continuous and intermittent RRT as complementary therapies in AKI patients. (*Not Graded*)**
- **5.6.2: We suggest using CRRT rather than standard intermittent RRT, for hemodynamically unstable patients. (*2B*)**
- **5.6.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (*2B*)**

CHAPTER 5.8:
DOSE OF RRT IN AKI

- **5.8.3: We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (*1A*)**

- **5.8.4: We recommend delivering an effluent volume of 20-25 ml/kg/h for CRRT in AKI *(1A).* This will usually require a higher prescription of effluent volume. (*Not Graded*)**

Prevention and Treatment of AKI

- No proven therapeutic intervention for prevention or treatment
- No proven benefit of over-dialysis
- No proven benefit of CRRT over IHD
- Apparent need for further research