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AKI

Prevalence of AKI and Importance of Early Detection
Pathogenesis of AKI and Markers of Cellular Injury

AACC Congress
Philadelphia
May 2015

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Disclosure

- I received research funds from
  - Astute Medical Inc.

- I have no other COI regarding this activity

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Outlines

- AKI
  - Prevalence
  - Major risk factors
  - Impact on patients
    - Mortality
    - CKD
    - ESRD
  - Pathogenesis
  - Markers of Cellular Injury
- Challenges in assessing AKI risk
  - Role of biomarkers

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Definition

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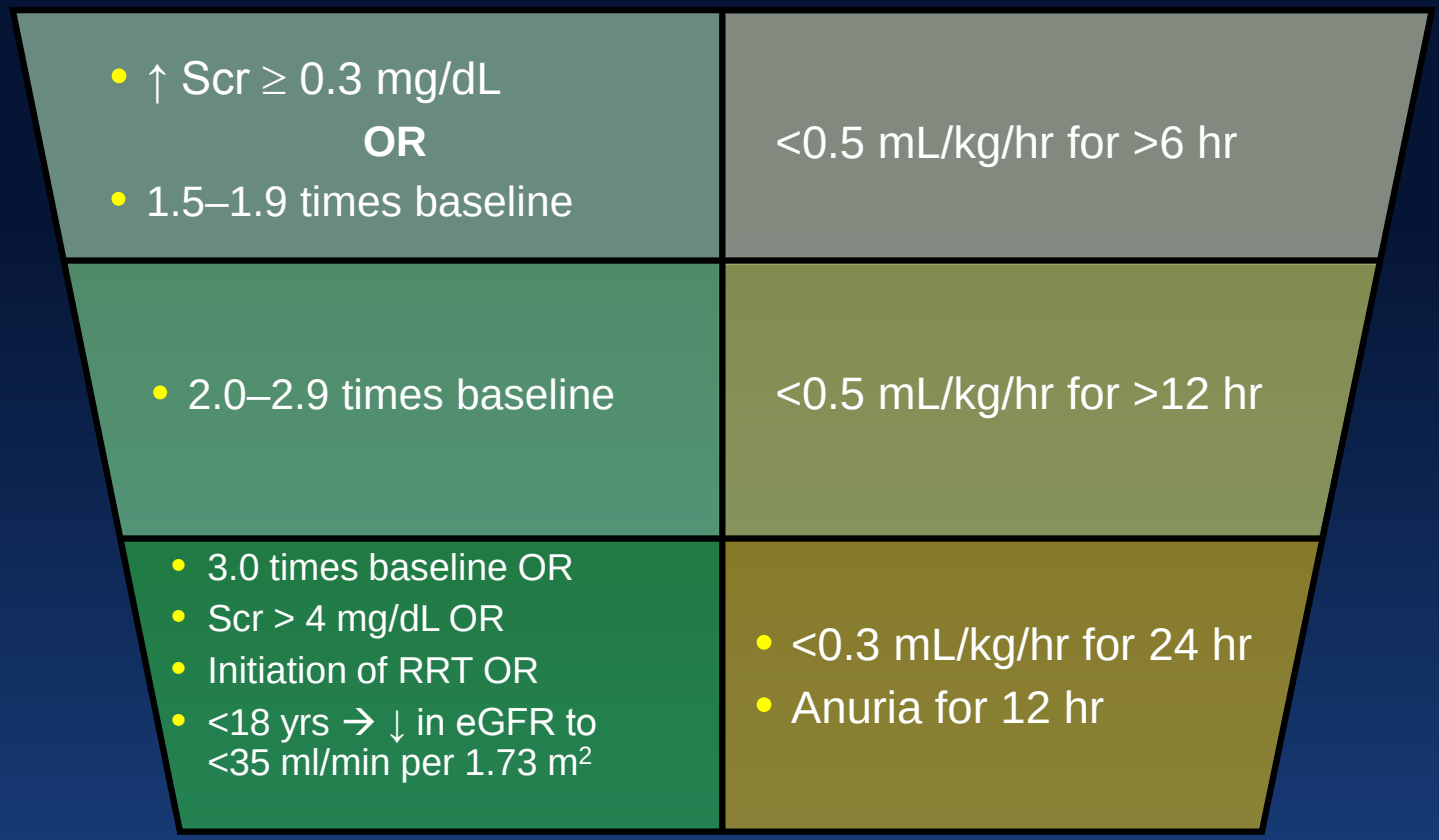
KDIGO Definition for AKI



Kidney International Supplements (2012) 2, 19–36

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Epidemiology

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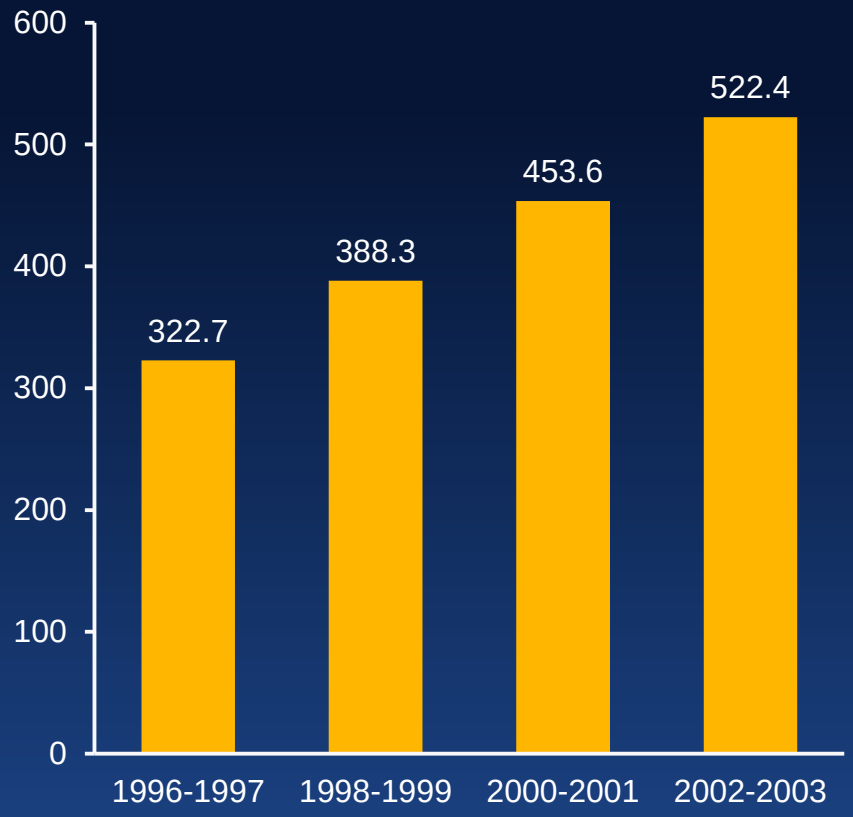
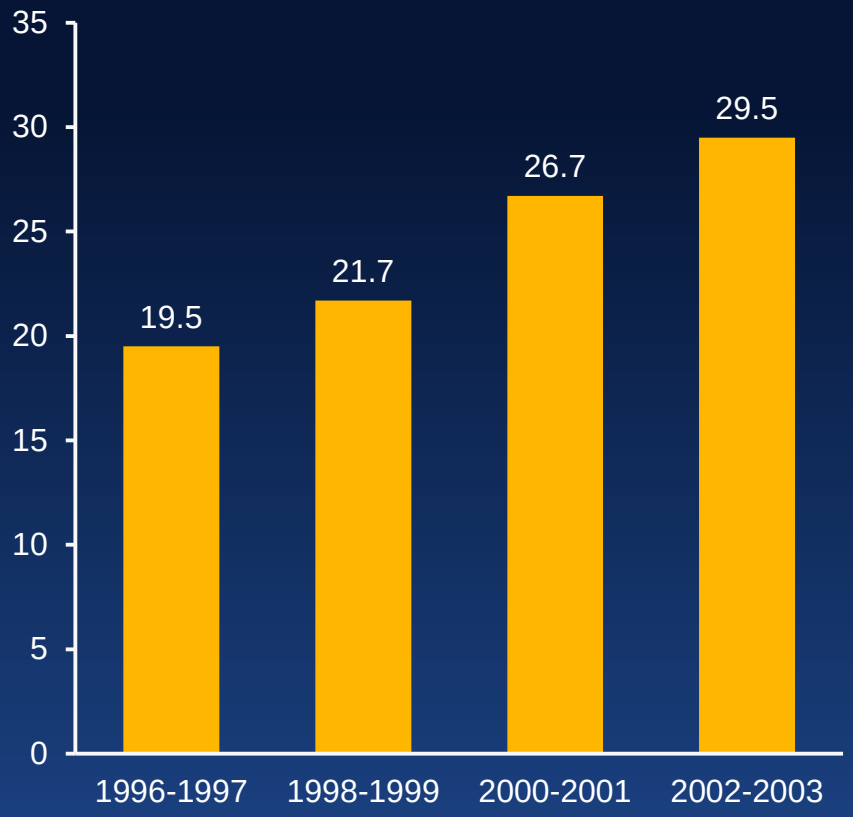
Incidence of AKI over time

Community-based incidence rates
(per 100,000 person-years)
of non-dialysis requiring AKI by calendar year



Community-based incidence rates
(per 100,000 person-years)
of dialysis-requiring AKI by calendar year



Hsu et al. Kidney International (2007) 72, 208–212

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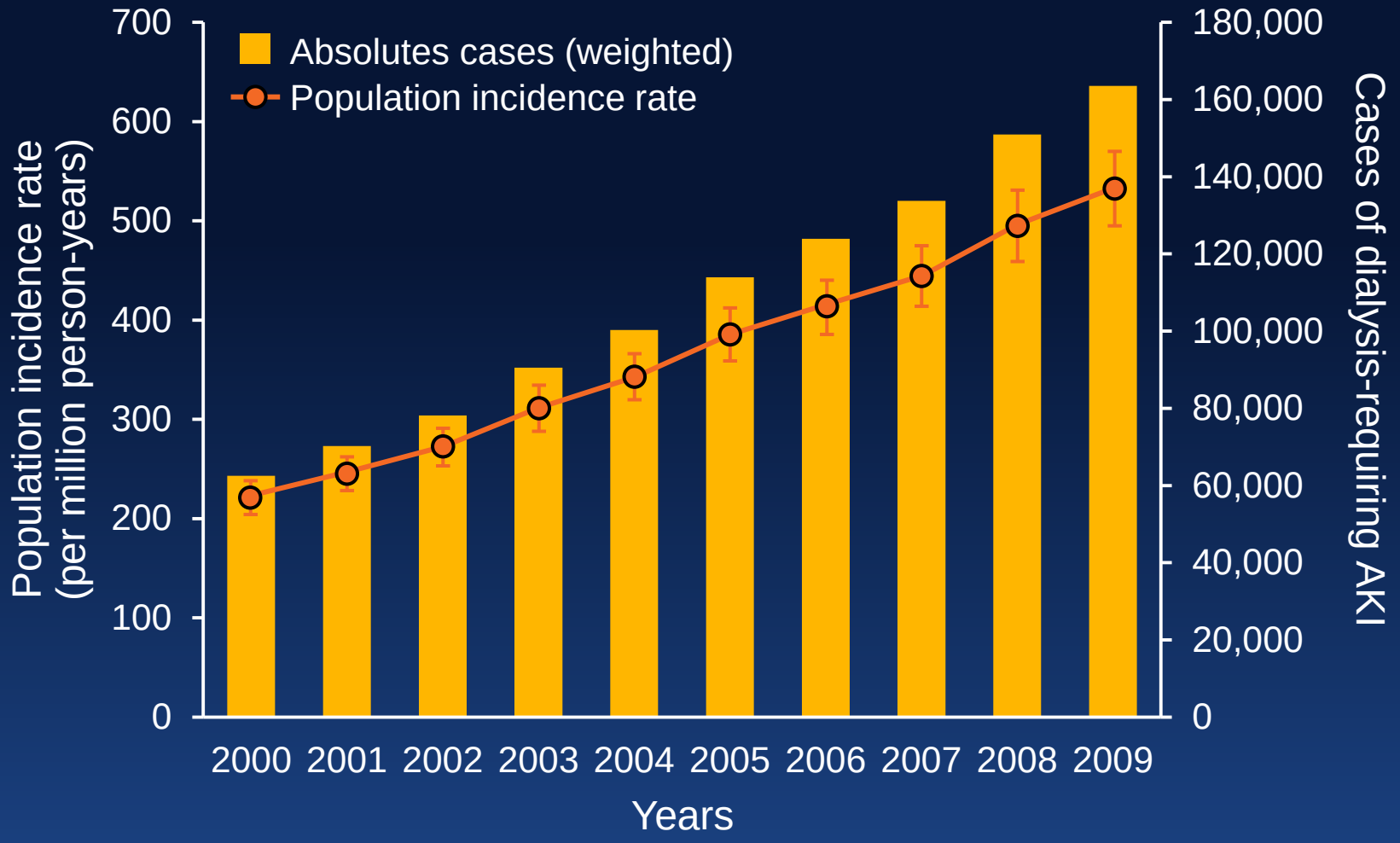
AKI incidence in last decade



Hsu et al; J Am Soc Nephrol 24: 37–42, 2013

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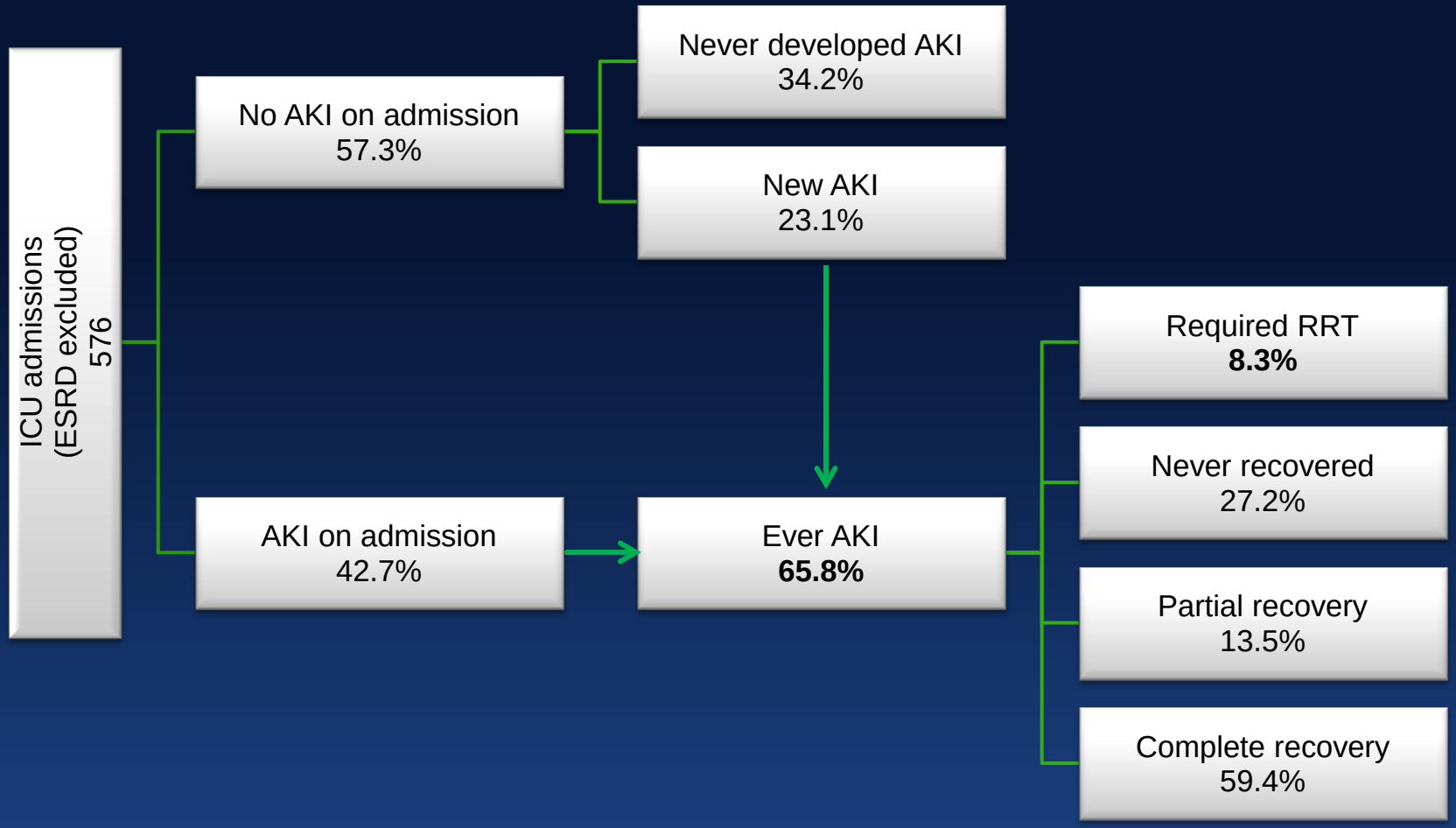
RRT epidemiology (NEFROINT data)



Piccinni et al. Minerva anestheiology 2011; 77:1-2

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Outcome

Survival after AKI

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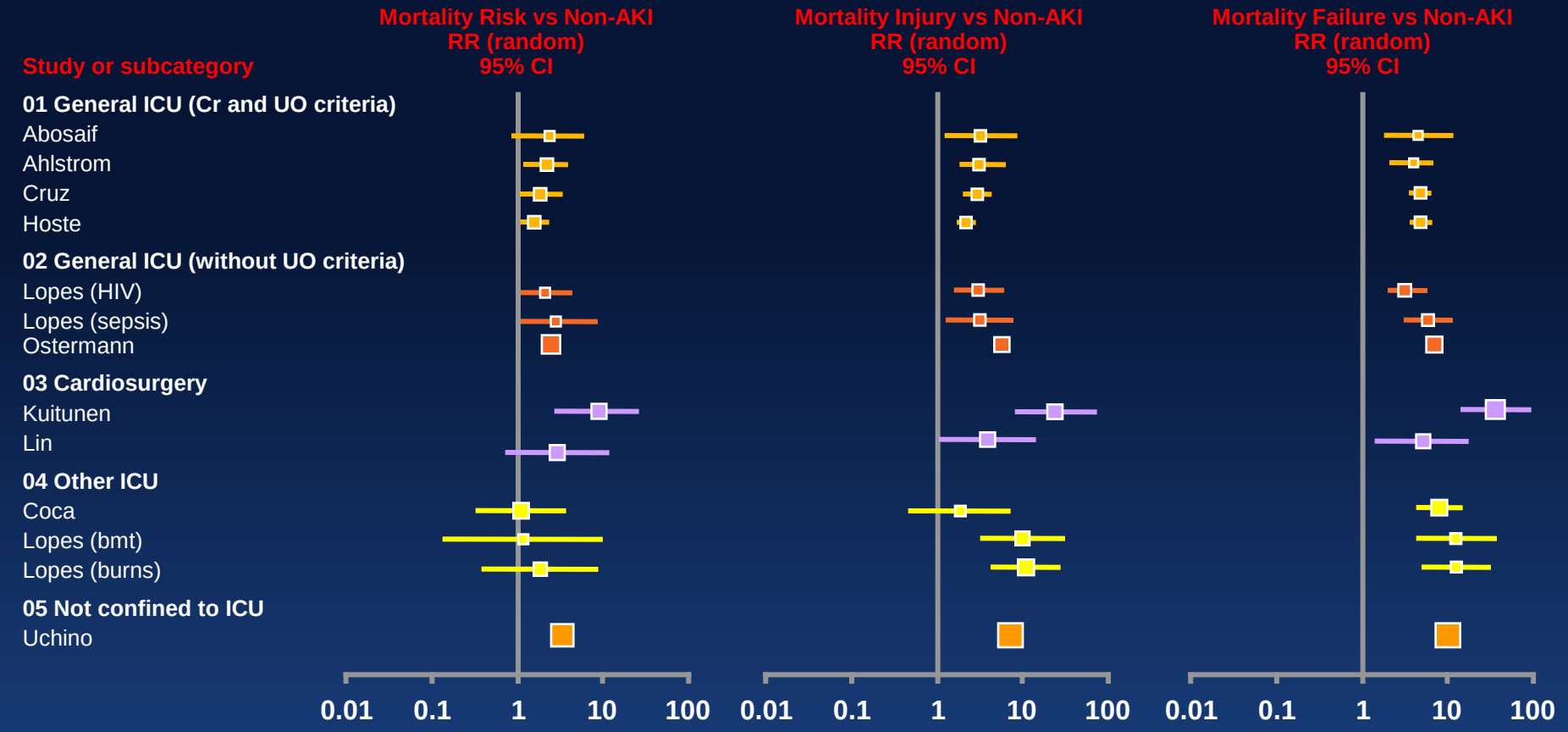
AKI and Mortality



Ricci Z: Kidney Int 73:538, 2008

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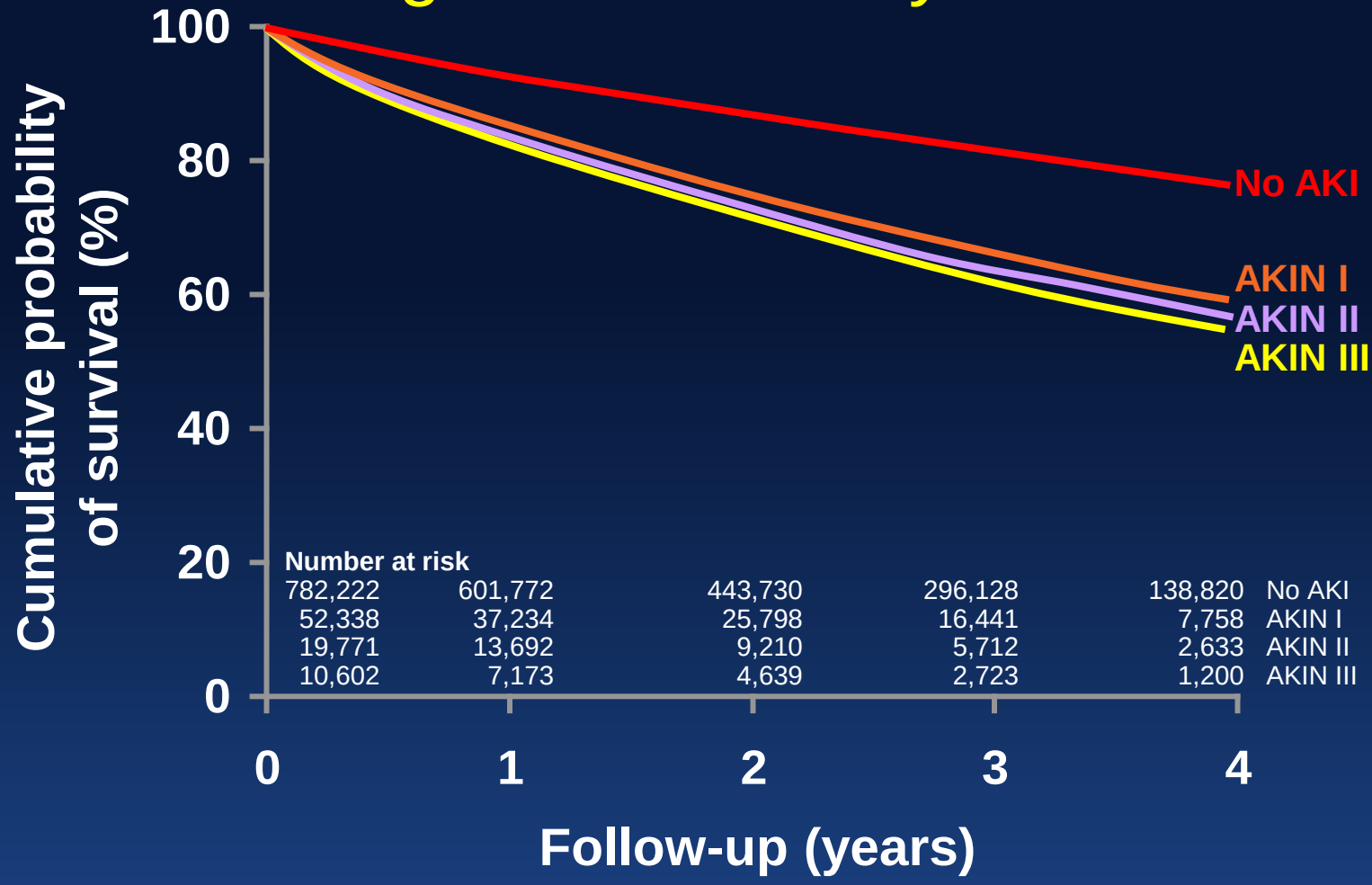
AKI and Long-Term Mortality



Lafrance et al: JASN 21(2):345, 2010

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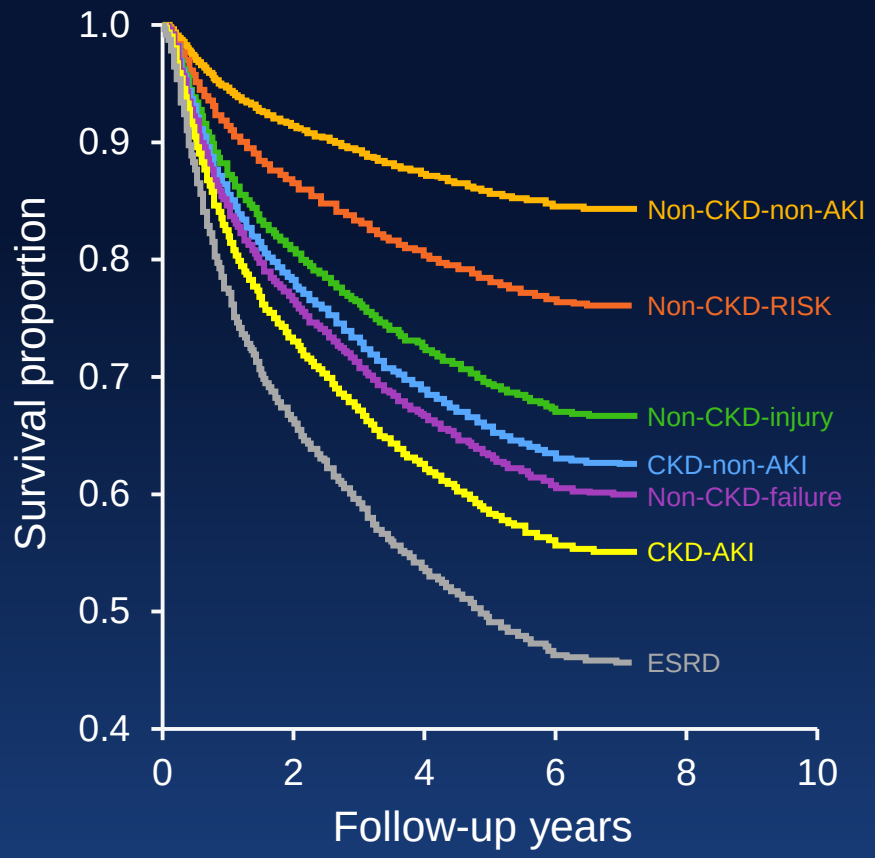
Long term survival

Stratified by CKD and AKI



Wu et al; Kidney International (2011) 80, 1222–1230

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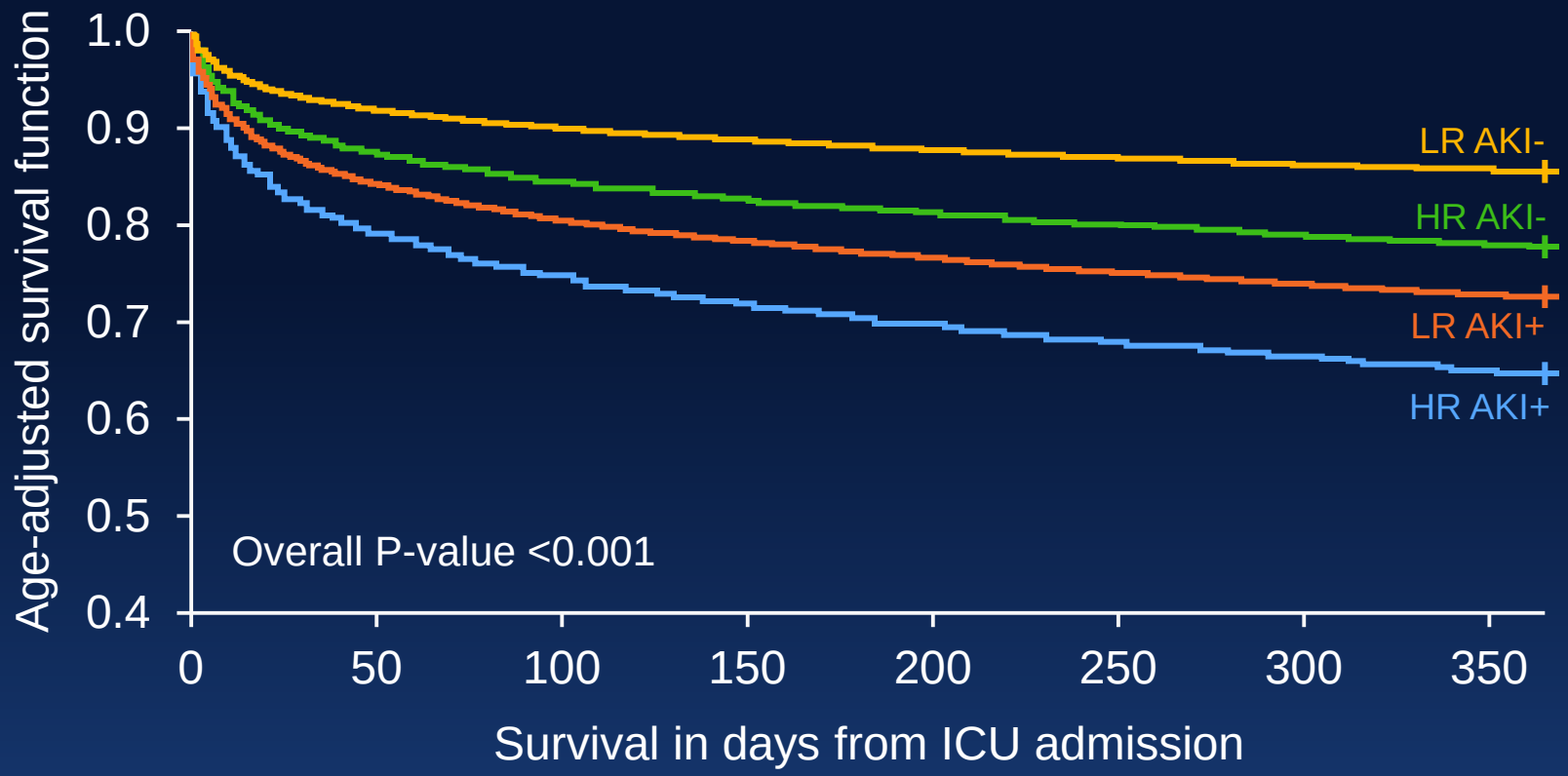
AKI in low and high risk patients



No. at risk

13,374	12,526	12,159	11,949	11,770	11,580	11,434	11,261
4,637	3,748	3,516	3,390	3,285	3,201	3,133	3,065
10,674	9,213	8,945	8,767	8,628	8,515	8,417	8,300
11,451	8,452	7,922	7,629	7,403	7,252	7,119	6,988

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Sileanu et al, Clin J Am Soc Nephrol; 2014

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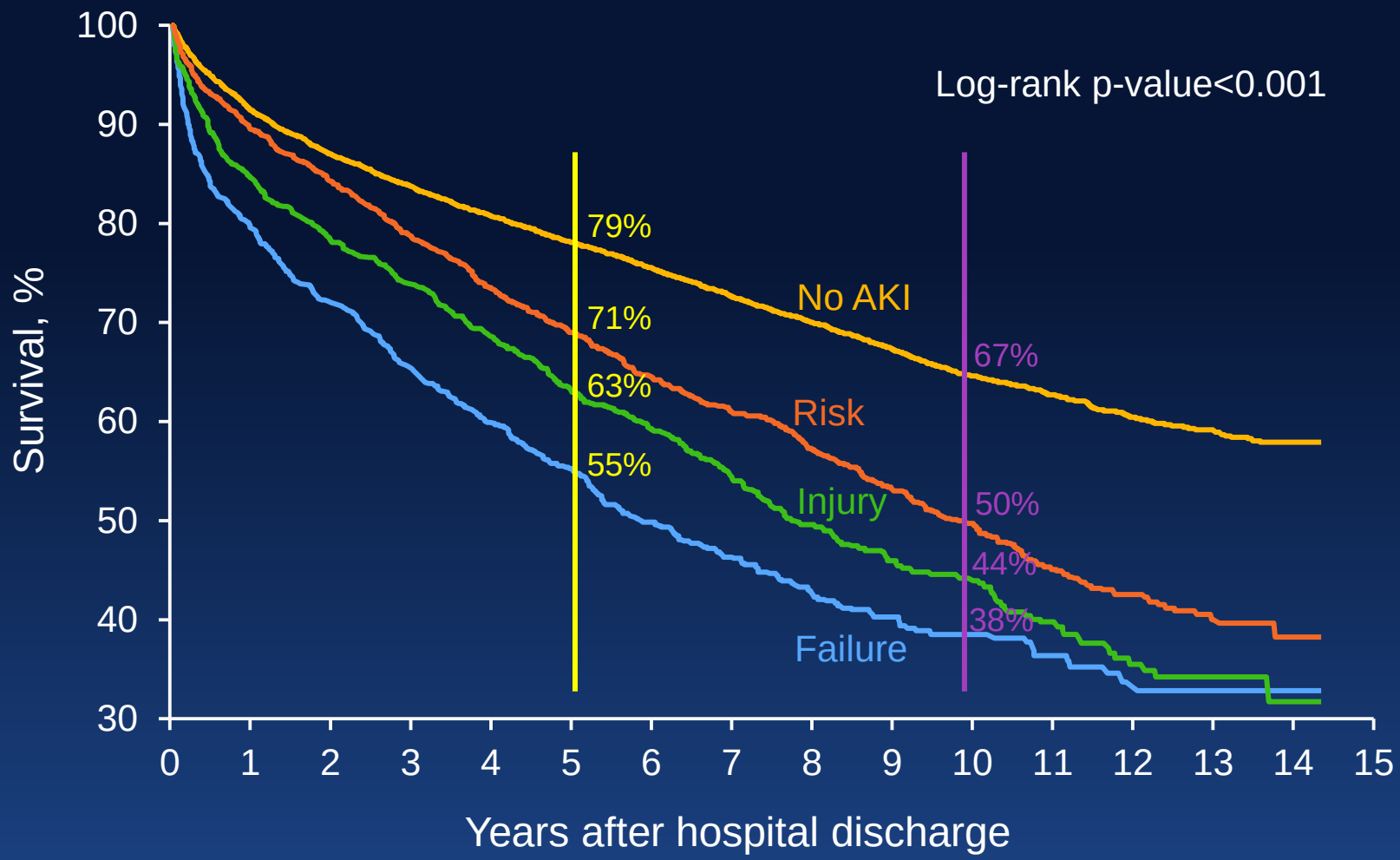
Survival After AKI in Critically Ill Surgical Patients



Bihorac and Segal: Ann Surg, 2009; Hobson and Bihorac: Circulation, 2009

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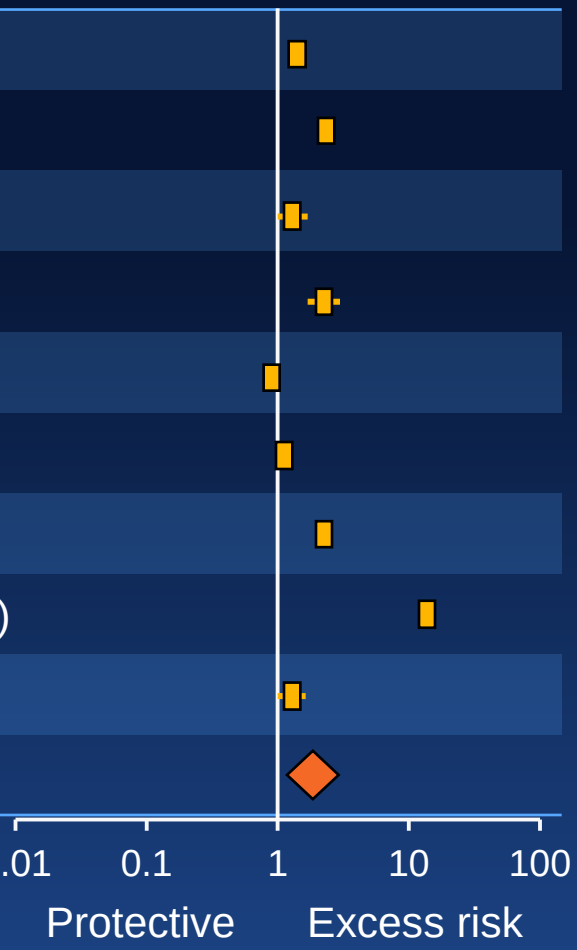
Mortality after AKI

Study or subgroup	Weight, %	HR IV, random, 95% CI
Newsome et al (14)	11.2	1.39 (13.5-1.43)
Ishani et al (20)	11.2	2.38 (2.31-2.46)
Hsu et al (10)	10.9	130 (1.03-1.64)
Lo et al (11)	10.8	2.30 (1.76-2.99)
Walk et al (17)	11.2	0.95 (0.89-1.02)
Choi et al (12)	11.2	1.20 (1.13-1.28)
Lafrance et al (18)	11.1	2.32 (2.04-2.63)
James et al (16)	11.2	12.99 (12.08-13.96)
Ishani et al (21)	11.1	1.38 (1.20-1.59)
Total (95% CI)	100.0	1.98 (1.26-3.11)



Heterogeneity: τ^2=0.47; χ^2=4,001.87, d.f.=8 (P<0.00001); I^2=100%. Test for overall effect: Z=2.96) P<0.003)

Coca et al. Kidney International (2012) 81, 442–448

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Outcome

CKD after AKI

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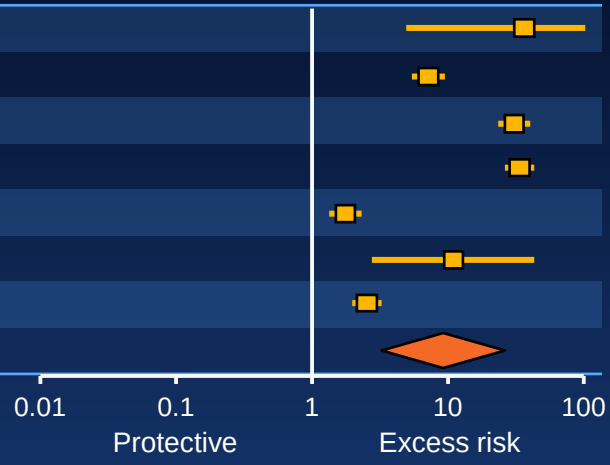
CKD after AKI

Study or subgroup	Weight (%)	HR IV, random, 95% CI
Weiss et al (13)	10.0	32.79 (4.30-249.77)
Amdur et al (22)	15.5	6.64 (5.05-8.74)
Lo et al (11)	15.5	28.08 (21.01-37.53)
James et al (16)	15.6	29.99 (24.32-36.99)
James et al (15, 23)	15.5	1.60 (1.20-2.14)
Ando et al (19)	12.4	9.91 (2.48-39.63)
Ishani et al (21)	15.6	2.33 (1.83-2.96)
Total (95% CI)	100.0	8.82 (3.05-25.48)

Heterogeneity: τ^2=1.87; χ^2=446.89, d.f.=6 (P<0.00001); I^2=99%. Test for overall effect: Z=4.02) P<0.0001)



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Coca et al. Kidney International (2012) 81, 442–448

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CKD risk factors

Variable	Definition
AKI severity	Repetitive episodes of AKI
	Degree of serum creatinine rise
	Need for RRT
Demographic	Increasing age
Causes of AKI	Mixed (multiple causes) vs. pure ATN
Biomarkers	Markers of renal recovery vs. ongoing inflammation
	Albumin

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Heung et al; Curr Opin Nephrol Hypertens 2012, 21:628–634

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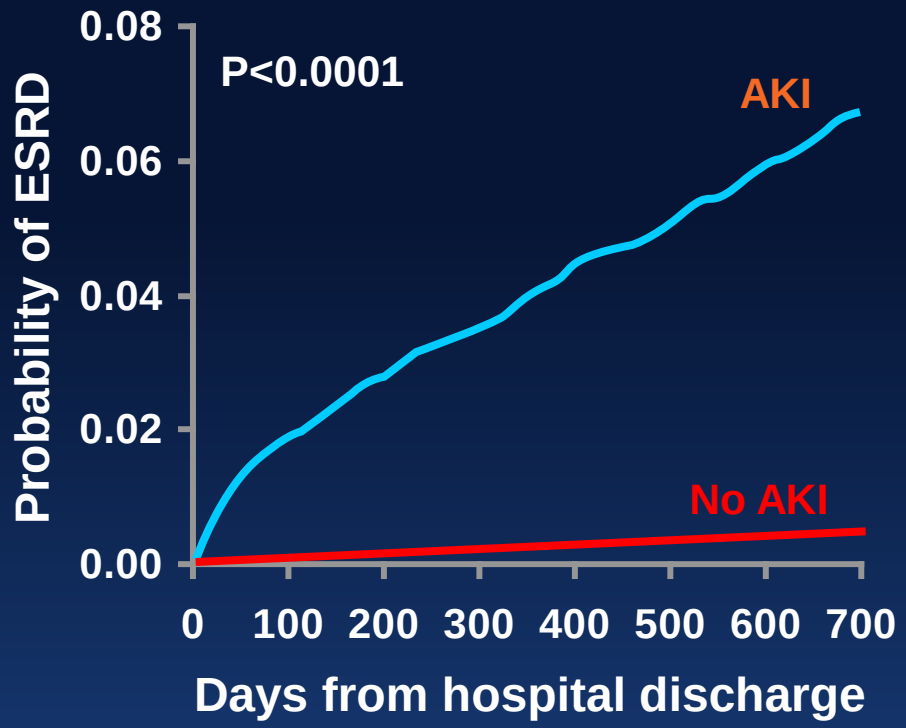
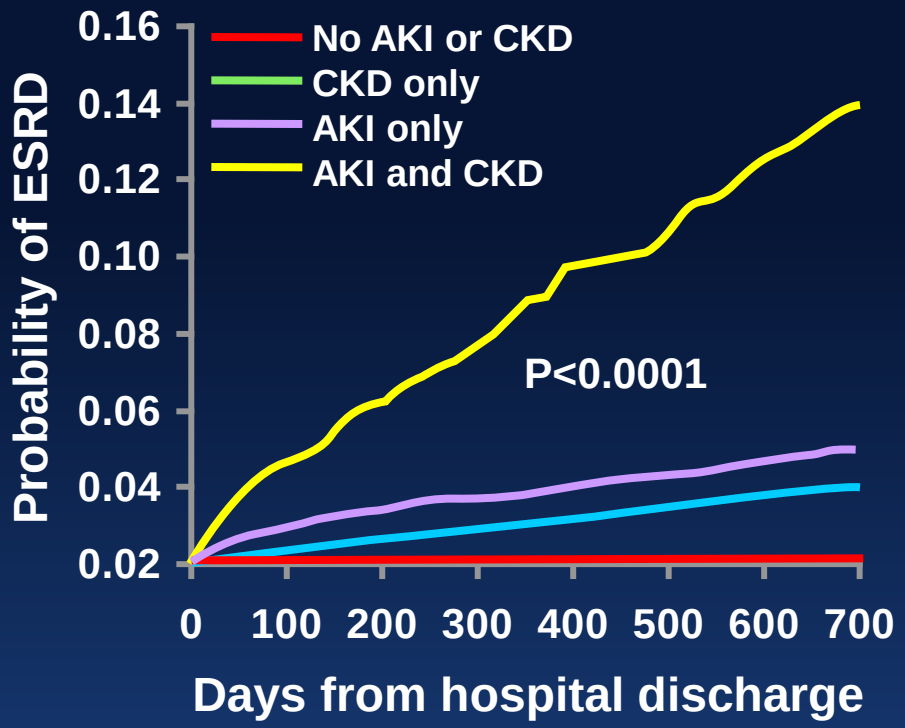
ESRD After AKI





Ishani, et al. *J Am Soc Nephrol* 20: 223–228, 2009

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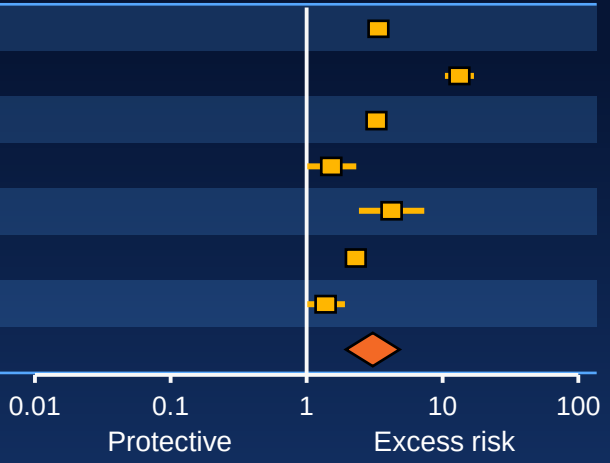
ESRD after AKI

Study or subgroup	Weight (%)	HR IV, random, 95% CI
Newsome et al (14)	15.0	3.26 (2.87-3.70)
Ishani et al (20)	14.8	12.99 (10.57-15.96)
Wald et al (17)	14.9	3.22 (2.70-3.85)
Hsu et al (10)	13.5	1.47 (0.95-2.28)
James et al (15, 23)	12.5	4.15 (2.32-7.41)
Lafrance et al (18)	15.0	2.33 (2.08-2.61)
Choi et al (12)	14.4	1.37 (1.02-1.84)
Total (95% CI)	100.0	3.10 (1.91-5.03)

Heterogeneity: τ^2=0.40; χ^2=252.85, d.f.=6 (P<0.00001); I^2=98%. Test for overall effect: *Z*=4.58) P<0.00001)



Coca et al. Kidney International (2012) 81, 442–448

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AKI risk factors

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- Age ≥65 years
- History of
  - CHF
  - Liver disease
  - CKD (eGFR <60)
  - AKI
  - DM
  - HTN
- Neurological impairment or disability
- Sepsis
- Hypovolemia
- Hematological malignancy
- Nephrotoxins
  - Contrast agents
  - NSAIDs
  - ACE inhibitors/ARBs
  - Aminoglycosides
  - Diuretics

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SA-AKI Risk Factors

- Sources of sepsis
  - Blood stream infection
    - GNB
    - Fungal
  - Abdominal and GU
  - Infective endocarditis
- Delayed administration of antimicrobial

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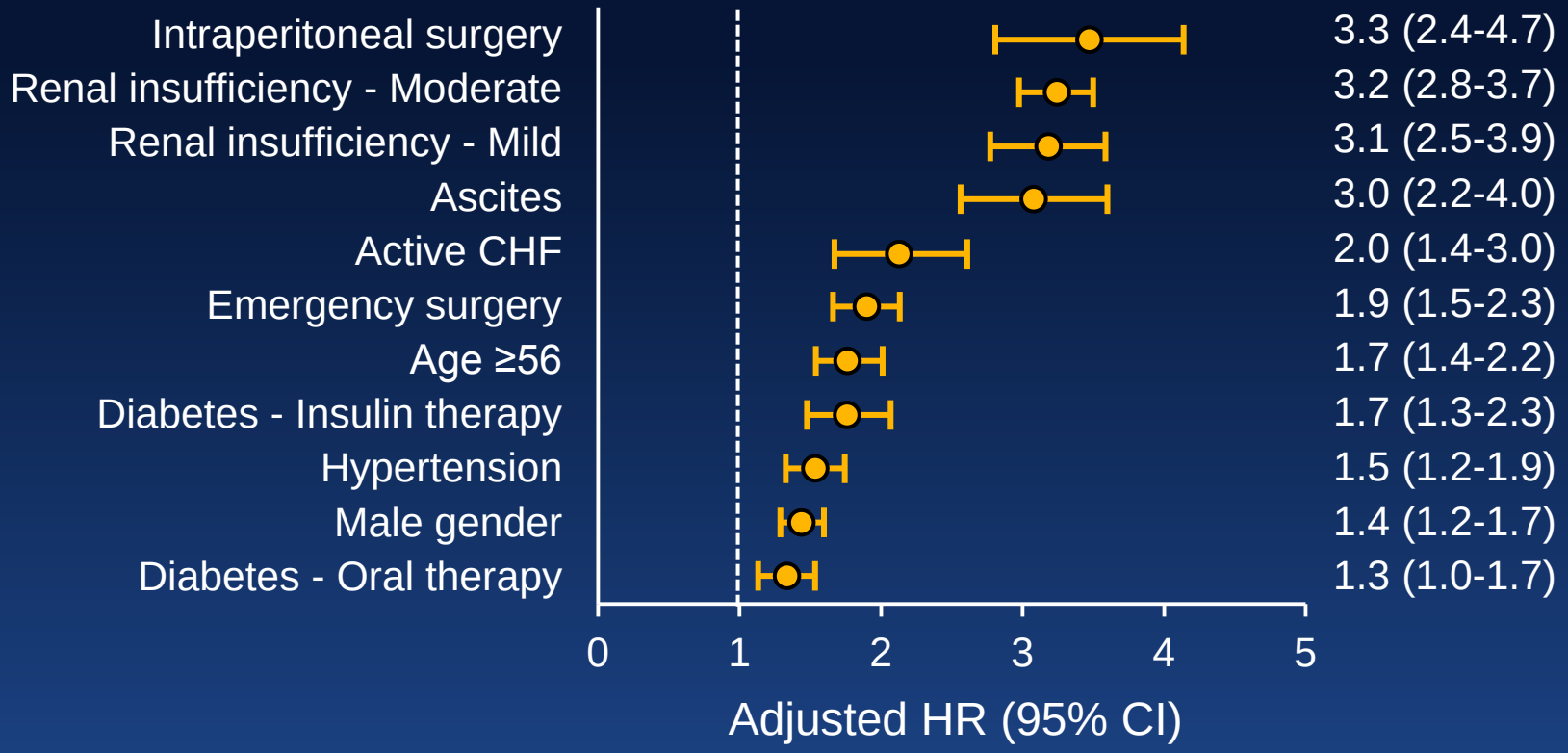
Anesthesiology 2009; 110:505–15
Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Development and Validation of an Acute Kidney Injury Risk Index for Patients Undergoing General Surgery

Results from a National Data Set

Sachin Kheterpal, M.D., M.B.A.,* Kevin K. Tremper, Ph.D., M.D.,† Michael Heung M.D.,‡ Andrew L. Rosenberg, M.D.,* Michael Englesbe, M.D.,§ Amy M. Shanks, M.S.,‖ Darrell A. Campbell, Jr., M.D.#



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Risk prediction

	Derivation Cohort, n=57,080			Validation Cohort, n=18,872		
Preoperative risk class	**Total patients, n**	**Acute kidney injury incidence, % (n)**	**HR (95% CI)**	**Total patients, n**	**Acute kidney injury incidence, % (n)**	**HR (95% CI)**
Class I (0-2 risk factors)	31,500	0.2 (66)		10,301	0.2 (25)	
Class II (3 risk factors)	12,576	0.8 (104)	4.0 (2.9-5.4)	4,218	0.8 (32)	3.1 (1.9-5.3)
Class III (4 risk factors)	7,933	1.8 (144)	8.8 (6.6-11.8)	2,625	2.0 (53)	8.5 (5.3-13.7)
Class IV (5 risk factors)	3,615	3.3 (118)	16.1 (11.9-21.8)	1,244	3.6 (45)	15.4 (9.4-25.2)
Class V (6+ risk factors)	1,456	8.9 (129)	**46.3 (34.2-62.6)**	484	9.5 (46)	46.2 (26.3-70.9)

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Diagnosis and Biomarkers

Traditional diagnostic tools

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Symptoms

- Urine flow
  - Polyuria
  - Oliguria/anuria
- Hematuria
- Dysuria
- Azotemia
  - Mental status changes
- Hypervolemia/hypertension vs. hypovolemia/hypotension
- Electrolyte and acid-base disorders
  - Kussmaul Breathing, weakness, arrhythmia
- Serositis

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Urinary Index

Laboratory test	Prerenal azotemia	ATN
Urine osmolality (mOsm/kg)	>500	<400
Urine sodium level (mEq/L)	<20	>40
Urine/plasma creatinine ratio	>40	<20
Fractional excretion of sodium (%)	<1	>2
Fractional excretion of urea (%)	<35	>35
Urinary sediment	Normal; occasional hyaline or fine granular casts	Renal tubular epithelial cells; granular and muddy brown casts

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Schrier: J Clin Invest 114(1):5, 2004

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Urinary Sediments

Sediment	Differential diagnosis
Normal or few Red blood cells White blood cells	Prerenal azotemia Arterial thrombosis or embolism Preglomerular vasculitis HUS or TTP Scleroderma crisis Postrenal azotemia
Granular casts	ATN (muddy brown) Glomerulonephritis or vasculitis Interstitial nephritis
Red blood cell casts	Glomerulonephritis or vasculitis Malignant hypertension Rarely interstitial nephritis
White blood cell casts	Acute interstitial nephritis or exudative glomerulonephritis Severe pyelonephritis Marked leukemic or lymphomatous infiltration
Eosinophiluria (>5%)	Allergic interstitial nephritis (antibiotics > NSAIDs) Atheroembolic disease
Crystalluria	Acute urate nephropathy Calcium oxalate (ethylene glycol toxicity) Acyclovir Indinavir Sulfonamides Radiocontrast agents

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Brenner and Rector: The Kidney, 8th edition

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Diagnosis and Biomarkers

Novel diagnostic tools

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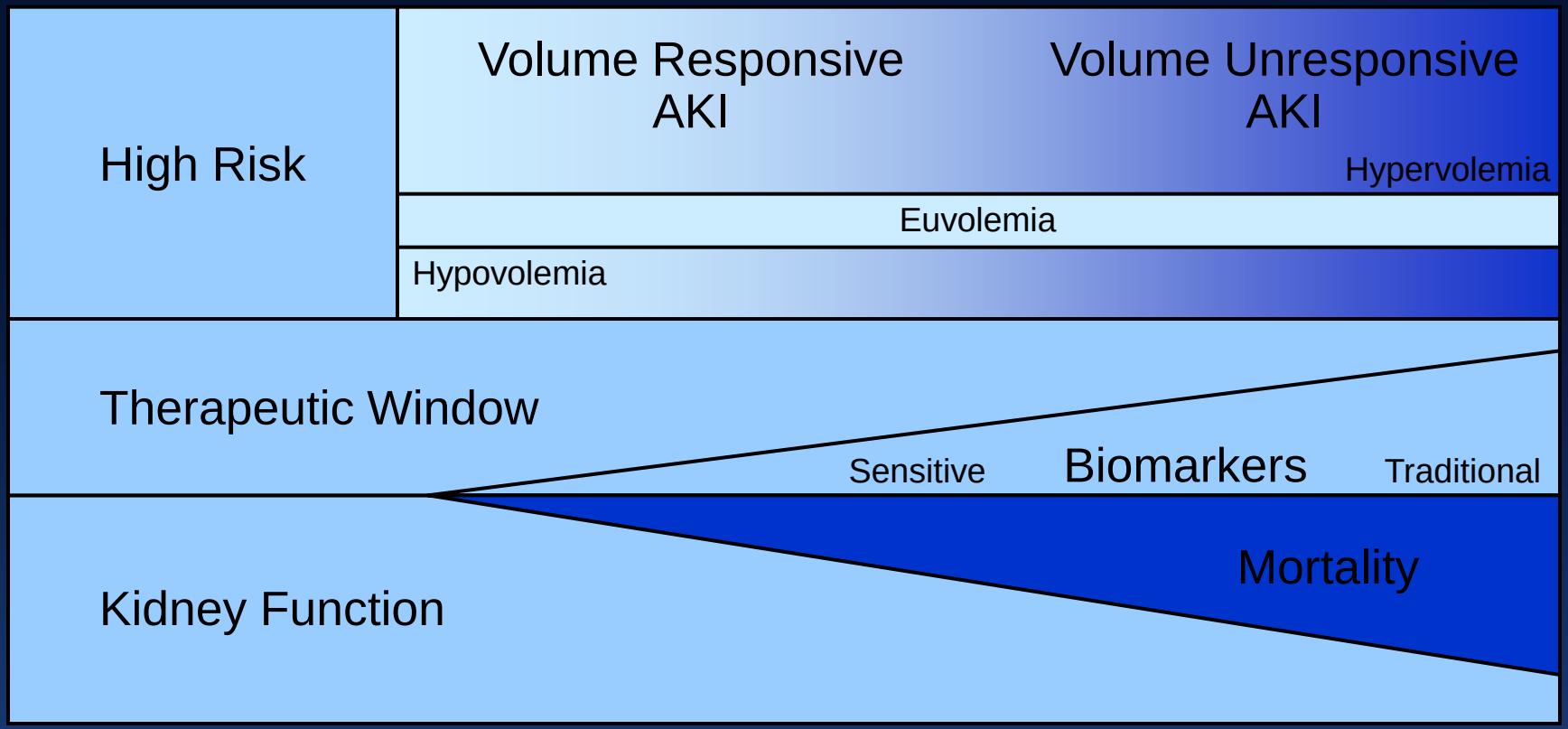
Therapeutic Window



Himmelfarb et al: Clin J Am Soc Nephrol 3:962, 2008

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Ideal biomarker

- Inexpensive
- Accurate
- Easy to measure at the point of care
- Correlate with severity of initial injury
- Sensitive to
  - Early subclinical injury
  - Recovery
  - Response to therapy

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Belcher et al. Am J Kidney Dis. 2011;57(6):930-940

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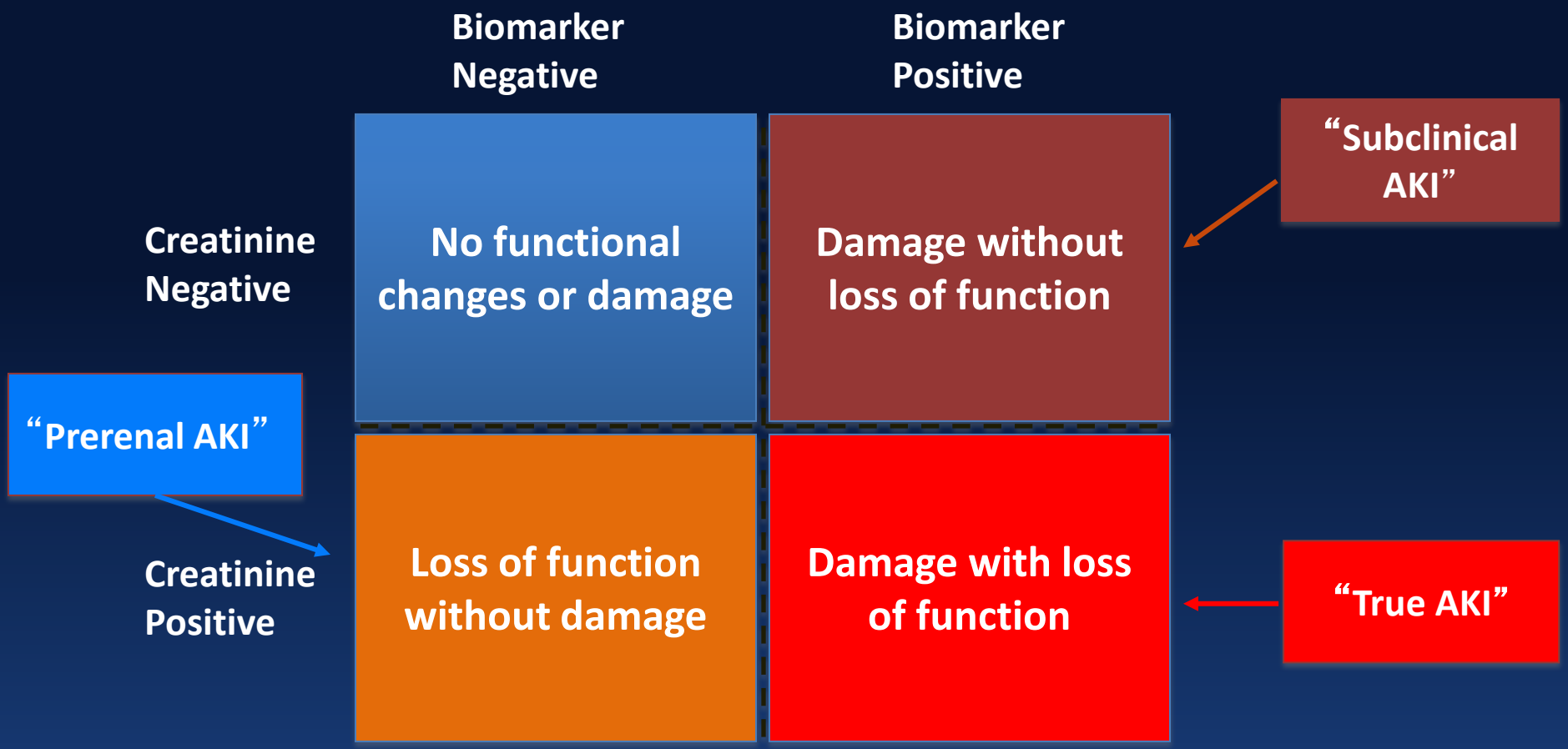
Traditional and novel biomarker integration



10th ADQI Consensus Conference. Adapted from Murray PT et al. Kidney International 2013

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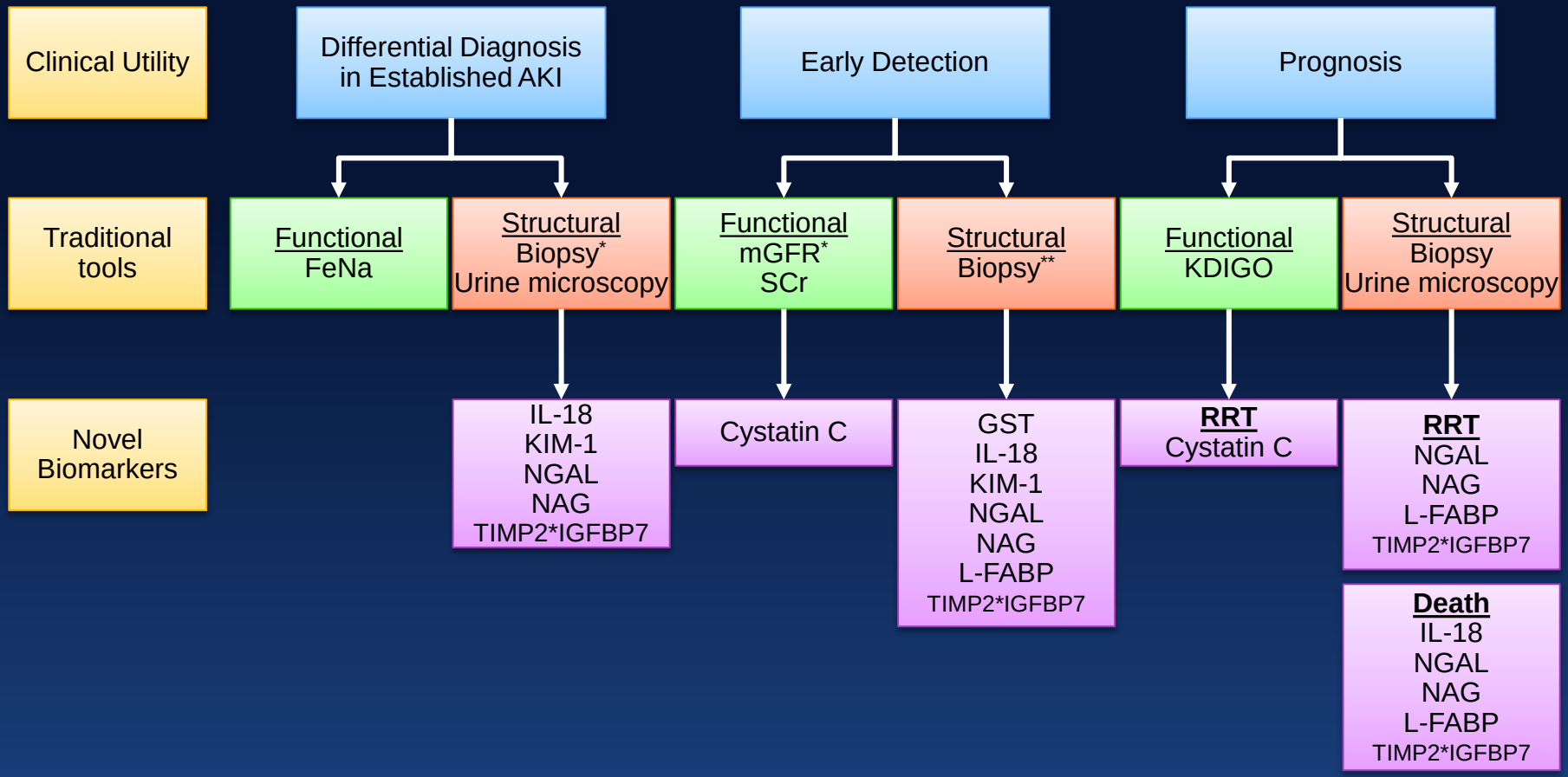
Current state



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Belcher et al. Am J Kidney Dis. 2011;57(6):930-940

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NGAL 2-3 Hours After CPB as the Predictor of AKI

Reference	Patients (no.)	Setting	AKI definition		Timing of NGAL measurement (after end of CPB)	AUC-ROC to predict AKI (plasma/urine)
			Creatinine increase	Timing of postop creatinine increase		
Mishra et al	71	Paediatric	>50%	Within 5 days	At 2 h	0.91/0.99
Dent et al	120	Paediatric	>50%	Within 5 days	At 2 h	0.96/–
Bennett et al	196	Paediatric	>50%	Within 5 days	At 2 h	–/0.95
Wagener et al	81	Adult	>50%	Within 5 days	At 3 h	–/0.74
Wagener et al	426	Adult	>50% or >0.3 mg/dL	Within 2 days	At 3 h	–/0.60
Koyner et al	72	Adult	>25% or need for RRT	Within 3 days	At ~2 h*	0.53/0.70
Haase-Fielitz et al	100	Adult	>50%	Within 5 days	At ~2 h*	0.80/–

Haase-Fielitz et al: NDT, May 27, 2009

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Urinary and Serum Biomarkers for the Diagnosis Of AKI: An In-depth Review of the Literature

Whereas biomarkers can increase our understanding of the pathophysiology of AKI, it appears that the promising results with new biomarkers for early detection and differential diagnosis of AKI in clinical practice can only be confirmed in the setting of children without co-morbidities and with a well-defined timing of renal injury. Results are far less robust when we search for validation in adult heterogenic populations, including patients with co-morbid conditions such as diabetes mellitus, vascular disease and CKD. Whereas AURoC values sometimes look impressive, applying levels of urinary or serum biomarkers for discrimination in individual patients is hampered by wide overlap between groups, which might result in many false positives. Biomarkers reflect a general degree of severity of disease, rather than being specific for kidney injury.

Vanmassenhove et al. Nephrol Dial Transplant (2012) 0: 1–20

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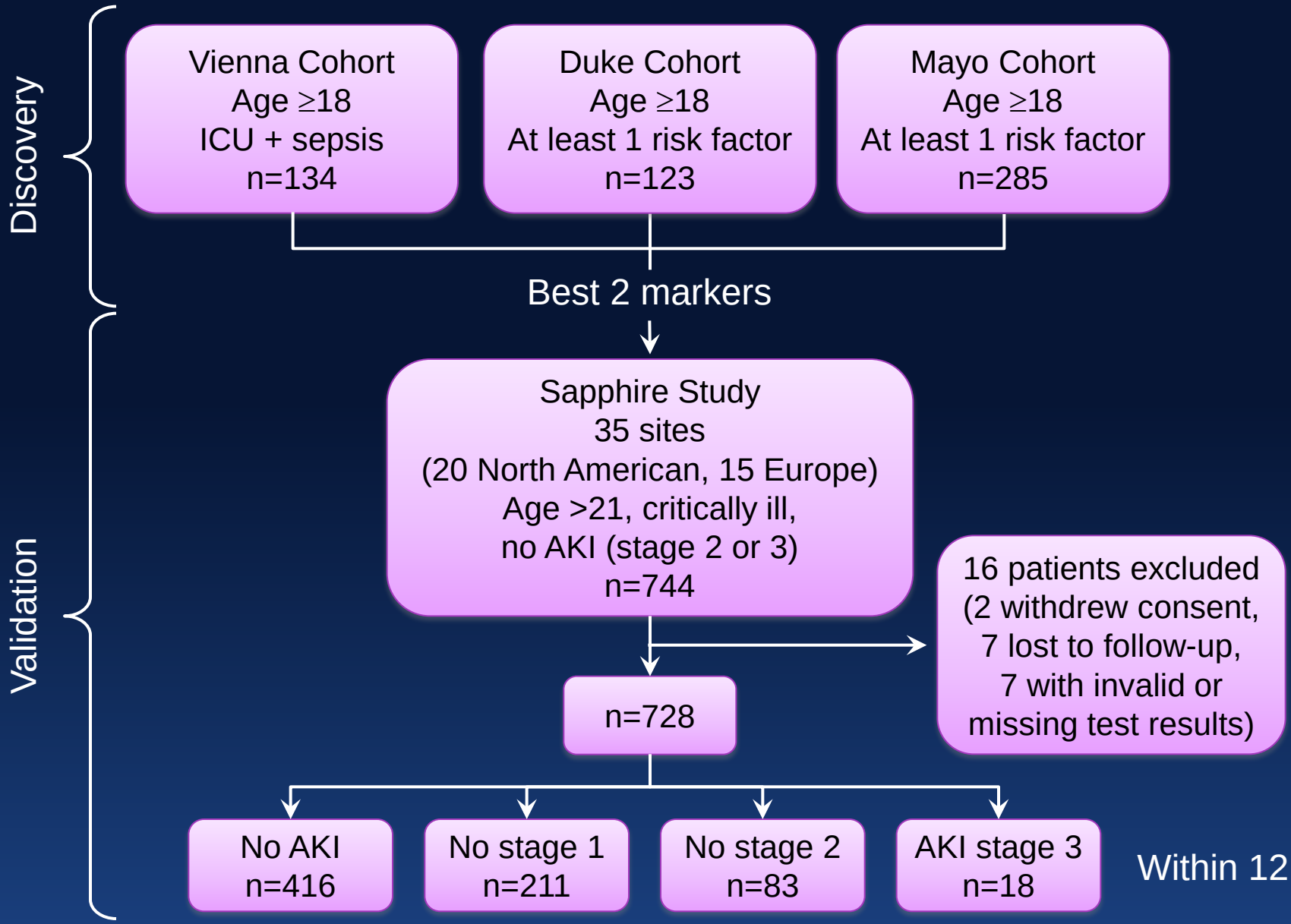

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Kashani et al. Critical Care 2013, 17:R25

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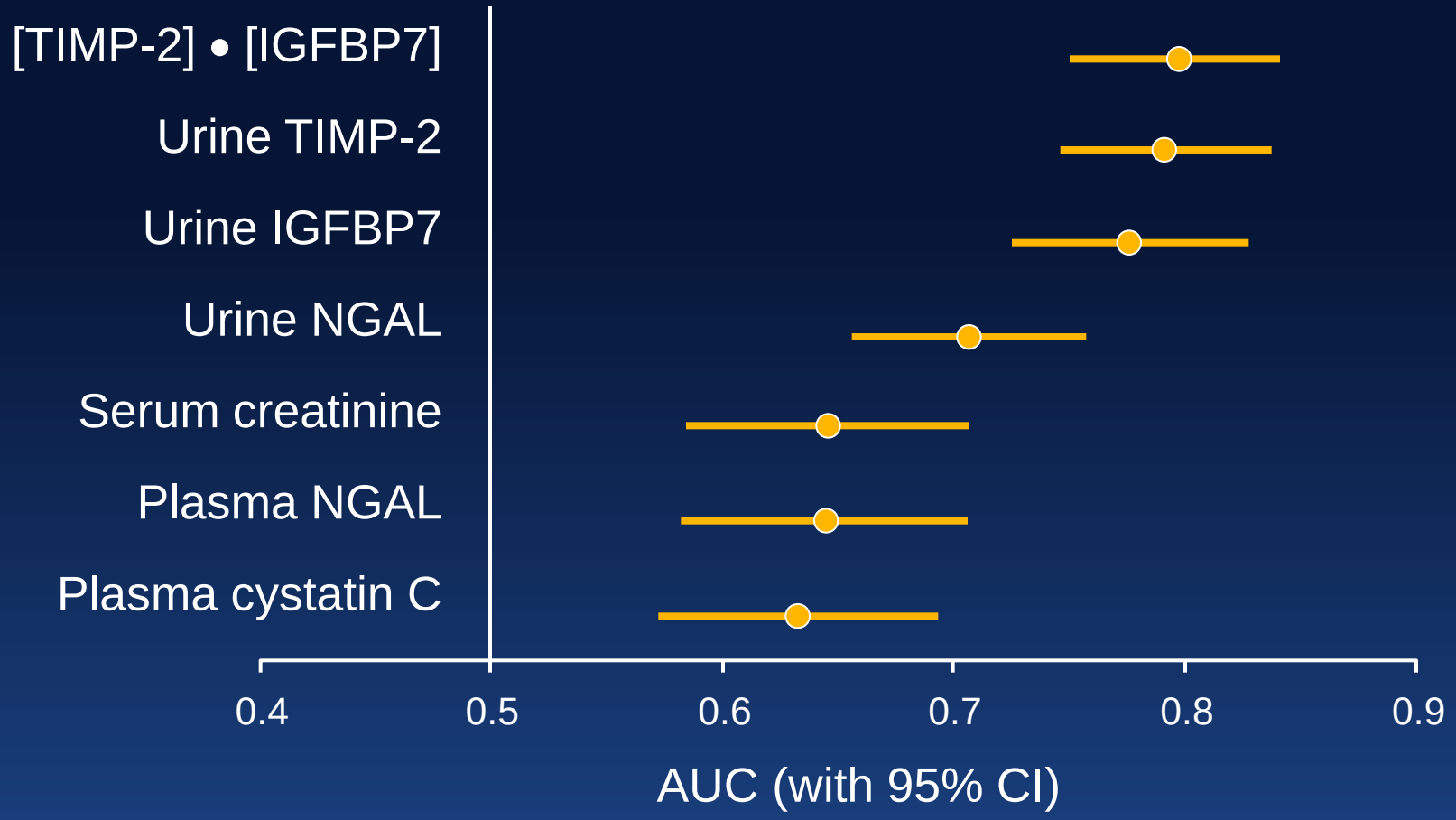
ROC-AUC – Comparison of Novel Markers



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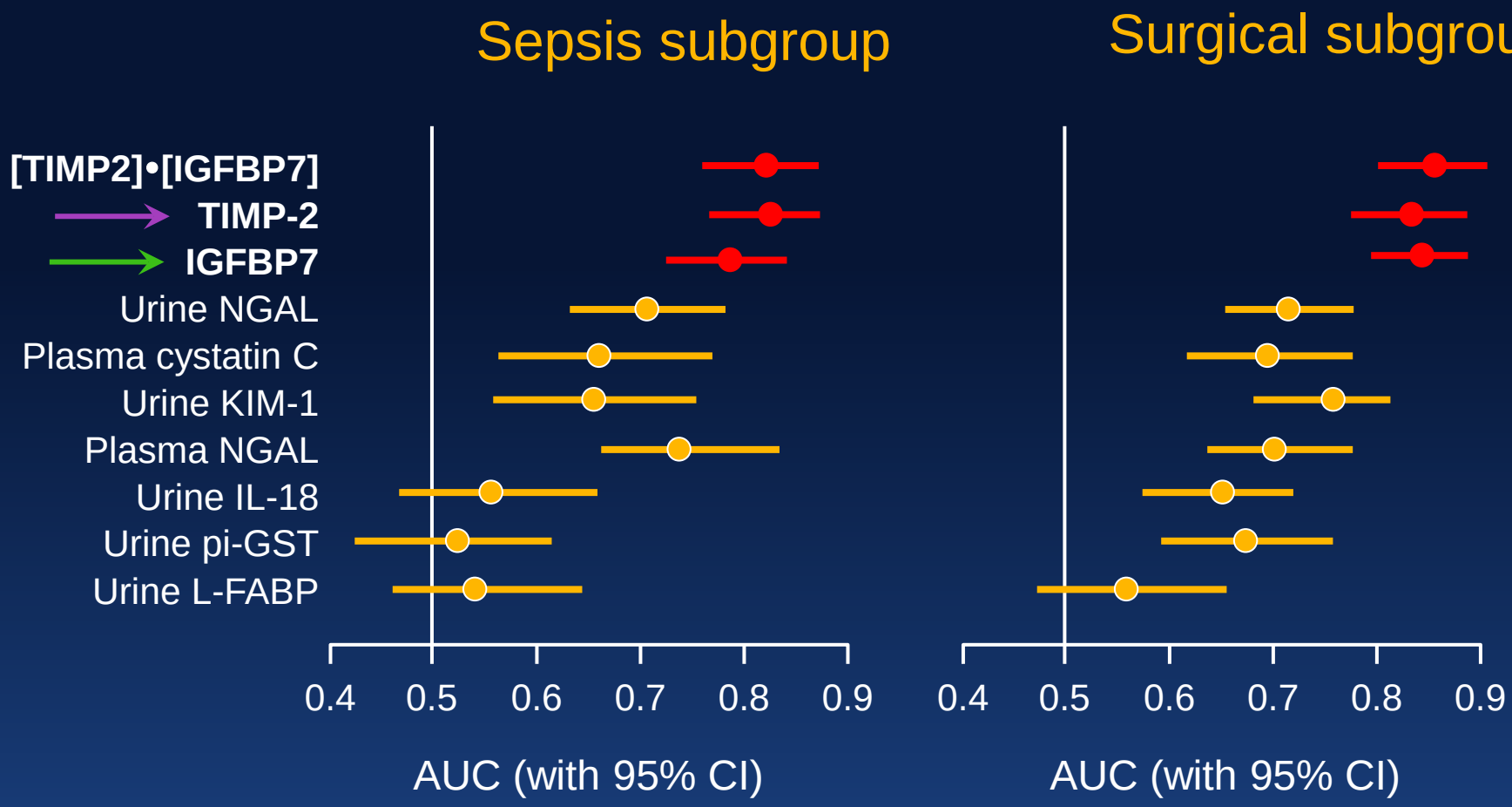

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Kidney Troponin

Period	ACS	AKI
1960s	LDH	Serum Creatinine
1970s	CPK, Myoglobin	Serum Creatinine
1980s	CK-MB	Serum Creatinine
1990s	Troponin T	Serum Creatinine
2000s	Troponin I	Serum Creatinine

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Kidney Troponin

Period	ACS	AKI
1960s	LDH	Serum Creatinine
1970s	CPK, Myoglobin	Serum Creatinine
1980s	CK-MB	Serum Creatinine
1990s	Troponin T	Serum Creatinine
2000s	Troponin I	Serum Creatinine
2010s	Troponin I	NGAL; KIM-1; CysC; IL18; TMIP2*IGFBP7; L-FABP

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Pathogenesis

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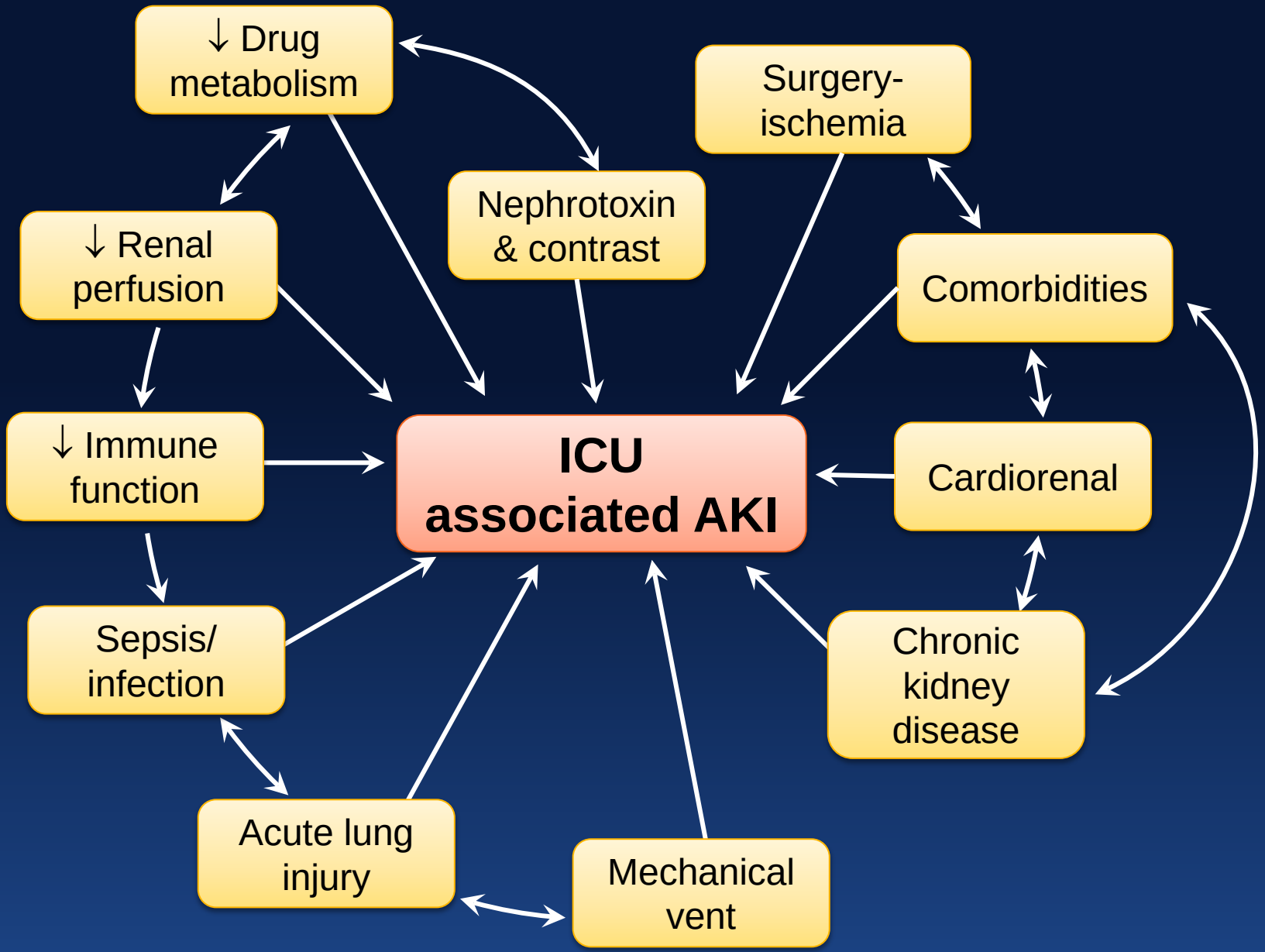

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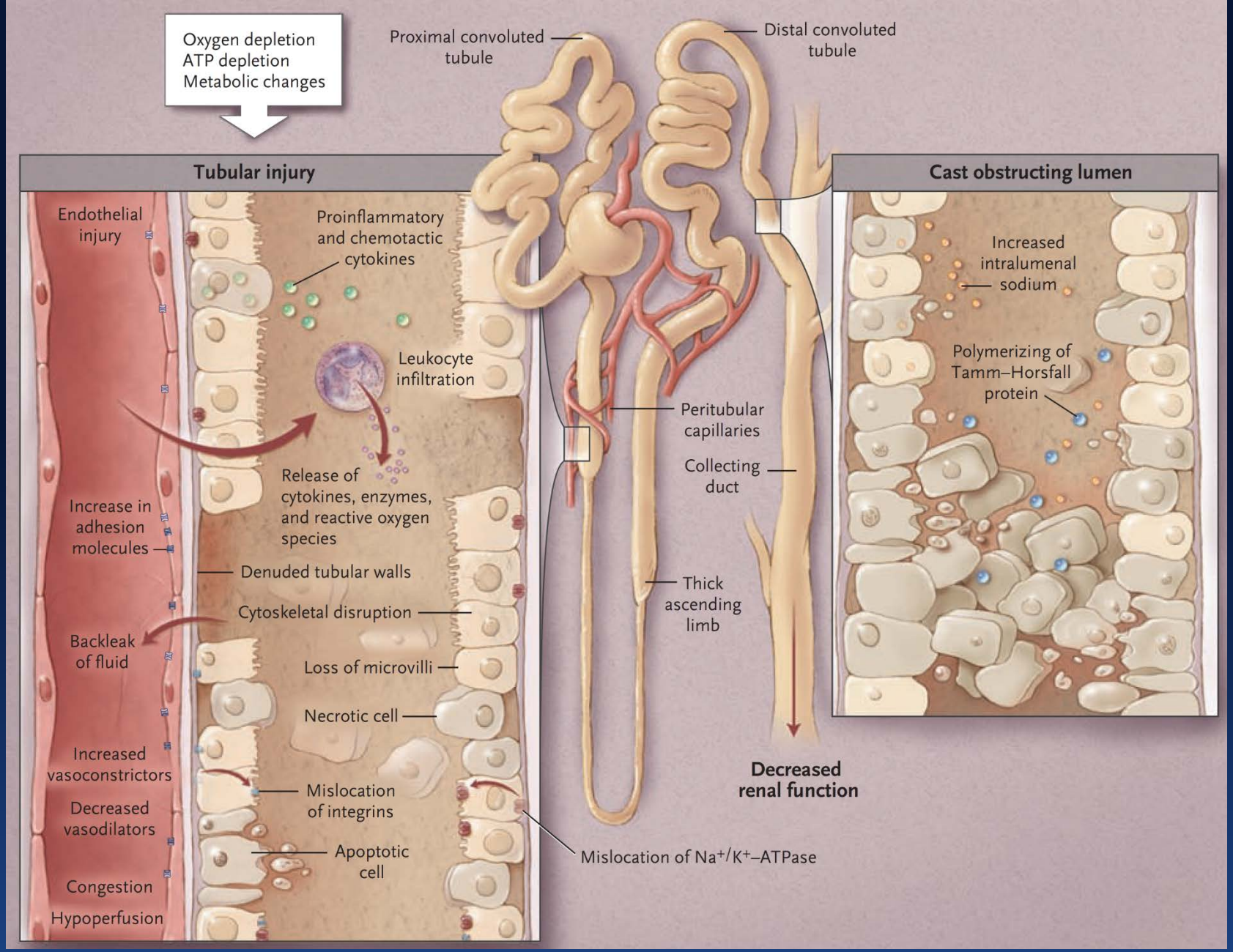

Abuelo et al, NEJM 2007, 357 (8)

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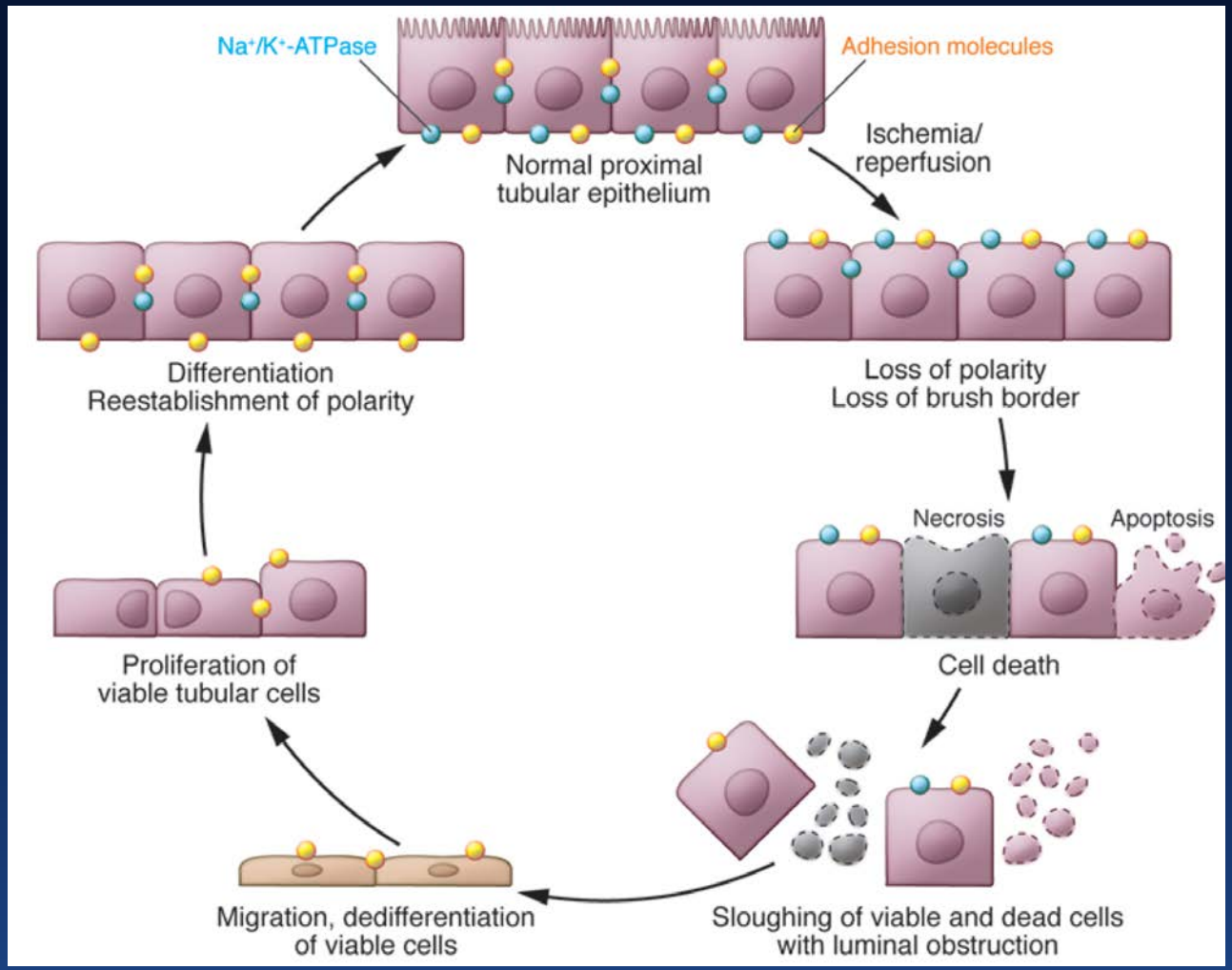
Tubular cells



Bonventre, et al. *J Clin Invest.* 2011;121(11):4210–4221

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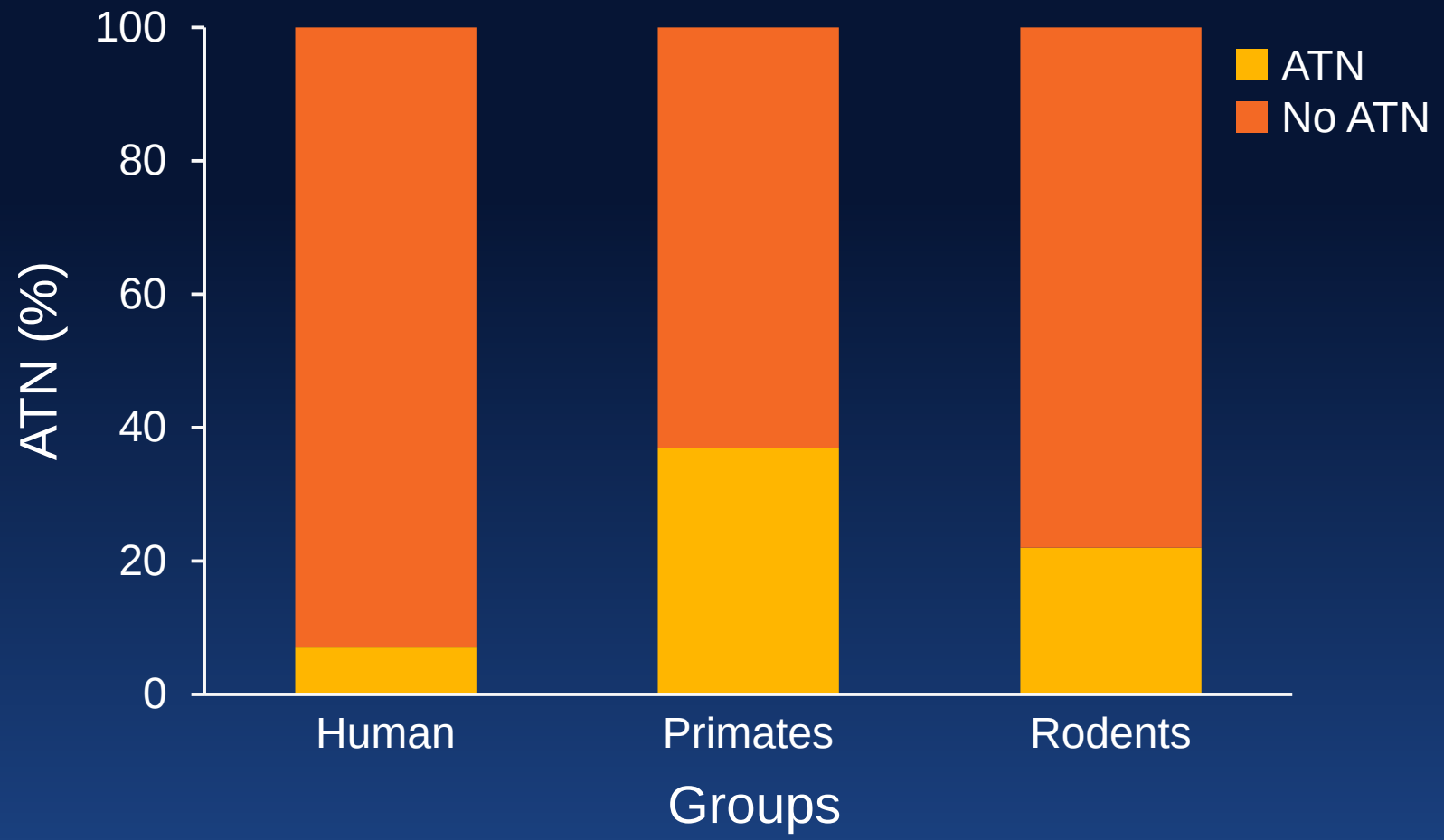
ATN found in biopsy samples



Critical Care 2008, 12:R38

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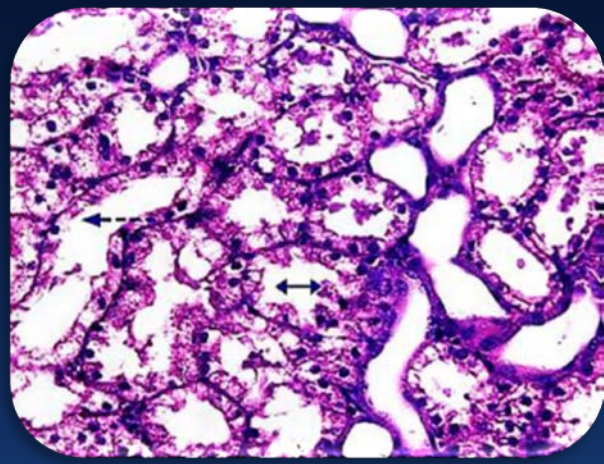
AKI pathology

Sepsis

- Patchy and heterogeneous tubular cell injury
- S_2, S_3 segment cell vacuolization (apical)
- Minimal necrosis/apoptosis
  - Disproportionate drop in GFR
- Renal vasodilation
- Increased or normal RBF
  - Decrease in capillary density
    - Decrease capillary continuous blood flow



Rosen et al. KI; 60(4): 1220-4

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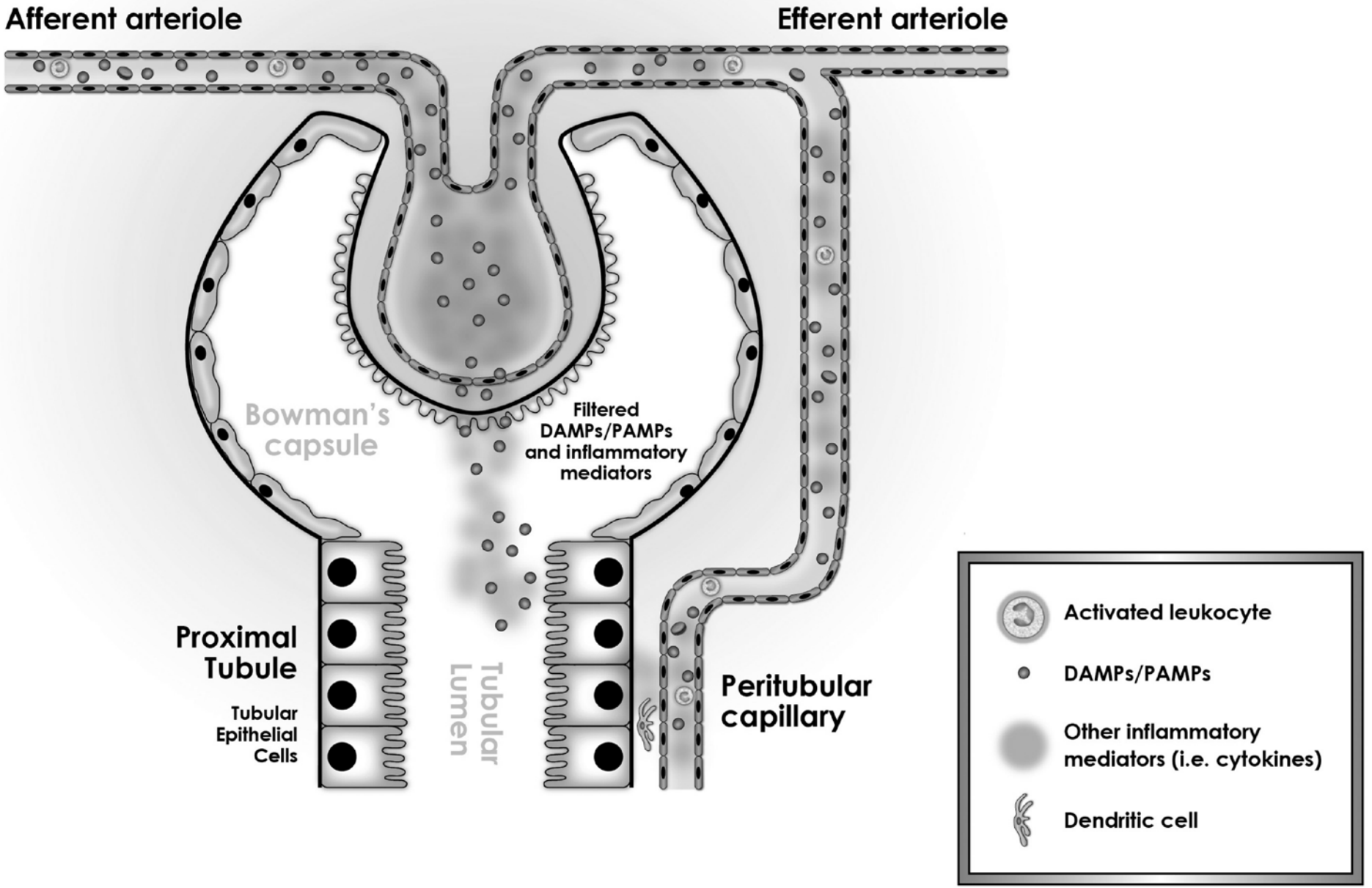

SHOCK, Vol. 41, No. 1, pp. 3Y11, 2014

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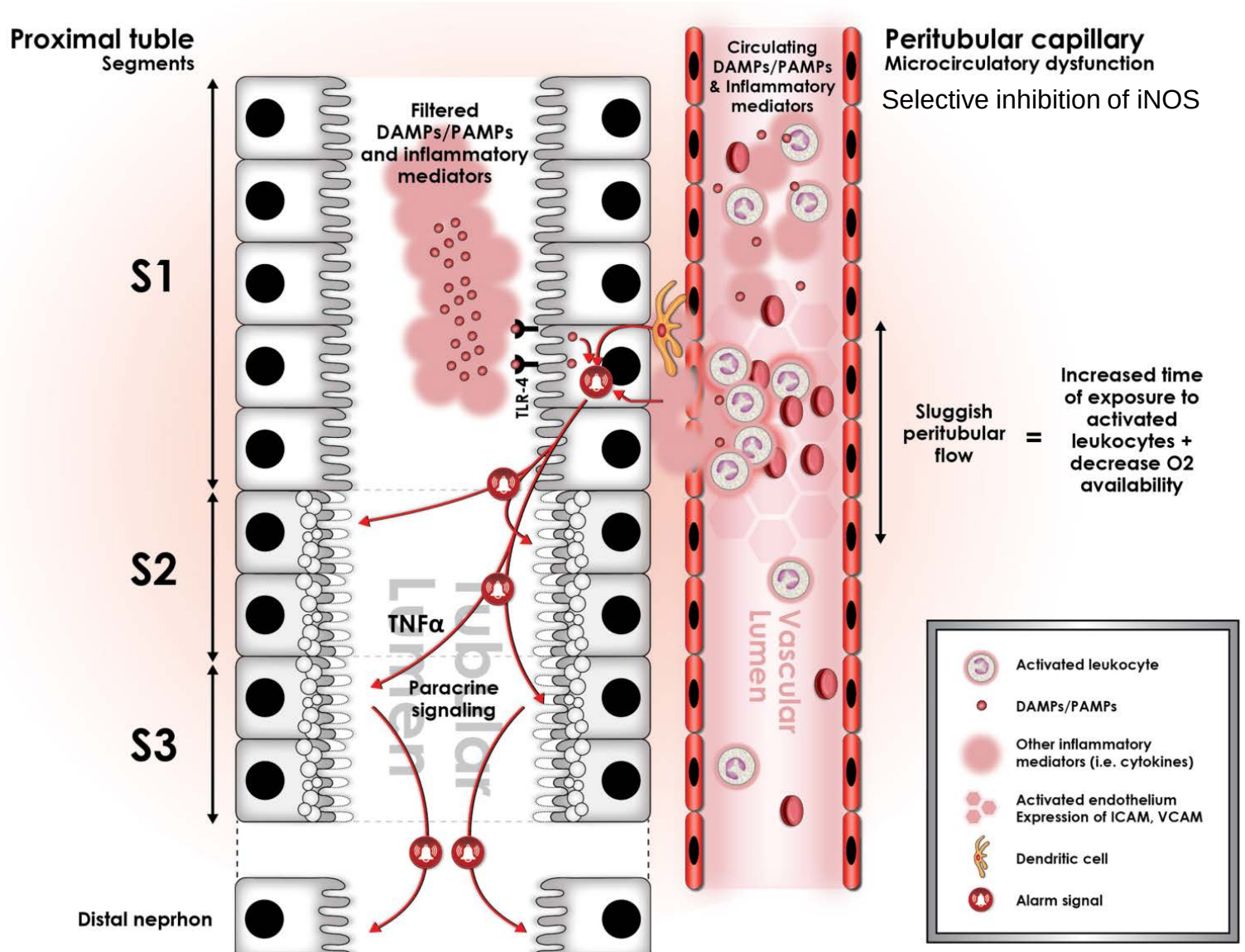

SHOCK, Vol. 41, No. 1, pp. 3Y11, 2014

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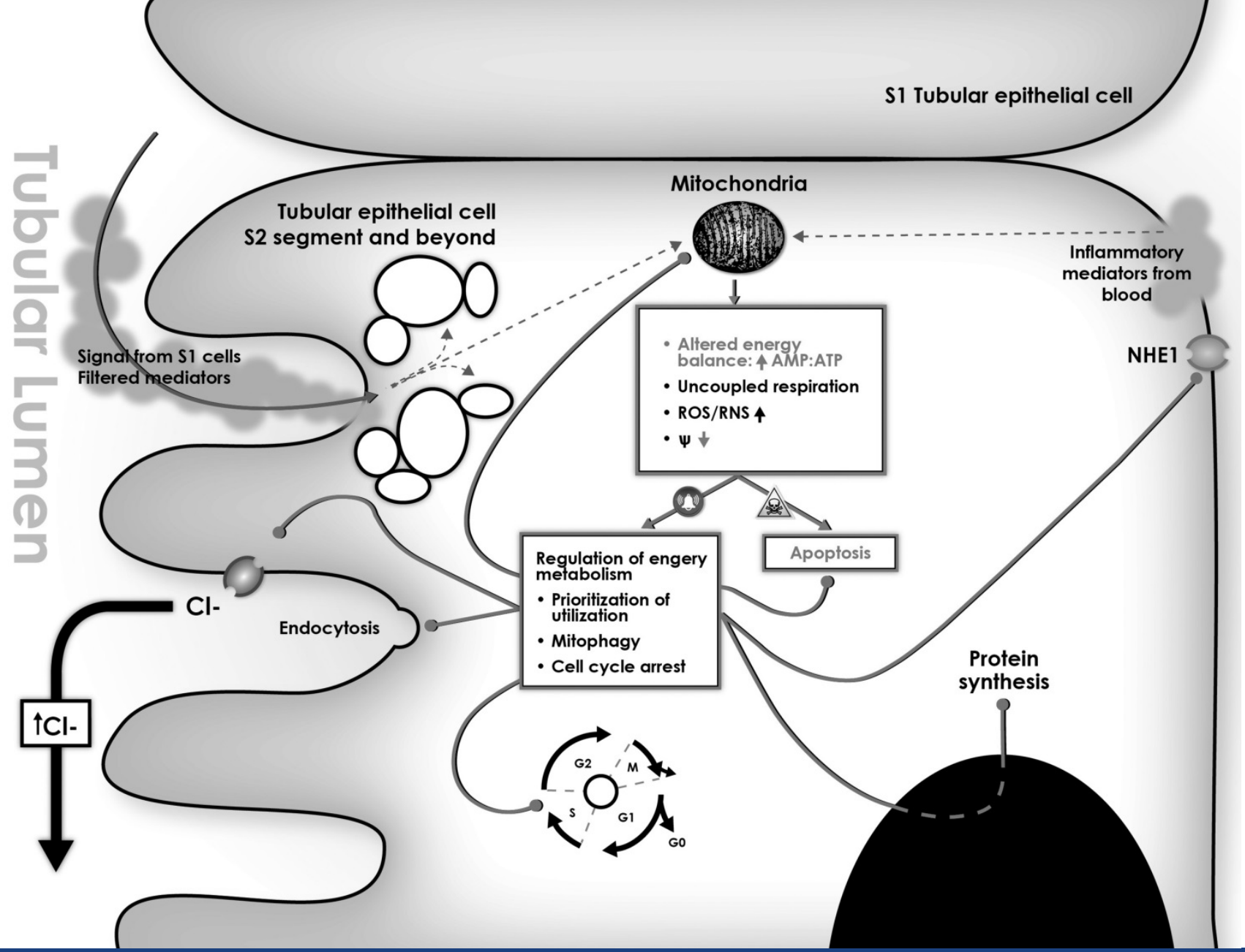

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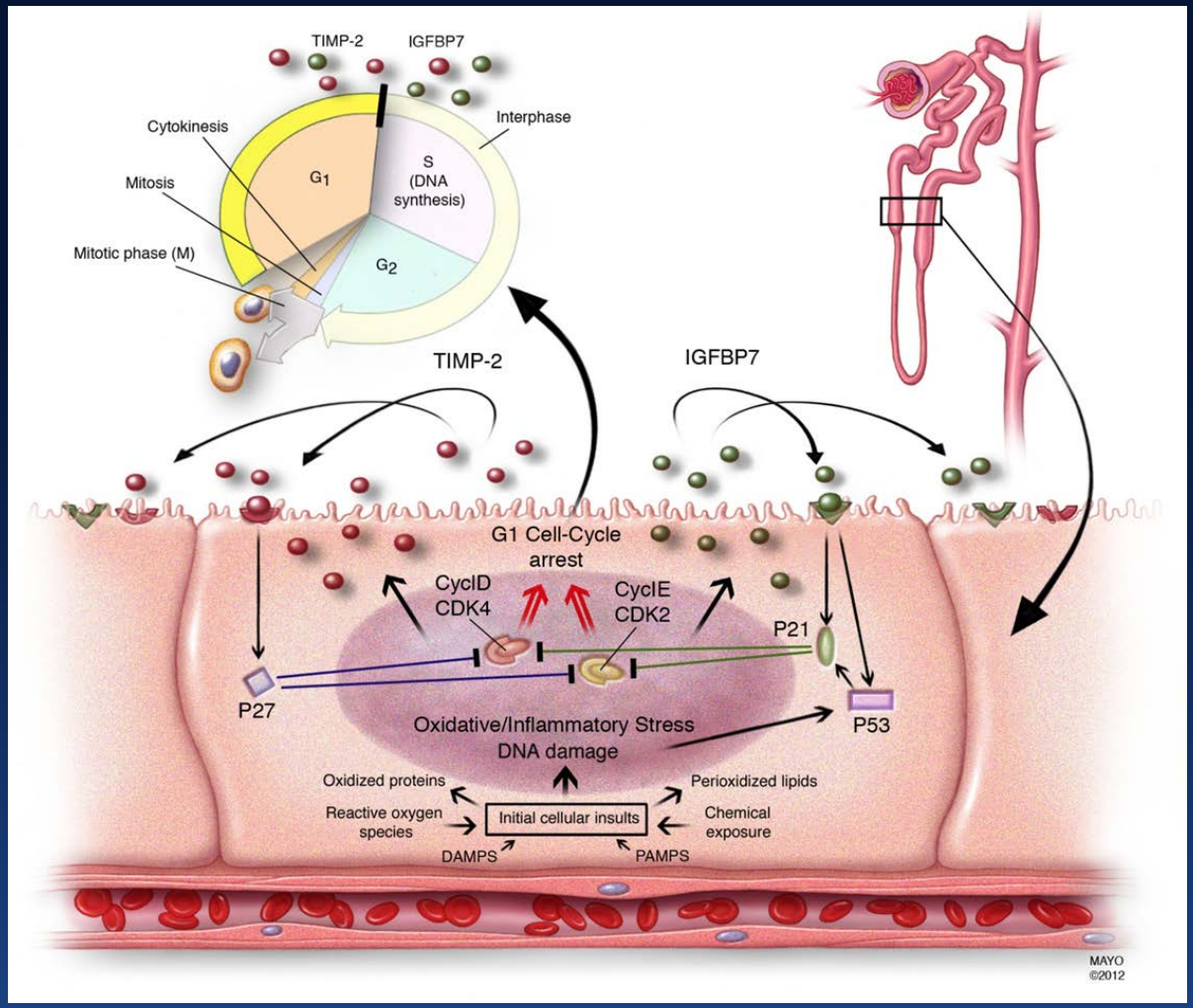
Cell cycle arrest biomarkers

$IGFBP_{7*}TIMP_2$



Kashani et al. Critical Care 2013, 17:R25

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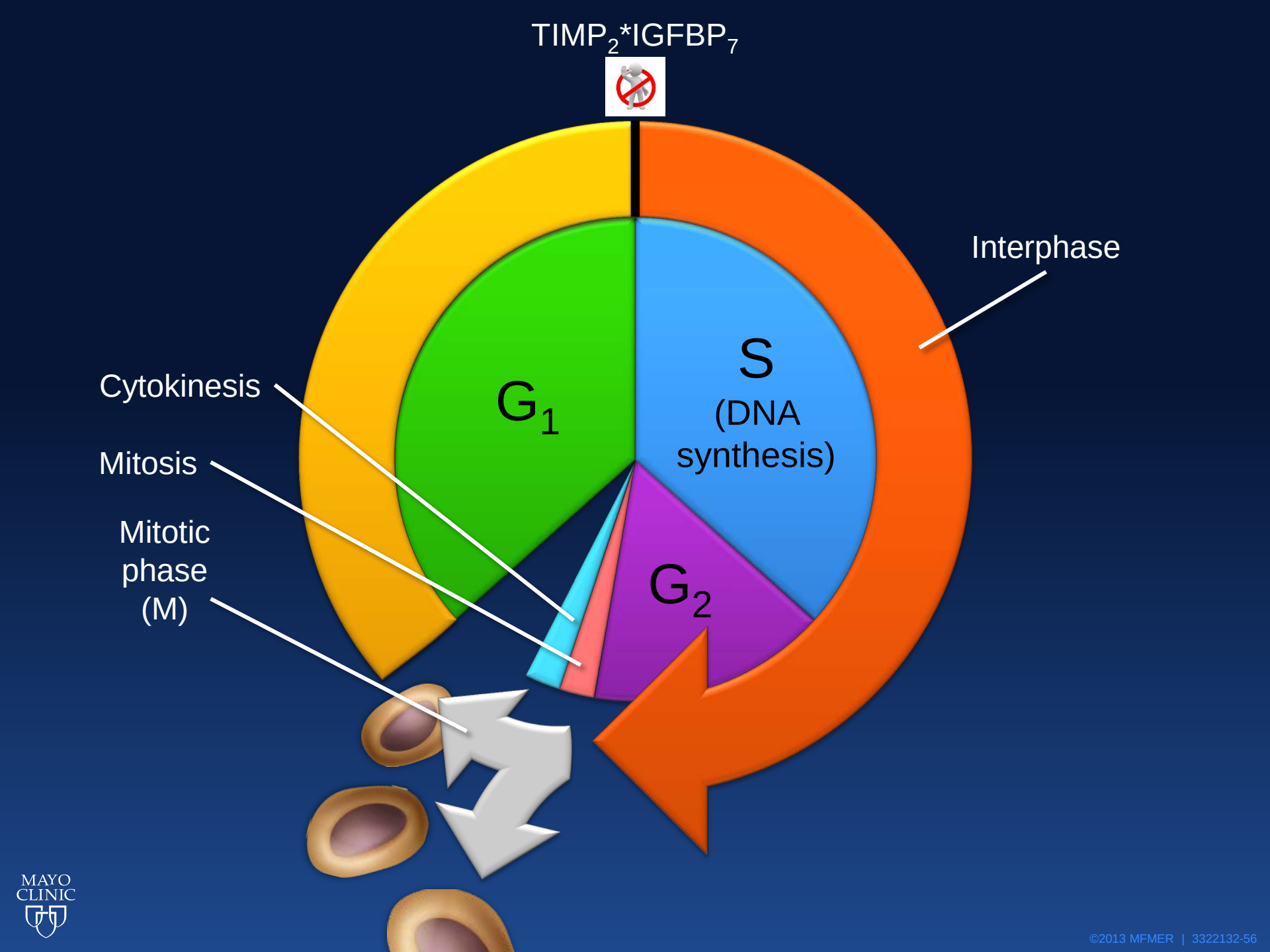

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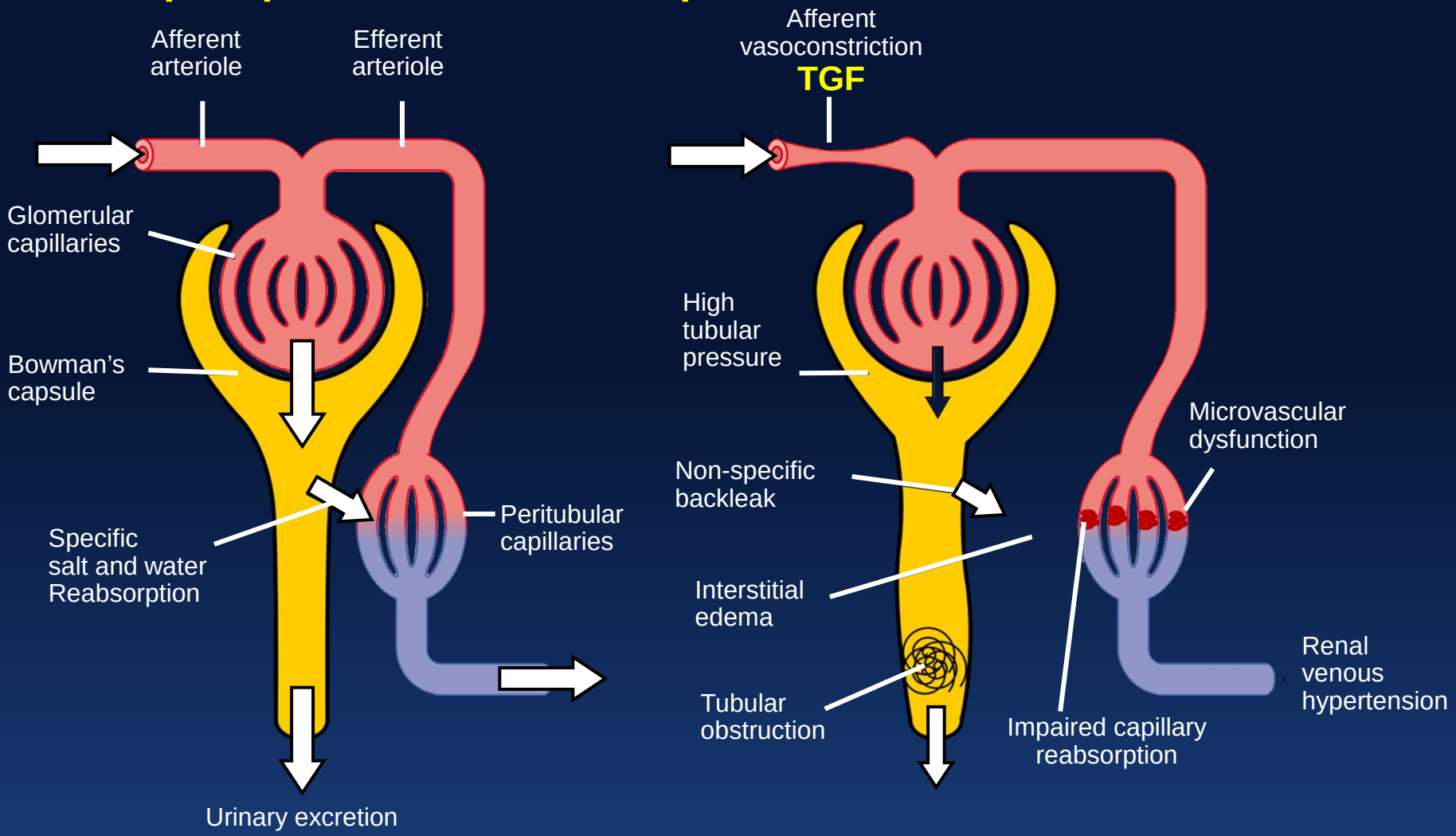
Disproportionate drop in GFR



Normal

Sustained AKI

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Semin Nephrol 35: 64-74

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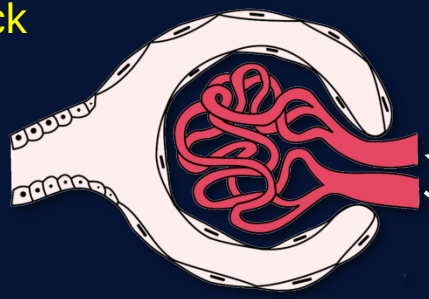
Hyperdynamic shock

Low GRF



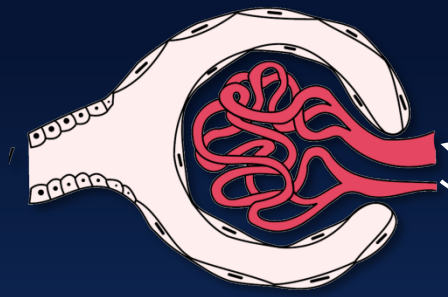
High cardiac output
Low systemic pressure

Efferent vasodilation

High RBF

Cardiogenic shock

Normal to low GFR



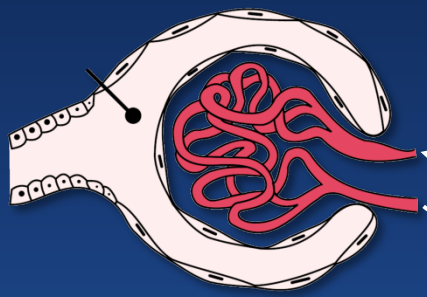
Low cardiac output
Low systemic pressure

Efferent vasoconstrictyion

Low RBF

Established AKI

Low to zero GFR



Normal cardiac output
Normal systemic pressure

Afferent vasoconstrictyion

Low RBF

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Potential therapeutic targets

- Attenuating early inflammatory response
- Cell-based therapy
  - Mesenchymal stem cells
  - Tolerized dendritic cells
- Activating late immunity
  - IL-7; IL-15
- Cellular targets
  - Mitochondrial biogenesis
  - Iron metabolism

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Potential therapeutic targets

- Molecular mechanisms of recovery
  - Autophagy
  - Cell cycle

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Take home points

- Incidence of AKI is rising
  - AKI is an independent risk factor
    - ICU, hospital and long term mortality
    - CKD
    - ESRD
- Traditional AKI diagnostic tools have limited performance
- Novel diagnostic and prognostic tools potentially improve the care of AKI patients

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Take home points

- AKI pathophysiology is very complex
  - Immune reactions
  - Microvascular dysfunction
  - Cellular adaptation
  - Necrosis and apoptosis

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Questions & Discussion

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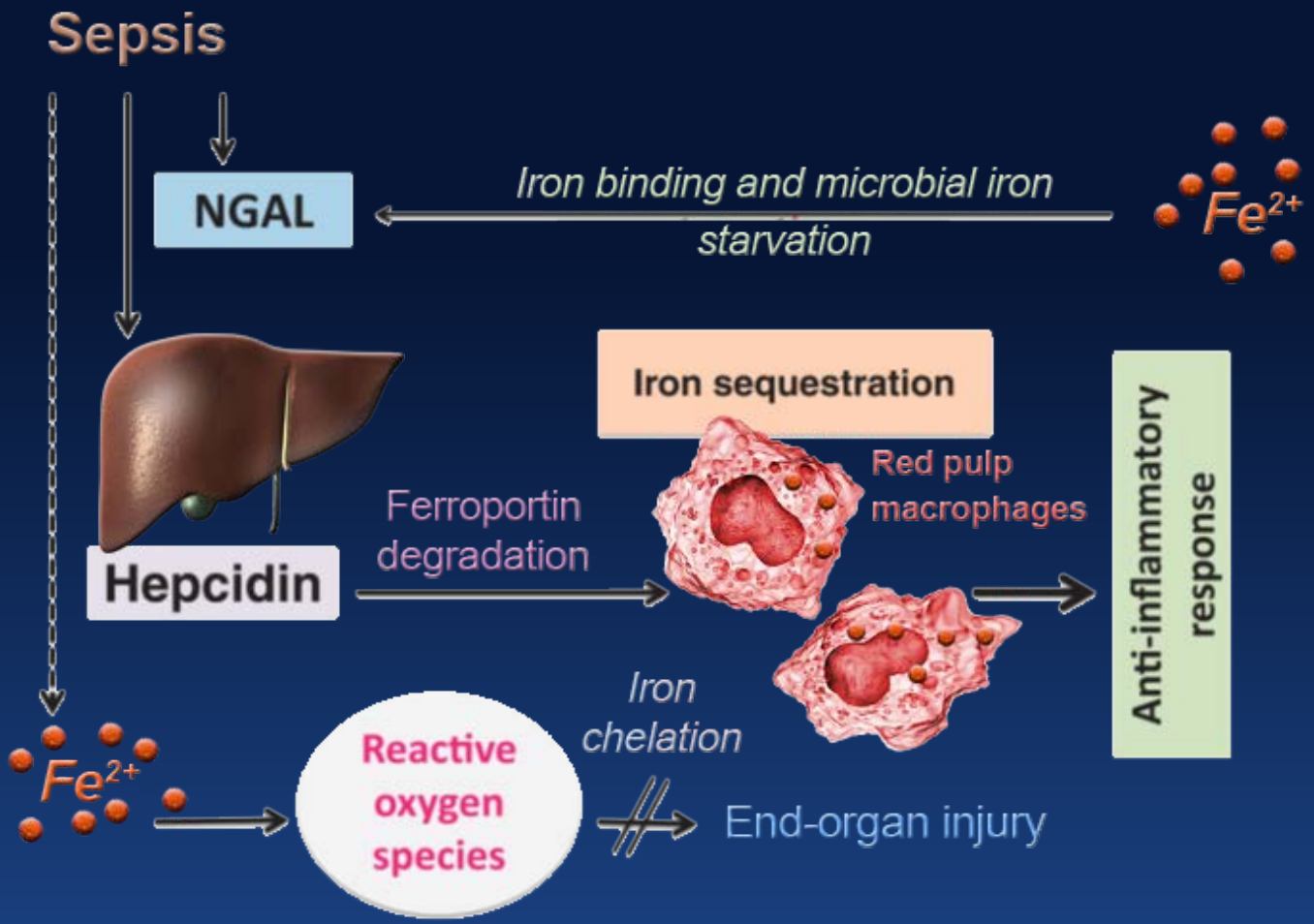
Iron Metabolism



Semin Nephrol 35: 38-52

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