POLTAVA STATE MEDICAL UNIVERSITY
Department of Anesthesiology and Intensive Care

Acute Kidney Injury

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Objectives

- Definition of AKI
- Epidemiology
- Causes
- Diuretics
- Fluid management
- Renoprotection

Definition

<u>Acute Kidney Injury (ARF)</u>

- Clinical syndrome denoted by decline in GFR (glomerular filtration rate)
  - With reduced excretion of nitrogenous waste (urea and creatinine)
  - Other uremic toxins

Measurement of Renal function

- Serum Cr used to estimate GFR:
- Problems:
  - SCr does not accurately reflect the GFR in non steady state
  - Creatinine is removed by dialysis
  - studies and clinical trials have used different cut-off values

Research

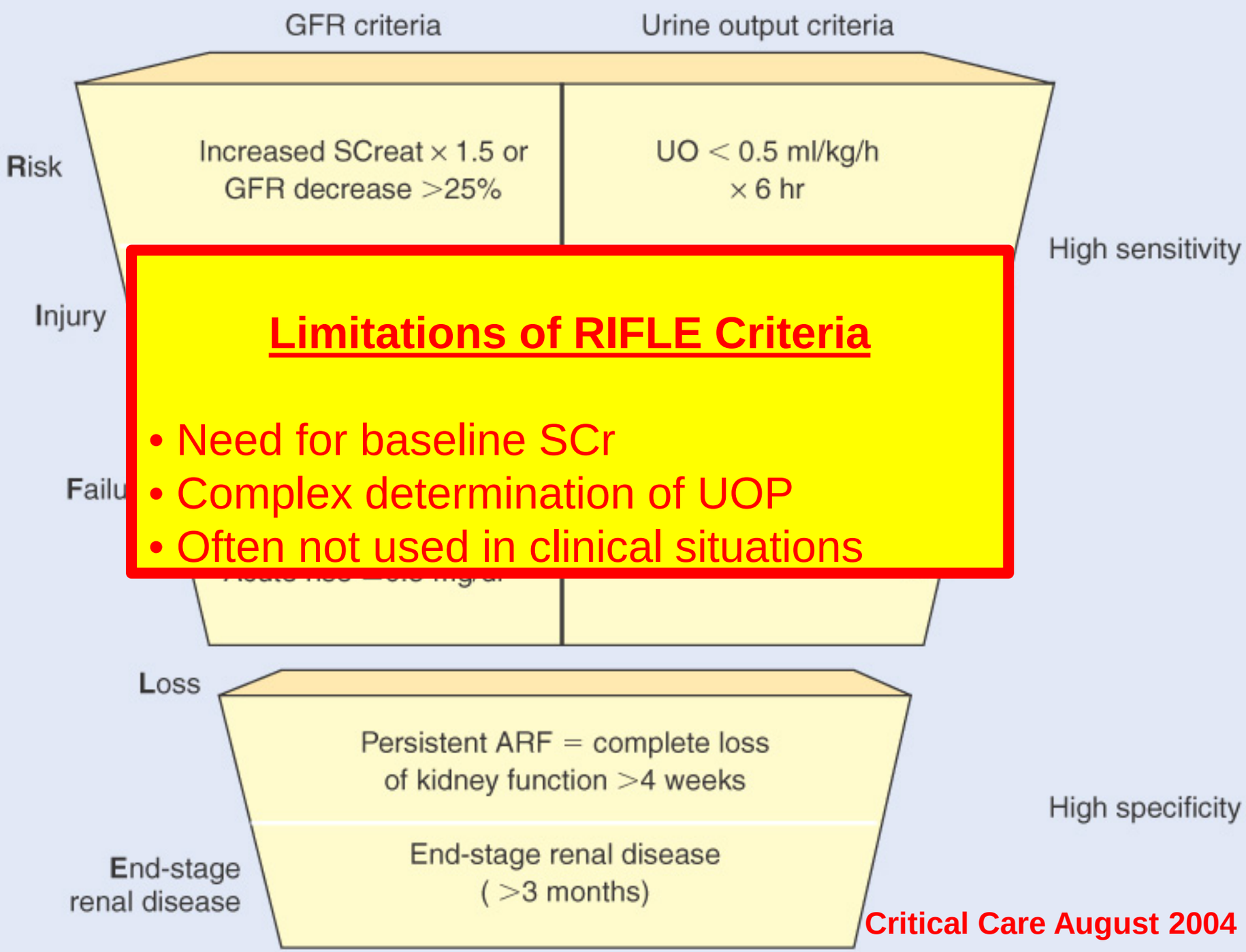
Open Access

Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group

Rinaldo Bellomo[1], Claudio Ronco[2], John A Kellum[3], Ravindra L Mehta[4], Paul Palevsky[5] and the ADQI workgroup[6]

Critical Care August 2004 Vol 8 No 4
Bellomo *et al.*

The RIFLE criteria for ARF



Limitations of RIFLE Criteria

- Need for baseline SCr
- Complex determination of UOP
- Often not used in clinical situations

Critical Care August 2004

Vol 8 No 4 Bellomo *et al*.

(Redrawn from Bellomo R: Defining, quantifying, and classifying acute renal failure. Crit Care Clin 2005;21:223–237.)

Improving Outcomes from Acute Kidney Injury

Bruce A. Molitoris,* Adeera Levin,† David G. Warnock,‡ Michael Joannidis,§ Ravindra L. Mehta,‖ John A. Kellum,¶ Claudio Ronco,** and Sudhir Shah;†† on behalf of the Acute Kidney Injury Network

ARF to AKI

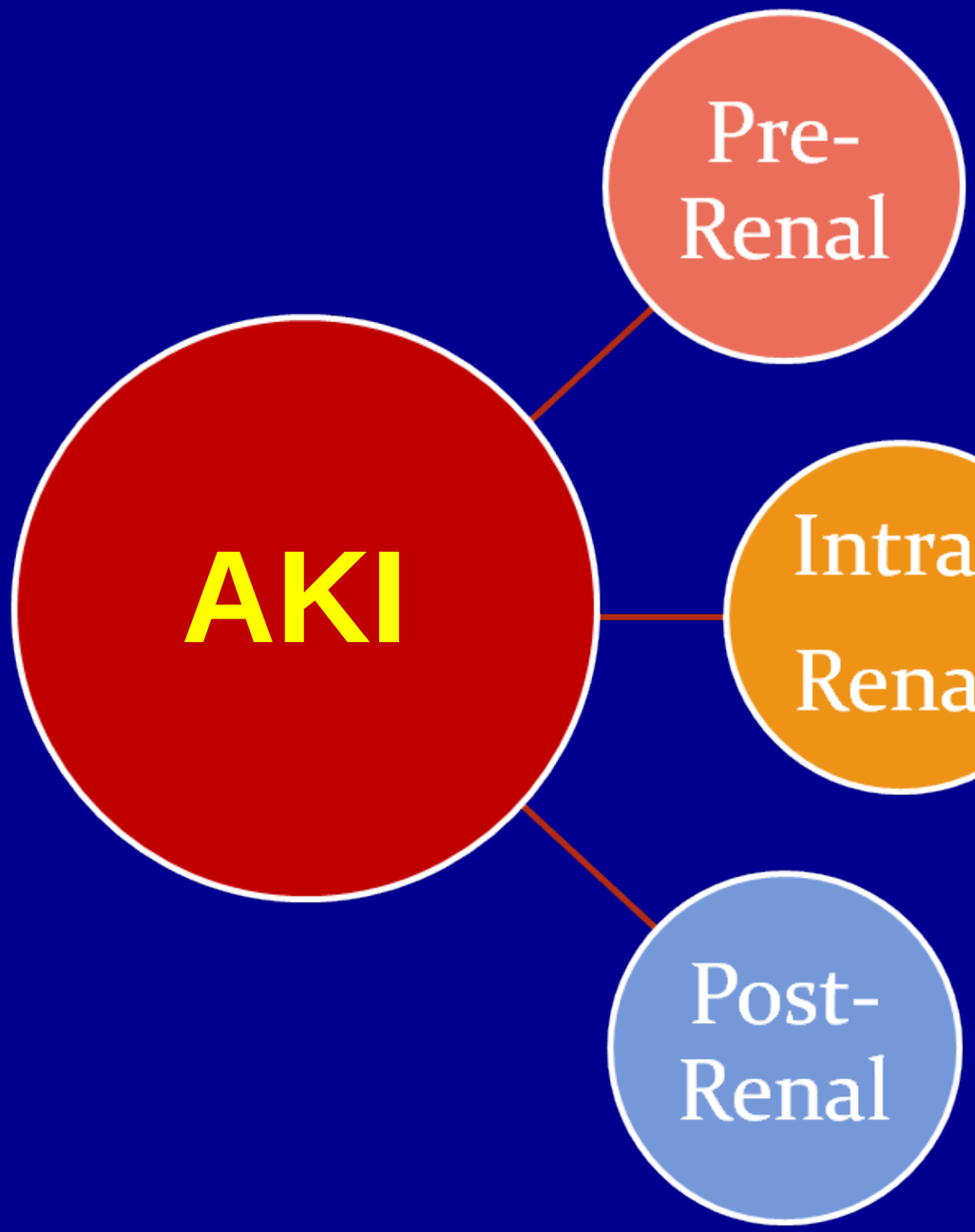
- Acute Renal failure (older term)
- ARF: rapid decline in GFR (hrs-week)
- AKIN recommended AKI
- AKI: spectrum of ARF including minor changes in GFR may be associated with adverse clinical outcomes
- Failure: reserved for severe impairment of renal function that renal replacement therapy is indicated/considered

JASN 18; 1987-1994, 2007

AKIN: Diagnostic Criteria

- An abrupt (within 48 h) reduction in kidney function currently defined by any of the following:
  - ***Absolute increase in serum creatinine of either 0.3 mg/dl***
  - ***A percentage increase in SCr of 50% or more***
  - ***A reduction in UOP (documented oliguria)***

Etiology of AKI



- **Hypoperfusion in which the integrity of renal parenchyma is preserved**

- ***Intrinsic AKI.*** **Involving renal parenchymal tissue**

- ***Obstructive AKI.*** **Acute obstruction of urinary flow**

Classification of AKI:

- Non Oliguria:
  - Urine output > 400 ml/24hr
- Oliguria:
  - Urine output < 400 ml/24 hr
- Anuria:
  - Urine output < 50 ml/24 hr

Other terms

- Azotemia:
  - Accumulation of nitrogenous waste
- Uremia:
  - Symptomatic AKI (eg MS changes, loss of appetite, tremors)

- Oliguria is a well-recognized and poor prognostic indicator in patients with AKI.

- The development of oliguria complicates clinical management, particularly for fluid balance.

- Use of diuretics therefore reflects attempt to convert oliguric state to non-oliguric state.

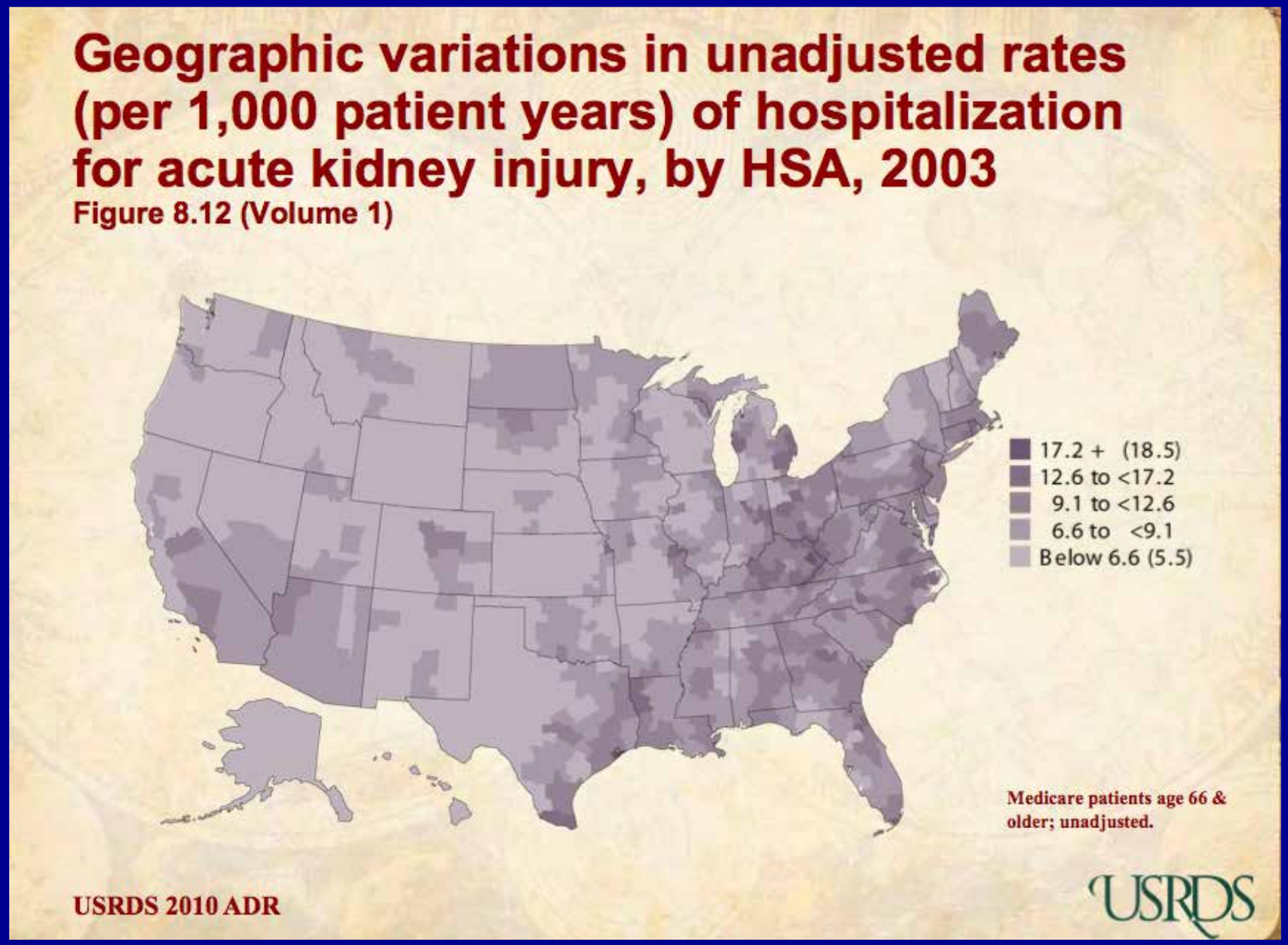
Bagshaw SM, Bellomo R, Kellum JA. Oliguria, volume over- load, and loop diuretics. Crit Care Med. 2008;36 Suppl:S172-8.
Uchino S. Outcome prediction for patients with acute kidneyinjury. Nephron Clin Pract. 2008;109:c217-23.

Epidemiology

- AKI à 1 million hospitalized patients in the United States.
- The incidence of AKI à is reported to occur in up to 5% to 7% of all hospitalized patients.
- Up to two thirds of critically ill patients.
- 5% to 6% of patients with AKI require renal replacement therapy
- Mortality rate in this population that requires renal replacement therapy is approximately 50% to 70%.
- AKI also significantly increases length of hospital stay
- AKI survivors are still at high risk for long-term adverse outcomes such as chronic kidney disease, end-stage renal disease, and premature death, even if the serum creatinine level returns to normal.
- Despite recent advances, the incidence of AKI has increased more than four-fold since 1998
- Approximate incidence is 500 per 10,000 population.
- Annual health cost due to AKI is more than 10 billion per year.

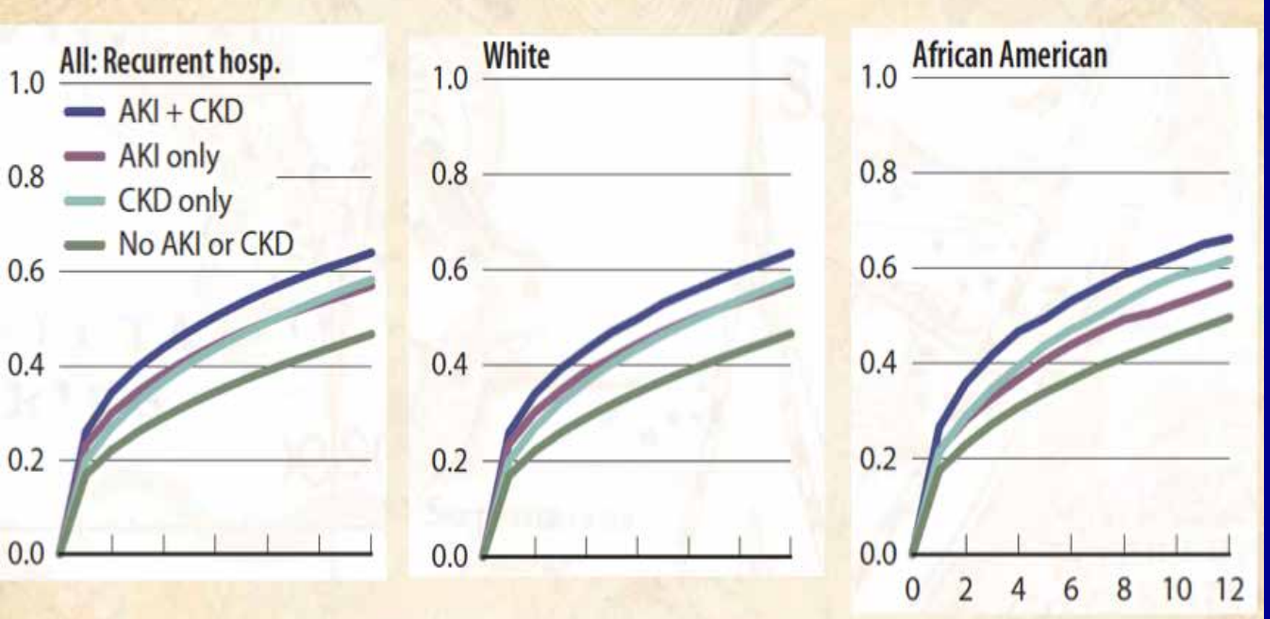
Waikar SS, Curhan GC, Wald R, McCarthy EP, Chertow GM. Declining mortality in patients with acute renal failure, 1988 to 2002. J Am Soc Nephrol. 2006;17:1143-50.Xue JL, Daniels F, Star RA, Kimmel PL, Eggers PW, MolitorisBA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol. 2006; 17:1135-42.Palevsky PM. Epidemiology of acute renal failure: the tip of the iceberg. Clin J Am Soc Nephrol. 2006;1:6-7.

Epidemiology



Epidemiology

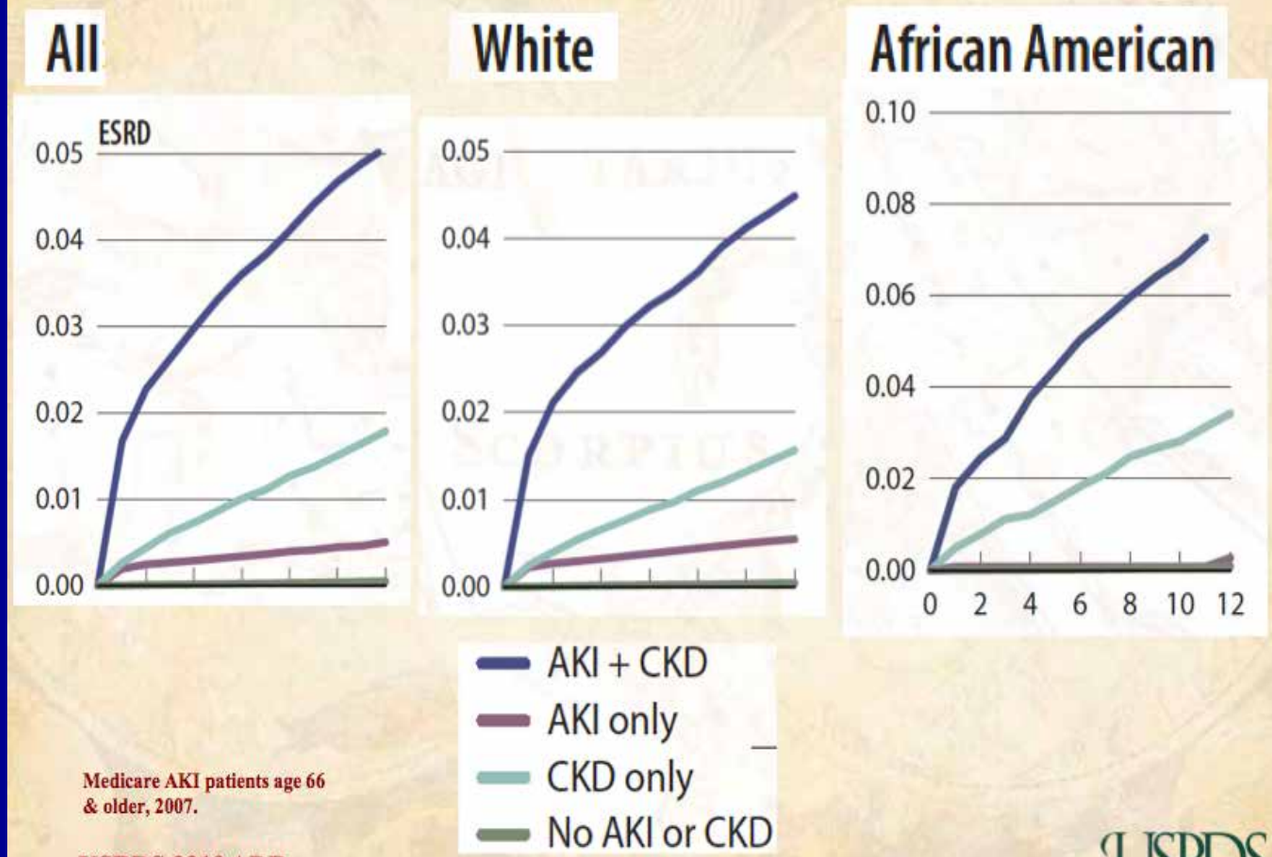
Probability of a recurrent hospitalization following hospitalization for AKI, by race, 2007



Medicare AKI patients age 66 & older, 2007.

USRDS 2010 ADR

Probability of ESRD following hospitalization for AKI, by race, 2007

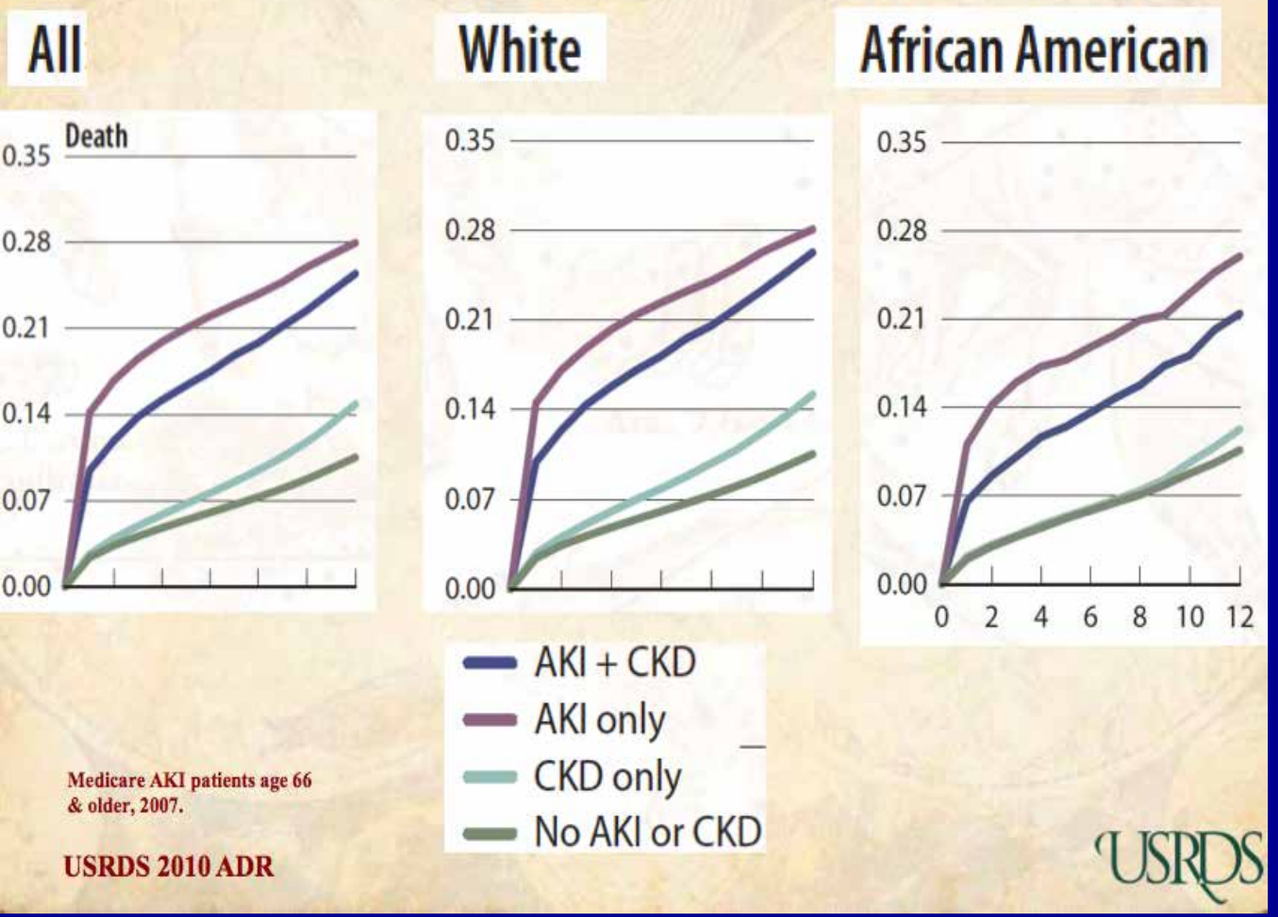


Medicare AKI patients age 66 & older, 2007.

USRDS 2010 ADR

Epidemiology

Probability of a recurrent hospitalization, ESRD, or death following hospitalization for AKI, by race, 2007

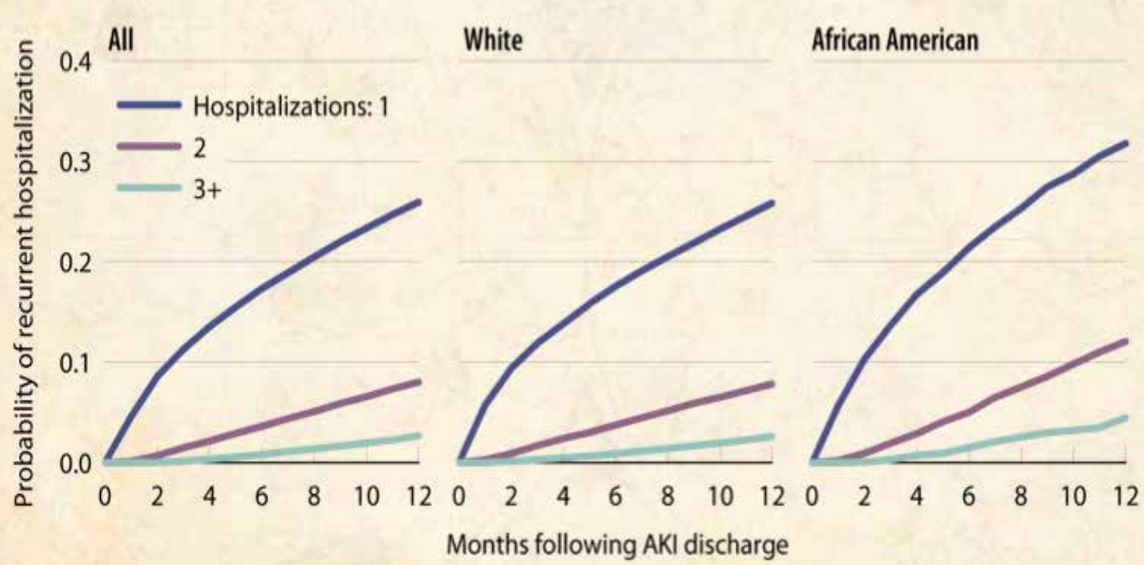


Medicare AKI patients age 66 & older, 2007.

USRDS 2010 ADR

Probability of a recurrent AKI hospitalization in Medicare patients, by race, 2008

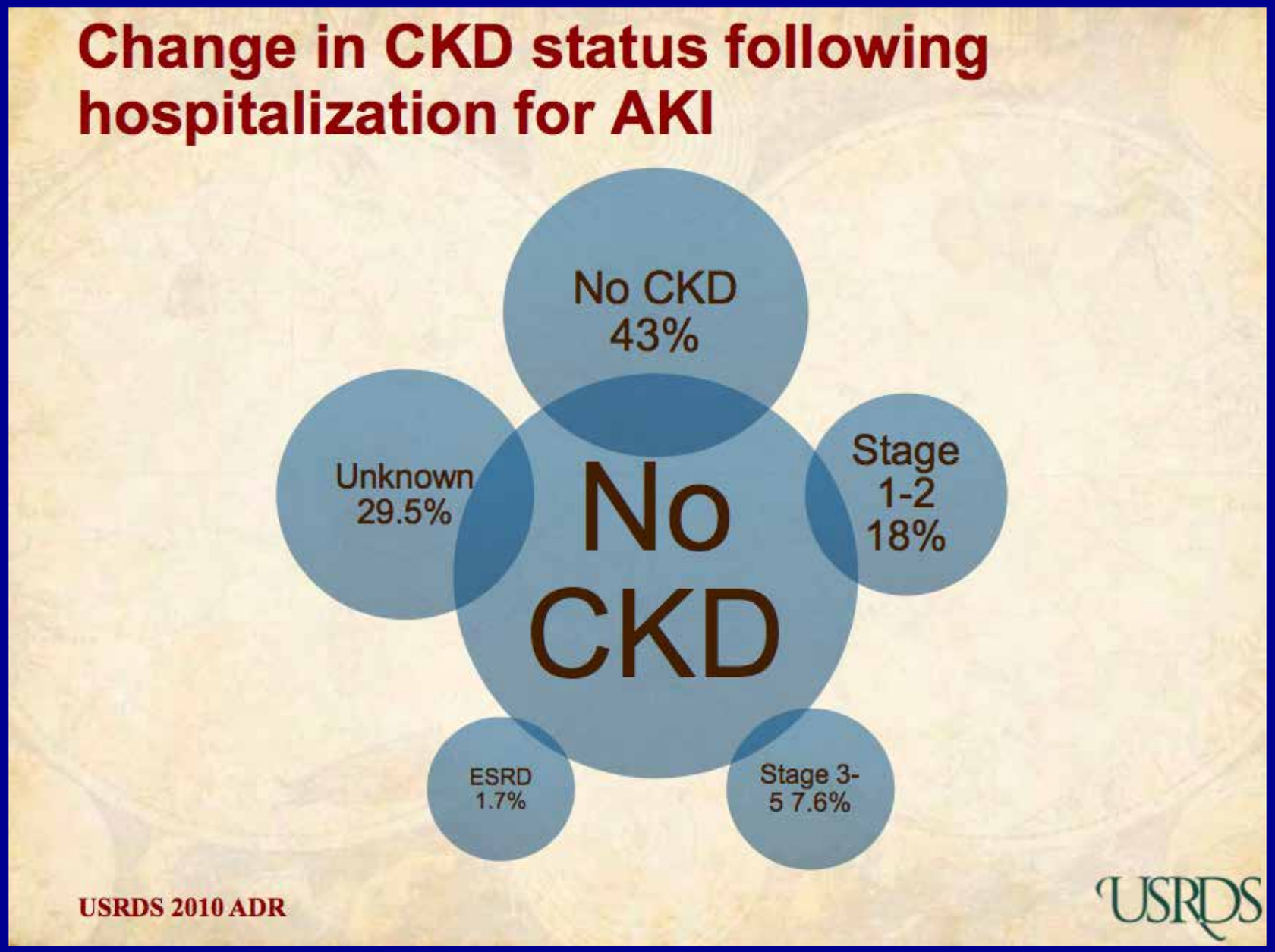
Figure 8.20 (Volume 1)



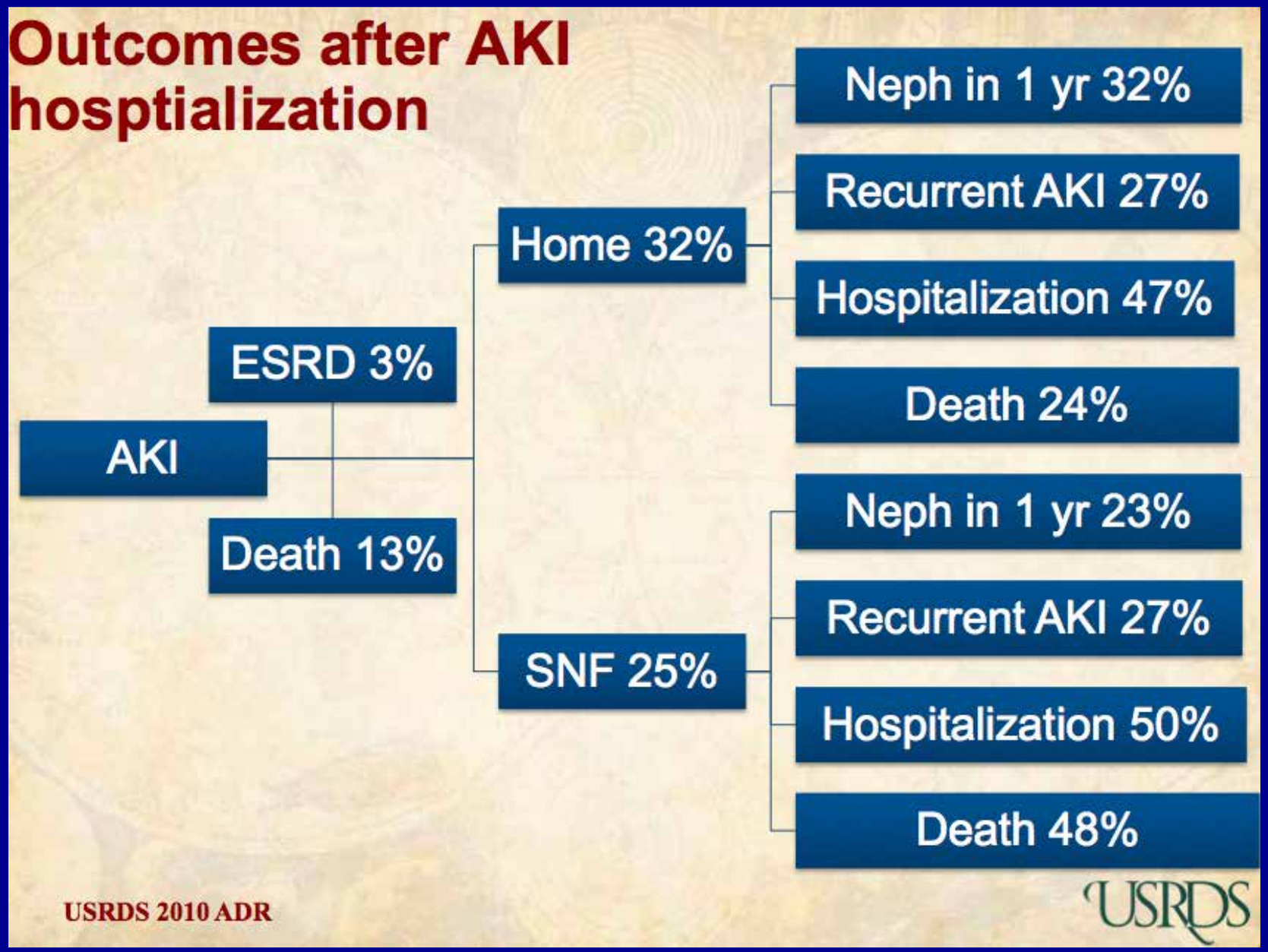
Medicare AKI patients age 66 & older, 2007.

USRDS 2010 ADR

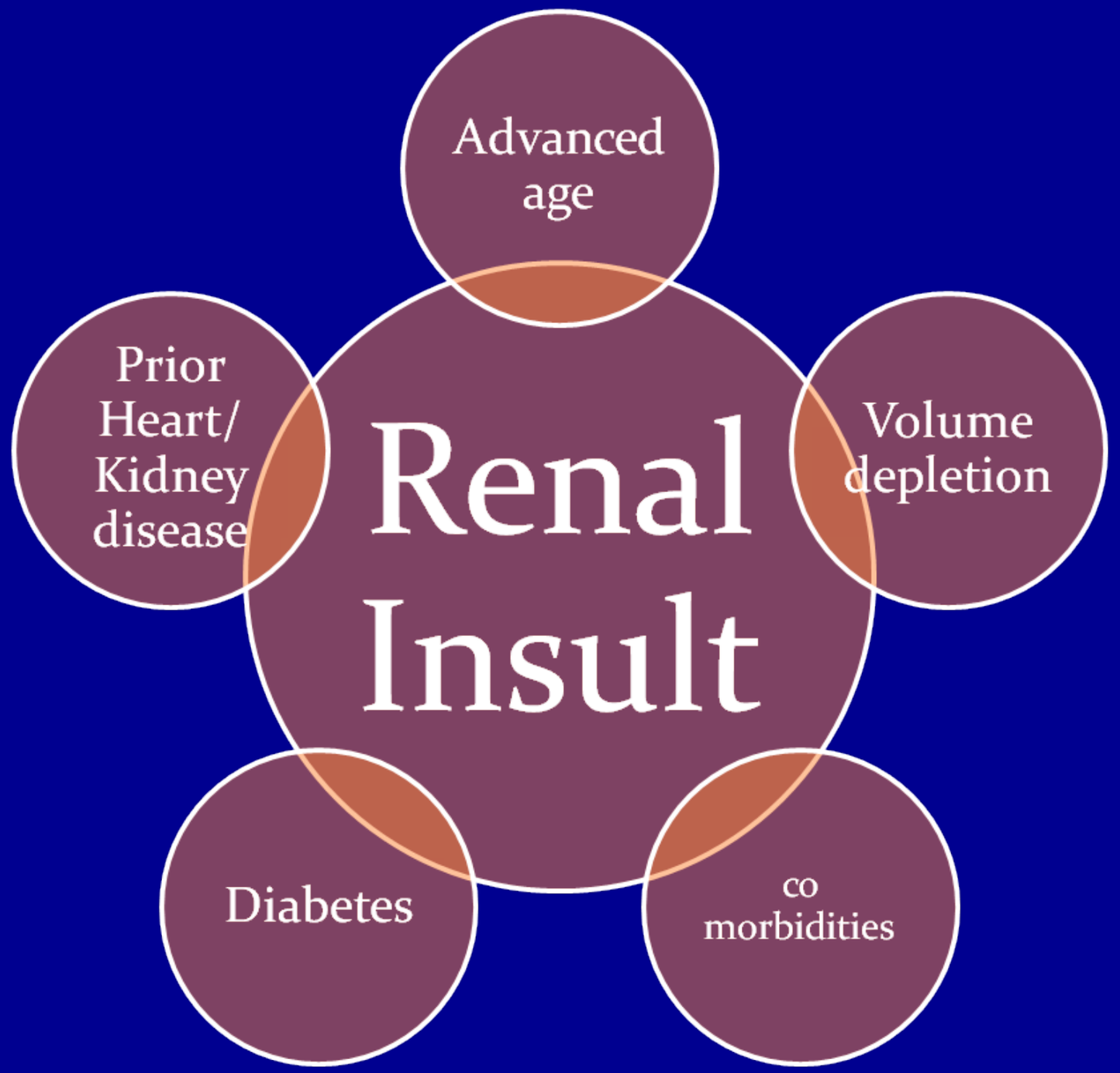
Epidemiology



Epidemiology



High Risk for AKI



Diuretics

- Definition
- Classes
- Practice vs. evidence

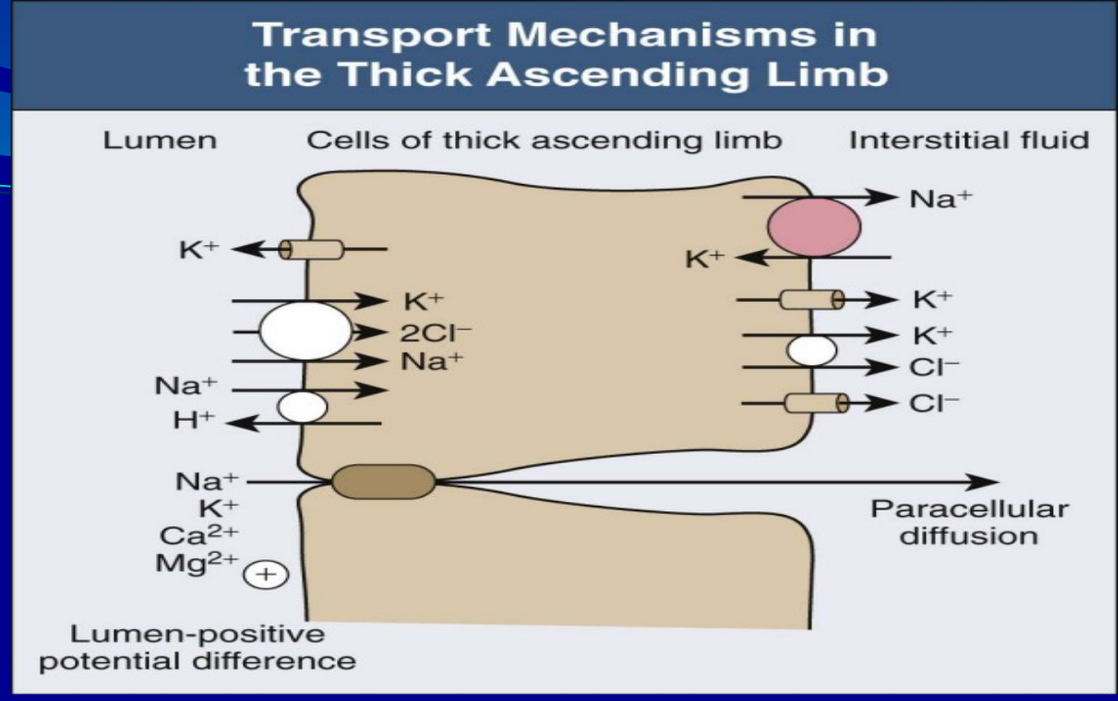
Definition:

These are the group of medications which act by diminishing sodium reabsorption at different sites in the nephron, thereby increasing urinary sodium and water losses

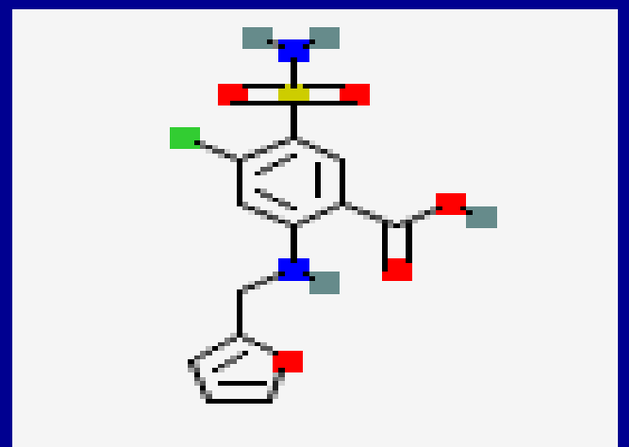
Classification

- Loop diuretics – TAL of Henle
- Thiazide-type diuretics-- distal tubule and connecting segment (and perhaps the early cortical collecting tubule)
- Potassium-sparing diuretics--aldosterone-sensitive principal cells in the cortical collecting tubule
- Acetazolamide and mannitol act at least in part in the proximal tubule
- Vassopressin receptor Antagonists

Loop Diuretics



- Fuoresemide, Bumetanide, Torsemide, ethacrynic acid.
- Furosemide is one of the most frequently prescribed drugs in the United States.
- The principle MOA involves blockade of the Na-K-2Cl transporter on the luminal side of the TAL of Henle.
- Expression of this transporter leads to sodium retention (accounting for high sodium reabsorption of up to 40% of filtered load that normally occurs in this nephron segment) and increases in medullary tonicity leading to increased water reabsorption.
- The expression of the Na-K-2Cl transporter is regulated via cyclic adenosine monophosphate pathways with vasopressin amplifying its expression and prostanoid prostaglandin E2 reducing its expression.



Pharmacokinetics

- Weak organic acid
- Highly protein bound.
- Secreted in urinary space, not filtered!
- Conditions e.g Metabolic acidosis, medications which are protein bound can interfere with their delivery
- Elimination half-life is 1 hour for bumetanide, 1.5 to 2 hours for furosemide, and 3 to 4 hours for torsemide.
- The average bioavailability of oral furosemide is 50%; however, it is highly variable, ranging from 10% to 100%.. In comparison, absorption of oral bumetanide and oral torsemide ranges from 80% to 100%, and hence their oral dose is equivalent to the intravenous dose
- The elimination half-life of furosemide is prolonged (from 1.5-2 to 2.8 h) in patients with renal insufficiency because both urinary excretion and renal metabolism are reduced. In comparison, bumetanide and torsemide are metabolized predominantly in the liver and hence their half-lives are not prolonged in patients with renal insufficiency.

Table 1. Pharmacokinetic data for select diuretics

	Oral Availability, %	Half-Life, hrs	Time to Maximum Serum Concentration, hrs
Loop diuretics			
Torsemide	80–100	3.5	~1.4
Furosemide	10–100	1.5	~2
Bumetanide	80–100	0.8	
Ethacrynic acid	~100	1	
Thiazide/thiazide-like diuretics			
Hydrochlorothiazide	70	~2.5	
Metolazone	65	Variable (see text)	
Chlorothiazide	9–56	~1.5	

Data from References 5, 7, 8, and 62.

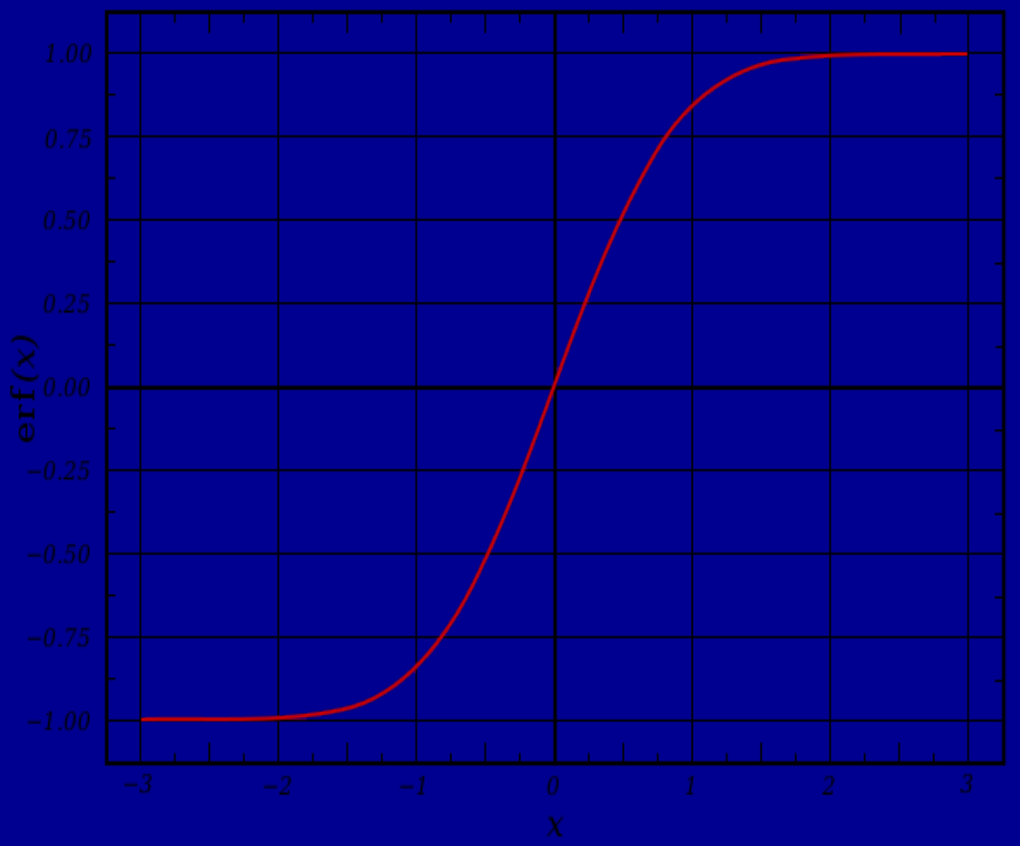
Pharmacokinetic data for select diuretics

Diuretics: Still the mainstay of treatment.
Wang, David; Gottlieb, Stephen

Critical Care Medicine. 36(1) Suppl:S89-S94, January 2008.
DOI: 10.1097/01.CCM.0000296272.68078.6B

Pharmacodynamics

- Diuretic response of Loop Diuretics correlates more with their urinary rather than plasma concentration.
- The relationship between the natriuretic response (measured by fractional excretion of sodium) and the amount of diuretic reaching the site of action is sigmoid shaped.
- This relationship is important clinically in establishing a threshold below which there will be no diuretic action and also a ceiling dose above which no additional diuretic action will take place.
- Thus, once a maximally effective dose of a loop diuretic agent is administered, the only way to increase response is to administer another class of diuretics which act downstream.



Pharmacodynamics

- Natriuretic effect depends on filtered sodium. Other concomitant factors such as heart failure, liver failure, volume depletion, and nonsteroidal anti-inflammatory agents significantly alter the pharmacodynamic properties of loop diuretics.

- Under these condition increasing doses do not produce added natriuresis, in fact frequent modest doses or continuous infusion are better.

- ***Loop diuretic tolerance*** from flooding of the distal nephron sites by the solute not reabsorbed from the loop of Henle à hypertrophy of collecting and connecting duct segments à an increase in the reabsorption of sodium at distal sites and a reduction in total diuresis.

- Bolus therapy vs. Continous

Pharmacodynamics

	Renal insufficiency		Nephrotic syndrome		Cirrhosis	Heart failure
	Moderate	Severe				
Mechanism of diminished response to Diuretic	Impaired delivery to the site of action		Diminished nephron responsiveness		Diminished nephron response	Diminished nephron response
			Binding of diuretic to urinary protein			
Therapeutic strategy	Sufficient doses to attain effective excretion rates of diuretic at the site of action		Increased frequency of effective dose		Increased frequency of effective dose	Increased frequency of effective dose
			Sufficient doses to attain effective excretion rates of unbound diuretic at the site of action			
Ceiling dose, mg (IV)						
Furosemide	80- 160	160- 200	80- 120		40	40- 80
Bumetanide	4-8	8-10	2-3		1	1-2
Tosemide	20-50	50-100	20-50		10	10-20

TRANSLATIONAL PHYSIOLOGYLoop diuretics: from the Na-K-2Cl transporter to clinical use

Pharmacodynamics

Doses for continuous intravenous infusion of loop diuretics					
	Creatinine clearance ml/min				
	All level	<25	25-75	>75	
	Intravenous loading dose, mg	Infusion rate, mg/ hr			
furosemide	40	20 then 40	10 then 20	10	
bumetanide	1	1 then 2	0.5 then 1	0.5	
torsemide	20	10 then 20	5 then 10	5	

Why Diuretics....

- Fluid dilemma in acquired AKI.

- *Reno – protection*
- *Ongoing trial*
- *Atrial Natriuretic peptide*
- *Final word*

Dilemmas of fluid management in acquired AKI

Table 1 | Reasons for decreased glomerular ultrafiltration in patients with acute kidney injury

Abnormality	Physiological effect	Consequence
Low systemic blood pressure Afferent arteriole vasoconstriction Efferent arteriole vasodilatation	Low glomerular hydrostatic pressure	Decreased glomerular filtration
Renal interstitial edema Extrinsic compression Tubular obstruction Failure of downstream tubular reabsorption	High intracapsular pressure	Decreased glomerular filtration
Low renal plasma flow	Rapid rise in oncotic pressure	Decreased glomerular filtration

Dilemmas of fluid management in acquired AKI

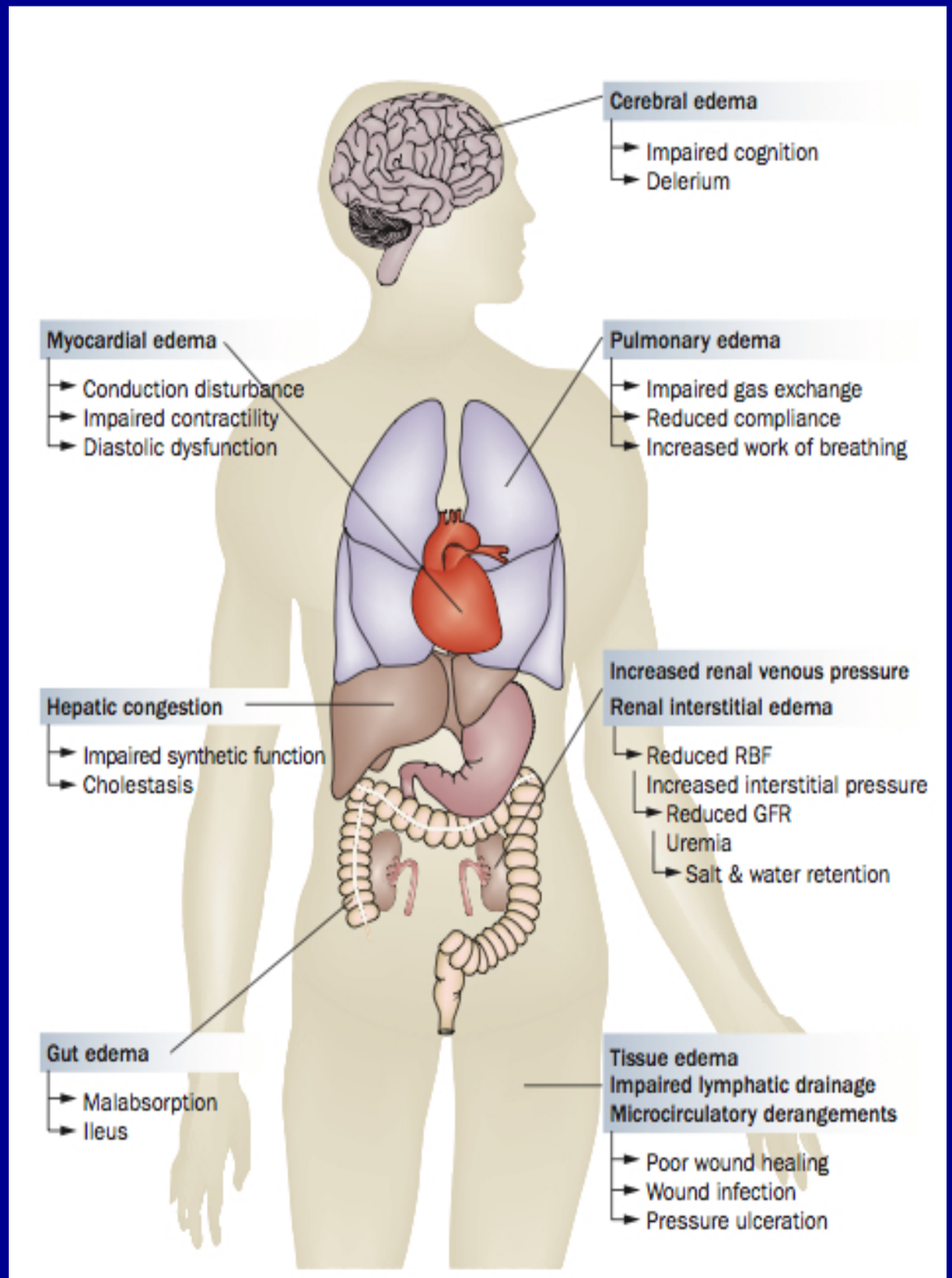


Figure 2 | Pathological sequelae of fluid overload in organ systems. Abbreviations: GFR, glomerular filtration rate; RBF, renal blood flow.

Dilemmas of fluid management in acquired AKI

Table 2 | Publications describing two groups of critically ill patients with differing fluid balances where a renal outcome was reported*

Reference	Study type	Population	*n*	Average fluid balance in less-positive group	Average fluid balance in more-positive group	Renal function measure	Renal outcome with more-restrictive fluid balance strategy	Principal outcome with more-restrictive fluid balance strategy
ARDS Clinical Trials Network (2006)[88]	Multicenter RCT	ARDS	1,000	–136 ml on day 7	+6,992 ml on day 7	Need for RRT; change in creatinine	No difference	Shorter duration of ventilation and ICU stay
Martin *et al.* (2005)[86]	Single-center RCT	Mixed ALI	40	–5,480 ml on day 5	–1,490 ml on day 5	Change in creatinine	No difference	Improved oxygenation
Martin *et al.* (2002)[85]	Single-center RCT	ALI after trauma	37	–3,300 ml on day 5	+500 ml on day 5	Change in creatinine	No difference	Improved oxygenation
Mitchell *et al.* (1992)[127]	Single-center RCT	Mixed ICU needing PAC	102	+142 ml	+2,239 ml	Change in creatinine	Small rise in creatinine	Shorter duration of ventilation and ICU stay
Bouchard *et al.* (2009)[25]	Retrospective observational	Mixed ICU with AKI	542	<10% rise	>10% rise	Dialysis independence	Improved	Decrease in mortality
Payen *et al.* (2008)[6]	Retrospective observational	Mixed ICU with or without AKI	3,147	–1,000 ml	+3,000 ml	Renal SOFA score	Improved	Decrease in mortality in patients with AKI
Vidal *et al.* (2008)[72]	Prospective observational	Mixed ICU with elevated or normal IAP	83	+5,000 ml	+9,000 ml	Renal SOFA score	Improved	Normal IAP associated with less organ failure and shorter ICU stay
Adesanya *et al.* (2008)[128]	Retrospective observational	Surgical ICU	41	+5 kg	+8.3 kg	Change in creatinine	No difference	Shorter duration of ventilation and ICU stay
McArdle *et al.* (2007)[87]	Retrospective observational	Surgical ICU	100	+7,500 ml	+10,000 ml	Change in creatinine	No difference	Decrease in postoperative complications
Arlati *et al.* (2007)[99]	Prospective observational	Burns ICU	24	+7,500 ml	+12,000 ml	Urine output	No difference	Decrease in organ dysfunction score

*See Supplementary Information online for systematic search strategy. Abbreviations: AKI, acute kidney injury; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; IAP, intra-abdominal pressure; ICU, intensive care unit; PAC, pulmonary artery catheter; RCT, randomized, controlled trial; RRT, renal replacement therapy; SOFA, sequential organ failure assessment.

Dilemmas of fluid management in acquired AKI

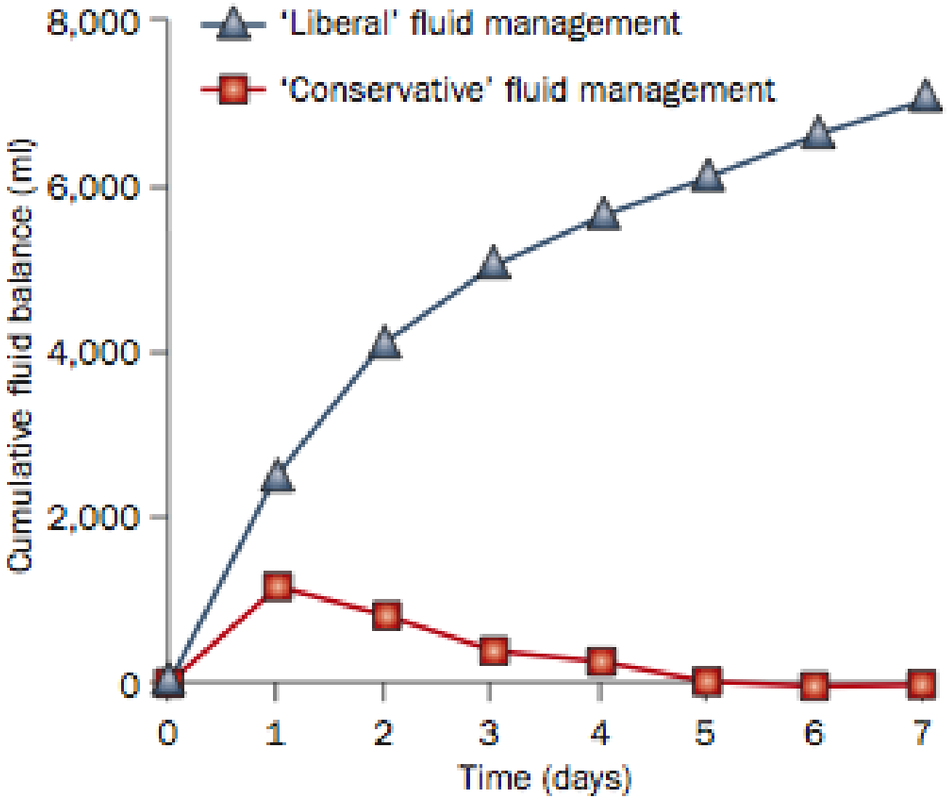


Figure 3 | Cumulative fluid balances achieved in the FACTT trial[88] of liberal (more-conventional) versus conservative (more-restrictive) fluid management strategies in critically ill patients with acute lung injury. No significant differences in renal outcome were found between groups but respiratory parameters were better in patients treated using the conservative approach.

Fluid and Catheter treatment trial (FaCtt)

- Patients were randomly assigned to a strategy involving either conservative or liberal use of fluids with concealed allocation in permuted blocks of eight
- Eligible patients were intubated and received positive-pressure ventilation, had a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) of less than 300
- Exclusion criteria were the presence of chronic conditions that could independently influence survival, impair weaning, or compromise compliance with the protocol; advanced cancer.

Why Diuretics....

- *Fluid dilemma in acquired AKI.*
- Reno - protection
- *Ongoing trial*
- *Atrial Natriuretic peptide*
- *Final word*

Unload the stressed kidney ?

- 1.Acute renal failure = “acute renal success”
- 2.

Acute renal failure is NOT an “acute renal success”—a clinical study on the renal oxygen supply/demand relationship in acute kidney injury

Redfors, Bengt MD, PhD; Bragadottir, Gudrun MD; Sellgren, Johan MD, PhD; Swärd, Kristina MD, PhD; Ricksten, Sven-Erik MD, PhD

Historical fact:

- The renal oxygen supply/demand relationship, are lacking and current views on renal oxygenation in the clinical situation of acute kidney injury are presumptive and largely based on experimental studies.

- Design: Prospectiv, two- group comparative study
- Setting: Cardiothoracic intensive care unit.
- Patients: Post cardiac surgery patients with (n= 12) and without (n= 37) AKI
- Measurement: 1. Renal blood flow (Renal vein thermodilution technique, Infusion clearance of PAHA) 2. Renal oxygen consumption. 3. GFR 4. Renal Oxygenation

Acute renal failure is NOT an "acute renal success"-a clinical study on the renal oxygen supply/demand relationship in acute kidney injury.

Redfors, Bengt; MD, PhD; Bragadottir, Gudrun; Sellgren, Johan; MD, PhD; Sward, Kristina; MD, PhD; Ricksten, Sven-Erik; MD, PhD

Critical Care Medicine. 38(8):1695-1701, August 2010.
DOI: 10.1097/CCM.0b013e3181e61911

Table 3. Systemic variables

	Control Group (n = 37)	AKI Group (n = 12)	*p* Value
MAP (mm Hg)	73.9 ± 1.1	73.5 ± 0.7	ns
CI (L/min/m^2)	2.63 ± 0.08	2.77 ± 0.16	ns
HR (beats/min)	75.4 ± 1.7	88.7 ± 6.1	ns
SVI (ml/beat/m^2)	35.3 ± 1.1	33.1 ± 3.1	ns
CVP (mm Hg)	7.6 ± 0.3	11.4 ± 0.8	<.001
PCWP (mm Hg)	10.1 ± 0.63	15.7 ± 1.01	<.001
SVRI (dynes · sec/cm^5/m^2)	2084 ± 71	1847 ± 88	.048
DO_2I (ml/min/m^2)	378 ± 11	396 ± 25	ns
VO_2I (ml/min/m^2)	101.6 ± 2.6	120.2 ± 4.3	.002
O_2Ex (%)	27.0 ± 0.7	31.6 ± 2.0	ns
SaO_2 (%)	98.3 ± 0.1	97.7 ± 0.4	ns
SvO_2 (%)	71.7 ± 0.7	66.8 ± 1.9	.020
Serum hemoglobin (g/L)	106.5 ± 2.0	105.4 ± 3.1	ns
Arterial lactate (mmol/L)	0.88 ± 0.08	1.53 ± 0.23	.020
Body temperature (°C)	36.5 ± 0.10	37.2 ± 0.27	.046

AKI, acute kidney injury; MAP, mean arterial pressure; ns, not significant; CI, cardiac index; HR, heart rate; SVI, stroke volume index; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; DO_2I, systemic oxygen delivery index; VO_2I, systemic oxygen consumption index; O_2Ex, systemic oxygen extraction; SaO_2, systemic arterial oxygen saturation; SvO_2, mixed venous oxygen saturation.

Values are means ± SEM.

Acute renal failure is NOT an "acute renal success"-a clinical study on the renal oxygen supply/demand relationship in acute kidney injury.

Redfors, Bengt; MD, PhD; Bragadottir, Gudrun; Sellgren, Johan; MD, PhD; Sward, Kristina; MD, PhD; Ricksten, Sven-Erik; MD, PhD

Critical Care Medicine. 38(8):1695-1701, August 2010.

Table 4. Renal variables obtained from the thermodilution and the infusion clearance techniques

	Control Group (n = 37)	AKI Group (n = 12)	*p* Value
RO_2Ex	0.097 ± 0.004	0.163 ± 0.009	<.001
Urine flow (ml/min)	3.73 ± 0.39	4.04 ± 0.48	ns
Thermodilution measurements			
RBF_{TD} (ml/min)	758 ± 40	477 ± 54	<.001
RVR (mm Hg/ml/min)	0.097 ± 0.005	0.146 ± 0.015	.01
GFR (ml/min)	74.7 ± 4.7	32.3 ± 3.6	<.001
FF	0.148 ± 0.006	0.109 ± 0.014	.022
Na^+ filtration (mmol/min)	10.2 ± 0.7	4.4 ± 0.4	<.001
Na^+ resorption (mmol/min)	9.7 ± 0.7	4.0 ± 0.4	<.001
FE_{Na}	0.050 ± 0.007	0.099 ± 0.019	.028
RDO_2 (ml/min)	110.0 ± 6.2	68.0 ± 7.2	<.001
RVO_2 (ml/min)	10.4 ± 0.6	11.0 ± 1.1	ns
Infusion clearance of PAH			
RBF_{IC} (ml/min)	822 ± 40	496 ± 34	<.001
ERBF (ml/min)	779 ± 37	375 ± 35	<.001
RVR (mm Hg/ml/min)	0.086 ± 0.004	0.131 ± 0.095	<.001
GFR (ml/min)	80.3 ± 4.2	33.6 ± 3.4	<.001
FF	0.148 ± 0.005	0.107 ± 0.014	.017
Na^+ filtration (mmol/min)	11.0 ± 0.6	4.6 ± 0.5	<.001
Na^+ resorption (mmol/min)	10.5 ± 0.6	4.2 ± 0.5	<.001
FE_{Na}	0.042 ± 0.004	0.093 ± 0.015	.008
RDO_2 (ml/min)	120,1 ± 6.6	70.9 ± 4.5	<.001
RVO_2 (ml/min)	11.4 ± 0.5	11.8 ± 0.8	ns
PAH extraction	0.85 ± 0.01	0.68 ± 0.04	.002

AKI, acute kidney injury; RO_2Ex, renal oxygen extraction; ns, not significant; RBF_{TD}, renal blood flow assessed by the thermodilution technique; RVR, renal vascular resistance; GFR, glomerular filtration rate; FF, filtration fraction; FE_{Na}, fractional excretion of sodium; RDO_2, renal oxygen delivery; RVO_2, renal oxygen consumption; RBF_{IC}, renal blood flow assessed by infusion clearance; ERBF, effective renal blood flow.

Values are means ± SEM.

Renal variables obtained from the thermodilution and the infusion clearance techniques

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Critical Care Medicine. 38(8):1695-1701, August 2010.
DOI: 10.1097/CCM.0b013e3181e61911

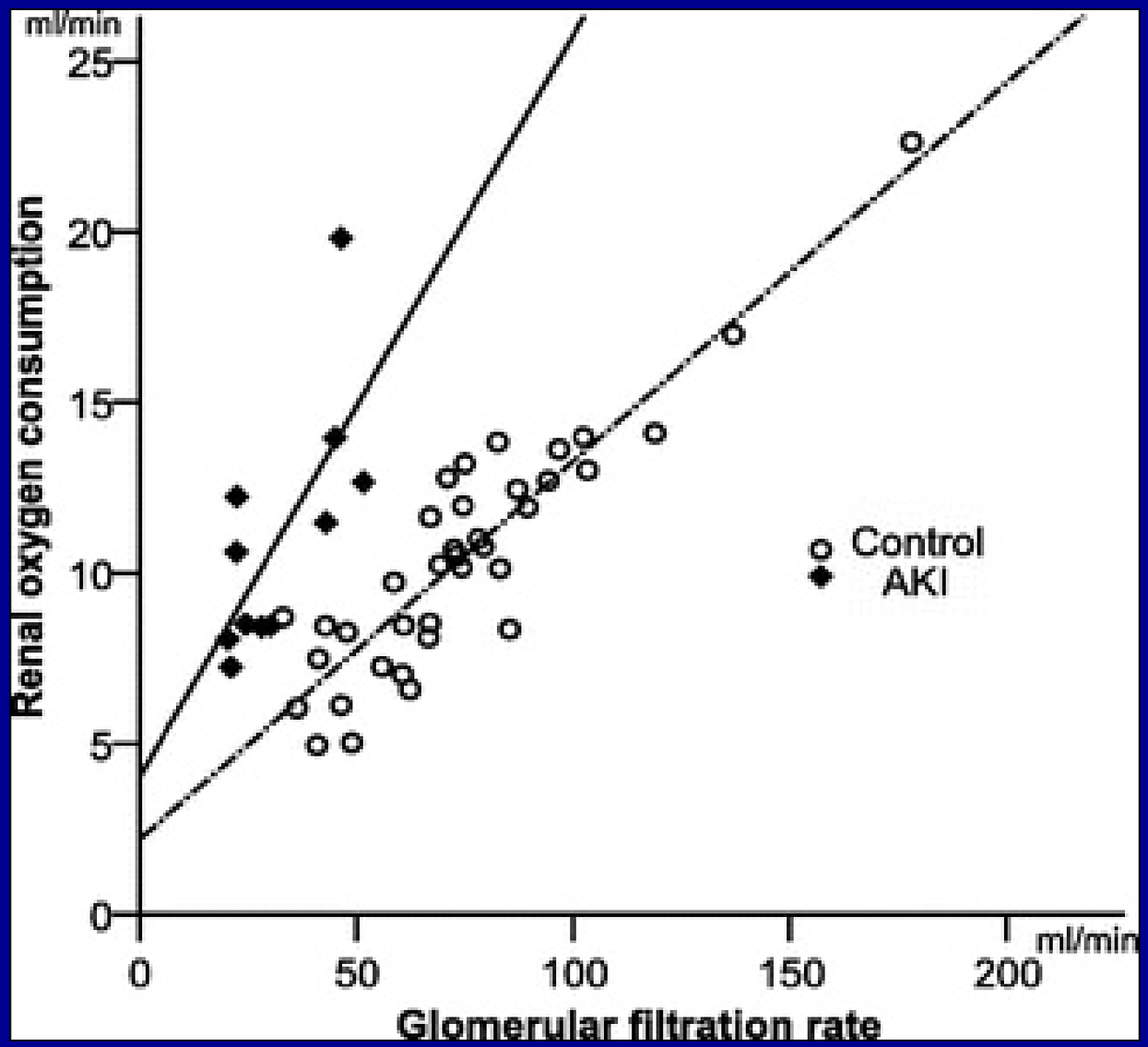

Figure 1. Shows the individual data on the relationship between renal oxygen consumption and glomerular filtration rate for the control group and patients with acute kidney injury (AKI). Note that the slope of the regression line was significantly (p = .04) higher in the AKI group compared with control.

Acute renal failure is NOT an "acute renal success"-a clinical study on the renal oxygen supply/demand relationship in acute kidney injury.

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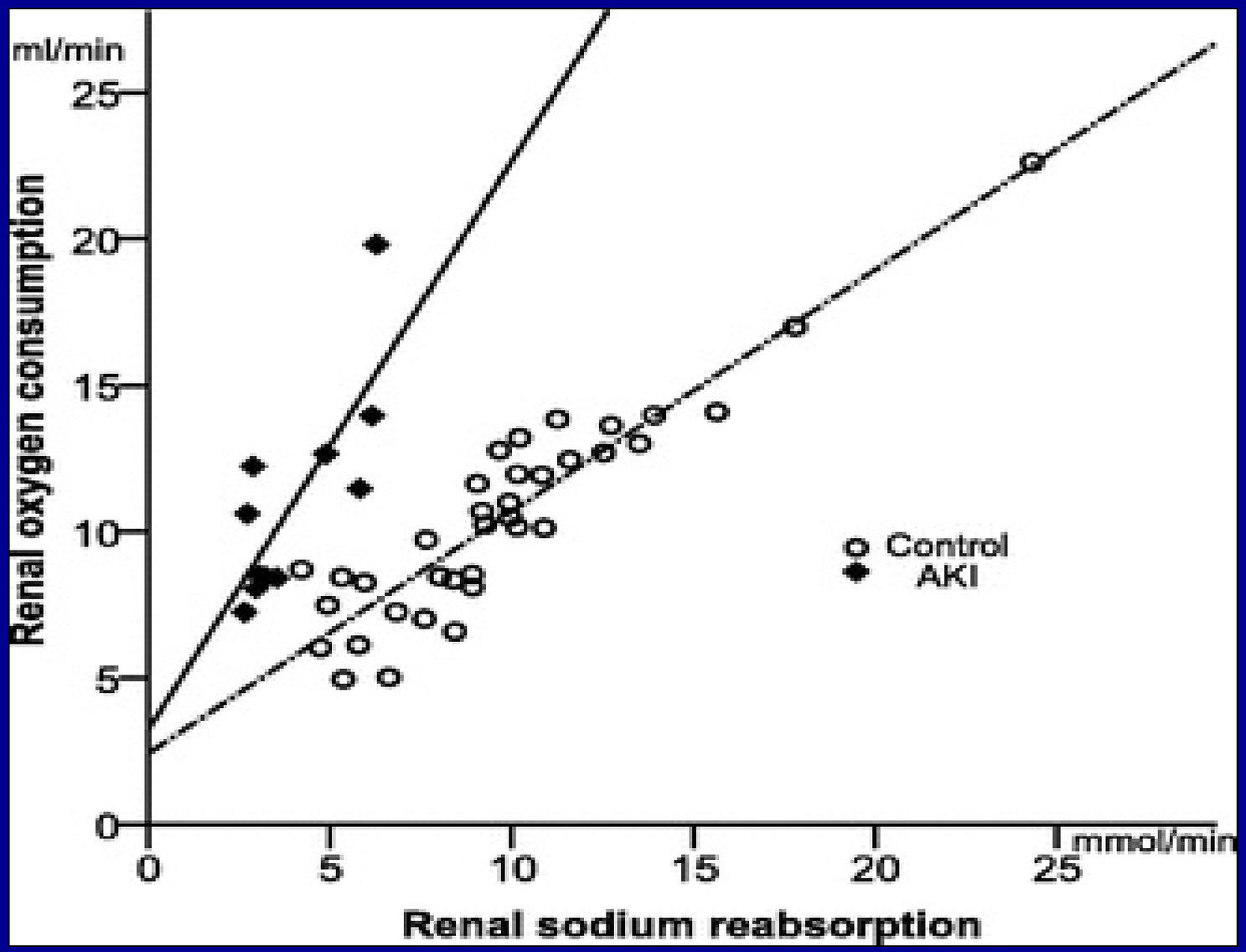

Shows the individual data on the relationship between renal oxygen consumption (RVO2) and renal sodium resorption for the control group (RVO2 = 2.43 + 0.82 x sodium resorption) and patients with acute kidney injury (AKI) (RVO2 = 3.27 + 1.94 x sodium resorption). Note that the slope of the regression line was significantly (p = .004) higher in the AKI group compared with control, whereas the intercepts of the regression lines did not differ significantly.

Acute renal failure is NOT an "acute renal success"-a clinical study on the renal oxygen supply/demand relationship in acute kidney injury.

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- Conclusion:
- Acute renal failure is not renal success.
- Renal oxygen consumption in and around time of AKI is significantly higher.
- The amount of oxygen consumed to absorb certain mmol of Na is significantly higher in AKI as compared to control.

- How can Diuretics be put to use in a condition which predisposes kidneys at risk of oxygen demand and supply mismatch !!!

Differential effect of human atrial natriuretic peptide and furosemide on GFR and renal oxygen consumption

Kristina Swärd[1], Felix Valsson[1], Johan Sellgren[1] and Sven-Erik Ricksten
Department of Cardiothoracic Anesthesia and Intensive Care, Sahlgrenska University Hospital, 41345 Gothenburg, Sweden

Variable	Control	Furosemide	P-value	h- ANP	P - value
Cardiac output (L/min)	5.6	6.1	<0.001	5.0	<0.05
Mean arterial pressure	80.2	80.6	NS	74	<0.001
Renal plasma flow	802	779	NS	655	<0.05
GFR (ml/min)	89.1	78.5	<0.001	97	<0.001
Na reabsorption mmol	12.0	7.7	<0.001	13.3	<0.01
Fena (%)	1.8	29.4	<0.001	5.4	<0.05
Urine flow (ml/min)	2.4	23.3	<0.001	4.7	<0.05
RVO2 consumption	11.1	7.9	<0.001	13.0	<0.001
O2 extraction (renal)	10.5	8.5	<0.05	13.3	<0.001

Sward et al ICM 2005

- Can Diuretics prevent AKI….

Experimental Evidence of Loop Diuretics

- The bulk of the kidney's metabolic activity is devoted to sodium reabsorption.
- The medullary thick ascending limb lives on thin balance. (partial pressure 15mm Hg) à prone to ischemic injury
- Experimental evidence has shown that loop diuretics:
- Increase oxygenation of renal tissue.
- Prevent renal adenosine 5' triphosphate depletion.
- Increases in glomerular filtration rate.
- Improvement in renal blood flow.
- Prevention of tubular obstruction by increasing tubular flow by flushing tubular debris.
- Low-dose furosemide can reduce ischemia/reperfusion injury by improving renal hemodynamics and attenuating ischemia-related changes in angiogenic gene transcription.
- Low-dose furosemide infusion also has been shown to attenuate ischemia/reperfusion-induced apoptosis.

Effects of Saline, Mannitol, and Furosemide on Acute Decreases in Renal Function Induced by Radiocontrast Agents

Richard Solomon, Craig Werner, Denise Mann, John D'Elia, and Patricio SilvaN Engl J Med 1994; 331:1416-142November 24, 1994

- Prospective study; 78 patients with CRI (mean [SD] SCr = 2.1 0.6 mg per deciliter who underwent cardiac angiography.
- Randomly assigned to receive 0.45 percent saline alone for 12 hours before and 12 hours after angiography,saline plus mannitol, or saline plus furosemide.
- The mannitol and furosemide were given just before angiography. Serum creatinine was measured before and for 48 hours after
- An acute radiocontrast-induced decrease in renal function was defined as an increase in the base-line SCr concentration of at

after the injection of radiocontrast agents.

Effects of Saline, Mannitol, and Furosemide on Acute Decreases in Renal Function Induced by Radiocontrast Agents

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Variable	P value	Saline N = 28	Mannitol and saline N = 25	P value	Furosemide and saline N = 25	P value
Changes in serum creatinine mg/dl						
24 hr after radiocontrast agent	0.003	0.0 +/-0.2	0.2 +/- 0.2	0.01	0.3 +/- 0.4	0.002
48 hr after radiocontrast agent	0.021	0.1 +/- 0.5	0.3 +/- 0.4	0.10	0.5 +/- 0.6	0.002
Incidence of acute renal dysfunction– no of patient %	0.05	3 (11)	7 (28)	0.16	10 (40)	0.02

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CONCLUSION:

- **In patients with chronic renal insufficiency who are undergoing cardiac angiography, hydration with 0.45 percent saline provides better protection against acute decreases in renal function induced by radiocontrast agents than does hydration with 0.45 percent saline plus mannitol or furosemide.**

Forced euvolemic diuresis with mannitol and furosemide for prevention of contrast-induced nephropathy in patients with CKD undergoing coronary angiography: a randomized controlled trial.

Majumdar SR, Kjellstrand CM, Tymchak WJ, Hervas-Malo M, Taylor DA, Teo KK.
Department of Medicine, University of Alberta, Edmonton, Alberta, Canada. Am J Kidney Dis. 2009 Oct;54(4):602-9. Epub 2009 Jun 17

- **BACKGROUND: Contrast-induced nephropathy is common in patients with coronary angiography. Mechanistically, forced euvolemic diuresis with mannitol and furosemide ought to prevent contrast-induced nephropathy.**

- **Objective: (1) undertake a randomized trial testing this hypothesis, and (2) conduct a meta-analysis of our findings with 2 earlier studies.**

- **STUDY DESIGN:(1) Randomized allocation-concealed controlled trial with blinded ascertainment of outcomes, and (2) random-effects meta-analysis of 3 trials.**

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES
Official Journal of the National Kidney Foundation

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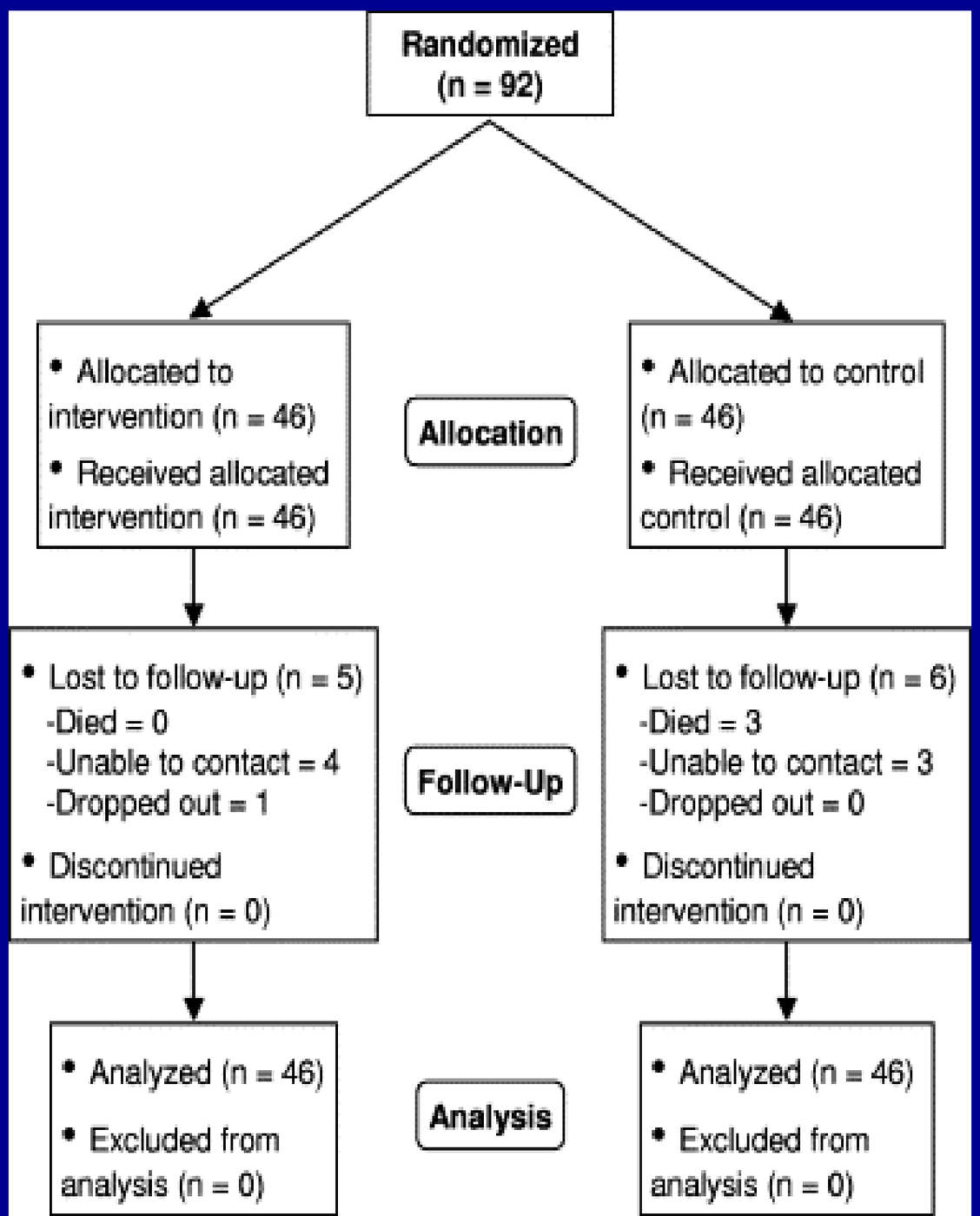

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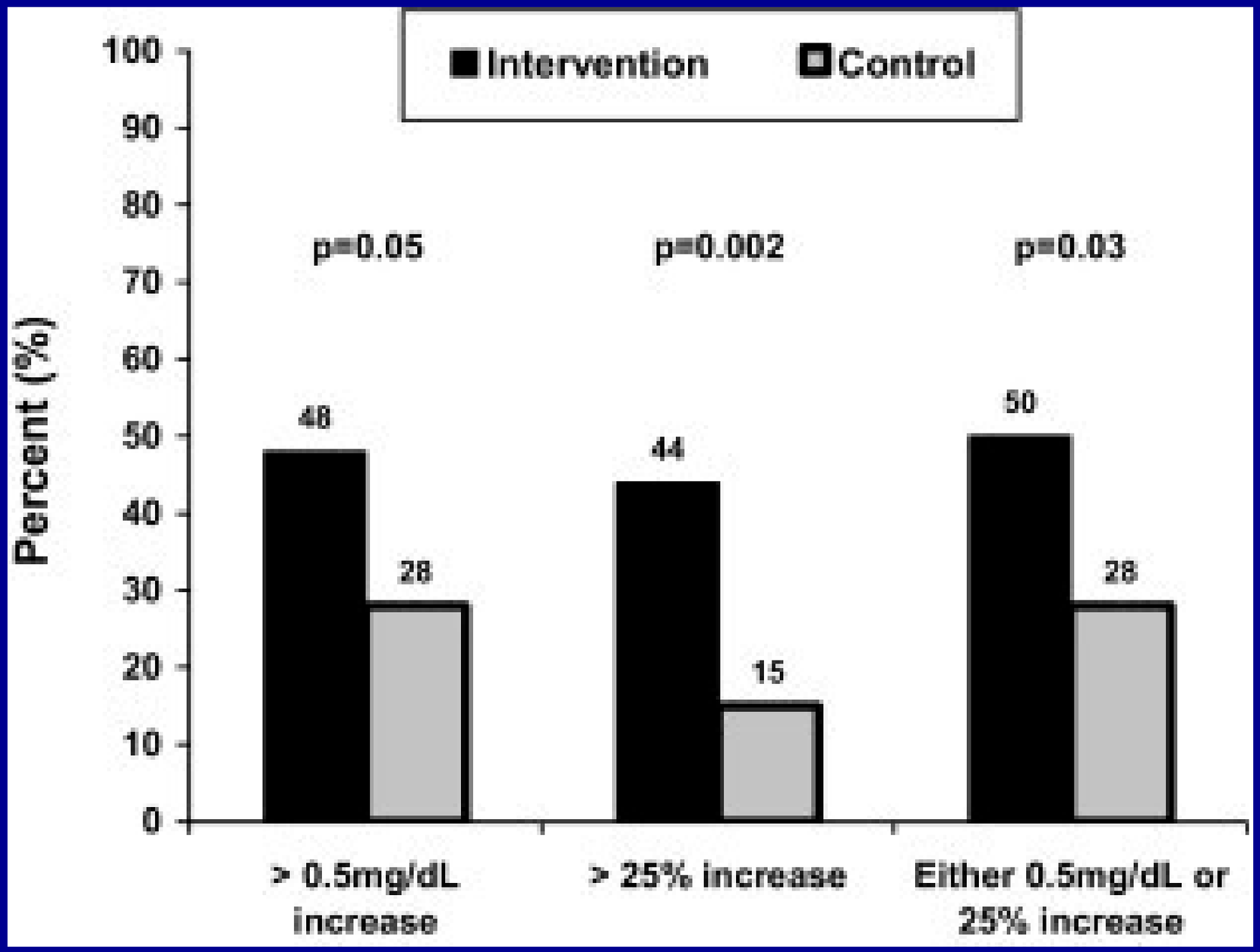

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Adverse clinical event	Intervention (n= 46)	Control (n = 46)	P
Dialysis	5 (11)	4 (9)	0.9
Doubling of creatinine or dialysis	6 (13)	4(9)	0.5
Death	0	3 (7)	0.1
Death or dialysis	5 (11)	7 (15)	0.5
Transfer to ICU	0	0	-
LENGTH OF STAY (D)	13 +/- 21	10 +/-	0.3

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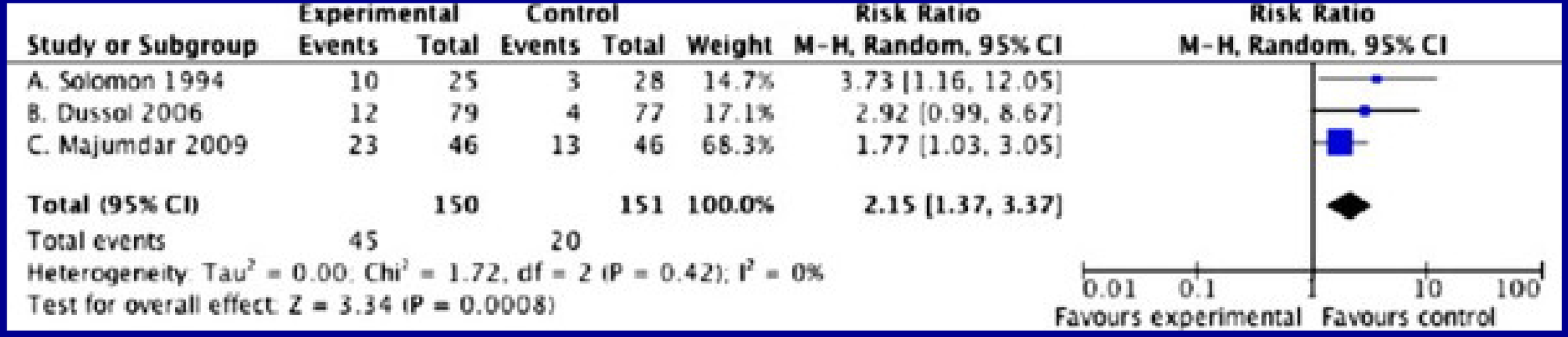

Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomized study

Shilliday IR, Quinn KJ, Allison ME.
Nephrol Dial Transplant. 1997 Dec;12(12):2592-6.

- Method:
- Total number of patients = 92
- All received IV dopamine 2 ug/kg body weight/ min throughout.
- 20 % mannitol 100ml q6h first 3 days
- Than in a double blind manner either furosemide, torsemide or placebo 3mg/kg body weight I.V q6h for 21 days or until renal recovery or Death.

Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomized study

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Demographis and clinical features				
	Torsemide	Furosemide	Placebo	P
Age (years)	58.7 +/- 13.8	59.2 +/-16.5	58.3 +/- 14.1	0.97
Sex (%)				
Male	53	50	63	
female	47	50	37	
Apache II score (pre-study)	19.6 +/- 4.5	19.1 +/- 7.2	18.4 +/- 5.8	0.77
Creatinine clearance (ml/min)	10 +/- 11	8 +/- 9	7 +/- 8	0.45
Hourly urine volume (ml/hr0	24 +/- 18	32 +/- 4.5	20 +/- 16	0.32

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Outcome of actual renal failure at day 21				
	Torsemide (%)	Furosemide (%)	Placebo (%)	P
Increase in urine flow	57	48	23	0.02
Renal recovery	17	28	23	0.56
dialysis	36	31	40	0.87
Death by 21 days No dialysis	47	41	37	0.73
Total death by 21 days	70	66	50	0.24

Final outcome by day 56 of people requiring dialysis			
	Torsemide (%)	Furosemide (%)	P
Death	64	60	42

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Diuretics, Mortality, and Nonrecovery of Renal Function in Acute Renal Failure

Ravindra L. Mehta, MD; Maria T. Pascual, RN, MPH; Sharon Soroko, MS M. Chertow, MD, MPH; for the PICARD Study Group

Secondary retrospective analysis from the Project to Improve Care in Acute Renal Disease (PICARD) database

- Population: 552 (64%) critically ill patients with AKI (defined as BUN>40 mg/dL, sCr>2 mg/dL or sustained rise >1 mg/dL above baseline.
- Intervention/Exposure: Diuretic use at any time in 7 days following nephrology consultation.
- Outcome: Death, non-recovery

Mehta et al JAMA 2002

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Diuretics, Mortality, and Nonrecovery of Renal Function in Acute Renal Failure

Ravindra L. Mehta, MD; Maria T. Pascual, RN, MPH; Sharon Soroko, MS M. Chertow, MD, MPH; for the PICARD Study Group

Diuretics were used in 59% (n= 326)		
Diuretics given on day 1	N%	Dose
Furosemide	203 (62)	80 (20- 320)
Bumetanide	106 (58)	10 (2- 29)
Metolazone	106 (33)	10 (5-20)
Hydrodiuril	13 (4)	-
Loop + thiazide	105 (32)	-

Table 1. Baseline Patient Characteristics on First Day of Nephrology Consultation*.

Table 1. Baseline Patient Characteristics on First Day of Nephrology Consultation*

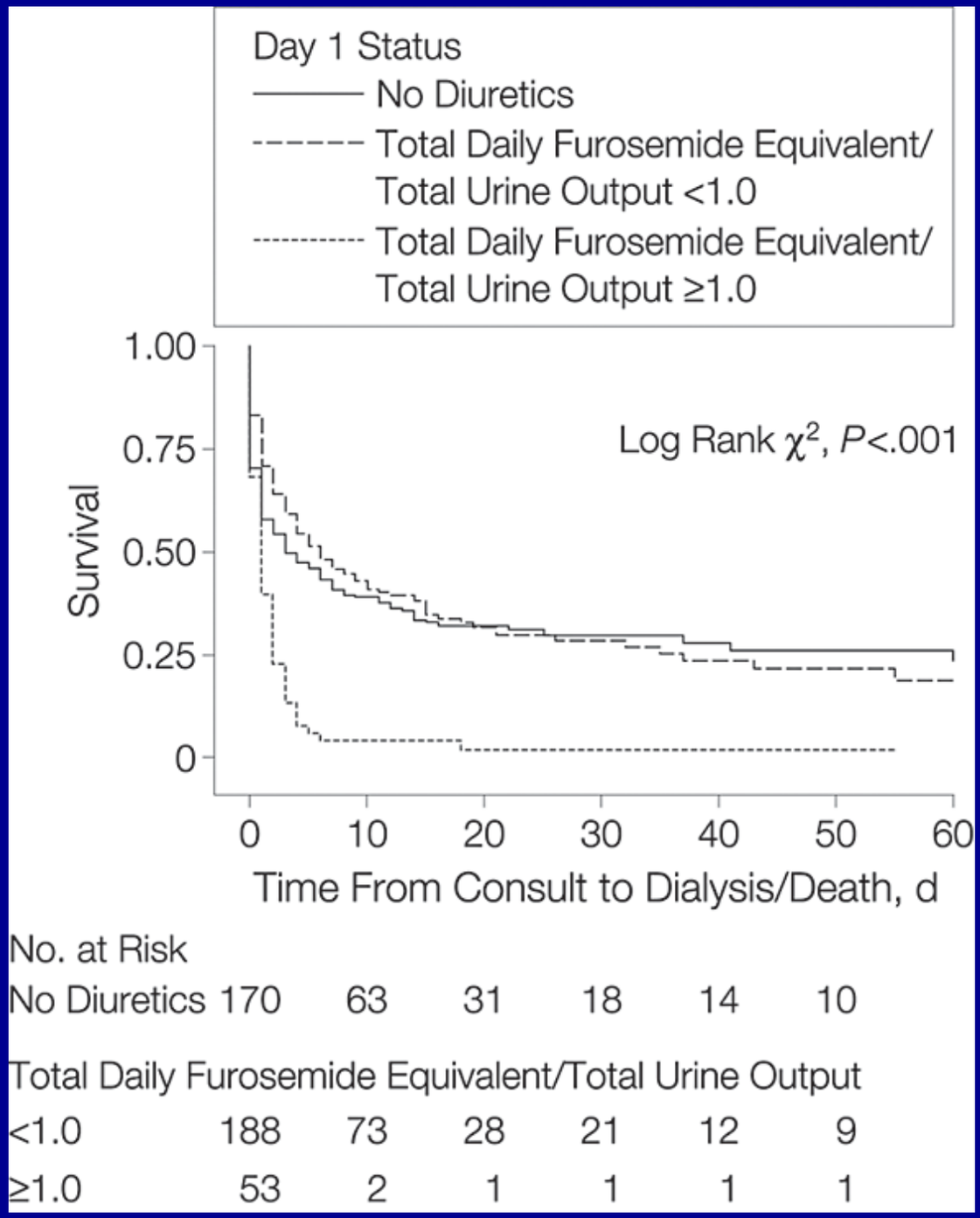
Demographics and History	No Diuretic (n = 226)	Diuretic (n = 326)	*P* Value
Age, mean (SD), y	53.8 (18.0)	58.1 (17.1)	.005†
Male, No. (%)	168 (74)	230 (71)	.33
Race, No. (%)			
White	125 (55)	203 (62)	.12†
African American	50 (22)	46 (14)	
Hispanic	2 (1)	5 (2)	
Asian	21 (9)	37 (11)	
Other or unknown	28 (12)	35 (11)	
Surgical, No. (%)	77 (65)	96 (62)	.28
Oliguria, No. (%)	71 (32)	100 (31)	.75
ARF on CRI, No. (%)	56 (25)	83 (26)	.86
Hyperkalemia, No. (%)‡	17 (8)	29 (9)	.57
History of CHF, No. (%)	30 (13)	87 (27)	<.001†
History of liver disease, No. (%)	49 (22)	54 (17)	.13†
Etiology of acute renal failure, No. (%)			
Ischemic	98 (43)	128 (40)	.34
Nephrotoxic	28 (12)	61 (19)	.05†
Multifactorial	43 (19)	49 (15)	.22†
Unknown	57 (25)	88 (27)	.64
Renal function			
Mean (SD) BUN, mg/dL	72.3 (43.4)	61.6 (34.6)	.001†
Mean (SD) creatinine, mg/dL	4.1 (3.3)	3.6 (1.9)	.02†
Median urine output, mL/d	955	888	.49
Physiologic indicators			
Temperature, mean (SD), °C	37 (1.2)	37 (1.1)	.63
Heart rate, mean (SD), beats/min	102 (24)	100 (22)	.24†
Systolic blood pressure, mean (SD), mm Hg	122 (33)	117 (29)	.07†
Diastolic blood pressure, mean (SD), mm Hg	61 (17)	59 (17)	.30
Arterial pressure, mean (SD), mm Hg	81 (21)	78 (20)	.19†
Central venous pressure, mean (SD), mm Hg§	15 (7)	15 (6)	.77
Pulmonary artery wedge pressure, mean (SD), mm Hg§	18 (8)	20 (7)	.04
Cardiac output, mean (SD), L/min§	8.5 (3.9)	6.9 (3.1)	<.001
Cardiac index, mean (SD), L/min/m^2§	4.6 (2.0)	3.7 (1.6)	<.001
Systemic vascular resistance, mean (SD), dynes·s·cm^{-5}§	728 (429)	903 (811)	.02
Po_2, mean (SD), mm Hg§	102 (48)	98 (49)	.43
Pco_2, mean (SD), mm Hg§	35 (9)	37 (9)	.11
pH, mean (SD)§	7.3 (0.1)	7.4 (0.1)	.21
APACHE III score, mean (SD)§	86.7 (32.9)	86.1 (30.5)	.84
APACHE II score, mean (SD)§	19.0 (7.8)	18.8 (7.4)	.54
Organ system failure, No. (%)			
Respiratory	143 (64)	241 (74)	.01†
Cardiac	75 (33)	148 (45)	.005†
Liver	75 (33)	109 (33)	.98
Hematologic	73 (32)	92 (28)	.29
Central nervous system	82 (36)	112 (34)	.61

*ARF indicates acute renal failure; CRI, chronic renal insufficiency; CHF, congestive heart failure; BUN, blood urea nitrogen; and APACHE, Acute Physiology and Chronic Health Evaluation. To convert milligrams per deciliter to micromoles per liter (creatinine), multiply by 88.4. To convert milligrams per deciliter to millimoles per liter (BUN), multiply by 0.357.
†Entry included as candidate variable for propensity score; physiologic variables not included in propensity score because not available on all or nearly all patients.
‡Hyperkalemia was defined as a potassium level of more than 6 mEq/L.
§For selected physiologic indicators, sample sizes range from 90 to 180 for "no diuretic" group and 133 to 260 for "diuretic" group.

Mehta, R. L. et al. JAMA 2002;288:2547-2553

JAMA

Figure 2. Time to Death or Dialysis From Day of Consultation in Intensive Care Unit Groups are stratified by day 1 status.



Mehta, R. L. et al. JAMA 2002;288:2547-2553

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Figure 1. Time Trends in Mean Serum Creatinine Levels, Mean Blood Urea Nitrogen Levels, and Median Urine Output Among the 416 Patients Who Survived for at Least 7 Days After Nephrology Consultation in the Intensive Care Unit (ICU) Groups are stratified by day 1 status: no diuretics vs diuretic therapy with response.

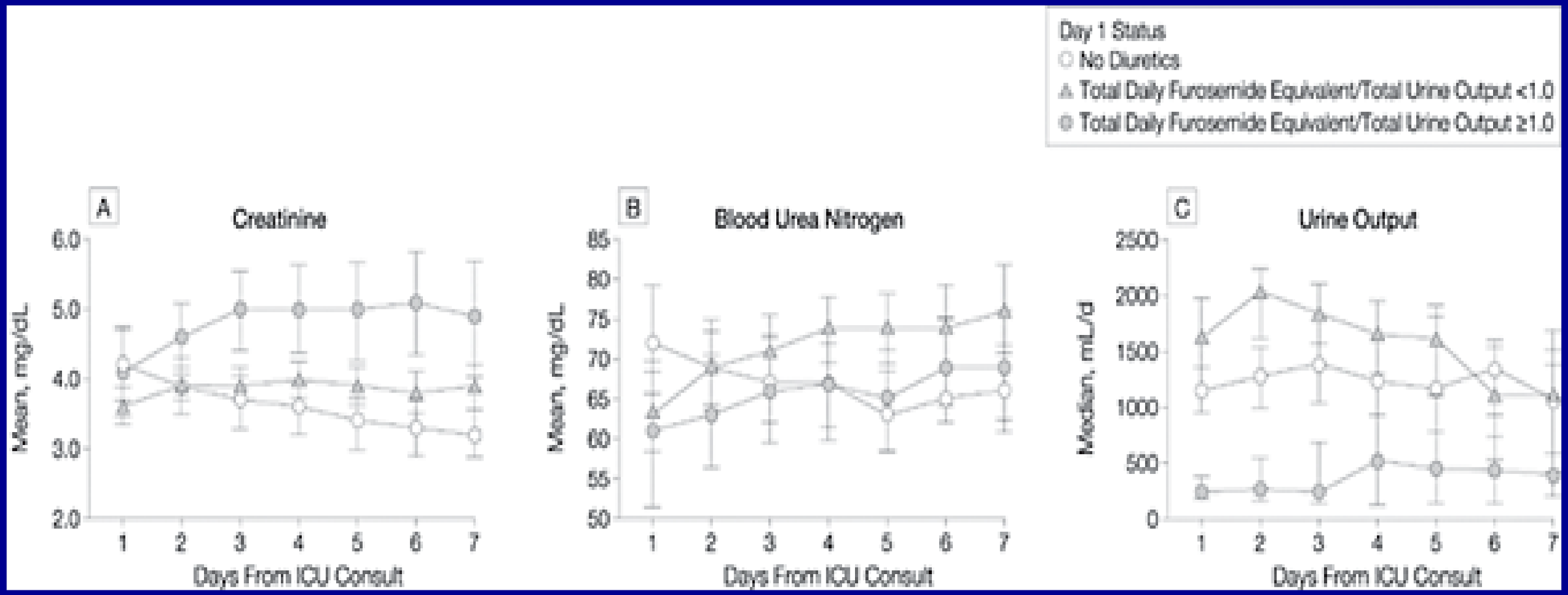

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Table 2. Effect of Diuretics on Mortality and Nonrecovery of Renal Function Compared With No Diuretic Use*.

Table 2. Effect of Diuretics on Mortality and Nonrecovery of Renal Function Compared With No Diuretic Use*

	OR (95% CI)		
Variable	**Unadjusted**	**Covariate Adjusted**	**Covariate and Propensity Score Adjusted**
In-hospital mortality	1.37 (0.97-1.92)	1.65 (1.05-2.58)	1.68 (1.06-2.64)
Nonrecovery of renal function	1.53 (1.08-2.15)	1.70 (1.14-2.53)†	1.79 (1.19-2.68)§
Death or nonrecovery	1.48 (1.02-2.12)	1.74 (1.12-2.68)‡	1.77 (1.14-2.76)‖

*Covariate adjusted for age; sex; log urine output; serum creatinine level; blood urea nitrogen level; respiratory, hepatic, and hematologic failure; and heart rate. The referent group was no diuretics; time was first day of intensive care unit consultation. OR indicates odds ratio; CI, confidence interval.
†Area under receiver operating characteristic (ROC) curve = 0.76; goodness-of-fit χ^2 P = .89.
‡Area under ROC curve = 0.82; goodness-of-fit χ^2 P = .39.
§Area under ROC curve = 0.85; goodness-of-fit χ^2 P = .84.
‖Area under ROC curve = 0.81; goodness-of-fit χ^2 P = .58.

Mehta, R. L. et al. JAMA 2002;288:2547-2553

Conclusion:
The use of diuretics in critically ill patients with acute renal failure was associated with an increased risk of death and nonrecovery of renal function.

JAMA

Diuretics and mortality in acute renal failure .

Uchino, Shigehiko; Doig, Gordon; Bellomo, Rinaldo; Morimatsu, Hiroshi; Morgera, Stanislao; Schetz, Miet; Tan, Ian; Bouman, Catherine; Macedo, Ettiene; Gibney, Noel; Tolwani, Ashita; Ronco, Claudio; Kellum, John
Beginning and Ending Support Therapy for the Kidney (B.E.S.T. Kidney) Investigator

Secondary analysis of the Beginning and Ending Support Therapy (BEST) for the Kidney database

- 1. Population: 1,731 critically ill patients with AKI (defined by: need for RRT; BUN>86 mg/ dL, K>6.5 mmol/L; oliguria <200mL/12hr; anuria)
- 2. Intervention/Exposure: Diuretic use after study enrolment
- 3. Outcome: In-hospital death

Diuretics and mortality in acute renal failure .

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Beginning and Ending Support Therapy for the Kidney (B.E.S.T. Kidney) Investigator

Diuretic use	N (%)
Any diuretic use	1.117 (60.8)
Furosemide	1.098 (98.3)
Other loop diuretic	29 (2.6)
Mannitol	22 (2.00
Metolazone	19 (1.7)
Spironalactone	18 (1.6)
Thiazide	14 (1.3)
other	14 (1.3)

Diuretics and mortality in acute renal failure *.

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Critical Care Medicine. 32(8):1669-1677, August 2004.
DOI: 10.1097/01.CCM.0000132892.51063.2F

Table 1. Baseline patient characteristics at the time of study inclusion

	Total	No Diuretics	Diuretics
No. of patients	1,743	626	1,117
Patient age, yrs[a,b]	67 (53–75)	64 (50–74)	68 (55–75)
Male gender, %	63.9	65.2	63.1
Body weight, kg	74 (63–85)	74 (60–85)	74 (64–84)
Premorbid renal function, %			
Normal	55.9	51.6	58.4
Chronic impairment[b]	29.7	28.8	30.3
Unknown	14.3	19.6	11.4
Premorbid Cr, μmol/L	97 (79–150)	99 (78–167)	97 (79–147)
Hospital to ICU, days[b]	1 (0–6)	1 (0–4)	2 (0–7)
ICU to study inclusion, days[a,b]	1.1 (0.3–3.8)	0.7 (0.1–2.6)	1.7 (0.5–4.6)
SAPS II[a,b]	48 (38–61)	50 (40–63)	47 (37–60)
Cr at ICU admission, μmol/L[a,b]	180 (110–310)	211 (117–383)	163 (106–283)
Urea at ICU admission, mmol/L[a,b]	14.9 (8.8–27.0)	16.5 (9.2–31.1)	14 (8.6–24.6)
Estimated Cr clearance, mL/min	35 (20–59)	31 (17–57)	37 (21–60)
Contributing factors to ARF, %			
Sepsis/septic shock[a,b]	46.8	52.0	43.8
Major surgery[a,b]	34.5	26.4	39.1
Low cardiac output[a,b]	26.7	21.3	29.7
Hypovolemia[a]	26.3	25.1	28.2
Drug induced[a,b]	19.0	18.2	19.4
Hepatorenal syndrome[a]	5.7	8.0	4.4
Obstructive uropathy[a,b]	2.8	3.5	2.3

Cr, creatinine; hospital to ICU, duration between hospital admission and intensive care unit admission; ICU to study inclusion, duration between ICU admission and study inclusion; SAPS, Simplified Acute Physiology Score; ARF, acute renal failure.

[a]Variable was associated with diuretic use and qualified for consideration in new propensity score (univariate logistic regression $p \leq .25$); [b]variable was associated with mortality (univariate logistic regression $p \leq .25$). Data are presented as median (interquartile range) or percentage.

Diuretics and mortality in acute renal failure *.

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Table 2. Diagnostic group at intensive care unit admission for patients with acute renal failure

	Total, %	No Diuretics, %	Diuretics, %
Medical admission			
Cardiovascular	11.1	10.5	11.5
Respiratory	13.3	13.6	13.1
Gastrointestinal	9.9	14.2	7.5
Neurologic	2.0	2.2	1.9
Sepsis	10.0	13.4	8.1
Trauma	2.0	3.2	1.3
Metabolic	3.7	5.3	2.8
Hematologic	4.6	5.1	4.4
Renal	2.2	3.0	1.7
Surgical admission			
Cardiovascular	23.2	9.4	30.9
Respiratory	1.8	2.6	1.4
Gastrointestinal	11.4	12.1	10.9
Neurologic	0.6	0.6	0.6
Trauma	2.3	2.1	2.4
Renal	0.9	1.0	0.9
Gynecologic	0.3	0.3	0.4
Orthopedic	0.6	1.3	0.3

Table 2. Diagnostic group at intensive care unit admission for patients with acute renal failure

Diuretics and mortality in acute renal failure *.

Uchino, Shigehiko; Doig, Gordon; Bellomo, Rinaldo; Morimatsu, Hiroshi; Morgera, Stanislao; Schetz, Miet; Tan, Ian; Bouman, Catherine; Macedo, Ettiene; Gibney, Noel; Tolwani, Ashita; Ronco, Claudio; Kellum, John

Critical Care Medicine. 32(8):1669-1677, August 2004.
DOI: 10.1097/01.CCM.0000132892.51063.2F

Table 3. Physiologic and laboratory variables for patients with acute renal failure

	Total		No Diuretics		Diuretics	
Heart rate, beats/min[a]	98	(84–112)	99	(84–115)	98	(84–112)
Respiratory rate, breaths/min[b]	18	(15–24)	20	(15–24)	18	(15–23)
Systolic AP, mm Hg[a,b]	112	(100–130)	111	(97–130)	114	(100–130)
Diastolic AP, mm Hg[a]	57	(50–66)	56	(49–66)	59	(50–66)
Mean AP, mm Hg[a,b]	75	(66–86)	75	(65–85)	75	(67–87)
SBP <100 mm Hg, %[a,b]		37.7		39.9		36.5
CVP, mm Hg[a,b]	13	(10–18)	13	(9–17)	14	(10–18)
PAC usage[b]		24.9%		23.0%		26.0%
PAOP, mm Hg	18	(15–22)	17	(14–21)	18	(15–22)
Glasgow Coma Scale score[a,b]	14	(10–15)	13	(8–15)	14	(11–15)
Mechanical ventilation, %[a,b]		75.4		72.4		77.1
Vasopressors/inotropes, %[a,b]		68.8		63.4		71.9
Urine output						
mL/6 hrs[a,b]	120	(40–379)	100	(25–350)	140	(50–400)
mL/24 hrs	675	(250–1509)	475	(189–1343)	756	(290–1638)
Furosemide						
mg/6 hrs		—		—	80	(20–200)
mg/24 hrs		—		—	240	(80–500)
RRT requirement, %[b]		71.5		66.8		74.2
WCC, $\times 10^3/\mu L$[b]	13.2	(8.9–19.3)	13.5	(8.2–20.3)	13.0	(9.1–19.0)
Platelet count, $\times 10^3/\mu L$[a,b]	127	(69–204)	136	(66–214)	126	(71–200)
Creatinine, μmol/L[a,b]	283	(187–407)	277	(172–432)	285	(194–399)
Urea, mmol/L[a,b]	27.5	(16.0–33.6)	28.3	(14.3–34.6)	27.0	(16.9–33.0)
Bilirubin, mmol/L[a,b]	19	(11–51)	20	(10–61)	18	(11–45)
Sodium, mmol/L[a]	139	(134–143)	139	(134–143)	139	(135–143)
Potassium, mmol/L[a]	4.5	(4.0–5.2)	4.5	(4.0–5.3)	4.5	(4.0–5.2)
Pao_2/Fio_2 ratio[a,b]	211	(141–301)	208	(141–305)	214	(141–300)
pH[a,b]	7.33	(7.25–7.40)	7.33	(7.23–7.40)	7.34	(7.26–7.41)

AP, arterial pressure; SBP, systolic blood pressure; CVP, central venous pressure; PAC, pulmonary artery catheter; PAOP, pulmonary artery occlusion pressure; RRT, renal replacement therapy; WCC, white cell count.

[a]Variable was associated with mortality (univariate logistic regression $p \leq 0.25$); [b]variable was associated with diuretic use and qualified for consideration in new propensity score (univariate logistic regression $p \leq 0.25$). Data are presented as median (interquartile range) or percentage.

Table 4. Outcomes of patients with acute renal failure

	Total	No Diuretics	Diuretics
Length of ICU stay, days	10 (5–22)	9 (4–20)	11 (5–22)
Length of hospital stay, days	22 (11–44)	21 (9–44)	23 (12–45)
ICU mortality, %	51.6	48.2	53.4
Hospital mortality, %	60.5	57.1	62.4
Hospital discharge without RRT, %	34.7	38.2	32.7
Hospital discharge with RRT, %	4.8	4.6	4.9

ICU, intensive care unit; RRT, renal replacement therapy.
Data are presented as median (interquartile range) or percentage.

Table 3. Physiologic and laboratory variables for patients with acute renal failure

Diuretics and mortality in acute renal failure .

Uchino, Shigehiko; Doig, Gordon; Bellomo, Rinaldo; Morimatsu, Hiroshi; Morgera, Stanislao; Schetz, Miet; Tan, Ian; Bouman, Catherine; Macedo, Ettiene; Gibney, Noel; Tolwani, Ashita; Ronco, Claudio; Kellum, John
Beginning and Ending Support Therapy for the Kidney (B.E.S.T. Kidney) Investigator

In- hospital mortality	OR (95% CI)
MODEL 1 (MEHTA et al)	1.21 (0.96 – 1.50)
MODEL 2 (PROPENSITY)	1.22 (0.96 – 1.60)
MODEL 3 (Multi collinearity)	1.22 (0.92- 1.60)

PICARD/ BEST Studies

Caveats to these studies:

- **1. Observational Confounding**
- **2. Selection/information bias**
- **3. Severe/advanced AKI at inclusion (sCr>3.5)**
- **4. No data on specifics of fluid resuscitation**
- **5. No data on fluid overload/ accumulation**
- **6. No data on timing of diuretic use**

The efficacy of loop diuretics in acute renal failure: Assessment using Bayesian evidence synthesis techniques

Sampath, Sriram MD (Gen Med); Moran, John L. FRACP, FJFICM, MD; Graham, Petra L. PhD; Rockliff, Sue BA, Grad Dip Lib; Bersten, Andrew D. MD, FANZCA, FJFICM; Abrams, Keith R. PhD

- Data Source: Randomized controlled trials or nonrandomized studies, 1966 to January 2007.
- Study Selection: Studies with assessable predefined end points, exclusive of those pertaining to acute renal failure prophylaxis or chronic renal failure.
- Data Extraction: Data extraction was performed jointly by the first two authors; independent study assessment was via standard checklist, unblinded.
- Data Synthesis: The primary outcome was mortality; secondary outcomes were time to renal function normalization and total number of dialyses

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Critical Care Medicine. 35(11):2516-2524, November 2007.
DOI: 10.1097/01.CCM.0000284503.88148.6F

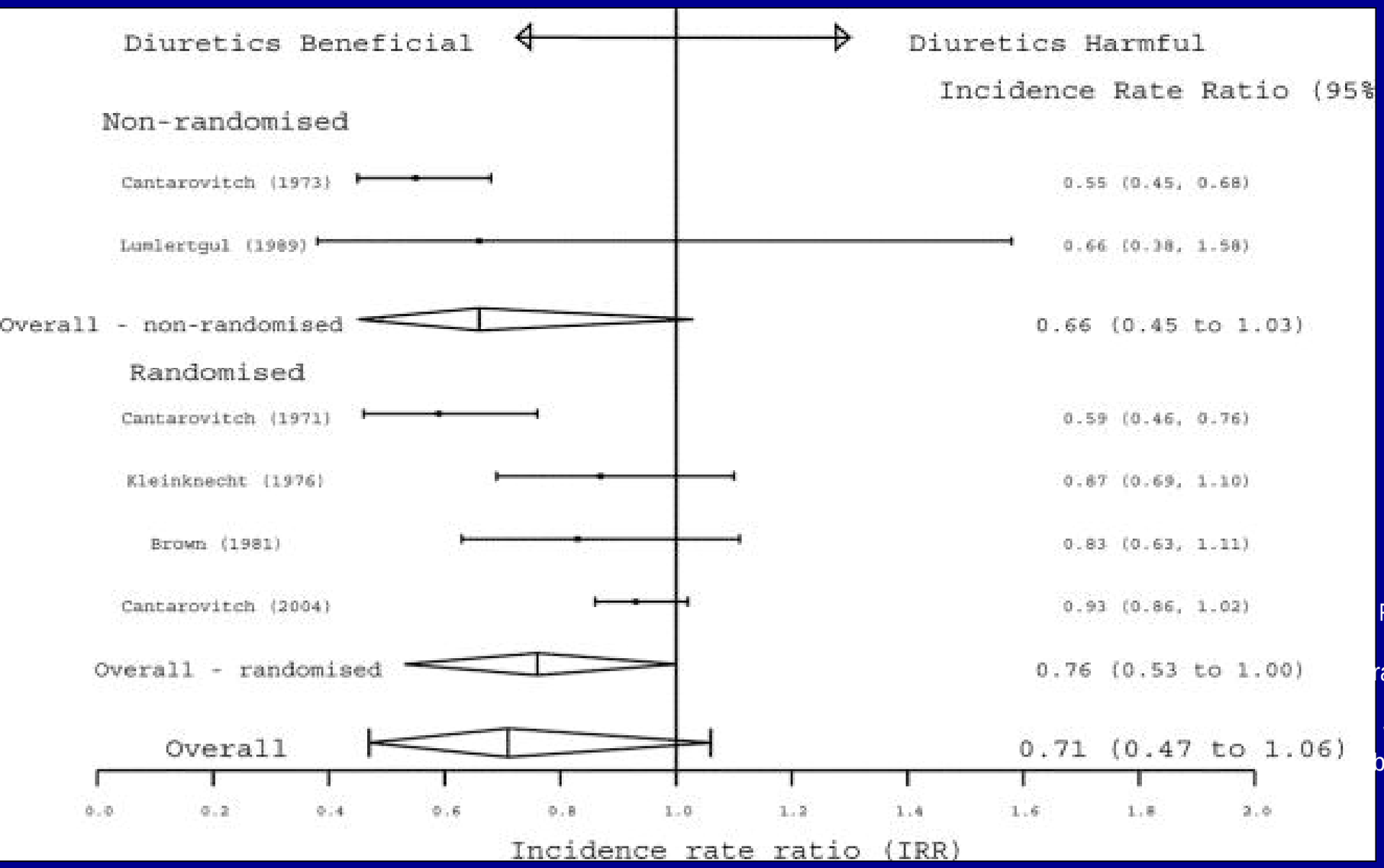

Figure 4. Forest plot showing effect of randomized and nonrandomized studies on dialysis rate, as incidence rate ratio. Small solid squares, study estimates; vertically capped horizontal lines, 95% credible intervals (CI); vertical lines within vertically capped diamond-shaped boxes, subgroup and overall point estimates and 95% CI; vertical straight line, the null effect.

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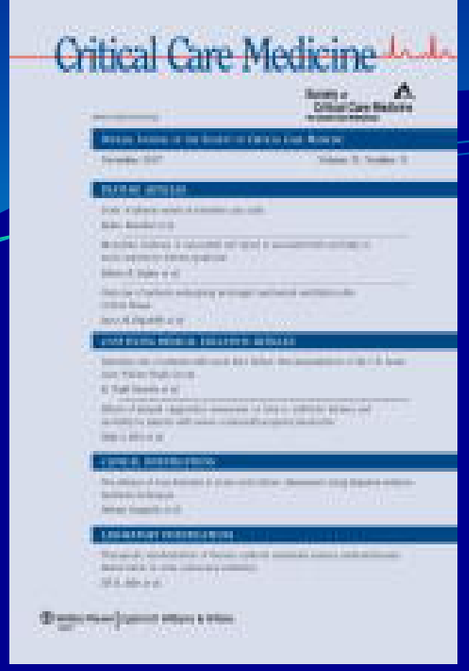
Table 1. Characteristics of studies included for meta-analysis

Lead Author (Reference No.)	Country Year	Study Type	Study Quality	Etiology	Mean Age	Gender Ratio, M/F	Study Features	Definition of ARF
Beroniade (26)	Rumania 1969	NR	3	Mixed	34	ND	Escalating drug dose	Not described
Cantarovich (28)	Argentina 1971	RCT	7	Mixed	ND	ND	Two subgroups in treatment arms combined for analysis	Urine output <400 mL/24 hrs
Cantarovich (29)	Argentina 1973	NR	5	Mixed	ND	ND	High dose of frusemide	Mannitol test
Chandra (31)	India 1975	NR	12	Mixed	41	ND	Adult and pediatric study, only adult data studied	Urine output <400 mL/24 hrs
Kleinknecht (32)	France 1976	RCT	11	Mixed	ND	31/35	Escalating up to 1200 mg/day of frusemide	Criteria defined
Minuth (35)	US 1976	NR	5	Mixed	55	76/28		Urine/blood variables
Borirakchanyavat (27)	Thailand 1978	NR	7	Leptospirosis	41	13/01	No dialysis required in any patient	Undefined
Brown (25)	UK 1981	RCT	14	Mixed	52	31/25	Initial 1 g of frusemide to both groups	Criteria defined
Lumlertgul (33)	Thailand 1989	NR	10	Malaria	24	8/0	Only two of five subgroups analyzable	Urinary indexes
Shilliday (36)	UK 1997	RCT	22	Mixed	58	42/34	Dopamine and mannitol given in both groups	Creatinine >180 mmol/L
Mehta (34)	US 2002	NR	18	Mixed	5	72/28	Preexisting renal dysfunction in 25% of patients	Criteria defined
Uchino (37)	Australia 2004	NR	17	Mixed	67	64/36	Preexisting renal dysfunction in 29% of patients	Criteria defined
Cantarovich (30)	France 2004	RCT	24	Mixed	58	67/33	Initial frusemide given to both groups	Criteria defined

M/F, male/female; ARF, acute renal failure; NR, nonrandomized study; ND, not described; RCT, randomized controlled trial; Mixed, mixed etiologies of ARF,

Table 1. Characteristics of studies included for meta-analysis



The efficacy of loop diuretics in acute renal failure: Assessment using Bayesian evidence synthesis techniques.

Sampath, Sriram; Moran, John; FRACP, FJFICM; Graham, Petra; Rockliff, Sue; BA, Grad; Bersten, Andrew; MD, FANZCA; Abrams, Keith

Critical Care Medicine. 35(11):2516-2524, November 2007.
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Table 2. Patient and therapy characteristics in trials studied

Lead Author (Reference No.)	Total No. of Patients	Control Deaths, No. (%)	Treatment Deaths, No. (%)	Control Survivors, No.	Treatment Survivors, No.	Dosage of Diuretic	Delivery Technique	Duration of Therapy	Deafness Incidence
Beroniade (26)	24	6 (50)	3 (25)	6	9	Frusemide 60–480 mg	Not described	Until onset of diuresis	ND
Cantarovich (28)	47	7 (54)	15 (44)	6	19	Frusemide 600–3200 mg fixed/geometric progression	IV infusion 30 mins to 10 hrs	Until onset of diuresis	ND
Cantarovich (29)	58	11 (58)	18 (46)	8	21	Frusemide 2000 mg/day	IV infusion	Until onset of diuresis	ND
Chandra (31)	17	3 (60)	5 (42)	2	7	Frusemide 200–2000 mg/day	IV infusion	Until onset of diuresis	2/16
Kleinknecht (32)	66	12 (36)	13 (39)	2	20	Frusemide 150–1200 mg	Intermittent IV infusion	Until onset of diuresis	ND
Minuth (35)	104	12 (48)	47 (59)	13	22	Frusemide 40–500 mg	Intravenous	Undefined	ND
Borirakchanyavat (27)	14	0	0	8	6	Frusemide 500 mg/day	IV	7–8 days	ND
Brown (25)	56	16 (57)	18 (64)	12	10	Frusemide 2 mg/min or 1 g tid	IV or oral	Defined biochemical/urinary criteria	2/56
Lumlertgul (33)	8	0	0	4	4	Frusemide 200 mg 6 hourly	IV	4 days	ND
Shilliday (36)	92	15 (50)	41 (68)	15	20	Frusemide or torasemide 3 mg/kg	IV bolus 6 hourly	21 days	1/92
Mehta (34)	552	110 (48)	184 (56)	116	142	Frusemide (median 80 mg)	Not known	Undefined	ND
Uchino (37)	1743	357 (57)	697 (62)	269	420	Frusemide (mean 240 mg/24 hrs)	Not known	Undefined	ND
Cantarovich (30)	330	50 (30)	59 (35)	114	107	Frusemide 25–35 mg/kg/day	IV or oral	Until renal recovery	3/166

ND, not defined; IV; intravenous.

The efficacy of loop diuretics in acute renal failure: Assessment using Bayesian evidence synthesis techniques.

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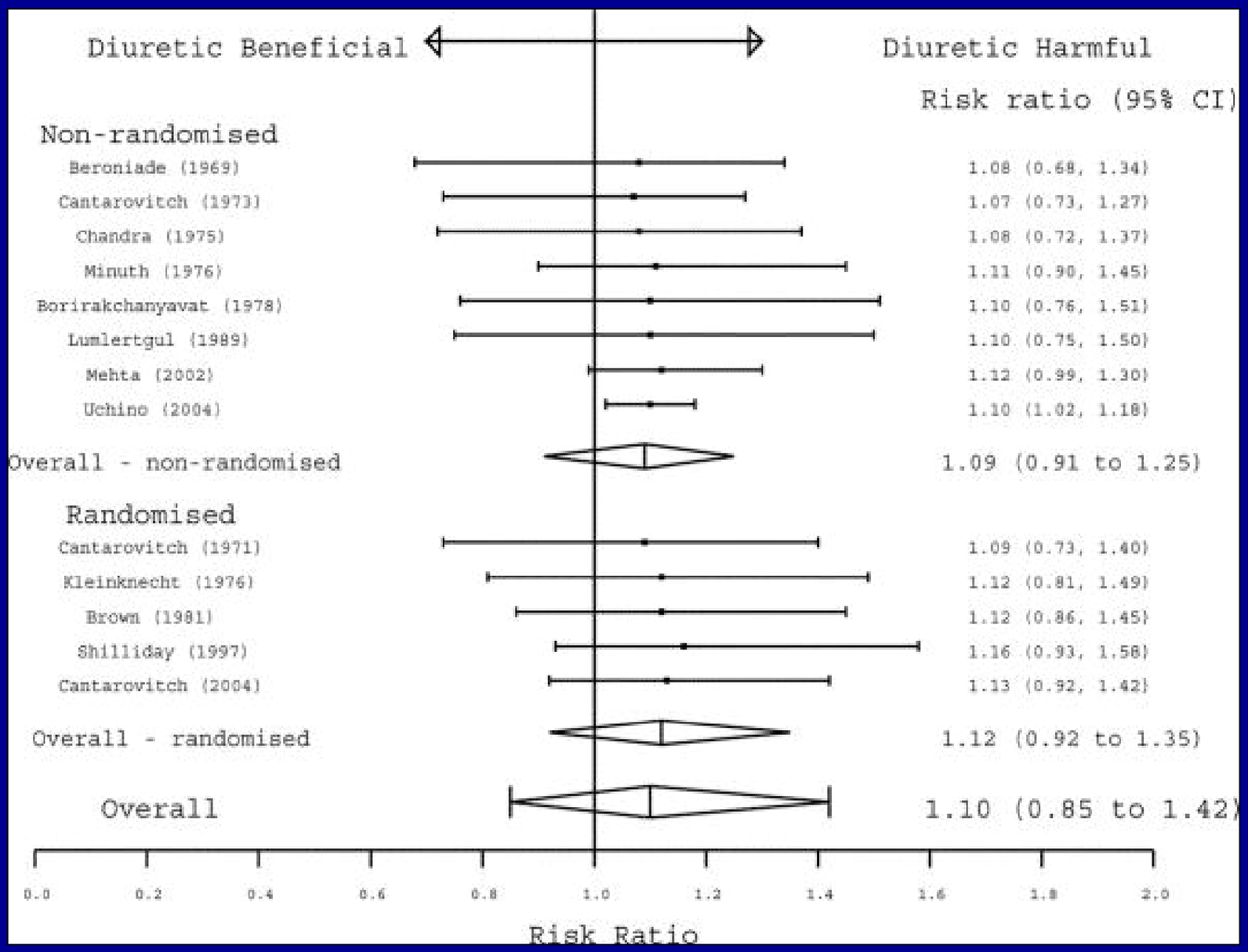

Figure 1. Forest plot showing effect of randomized and nonrandomized studies on mortality treatment effect as risk ratio. Small solid squares, study estimates; vertically capped horizontal lines, 95% credible intervals (CI); vertical lines within vertically capped diamond-shaped boxes, subgroup and overall point estimates and 95% CI; vertical straight line, the null effect.

The efficacy of loop diuretics in acute renal failure: Assessment using Bayesian evidence synthesis techniques.

Sampath, Sriram; Moran, John; FRACP, FJFICM; Graham, Petra; Rockliff, Sue; BA, Grad; Bersten, Andrew; MD, FANZCA; Abrams, Keith

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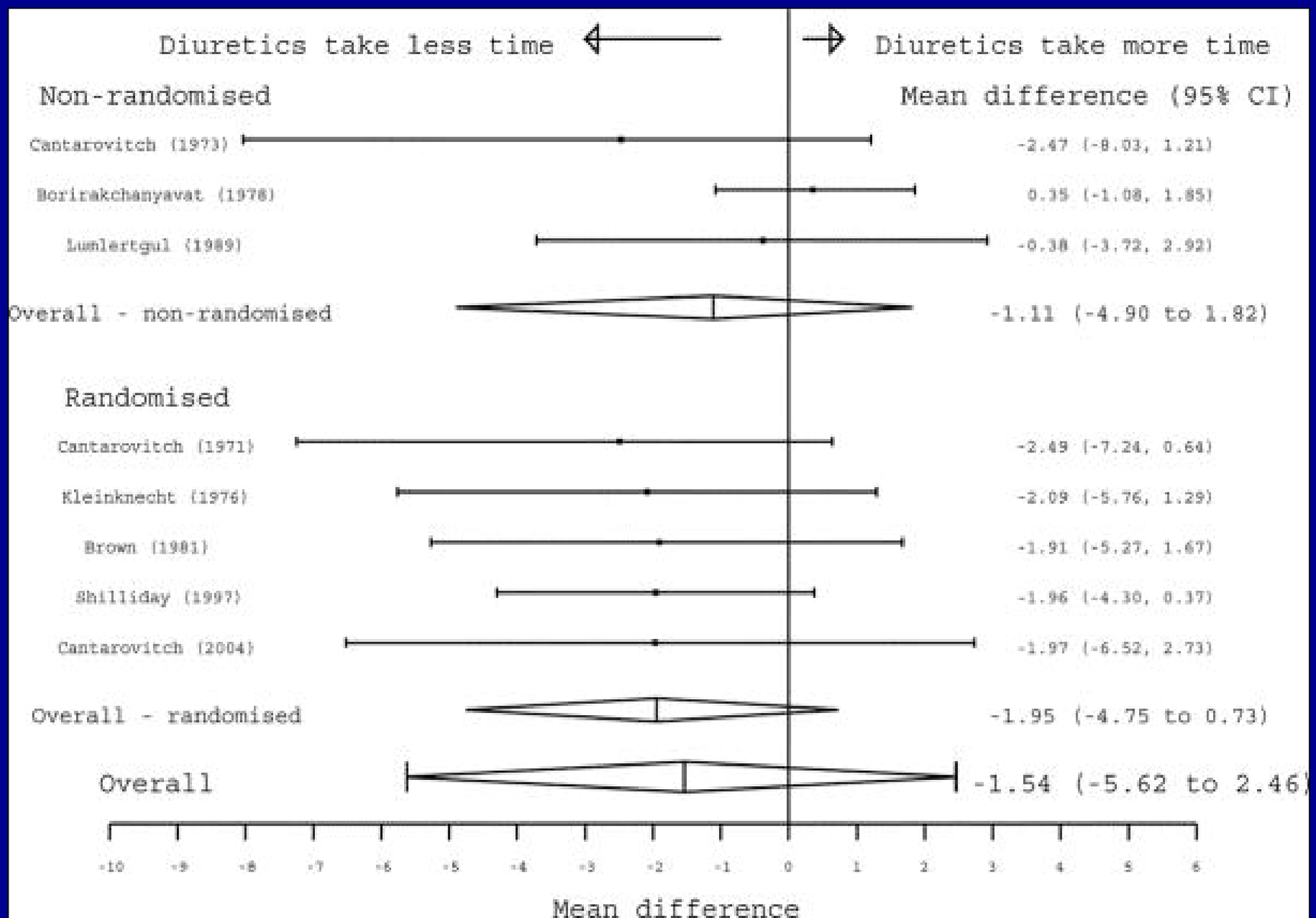


Figure 2. Forest plot showing effect of randomized and nonrandomized studies on time taken to normalize creatinine/urea, as mean difference (days). Small solid squares, study estimates; vertically capped horizontal lines, 95% credible intervals (CI); vertical lines within vertically capped diamond-shaped boxes, subgroup and overall point estimates and 95% CI; vertical straight line, the null effect.

The efficacy of loop diuretics in acute renal failure: Assessment using Bayesian evidence synthesis techniques

- Conclusion:
- The use of loop diuretics was found to significantly decrease the oliguric period by a mean of 7.7 days

Table 1. Randomized Controlled Trials Addressing Loop Diuretics in the Management of AKI

Study	Setting	Number of Patients: Intervention Arm	Number of Patients: Control Arm	Intervention	Control	Reported Clinical Outcomes	Notes
Trials addressing prevention of AKI							
Solomon et al,[78] 1994	Cardiac angiography	25	28	Saline 0.45% at 1 mL/kg/h for 12 h before and after angiography plus 80 mg furosemide intravenously 30 min before angiography	Saline 0.45% at 1 mL/kg/h for 12 h before and after angiography	AKI Need for dialysis	AKI defined as increase in the baseline serum creatinine concentration of at least 0.5 mg/dL within 48 h after the injection of radiocontrast agents Trial also had a third arm that received saline 0.45% with mannitol
Lassnigg et al,[76] 2000	Cardiac surgery	41	40	Furosemide infusion 2.5 mg/h since induction of anesthesia until 48 h after surgery or discharge from ICU	Saline 0.9% infusion since induction of anesthesia until 48 h after surgery or discharge from ICU	AKI Need for dialysis Mortality	AKI defined as increase in the baseline serum creatinine concentration of at least 0.5 mg/dL within 48 h Trial also had a third arm that received dopamine infusion
Mahesh et al,[80] 2008	Cardiac surgery	21	21	Furosemide infusion at 4 mg/h since induction of anesthesia until 12 h after surgery	Saline 0.9% infusion at 2 mL/h since induction of anesthesia until 12 h after surgery	AKI Need for dialysis Mortality	AKI defined as >50% increase in serum creatinine postoperatively, or >1.4 mg/dL, or requirement for dialysis, or all of these Patients were at risk for post-surgery AKI with ≥1 of the following criteria: serum Cr > 1.4 mg/dL, EF < 50%, DM, combined CABG and valve surgery, redo cardiac surgery
Majumdar et al,[89] 2009	Cardiac angiography	46	46	Intervention solution consisted of saline 500 mL 0.45%, 15 mmol of potassium chloride, 25 g of mannitol, and 100 mg of furosemide at 125 mL/h for 4 h	Saline hydration protocol	AKI Need for dialysis Mortality	AKI defined as a 0.5-mg/dL absolute or 25% relative increase in creatinine level within 48 hours of the procedure In all study patients, urine output was replaced with half-normal saline milliliter per milliliter each hour during and for 12 hours after angiography

Trials addressing treatment of AKI							
Cantarovich et al,[82] 1971	AKI with urine output <400 mL/d and no response to mannitol 60 g within 24 h	34	13	Group 1: furosemide 600 mg/d until diuresis >2 L/d Group 2: geometric progression of furosemide dose from 100 to 3,200 mg/d	Conventional treatment (details not known)	Mortality	
Karayannopoulos,[83] 1974	Established AKI	10	10	Furosemide 1 g initially and increased to 3 g over a period of 7 d if no response	Conventional treatment (details not known)	Need for dialysis	Unclear how AKI was defined

Study	Setting	Number of Patients: Intervention Arm	Number of Patients: Control Arm	Intervention	Control	Reported Clinical Outcomes	Notes
Kleinknecht et al,[84] 1976	Oliguric AKI (no underlying CKD)	33	33	Furosemide 3 mg/kg every 4 h to maintain urine output 20-100 mL/h and 6 mg/kg/h if diuresis remained <20 mL/h, 1.5 mg/kg if diuresis between 100 and 150 mL/h, and no furosemide if diuresis >150 mL/h	Placebo (details not known)	Need for dialysis Mortality	Urine output in the intervention arm was replaced by dextrose 5% with 6 g/L sodium chloride and 1.5 g/L potassium chloride
Hager et al,[87] 1996	Major abdominal, chest or vascular surgery patient entering ICU with moderate post-surgery renal impairment	62	59	Furosemide infusion at 1 mg/h since admission to ICU to discharge	Dextrose 5% infusion since admission to ICU to discharge	Need for dialysis Mortality	Enrolled patients in both groups had moderate renal impairment after surgery before initiation of the trial medication
Shilliday et al,[79] 1997	AKI not caused by to prerenal or post-renal causes	32 (Furosemide) 30 (Torsemide)	30	Furosemide or torsemide at 3 mg/kg every 6 h (reduced to 2 mg/kg then 1 mg/kg if the serum creatinine level improved and stopped when renal function recovered) for 21 d or until recovery or death	Placebo (details not known)	Need for dialysis Mortality	All patients also received dopamine 2 μg/kg/min and mannitol 20% 100 mL/6 h
Cantarovich et al,[81] 2004	AKI requiring dialysis	166	164	Furosemide 25 mg/kg/d infusion changed to 35 mg/kg/d oral when tolerated	Placebo (details not known)	Renal recovery Mortality	
van der Voort et al,[85] 2009	Mechanically ventilated patients coming off of continuous veno-veno hemofiltration	36	35	Furosemide 0.5 mg/kg/h infusion continued until the recovery of renal function or until a new hemofiltration session was started	Placebo infusion (details not known)	Need for dialysis Mortality	The criteria to restart hemofiltration were based on the institutional practice
Trials comparing different doses of loop diuretics							
Brown et al,[80] 1981	AKI after trauma or surgery (not related to obstruction or volume depletion)	28	28	Furosemide 4 mg/min for 4 h followed by 2 mg/min infusion or oral furosemide 1 g to maintain urine output 150-200 mL/h until serum creatinine <3.39 mg/dL without dialysis	Furosemide 4 mg/min for 4 h	Need for dialysis Mortality	
Kunt et al,[88] 2009	Cardiac surgery	50	50	Furosemide intermittent bolus at 1-3 mg/kg every 4 h until 48 h after surgery or discharge from ICU	Furosemide infusion at 20 mg/h until 48 h after surgery or discharge from ICU	AKI Need for dialysis Mortality	Both groups received dopamine infusion at 2-3 μg/kg/min

Why Diuretics....

- *Fluid dilemma in acquired AKI*.
- *Reno – protection*
- Ongoing trial

- *Atrial Natriuretic peptide*
- *Final word*

The Effect of Loop Diuretics on Severity and Outcome of Acute Kidney Injury

ClinicalTrials.gov Identifier: NCT01275729
Sponsor: University of Chicago

Inclusion Criteria:

- 18 yrs or older
- increase in serum creatinine of 0.3 mg/dl within 48 hours or an increase of greater than or equal to 150% from baselinie or sustained oliguria (UOP < 0.5 cc/kg/hr for 6 hours with the last 48hours)
- written informed consentpatients
- with an indwelling bladder catheter

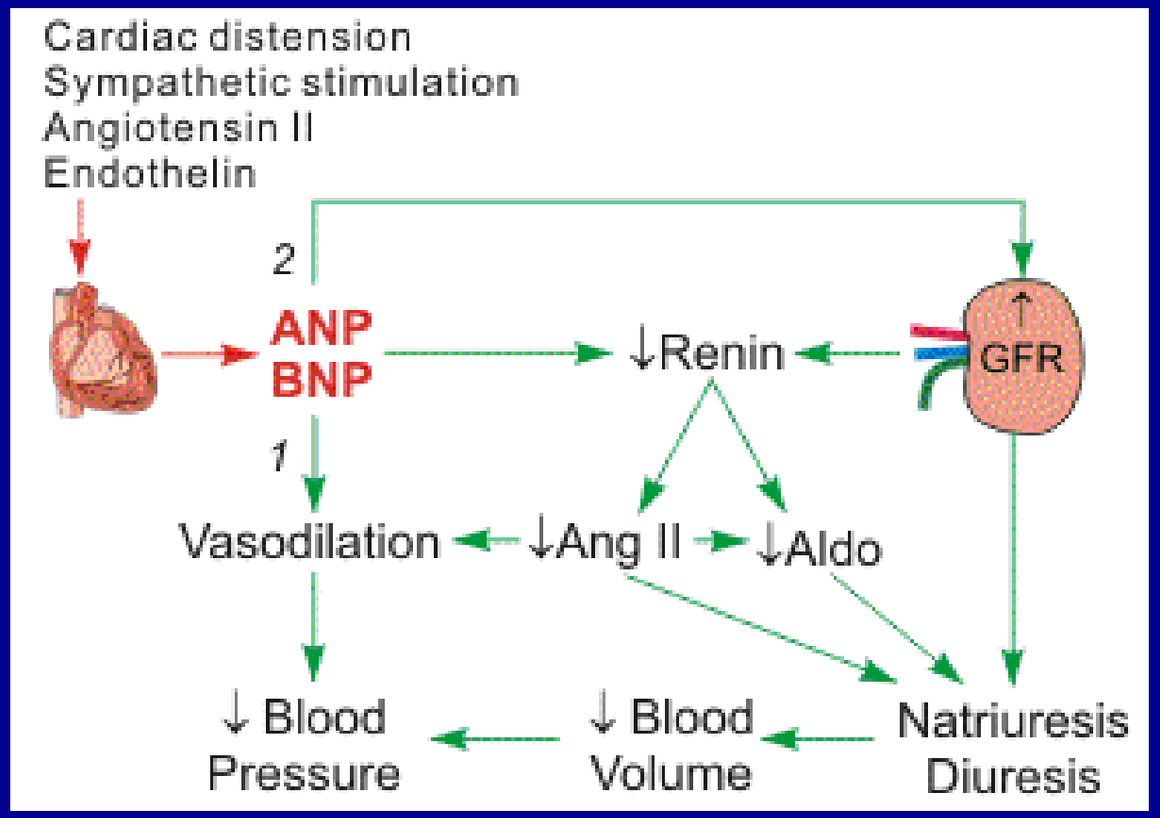
Exclusion Criteria:

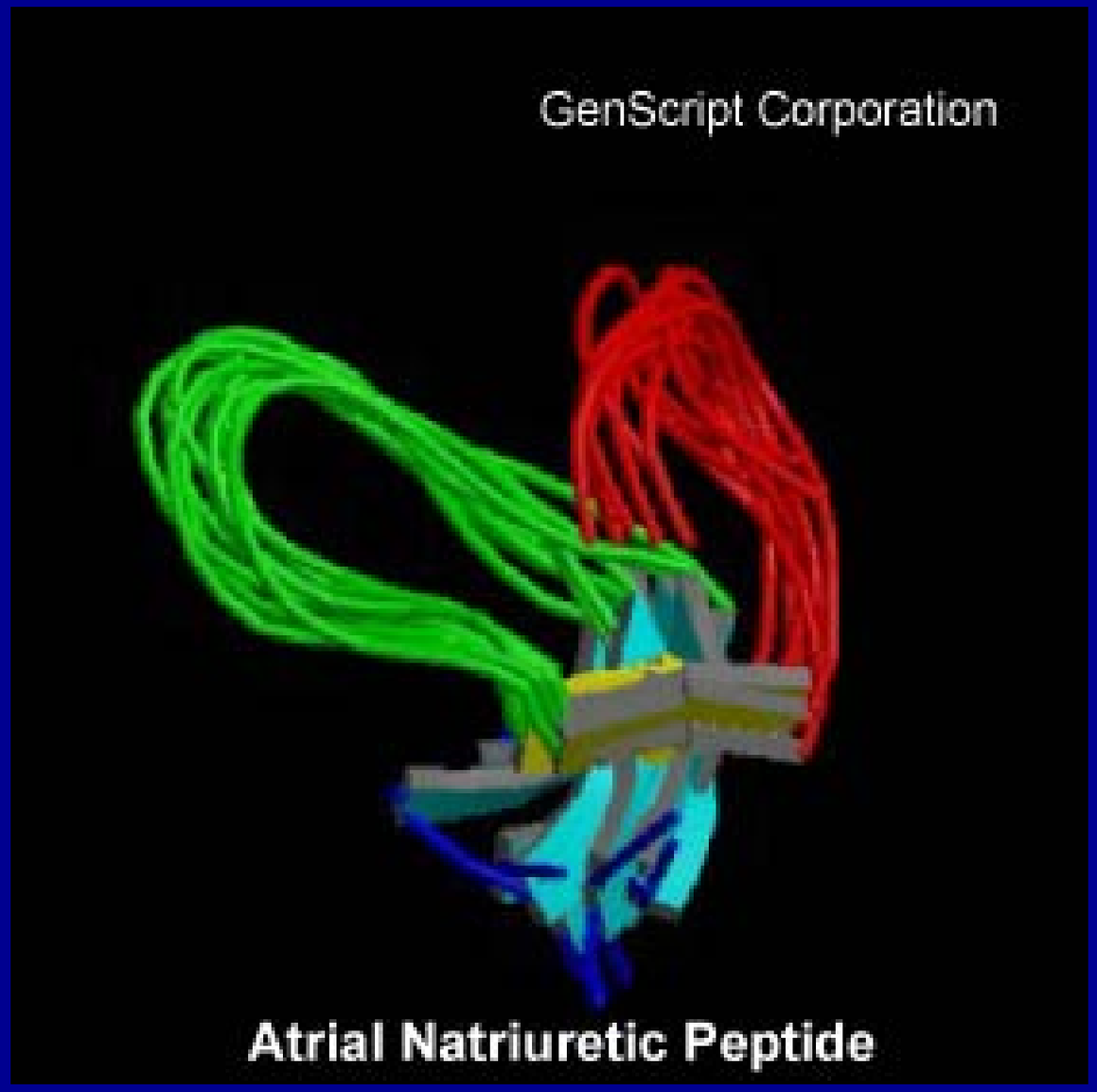
- Voluntary refusal
- Patients with advanced chronic kideny disease - as defined by a baseline GFR < 30 ml/min (MDRD)
- history of renal transplant
- Pregnant patients
- Allergy / Sensitivity to Loop diuretics (furosemide)
- Pre-renal AKI defined by a FENa of < 1% and no urinary casts under-resuscitated per the treating clinical teamactive bleed
- Post renal AKI evidence of hydro-ureter clincal scenario wherein obstruction is considered a likely possibility

Why Diuretics....

- *Fluid dilemma in acquired AKI*.
- *Reno – protectionOngoing trial*
- Atrial Natriuretic peptide
- *Final word*

Atrial Natriuretic Peptide





Natriuretic peptide (NP) family

- ANP : -atrial natriuretic peptide (28 a.a.)
  -ANP : dimmeric form of human ANP
  N-terminal proANP (98 a.a.)
- BNP : brain natriuretic peptide (32 a.a.)
  N-terminal proBNP (76 a.a.)
- CNP : C-type natriuretic peptide (22 and 53 a.a.)

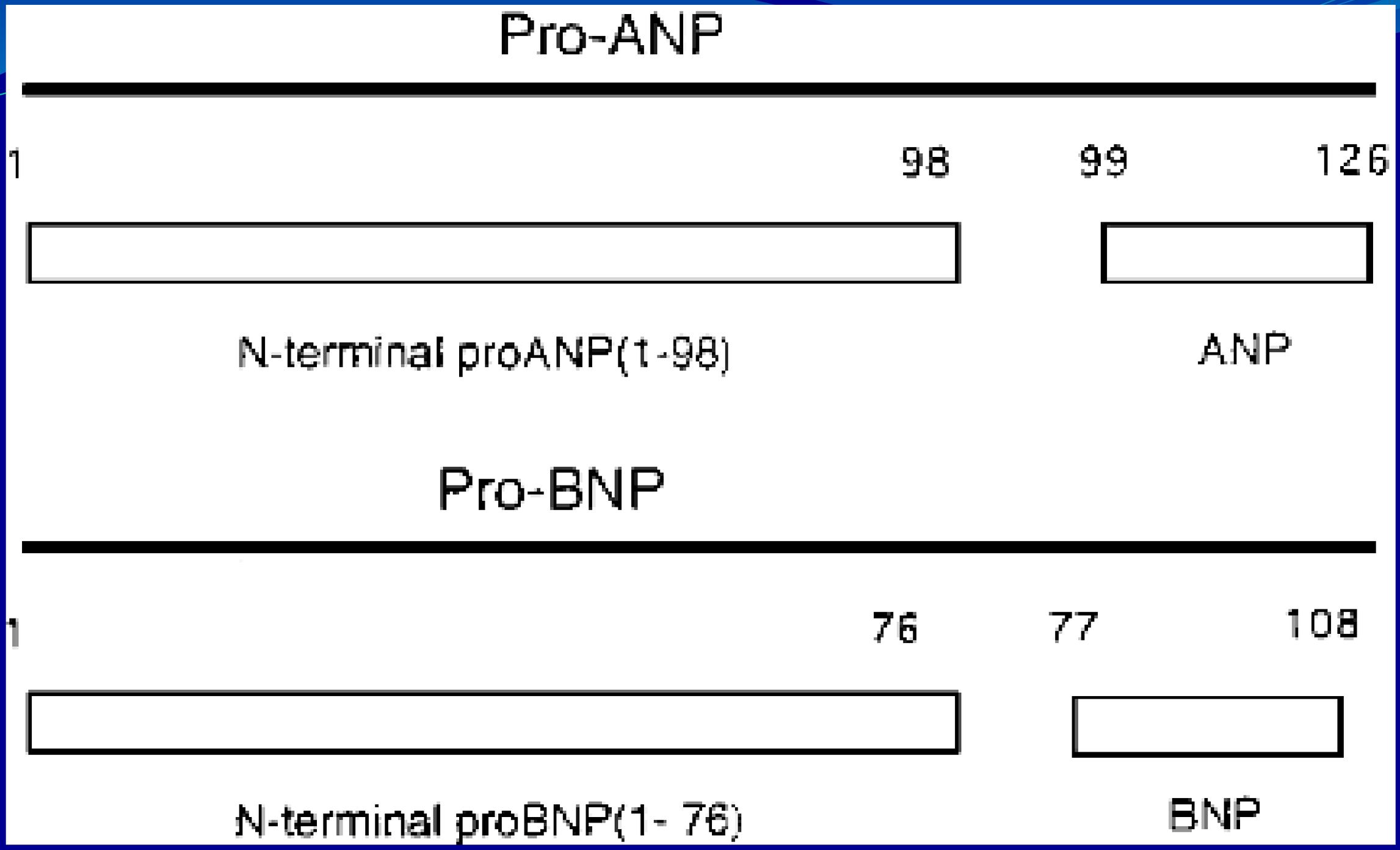
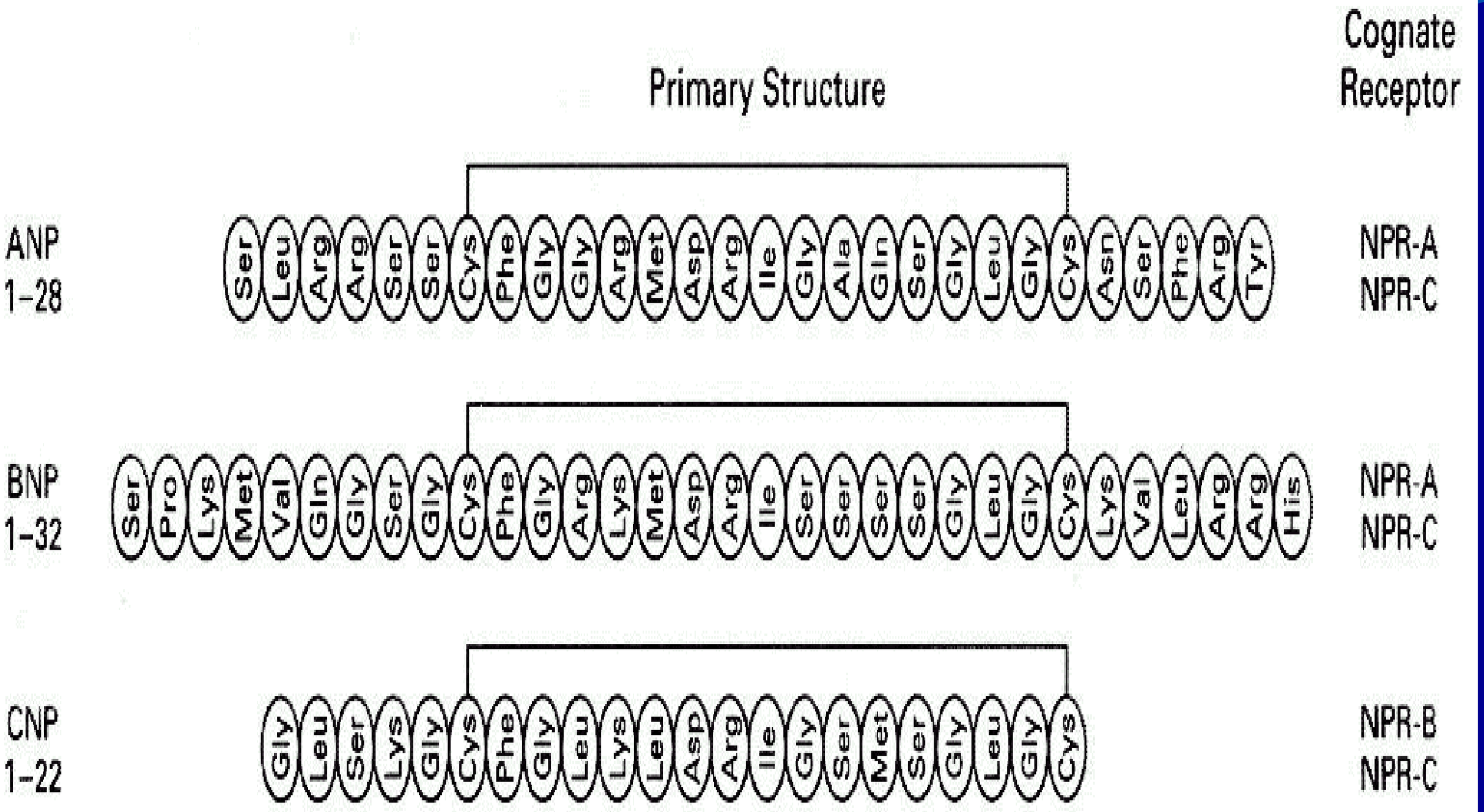


Fig. Schematic representation of the ANP and BNP precursors with sequence numbering defining low-molecular-mass forms, N-terminal forms and high-molecular-mass precursors



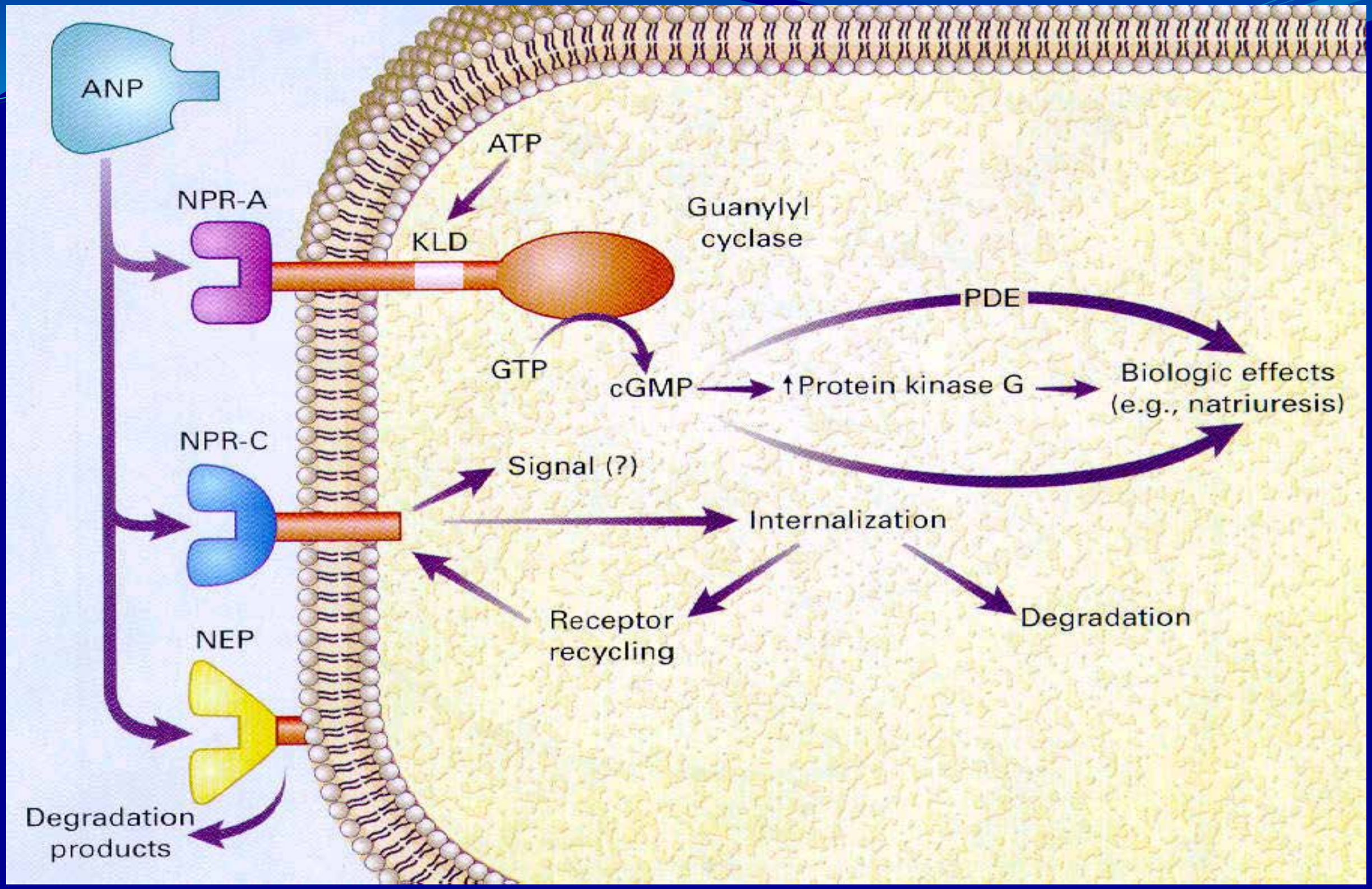
Amino Acid Sequences of the Three Human Natriuretic Peptides

-atrial natriuretic peptide(ANP)

- Prohormone (Pro-ANP) in cardiac tissue is cleaved into two fragments :

  N-terminal fragment (ANP 1-98)

  C-terminal 28a.a. peptide (ANP 99-126)
- mRNA has been found in many tissues but is most abundant in the atria of the heart
- Urodilatin (ANP 95-126)



Action of Atrial Natriuretic Peptide at Target Cells

Physiology

- ANP and BNP concentrations increase in response to volume expansion and pressure overload of the heart
- natriuretic-peptide family counterbalance the effects of the renin-angiotensin-aldosterone system

Physiology

ANP and BNP have been shown to be physiological antagonists of the effects of

(1) angiotensin II on vascular tone

(2) aldosterone secretion

(3) renal-tubule sodium reabsorption

(4) vascular-cell growth

Conditions investigated for possible uses of plasma natriuretic peptides

- Identification of LV hypertrophy in hypertension
- Recognition of obstructive hypertrophic cardiomyopathy
- Detection of LV diastolic dysfunction
- Screening for mild heart failure
- Evaluation of LV systolic dysfunction
- Assessment of severity of congestive heart failure
- Monitoring of therapy in congestive heart failure
- Estimation of infarct size after myocardial infarction
- Prognostic outcome after myocardial infarction
- Prediction of mortality in the elderly

Therapeutic potential

ANP and BNP infusion

- Decrease

  right-atrial and pulmonary-capillary pressure

  renin and aldosterone concentration

- Increase

  urinary sodium and water excretion

Atrial Natriuretic factor in Oliguric Acute Renal Failure

- 222 patients with oliguric acute renal failure were enrolled into a multicenter, randomized, double-blind, placebo-controlled trial.
- Designed to assess prospectively the safety and efficacy of ANP compared with placebo.
- Subjects were randomized to treatment with a 24-hour infusion of ANP (anaritide, 0.2 microgram/kg/min; synthetic form of human ANP) or placebo.
- Dialysis and mortality status were followed up for 60 days.
- The primary efficacy end point was dialysis-free survival through day 21.

Atrial Natriuretic factor in Oliguric Acute Renal Failure

Characteristics	Anaritide (n= 108)	Placebo (n= 114)	All subjects
Age (y)	64 +/- 16	65 +/- 15	64 +/- 16
Sex (% men)	56	53	55
Ethnicity (% white)	80	82	81
Medical status at presentation			
In ICU (%)	85	89	87
On Respirator (%)	54	63	59
Acute medical condition (%)			
Myocardial infarction in 48 h before randomization	12	10	11
Gastrointestinal bleed	5	7	6
Hepatic dysfunction	16	20	18
Pancreatitis	5	7	6
DIC	13	9	11
Thrombocytopenia	22	13	18
Anemia	12	17	14
Arrythmia requiring treatment (%)	25	16	20
Infection (%)	46	47	47
Sepsis (%)	38	35	35
ARDS (%)	13	13	13
CV failure (%)	46	47	47

Atrial Natriuretic factor in Oliguric Acute Renal Failure

Characteristics	Anaritide (n= 108)	Placebo (n= 114)	All subjects
Chronic medical condition (%)			
Diabetes	34	31	35
CRI	15	18	13
Hepatic cirrhosis	5	4	5
Immune defeciency	6	5	6
Hypertension (%)	58	56	57
CHF (%)	36	27	32
CAD	49	45	47
CHRONIC ARRYTHMIA (%)	22	10	16
Active malignancy (%)	7	6	7
Renal function measurement			
Mean SCr	4.3	4.1	4.2
Mean CrCl	8.0	5.1	6.4

Atrial Natriuretic factor in Oliguric Acute Renal Failure

	Anaritide	Placebi	All subjects
Primary cause for ATN (%)			
Ischemic	58	49	54
Nephrotoxic	21	16	18
Multifactorial	20	35	28
Risk factor for ATN (%)			
Radiocontrast dye	34	37	36
Aminoglycoside	16	18	17
Amphotericin B	1	1	1
Hemolysis/ rhabd	10	10	10
Cardiac surgery	17	22	19
Vascular surgery	5	13	9
Other surgery	23	23	23
Hypotension	65	60	62
Sepsis	34	31	32
Hemorrhage/hypovolemia	30	33	32
CV failure	30	18	24

Cause of ATN in Anaritide and placebo group

Atrial Natriuretic factor in Oliguric Acute Renal Failure

		No. of patients	Anaritide (%)	Placebo (%)	P
Study population as a whole			21	15	.22
Age <65		84	21	18	.75
Age >65		138	22	13	.18
Men		121	22	17	.51
Women		101	22	14	.30
Diabetes		69	22	26	.68
No diabetes		145	21	10	.06
History of CHF		68	26	17	.33
Sepsis		74	11	11	.94
Causes of ATN					.88
Ischemia			18	17	.24
Nephrotoxic			41	24	.70
Multifactoria			14	10	.573
ARF + 1 other organ failure		50	24	17	.68
ARF + multi organ failure		109	11	9	.45
ARF without multi organ failure		55	39	29	

Dialysis free survival through day 21

Atrial Natriuretic factor in Oliguric Acute Renal Failure

Systolic blood pressure during study drug infusion			
Blood pressure	Anaritide (n= 105)	Placebo (n= 109)	P
Systolic Bp at baseline (mm)	123 +/- 23.6	125.1 +/- 23.3	0.719
Minimum SBP during infusion (mm)	90.3 +/- 18.8	100.7 +/- 22.2	<0.001
Maximum absolute decrease in SBP during infusion	33.6 +/- 20.4	23. +/- 19.1	0.001

Why Diuretics....

- *Fluid dilemma in acquired AKI*.
- *Reno – protection*
- *Ongoing trial*
- *Atrial Natriuretic peptide*

- Final word

Diuretics in the management of acute kidney injury: a multinational survey.

Bagshaw SM, Delaney A, Jones D, Ronco, C Bellomo R
Division of Critical Care Medicine, University of Alberta Hospital, University of Alberta, Edmonton, Alta., Canada, Contrib Nephrol. 2007;156:236-49

- **BACKGROUND: To determine the practice patterns of diuretic use by clinicians.**
- **METHODS:Multinational, multicenter survey of intensive care and nephrology clinicians that utilized an 18-question self-reported questionnaire.**

Private and regional hospitals	22.5%
Use of furosemide	67.1%
Primary route of delivery	
---Intravenous	71.9%
---Bolus dosing	43.3%
Deciding factors for dosing	
---current serum creatinine	73.6%
---urine output	73.4%
---blood pressure	59.7%
---central venous pressure	65.2%
---risk of ototoxicity	62.4%
---pulmonary edema	86.3%
Commonly used in conditions	
---rhabdomyolysis	55.6%
---major surgery	56%
---cardiogenic shock	56.2%
---sepsis	49.5%
---prior to RRT	57.7%
---During recovery after RRT	33.9%
Taret UOP of >0.5 – 1.0ml/kg/hr	76.6%
Can Diuretics reduce mortality- NO	74.3%
Can diuretics reduce need of RRT- NO	50.8%
Can diuretics reduce duration of RRT- NO	57.8%
Readiness to participate in RCT	72.4%

Literature

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- Pavkov ME, Collins AJ, Coresh J, Nelson RG. Kidney Disease in Diabetes. In: Cowie CC, Casagrande SS, Menke A, et al., eds. Diabetes in America. 3rd ed. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (US); August 2018.

Questions for the next lecture

- What causes kidney damage during shock?

- What in case of shock resuscitation is carried out simultaneously with a stop of bleeding and infusion therapy