INTERNISTISCHE INTENSIVSTATION INNSBRUCK

Ten Myths about Furosemide

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Conflicts of interest

Speaker

- Fresenius
- Baxter
- Braun
- CLS Behring
- Biomerieux

Consultant

- Baxter
- Fresenius
- Novartis
- Sandoz
- AmPharma
- Takeda

Epidemiological Facts

Myths..

4.9%) receive diureti

- F nly used ts) in the ICU

Myths..

Myths..

- Median

Myths..

- 14% receive conti ut bolus)

Myths..

Myths..

McCoy IE et al , Plos One 2019, 14(5):e0217911,
McMahon BA & Chawla LS, Ren Fail (2021) 43 (1):830-9

Myth #1

Furosemide causes AKI

No, it does not…

unless you cause severe hypovolemia

Rationale for Loop Diuretics in AKI

- Direct renal vasodilator
- Attenuate medullary hypoxia by inhibiting Na+/K+/2Cl- pump to reduce tubular O2 demand
- Attenuate ischemic/reperfusion-induced apoptosis and associated gene transcription
- Mitigate/treat fluid overload/accumulation
- Caveat: Ototoxicity/Pancreatitis at doses > 800mg/day

Kramer et al KI 1980; Aravindan et al Ren Fail 2007; Aravindan et al Ren Fail 2006; Grams et al CJASN 2011

Myth #2

Furosemide and fluids together can prevent AKI in high-risk patients

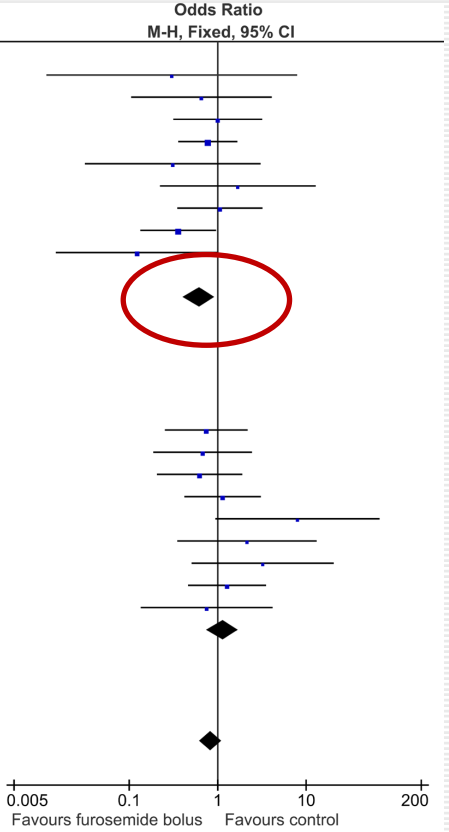
Probably not

Intermittent furosemide administration in patients with or at risk for acute kidney injury: Meta-analysis of randomized trials

28 studies randomizing 3,228 patients were included
No difference overall mortality between the two groups (OR = 0.84; 95% CI 0.63 to 1.13; p-value = 0.25; I2 = 0%)

CM trials

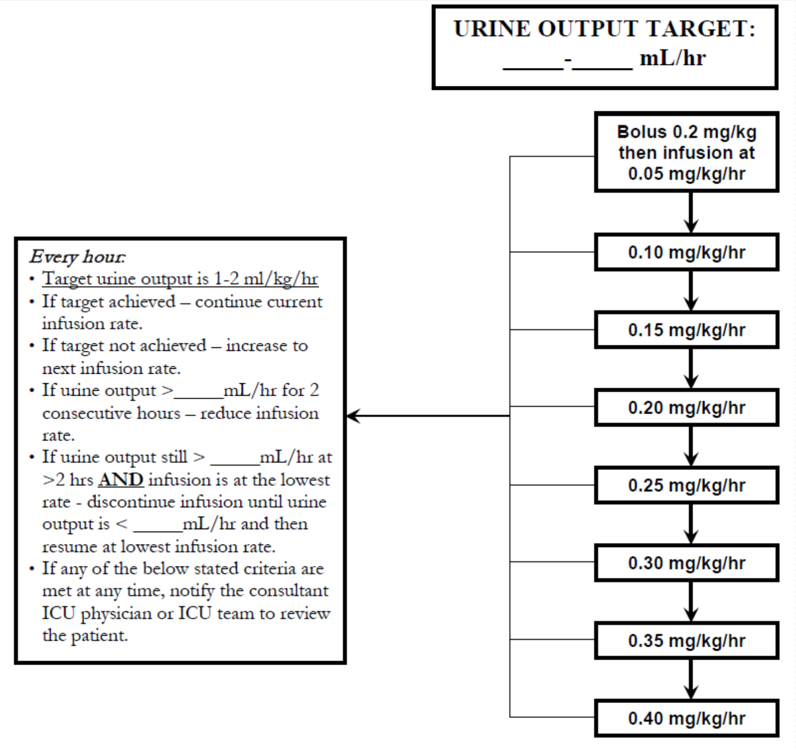
Study or Subgroup	Furosemide bolus Events	Furosemide bolus Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.1.1 Prevention						
Allen 2010	0	21	1	20	1.5%	0.30 [0.01, 7.87]
Barbanti 2015 PROTECT-TAVI	2	56	3	56	2.9%	0.65 [0.11, 4.07]
Briguori 2011 REMEDIAL-II	6	146	6	146	5.8%	1.00 [0.31, 3.18]
Felker 2011 DOSE	13	156	16	152	15.1%	0.77 [0.36, 1.67]
Marenzi 2012 MYTHOS	1	87	3	83	3.1%	0.31 [0.03, 3.04]
Mojtahedzadeh 2004	3	11	2	11	1.5%	1.69 [0.22, 12.81]
Ostermann 2007	9	26	10	30	6.2%	1.06 [0.35, 3.21]
Palazzuoli 2014 Diur-HF	8	39	18	43	13.8%	0.36 [0.13, 0.96]
Usmiani 2016 AKIGUARD	1	57	8	63	7.6%	0.12 [0.01, 1.01]
Yayla 2015	0	14	0	15		Not estimable
Subtotal (95% CI)		**613**		**619**	**57.4%**	**0.62 [0.41, 0.94]**
Total events	43		67			
Heterogeneity: Chi² = 6.79, df = 8 (P = 0.56); I² = 0%						
Test for overall effect: Z = 2.23 (P = 0.03)						
4.1.2 Treatment						
Brown 1981	16	28	18	28	7.8%	0.74 [0.25, 2.17]
Cantarovich 1971	15	34	7	13	5.7%	0.68 [0.19, 2.44]
Cantarovich 1973	18	39	11	19	8.1%	0.62 [0.21, 1.89]
Kleinknecht 1976	13	33	12	33	7.4%	1.14 [0.42, 3.08]
Kunt 2009	7	50	1	50	0.9%	7.98 [0.94, 67.46]
Schuller 1997	5	19	2	14	1.7%	2.14 [0.35, 13.12]
Shah 2014	3	30	2	60	1.2%	3.22 [0.51, 20.42]
Shilliday 1997	20	32	17	30	6.7%	1.27 [0.46, 3.52]
Vargas Hein 2005	3	14	4	15	3.1%	0.75 [0.14, 4.17]
Subtotal (95% CI)		**279**		**262**	**42.6%**	**1.14 [0.75, 1.72]**
Total events	100		74			
Heterogeneity: Chi² = 7.54, df = 8 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)		**892**		**881**	**100.0%**	**0.84 [0.63, 1.13]**
Total events	143		141			
Heterogeneity: Chi² = 16.78, df = 17 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
Test for subgroup differences: Chi² = 4.06, df = 1 (P = 0.04), I² = 75.4%						

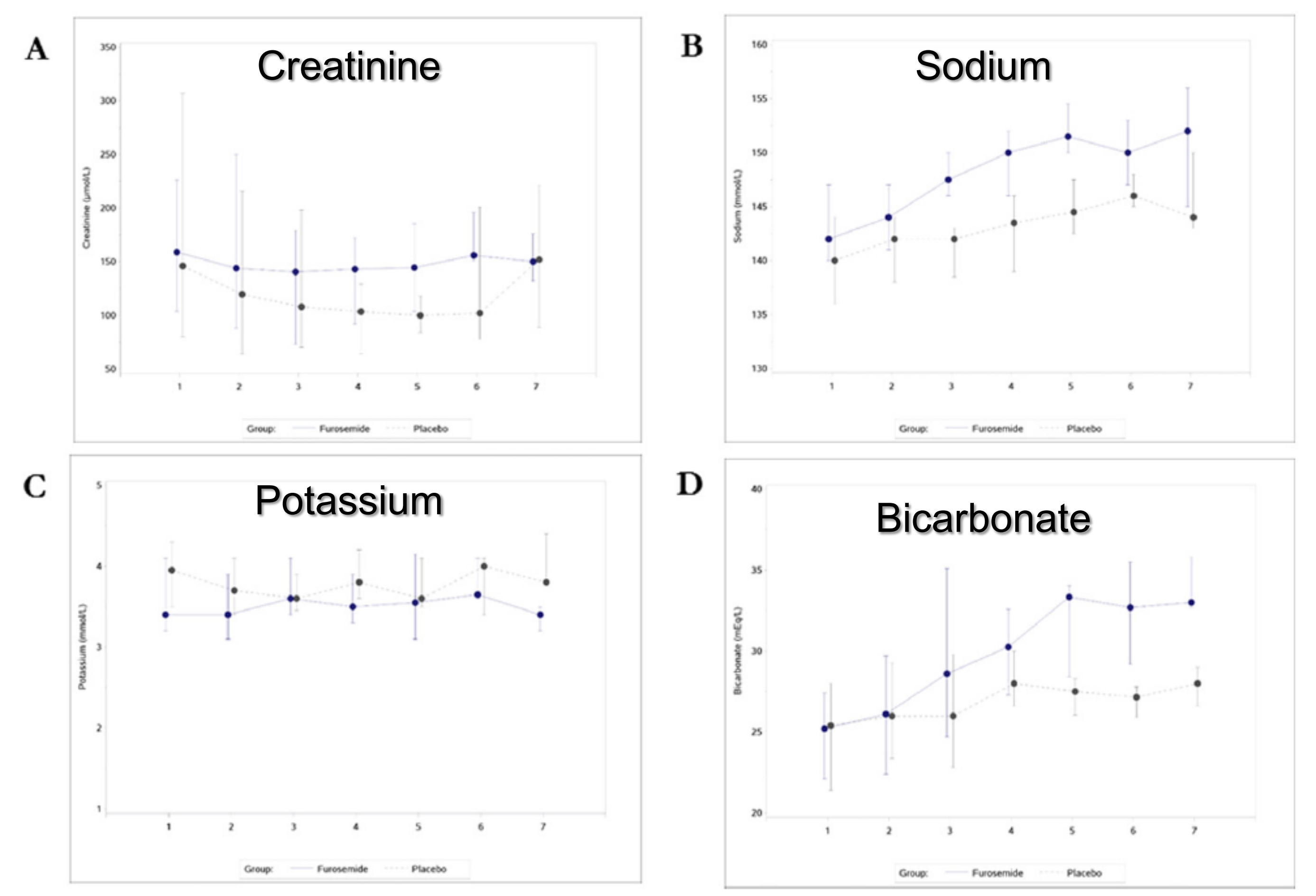


Bove T et al, PLoS ONE 13(4): e0196088. 2018

The effect of low-dose furosemide in critically ill patients with early acute kidney injury: A pilot randomized blinded controlled trial (the SPARK study)

2000 mg of furosemide in 500 mL of 0.9% saline





Bagshaw SM et al, Journal of Critical Care 42 (2017) 138–146

Myth #3

Furosemide is contraindicated in AKI.

No, it is not

Intermittent furosemide administration in patients with or at risk for acute kidney injury: Meta-analysis of randomized trials

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No difference overall mortality between the two groups (OR = 0.84; 95% CI 0.63 to 1.13; p-value = 0.25; I2 = 0%)

Treatment trials

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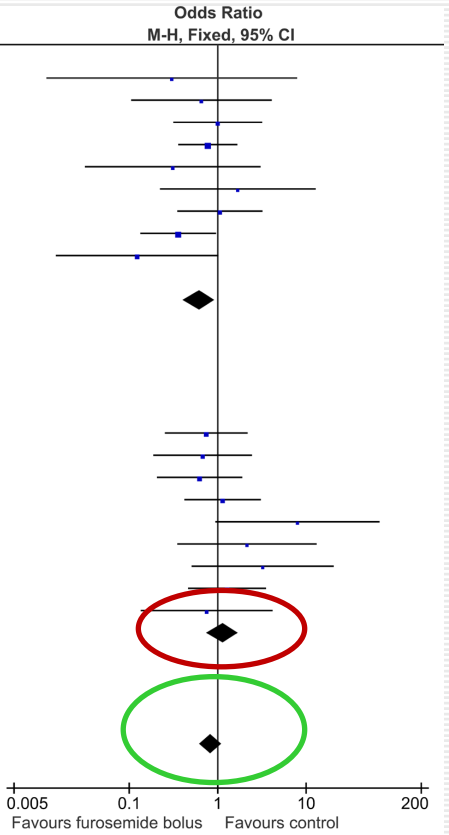


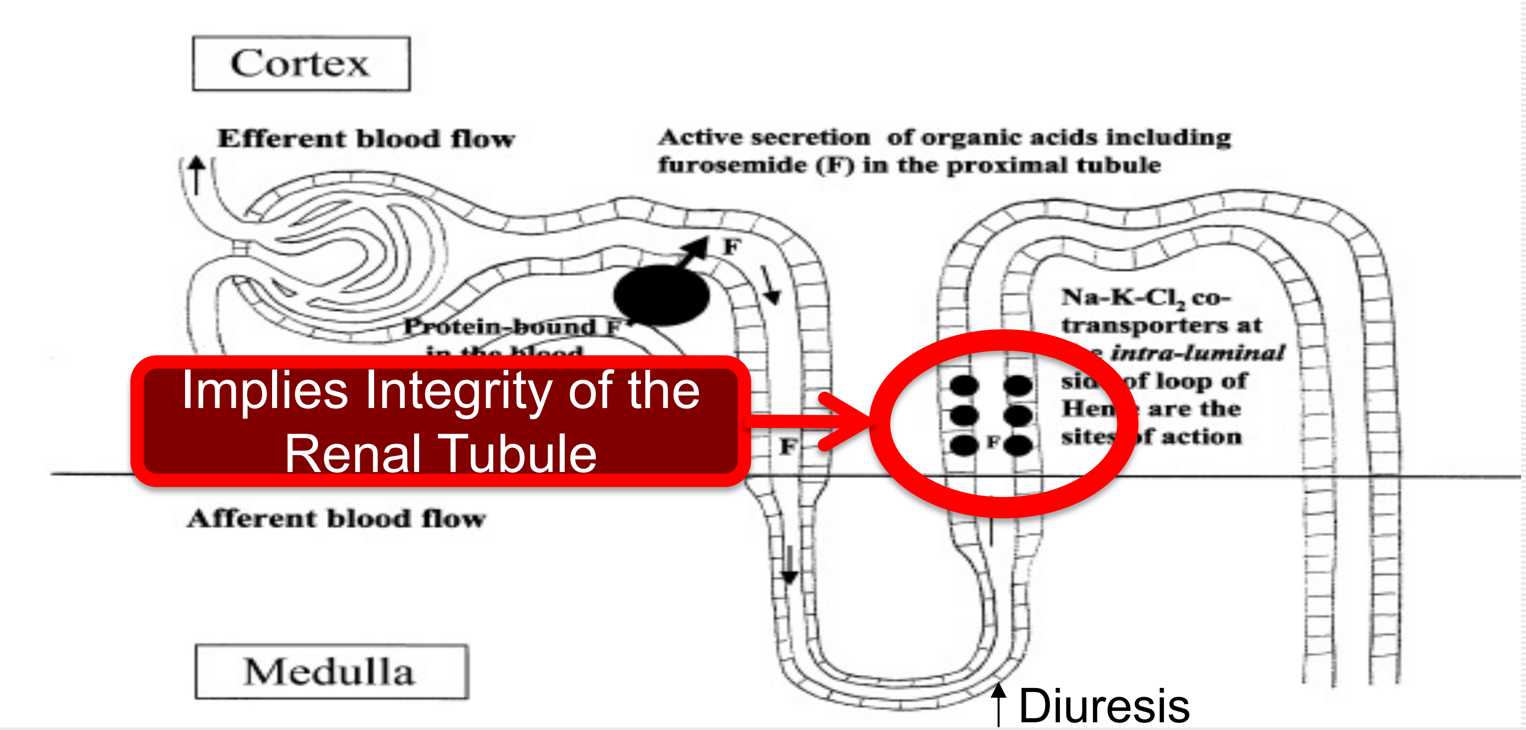
Bove T et al, PLoS ONE 13(4): e0196088. 2018

Myth #4

Frusemide can kick-start kidney function.

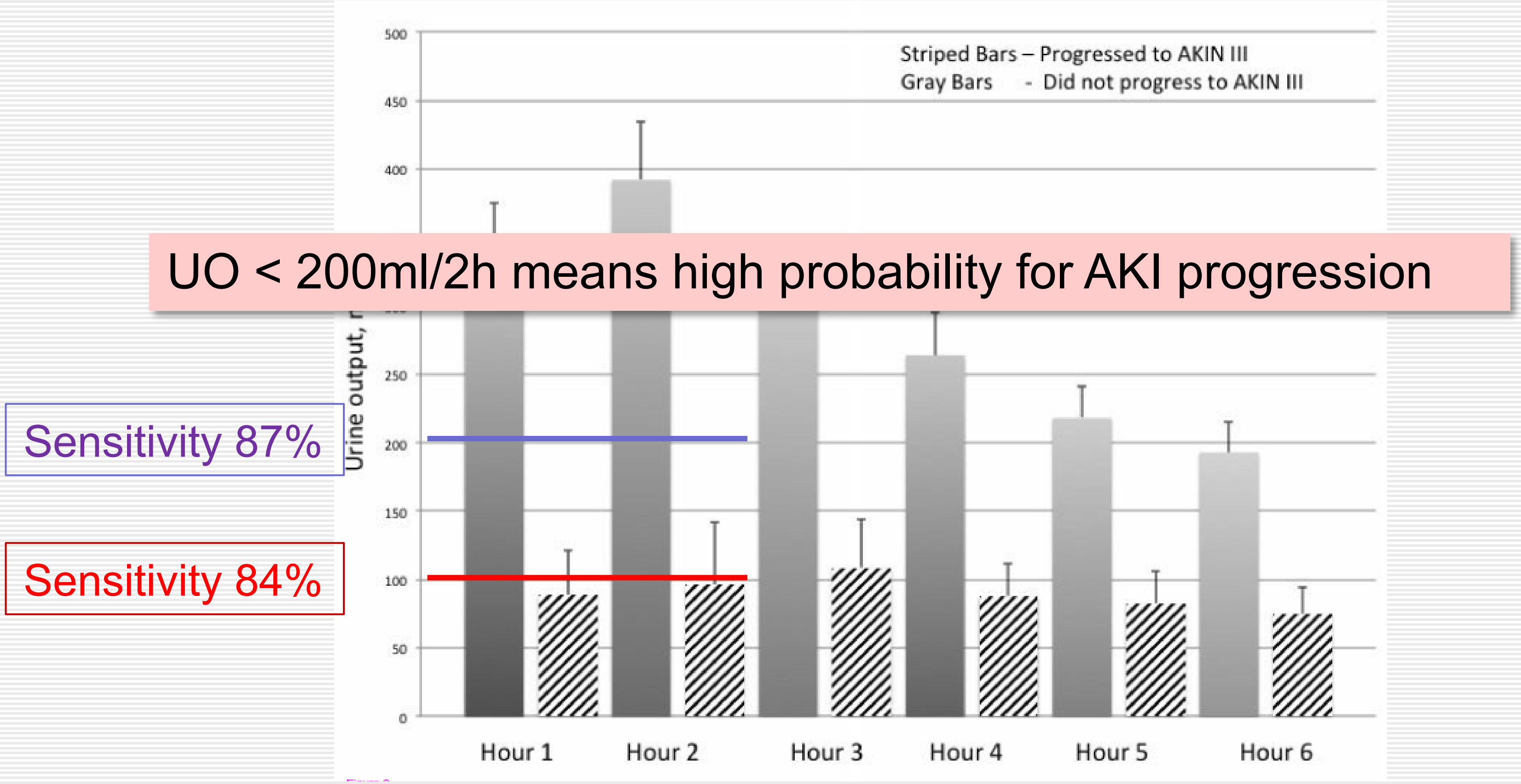
No, this is not the case

Physiology of Furosemide



Development and standardization of a furosemide stress test to predict the severity of acute kidney injury

Urinary Output response to **1.0-1.5 mg/kg furosemide** in patients with AKI stage I or II



Chawla LS et al, Crit Care 2013, 17:R207

Myth #5

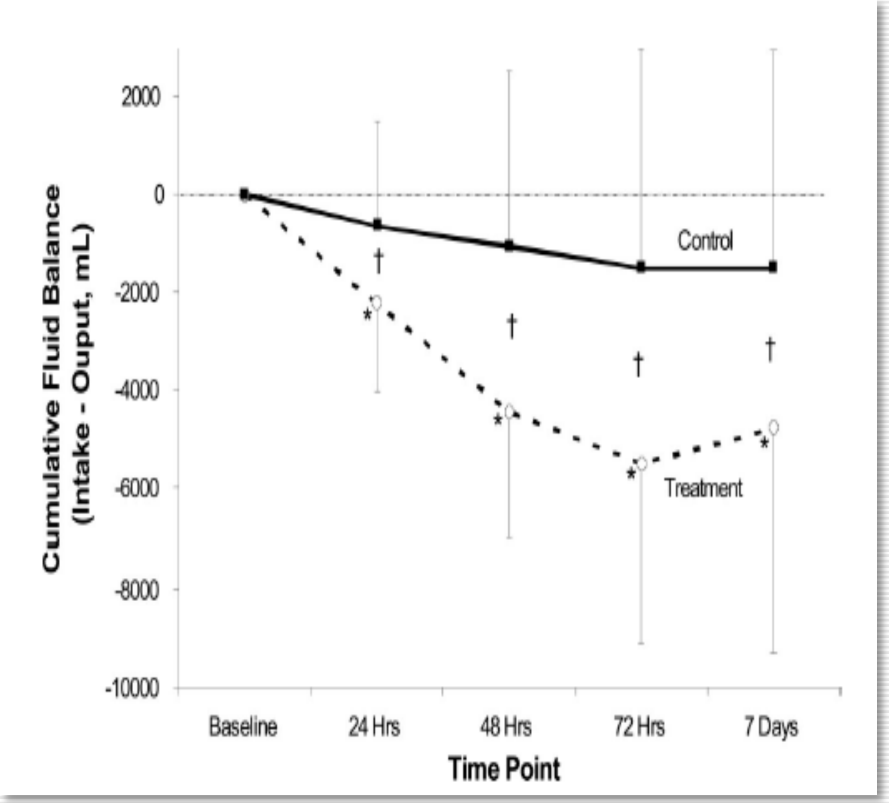
Frusemide works better if given together with albumin.

It depends

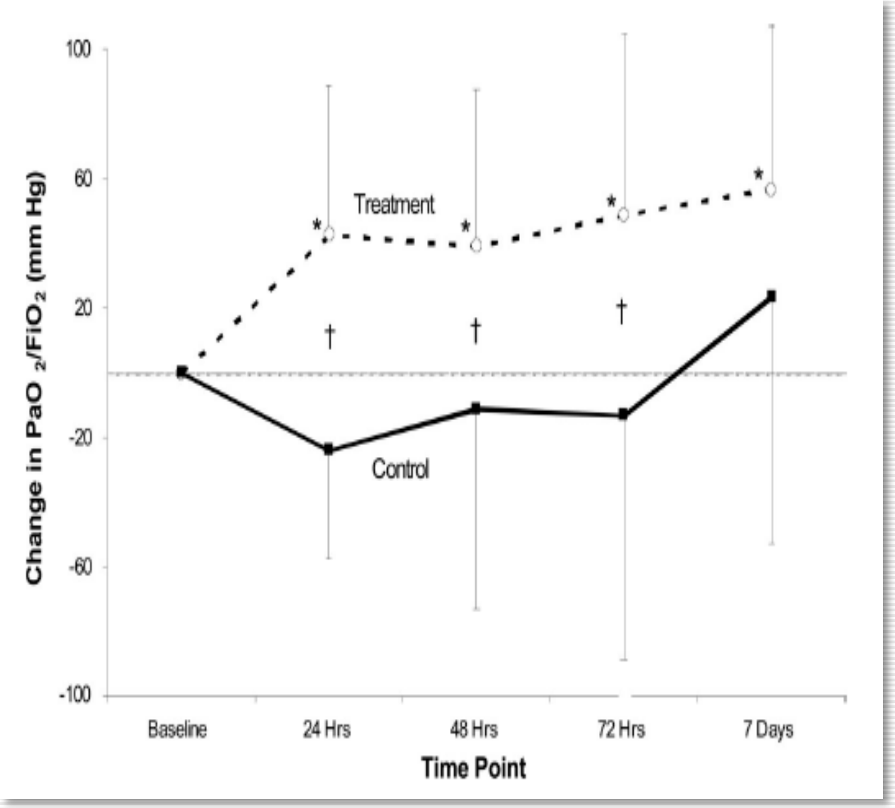
Furosemide with or without albumin in hypoproteinemic patients with ALI

RCT (n=40): furosemide 3-5 mg/h (max.10 mg/h) + albumin 25g q8h vs. placebo

Cumulative fluid balance



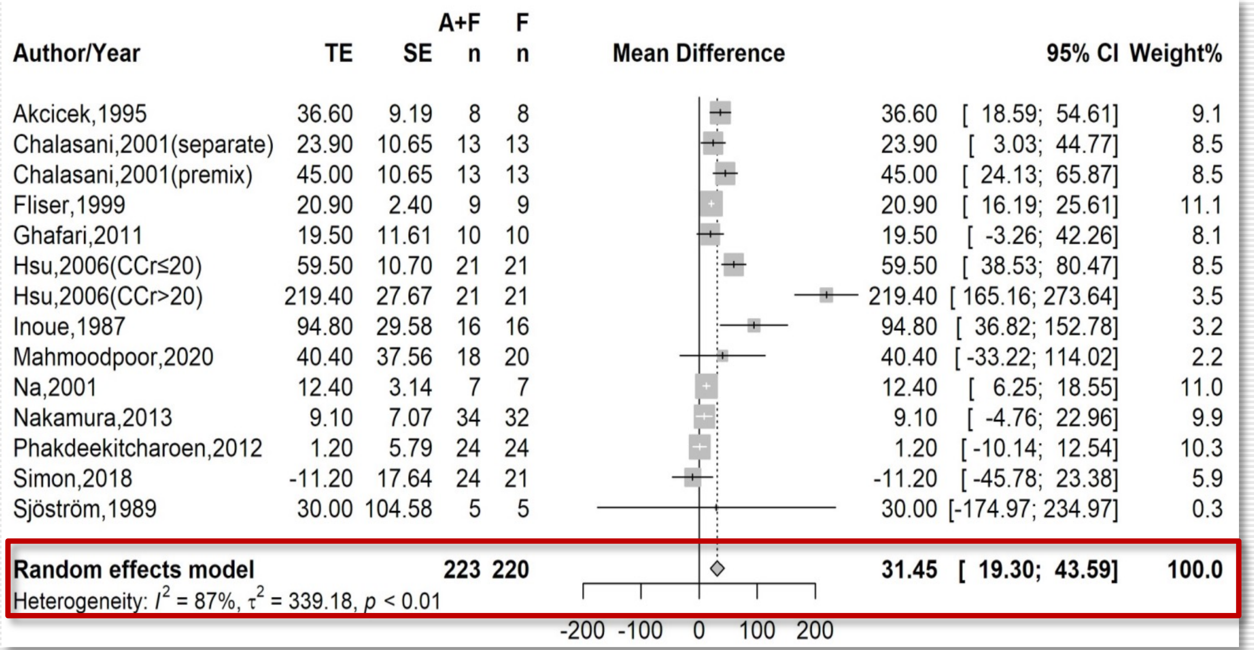
Change in paO_2/FiO_2



Martin G et al, Crit Care Med. 2005 Aug; 33(8):1681-7.

Diuretic effect of co-administration of furosemide and albumin in comparison to furosemide therapy alone: An updated systematic review and meta-analysis

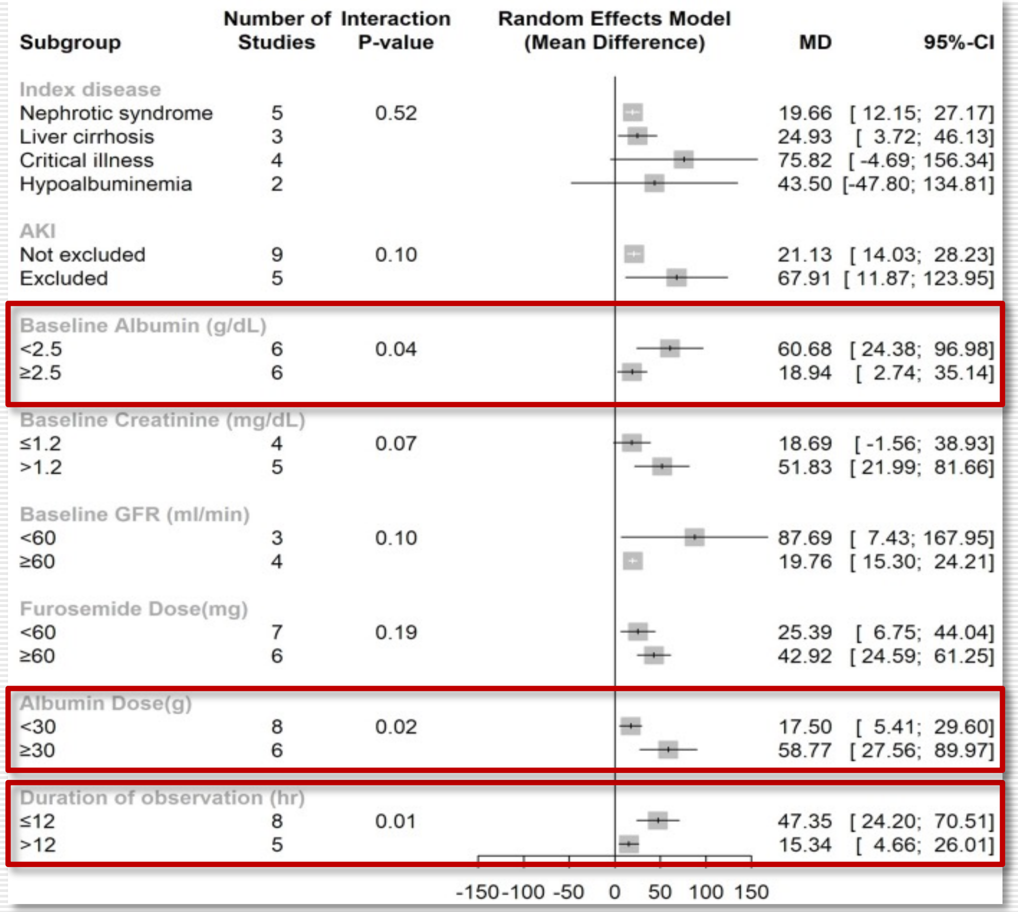
Treatment effect of co-administration furosemide with albumin on urine output rate.



Author/Year	TE	SE	A+F n	F n	95% CI	Weight%
Akcicek,1995	36.60	9.19	8	8	36.60 [18.59; 54.61]	9.1
Chalasani,2001(separate)	23.90	10.65	13	13	23.90 [3.03; 44.77]	8.5
Chalasani,2001(premix)	45.00	10.65	13	13	45.00 [24.13; 65.87]	8.5
Fliser,1999	20.90	2.40	9	9	20.90 [16.19; 25.61]	11.1
Ghafari,2011	19.50	11.61	10	10	19.50 [-3.26; 42.26]	8.1
Hsu,2006(CCr≤20)	59.50	10.70	21	21	59.50 [38.53; 80.47]	8.5
Hsu,2006(CCr>20)	219.40	27.67	21	21	219.40 [165.16; 273.64]	3.5
Inoue,1987	94.80	29.58	16	16	94.80 [36.82; 152.78]	3.2
Mahmoodpoor,2020	40.40	37.56	18	20	40.40 [-33.22; 114.02]	2.2
Na,2001	12.40	3.14	7	7	12.40 [6.25; 18.55]	11.0
Nakamura,2013	9.10	7.07	34	32	9.10 [-4.76; 22.96]	9.9
Phakdeekitcharoen,2012	1.20	5.79	24	24	1.20 [-10.14; 12.54]	10.3
Simon,2018	-11.20	17.64	24	21	-11.20 [-45.78; 23.38]	5.9
Sjöström,1989	30.00	104.58	5	5	30.00 [-174.97; 234.97]	0.3
Random effects model			**223**	**220**	**31.45 [19.30; 43.59]**	**100.0**

Heterogeneity: $I^2 = 87\%$, $\tau^2 = 339.18$, $p < 0.01$

13 studies with 422 patients



Subgroup	Number of Studies	Interaction P-value	MD	95%-CI
Index disease				
Nephrotic syndrome	5	0.52	19.66	[12.15; 27.17]
Liver cirrhosis	3		24.93	[3.72; 46.13]
Critical illness	4		75.82	[-4.69; 156.34]
Hypoalbuminemia	2		43.50	[-47.80; 134.81]
AKI				
Not excluded	9	0.10	21.13	[14.03; 28.23]
Excluded	5		67.91	[11.87; 123.95]
Baseline Albumin (g/dL)				
<2.5	6	0.04	60.68	[24.38; 96.98]
≥2.5	6		18.94	[2.74; 35.14]
Baseline Creatinine (mg/dL)				
≤1.2	4	0.07	18.69	[-1.56; 38.93]
>1.2	5		51.83	[21.99; 81.66]
Baseline GFR (ml/min)				
<60	3	0.10	87.69	[7.43; 167.95]
≥60	4		19.76	[15.30; 24.21]
Furosemide Dose(mg)				
<60	7	0.19	25.39	[6.75; 44.04]
≥60	6		42.92	[24.59; 61.25]
Albumin Dose(g)				
<30	8	0.02	17.50	[5.41; 29.60]
≥30	6		58.77	[27.56; 89.97]
Duration of observation (hr)				
≤12	8	0.01	47.35	[24.20; 70.51]
>12	5		15.34	[4.66; 26.01]

Lee TH et al, PLoS ONE 16(12): e0260312, 2021

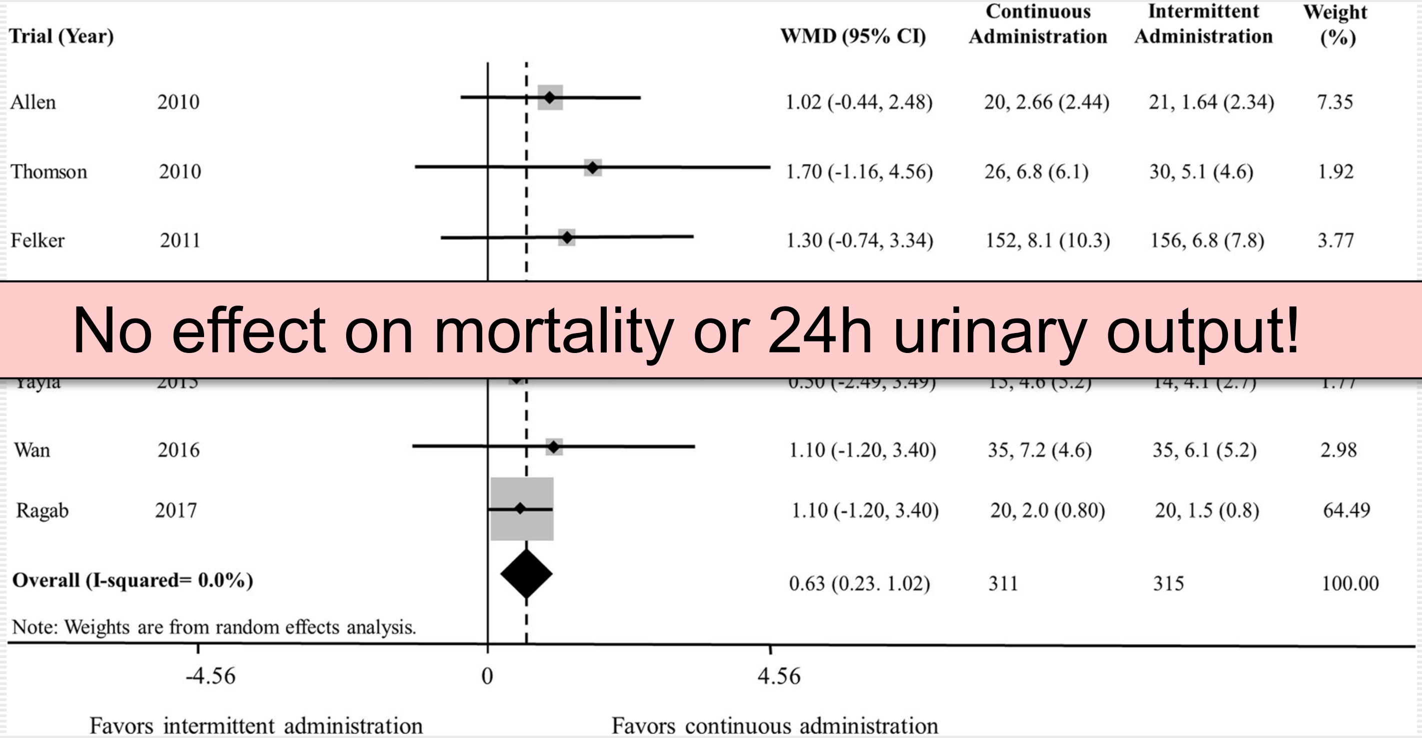
Myth #6

Furosemide infusion is more effective than furosemide bolus.

Not really

Continuous versus intermittent administration of furosemide in acute decompensated heart failure: a systematic review and meta-analysis

Body weight reduction



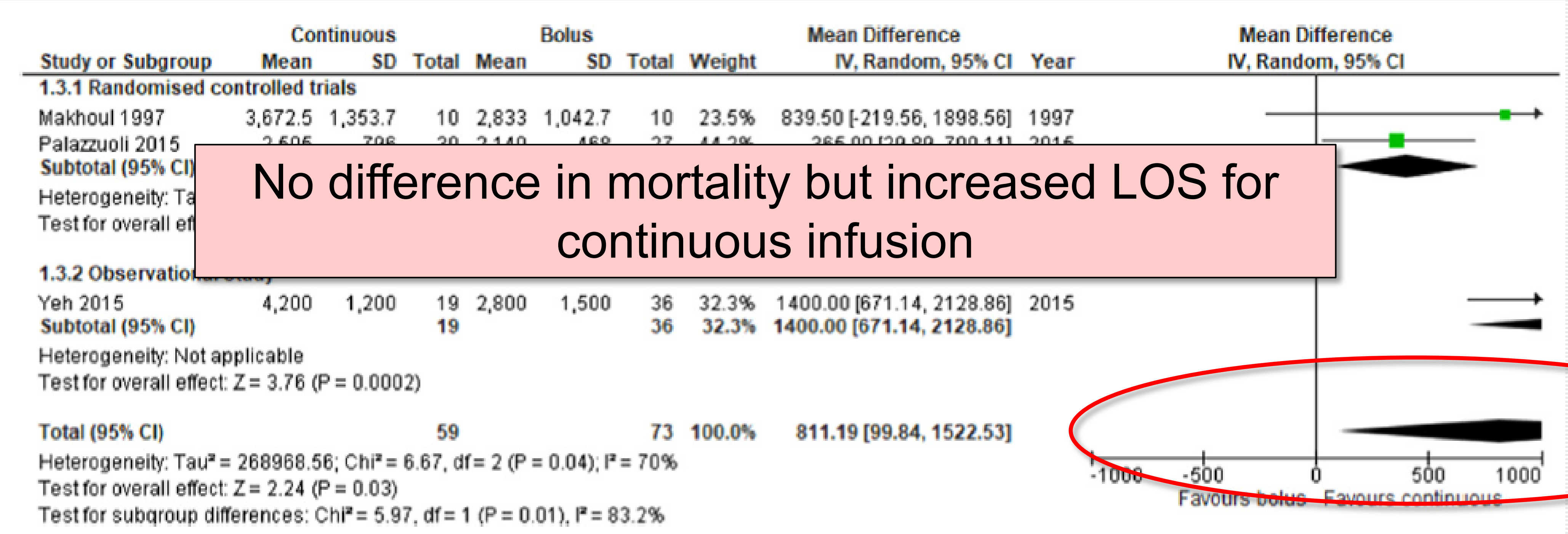
No effect on mortality or 24h urinary output!

No differences in hypokalemia, hyponatremia, increased serum creatinine level, and hypotension were noted.

Kuriyama A et al, Heart Failure Reviews 2018

Continuous Infusion versus Intermittent Bolus Injection of Furosemide in Critically Ill Patients: A Systematic Review and Meta-analysis

Urine Output in the first 24 h



No difference in mortality but increased LOS for continuous infusion

Ng K T et al, J Cardiothorac Vasc Anesth 32 (2018) 2303–2310

Myth #7

Furosemide can prevent RRT.

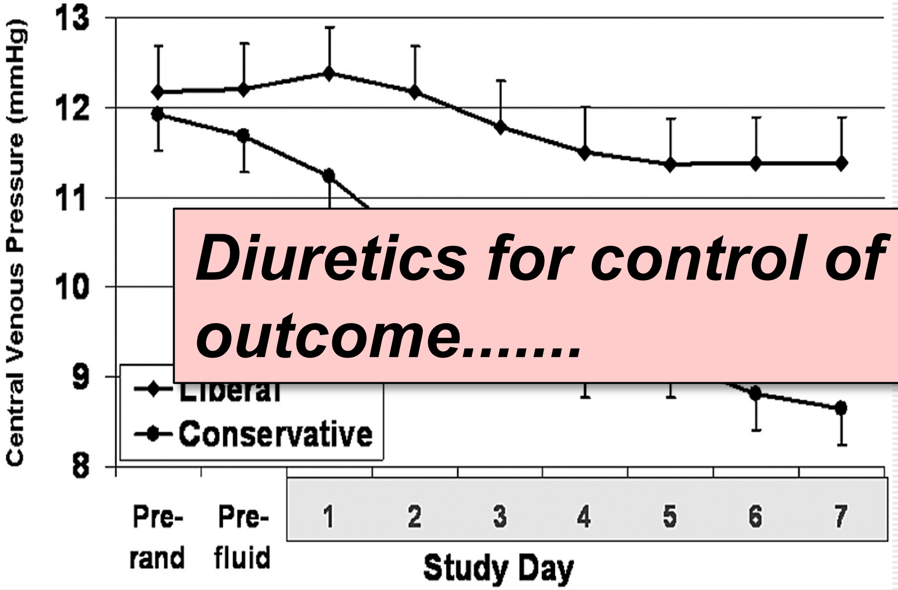
No, it can´t

Fluid balance, diuretic use, and mortality in acute kidney injury Fluid and Catheter Treatment Trial (FACTT)

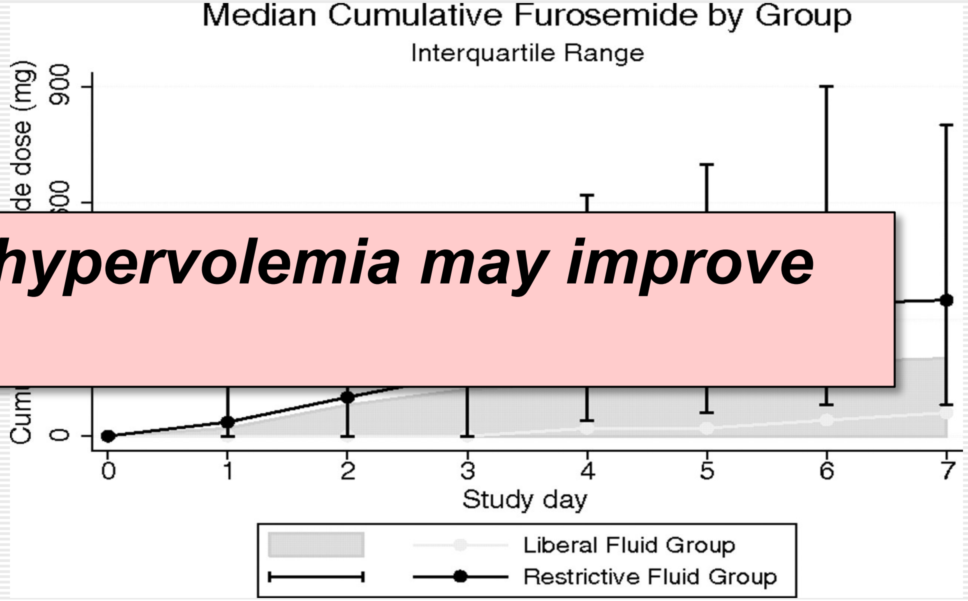
Fluid balance / week	
Conserv. Strategy (n=503):	Liberal Strategy (n=498):
-136 (± 491) ml	**+ 6992 (±502) ml**

Pat. on RRT: conservative 10% liberal 14% (p=0.06)

CVP



Furosemide

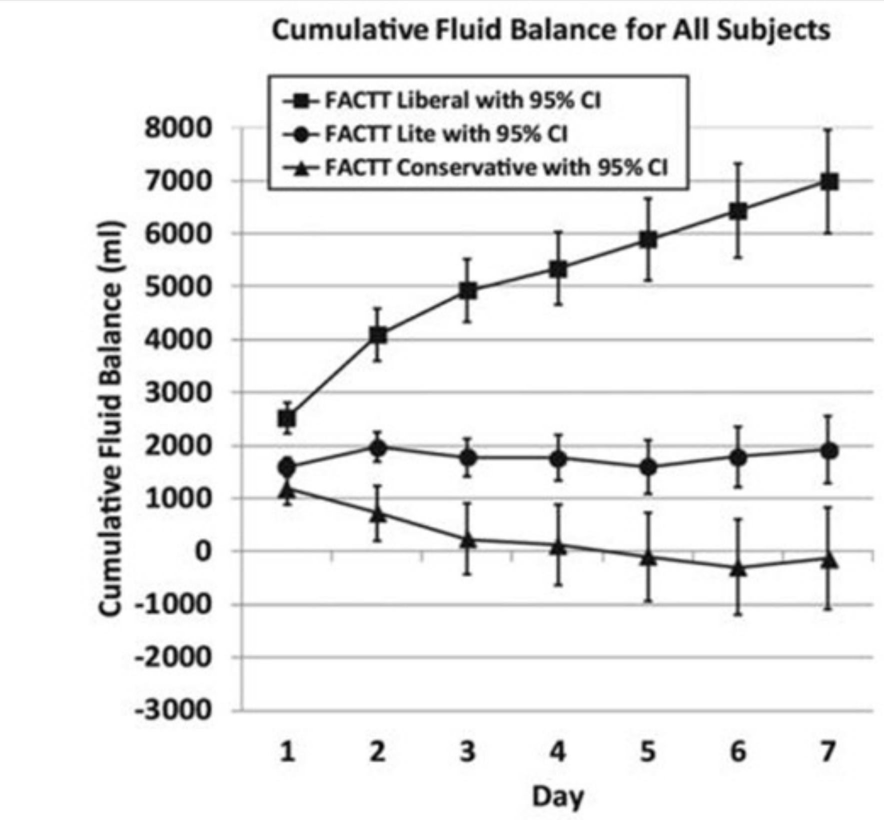


Diuretics for control of hypervolemia may improve outcome.......

ARDS Clinical Network Trial, NEJM 2006

Grams M E et al. CJASN 2011;6:966-973

Fluid Management With a Simplified Conservative Protocol for the Acute Respiratory Distress Syndrome



Outcome	FACTT Lite (n = 1,124) (%)	FACTT Conservative (n = 503) (%)	FACTT Liberal (n = 497) (%)	p Lite Versus Conservative	p Lite Versus Liberal
Ventilator-free days	14.9±0.3	14.6±0.5	12.1±0.5	0.61	< 0.001
ICU-free days	14.4±0.3	13.4±0.4	11.2±0.4	0.054	< 0.001
60-day mortality	249 (22)	128 (25)	124 (28)	0.15	0.007
Adjusted 60-day mortality[a]	272 (24)	123 (25)	127 (25)	0.91	0.56
New onset shock[b]	104 (9)	67 (13)	55 (11)	0.007	0.18
Acute kidney injury before adjustment for fluid balance	653 (58)	288 (57)	253 (51)	0.72	0.006
Acute kidney injury after adjustment for fluid balance	631 (56)	290 (58)	328 (66)	0.60	< 0.001

FACTT = Fluid and Catheter Treatment Trial.

Furosemide: ~70 mg/d ~140 mg/d ~25 mg/d

Grissom C et al, Critical Care Medicine. 43(2):288-295, 2015

Myth #7

Furosemide can prevent RRT.

No, it can´t

but it may allow for better fluid management
and buy the patient time to recover

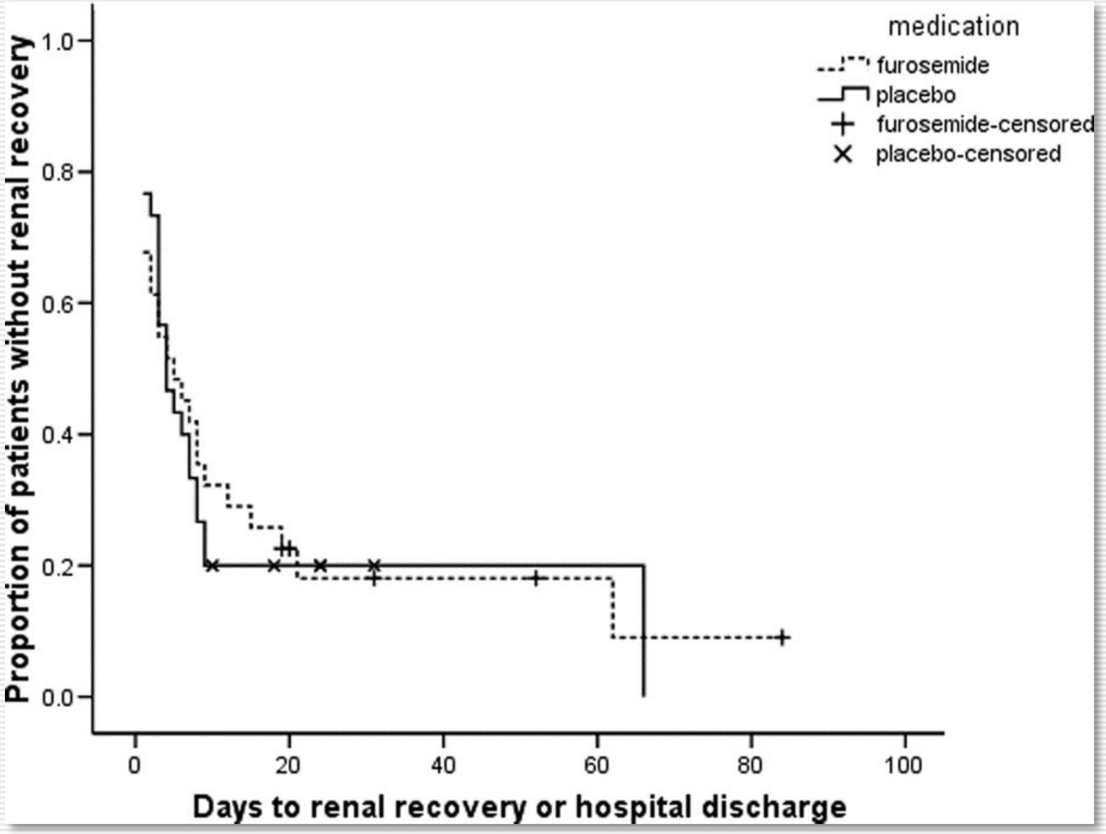
Myth #8

Furosemide helps to wean anuric patients from RRT.

No, it does not

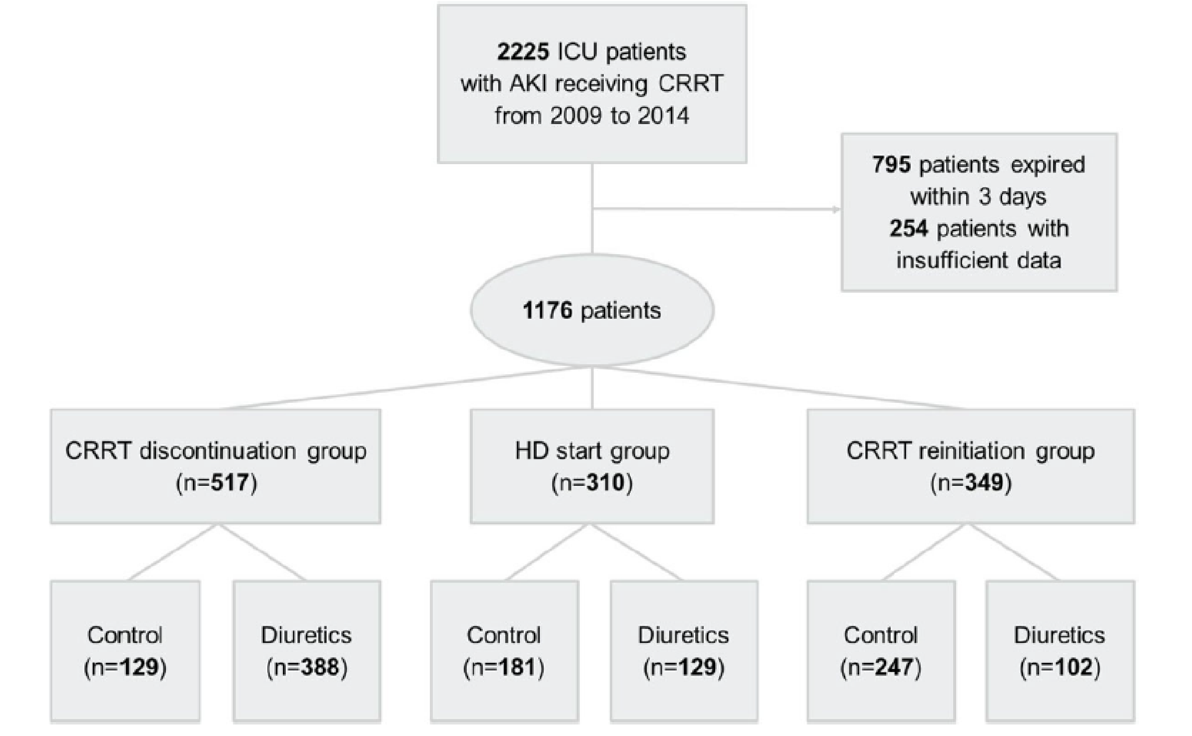
Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: a double blind randomized controlled trial

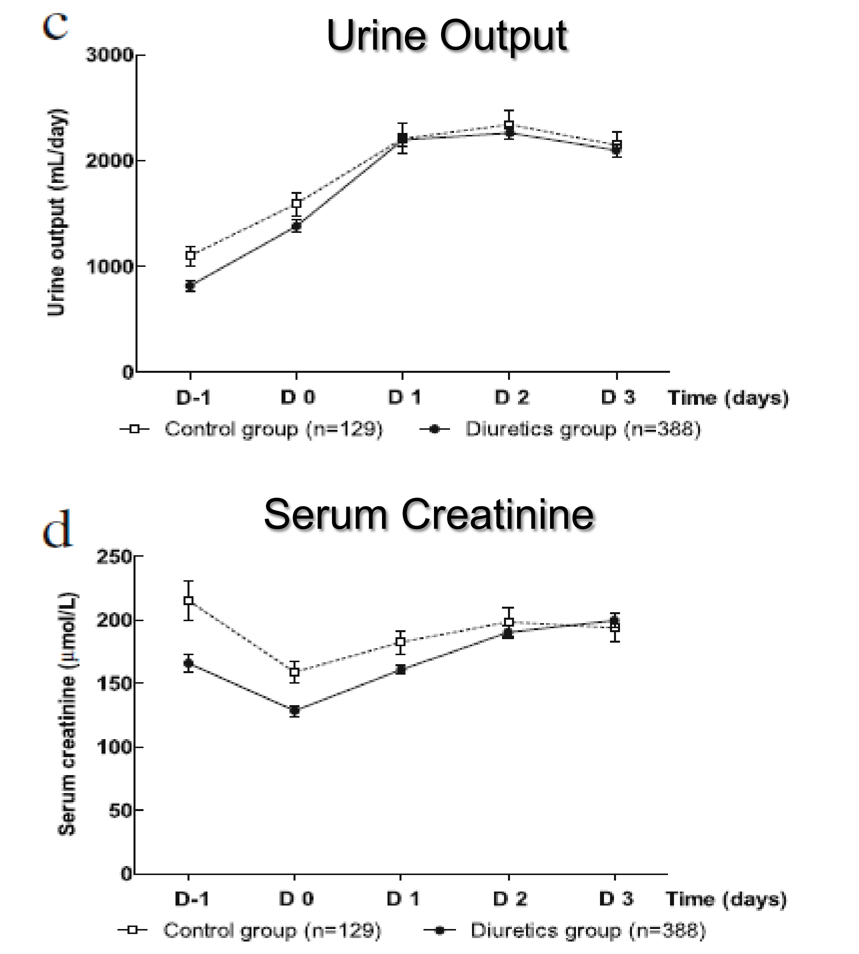
Single centre RCT,
N=72 ICU patients



Van der Voort PH, et al, Crit Care Med 2009 37(2):533-8.

Association between diuretics and successful discontinuation of continuous renal replacement therapy in critically ill patients with acute kidney injury





Jeon et al. Critical Care (2018) 22:255

Myth #9

Frusemide-induced diuresis after AKI implies full renal recovery.

No, it does not

Discontinuation of continuous renal replacement therapy (B.E.S.T kidney)

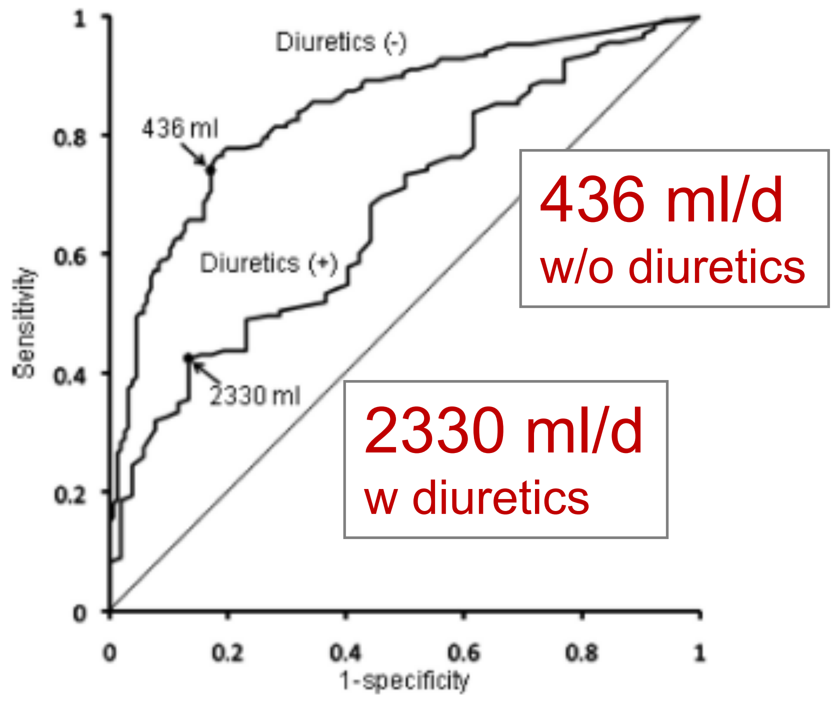


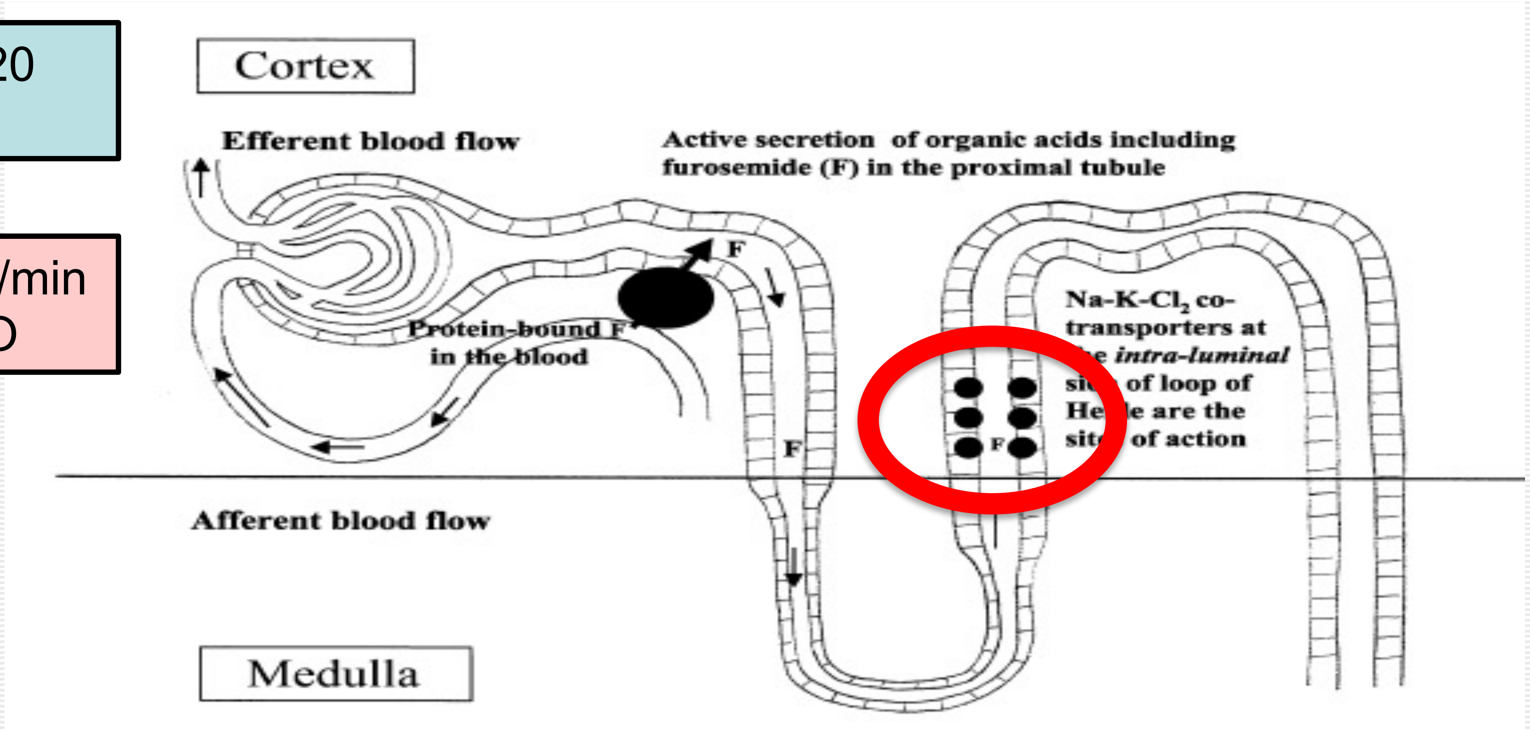
Figure 3. Impact of diuretics use on predictive ability of urine output. The area under the receiver operating characteristics curve of urine output for successful discontinuation of continuous renal replacement therapy was 0.671 (0.585–0.750) with diuretics and 0.845 (0.799–0.883) without diuretics. Urine output of 436 mL/day for patients without diuretics and of 2330 mL for those with diuretics had the highest accuracy.

Uchino et al, Crit Care Medicine 2009

Physiology of Furosemide

normal GFR=90-120 ml/min

Reduced GFR=50 ml/min still is sufficient UO



UO = 2400 ml/h (40 ml/min)

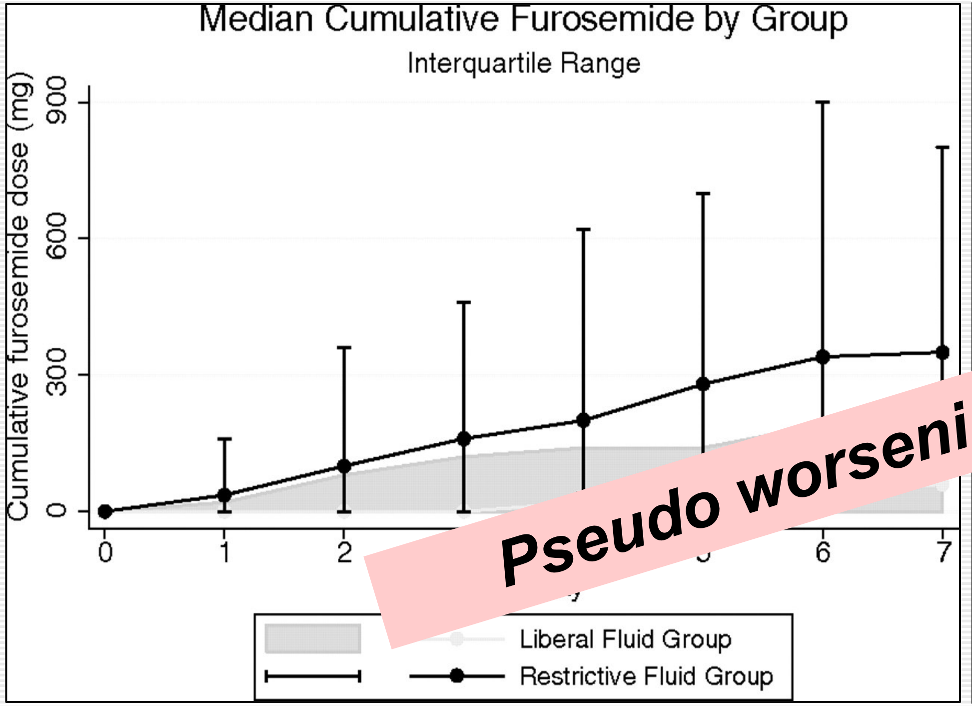
Myth #10

Frusemide should be stopped if serum creatinine is increasing, indicating worsening renal function

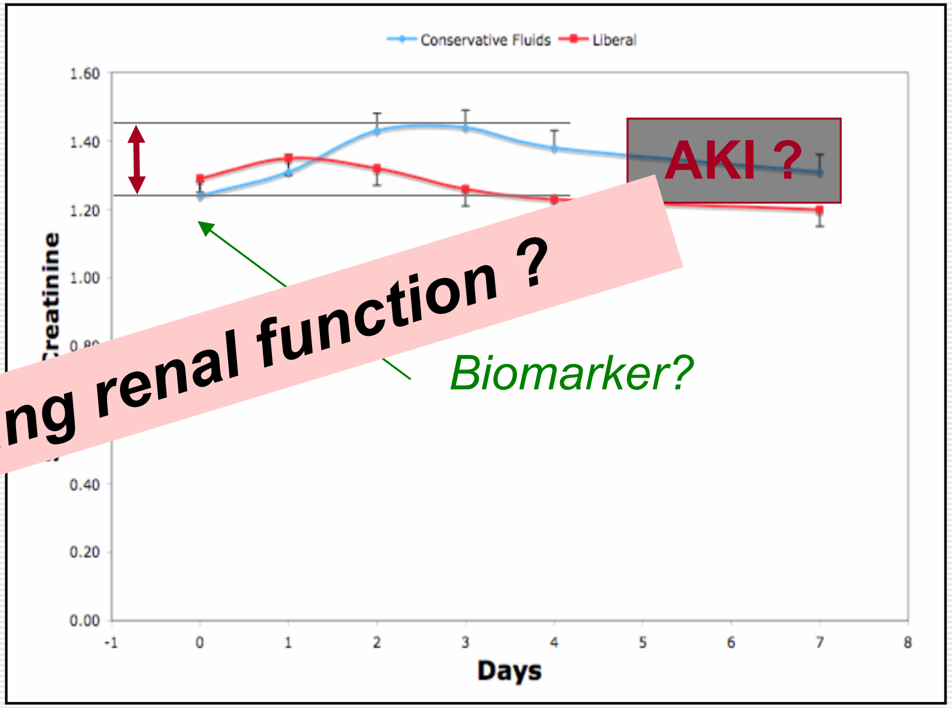
No, not necessarily

Furosemide Doses and Changes in Serum Creatinine During the FACTT Trial

Furosemide Dose



Serum Creatinine



Grams M E et al. CJASN 2011;6:966-973

ARDS Clinical Network Trial, NEJM 2006

Diuretic response in acute heart failure: clinical characteristics and prognostic significance

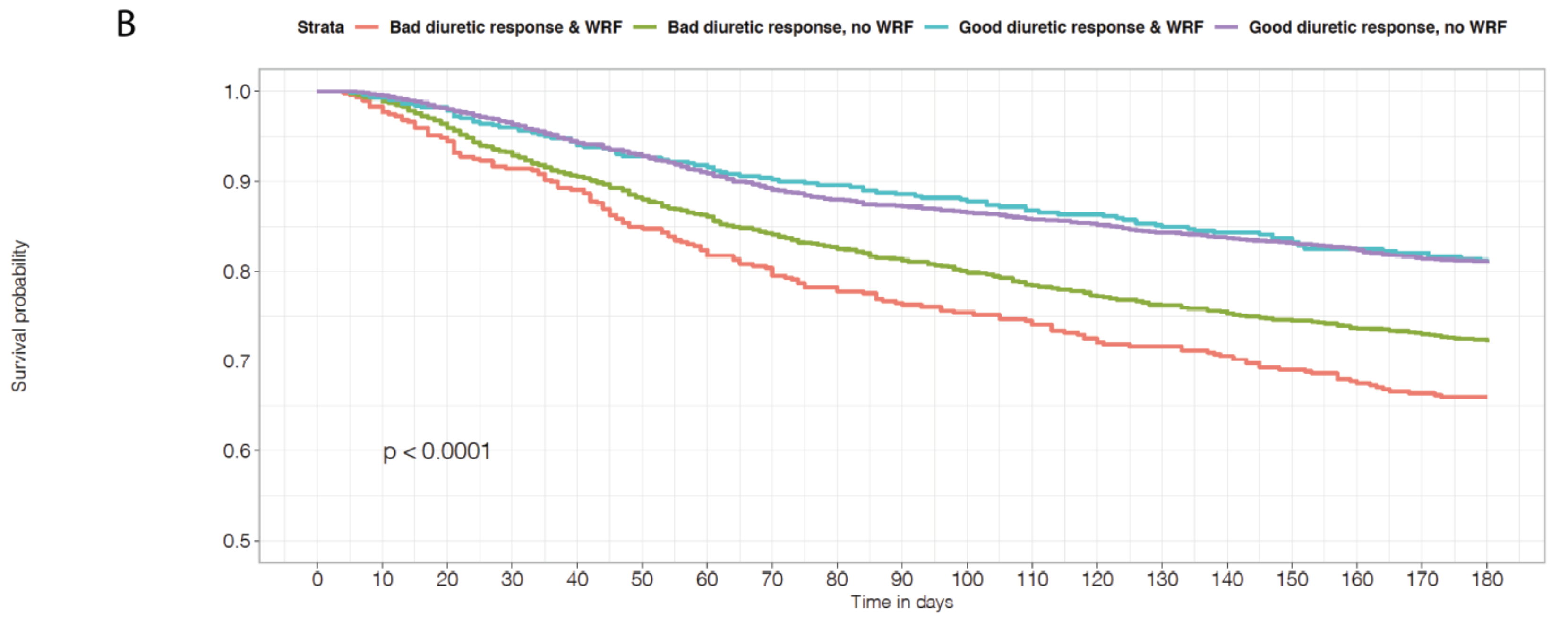
Table 3 Clinical, rehospitalization, and mortality outcomes per quintile of diuretic response

Diuretic response (kg/40 mg furosemide)	−1.33 (−1.95 to 0.07) (*n* = 349)	−0.70 (−0.80 to −0.60) (*n* = 349)	−0.38 (−0.44 to −0.33) (*n* = 351)	−0.18 (−0.24 to −0.13) (*n* = 347)	0.00 (−0.04 to 0.18) (*n* = 349)	*P* for trend
Weight change Day 1–4 (kg)	−5.7 ± 3	−3.9 ± 2	−2.8 ± 1.8	−2.1 ± 1.6	0.5 ± 2.1	<0.001
Total diuretic dose, Day 1–3 (mg)	130 (100–180)	200 (140–280)	240 (160–400)	380 (240–607.5)	330 (200–640)	<0.001
Thiazide diuretics during admission	15.2 (53)	18.3 (64)	16.8 (59)	23.6 (82)	21.2 (74)	0.009
Inotropes during admission [% (*n*)]	2 (7)	1.4 (5)	4 (14)	8.6 (30)	14.6 (51)	<0.001
Inotropes or vasodilators during admission [% (*n*)]	13.8 (48)	12 (42)	14.8 (52)	19 (66)	21.8 (76)	<0.001
WRF, Day 7 [% (*n*)]	21.9 (75)	16 (54)	18.2 (62)	26.8 (90)	25.1 (84)	0.016
WRF, Day 14 [% (*n*)]	21.9 (75)	18.6 (63)	22 (75)	25 (84)	29.6 (99)	0.003
Treatment failure due to death [% (*n*)]	0.3 (1)	0.9 (3)	0.3 (1)	0.9 (3)	1.1 (4)	0.218
Treatment failure due to worsening Heart failure (%(*n*))	3.4 (12)	4.9 (17)	5.7 (20)	14.1 (49)	18.3 (64)	<0.001
Treatment failure due to WRF [% (*n*)]	11.4 (39)	8.9 (30)	10 (34)	14.1 (47)	16 (53)	0.011
Treatment failure due to HF rehospitalization (%(*n*))	0.3 (1)	0 (0)	0.3 (1)	0.3 (1)	0.3 (1)	0.722
Haemoconcentration on Day 4 [% (*n*)]	65.8 (156)	66.4 (176)	61.6 (165)	55.7 (151)	47.1 (123)	<0.001
180-day mortality [% (*n*)]	8 (28)	12.6 (44)	14 (49)	21.9 (76)	24.9 (87)	<0.001
60-day Heart failure rehospitalization [% (*n*)]	7.4 (26)	8.9 (31)	15.7 (55)	19 (66)	23.2 (81)	<0.001
60-day death or renal or cardiovascular rehospitalization [% (*n*)]	15.8 (55)	19.2 (67)	27.9 (98)	35.2 (122)	38.4 (134)	<0.001

Unadjusted incidence rates are reported.
WRF, worsening renal function; HF, heart failure.
WRF ≥ 0.3 mg/dL creatinine increase from baseline.

Valente MAE et al, European Heart Journal (2014) 35, 1284–1293

Worsening renal function in acute heart failure in the context of diuretic response



Number at risk

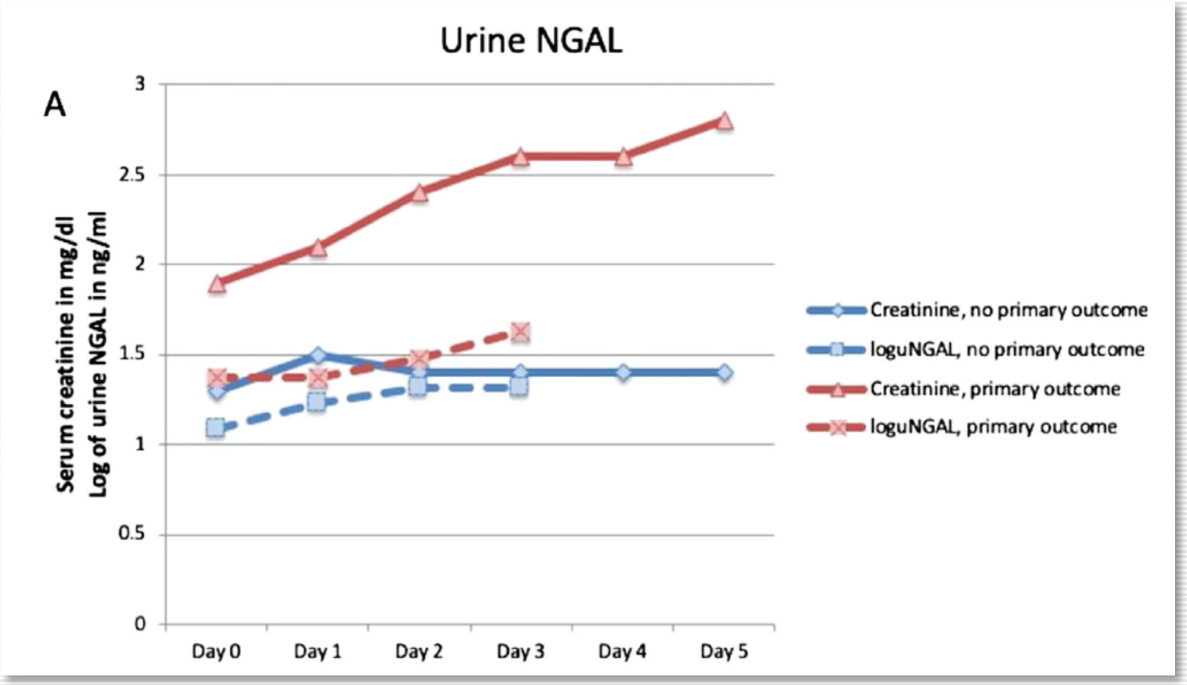
Bad diuretic response & WRF	470	462	443	427	413	392	379	370	360	352	344	340	330	326	320	312	305	299	255
Bad diuretic response, no WRF	1845	1829	1771	1710	1657	1610	1574	1534	1504	1478	1452	1421	1398	1375	1361	1340	1323	1313	1139
Good diuretic response & WRF	502	498	492	480	472	464	458	449	444	439	435	428	424	417	412	409	403	401	359
Good diuretic response, no WRF	2551	2541	2499	2453	2397	2358	2307	2260	2223	2206	2187	2164	2148	2120	2105	2091	2073	2043	1794

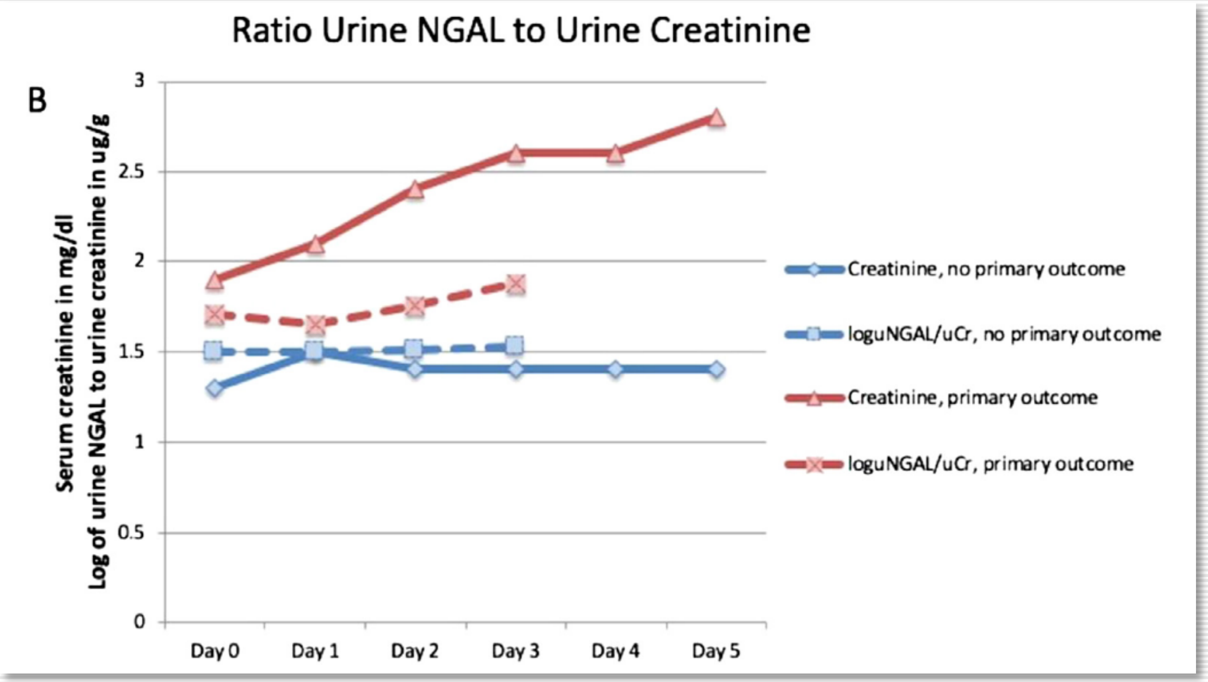
Secondary analysis of PROTECT (n=1698) and RELAX_AHF-2 (n=5586) investigating impact of WRF (increase in Serum creatinine $\geq$ 0.3 mg/dl – day 4) by diuretic response (kg weight loss/40 mg furosemide equivalent baseline—day 4) with regard to (cardiovascular) death

Emmens JE et al, European Journal of Heart Failure (2022) **24**, 365–374

Utility of Urine Neutrophil Gelatinase-Associated Lipocalin for Worsening Renal Function during Hospitalization for Acute Heart Failure: Primary Findings of the Urine N-gal Acute Kidney Injury N-gal Evaluation of Symptomatic Heart Failure Study (AKINESIS)

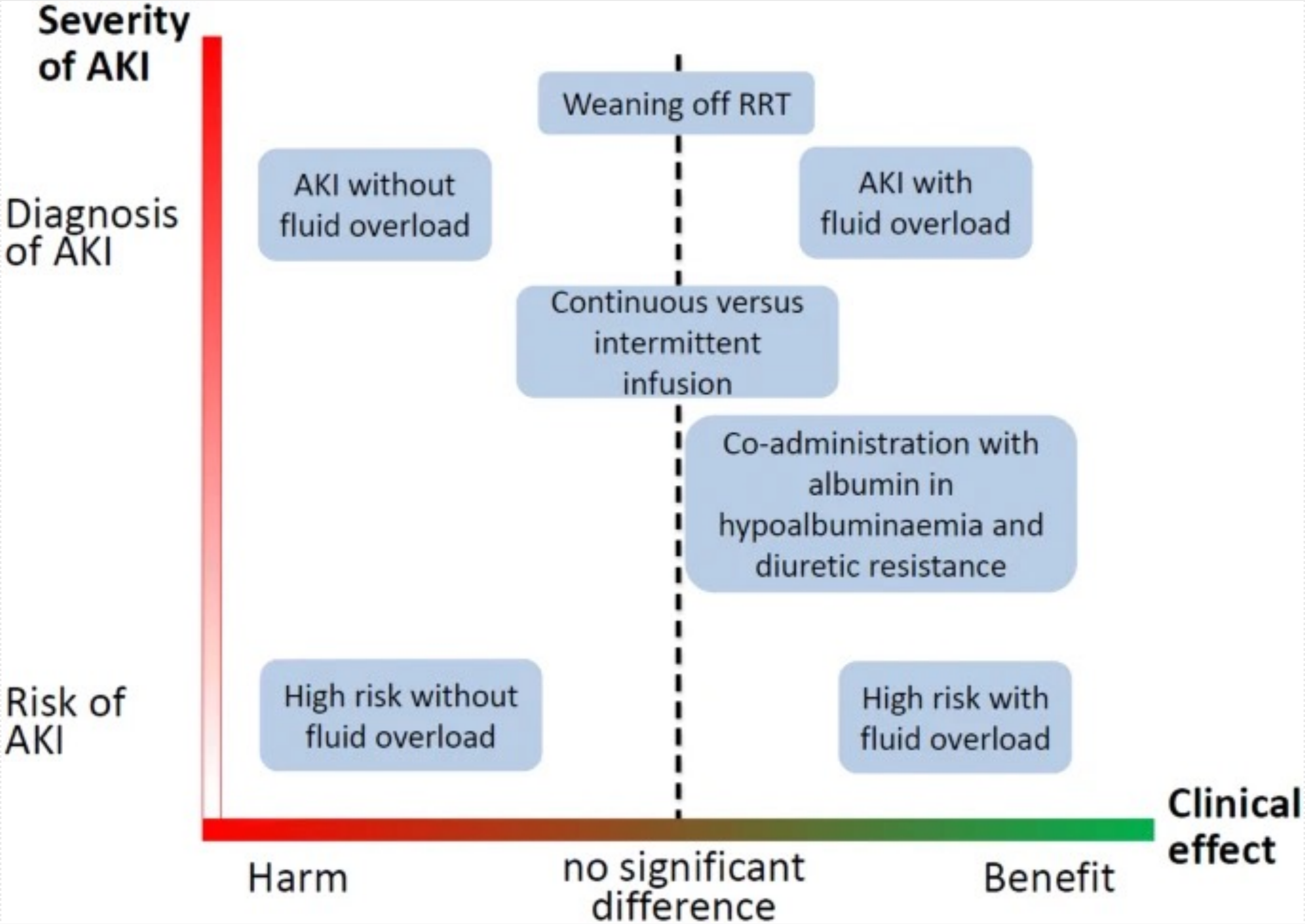
Mean values of creatinine and uNGAL in patients with and without primary outcome (WRF or initiation of RRT within 5 days of hospitalization compared to the first measured serum creatinine level)





Murray PT et al, J Card Fail 2019 Aug;25(8):654-665.

Use of Furosemide Summary



Intensive Care Med (2019) 45:545–548

Thanks for your attention

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