WORSENING OF RENAL FUNCTION AFTER RAS INHIBITION IN DECOMPENSATED HEART FAILURE: CLINICAL IMPLICATIONS

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MAJOR KEY POINTS

- A small initial increase in serum creatinine (up to 30%) strongly correlates with slower CKD progression in diabetes
- In Heart Failure the same initial increase is an indicator of poor renal reserve and may be associated with higher short term CV event rates.

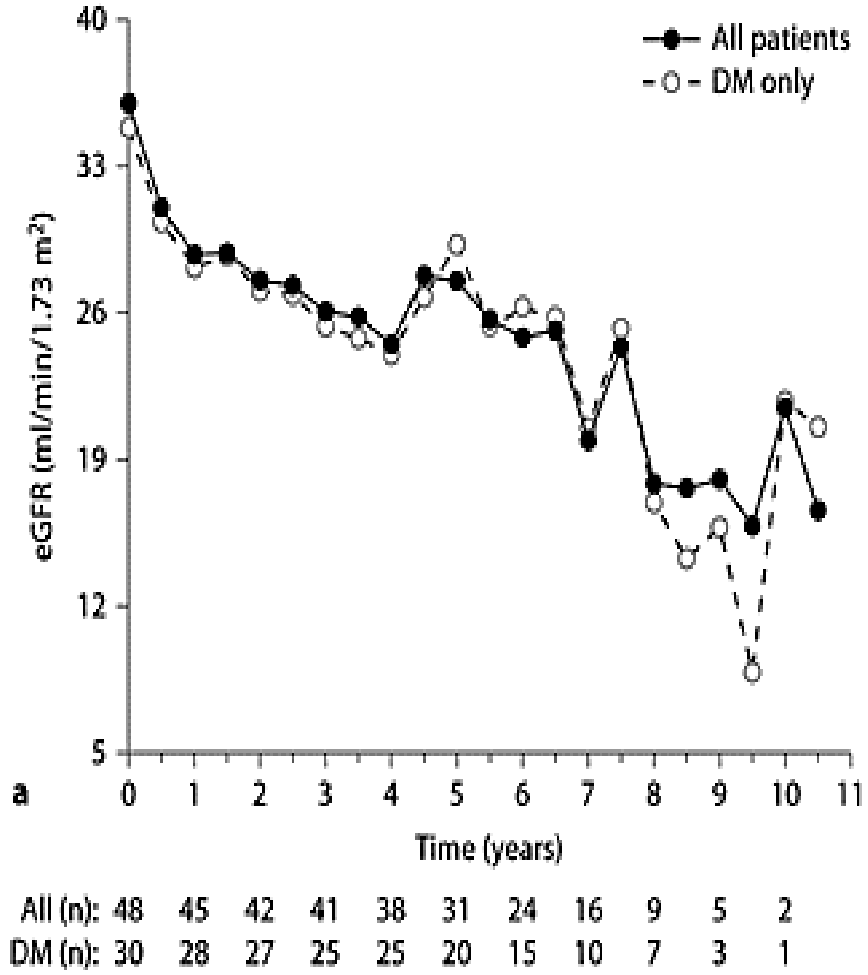
Baseline demographics and clinical characteristics use of RAS Blockers in Stage 3b CKD

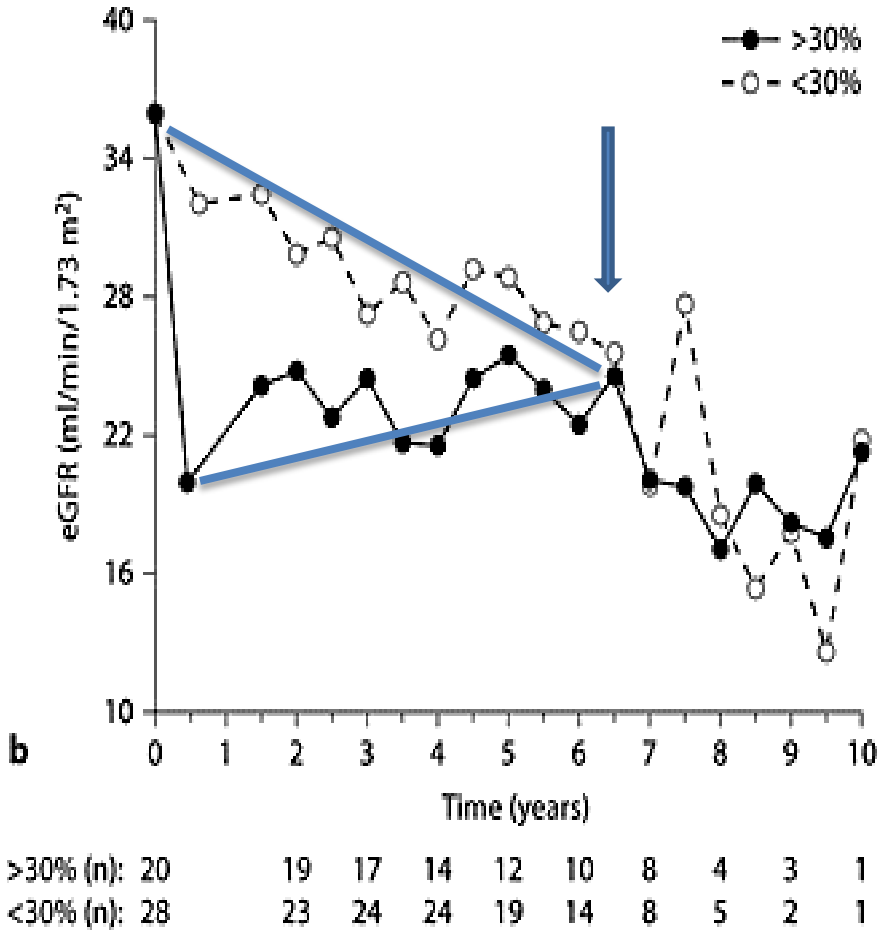
	All patients	Diabetics only	Cr ↑ >30%	Cr ↑ <30%
Age, years	64.2 ± 11.5	66.5 ± 8.2	65.3 ± 11.8	63.4 ± 11.4
Patients	48	30	20	28
Male, %	58.3	46.7	35*	75
Diabetes, %	62.5	100	65.0	60.7
SBP, mm Hg	151.7 ± 23.6	151.4 ± 22.7	159.75 ± 26.8+	145.9 ± 19.6
eGFR, ml/min/1.73 m^2	36.0 ± 14.3	34.9 ± 12.3	35.9 ± 13.1	36.2 ± 15.2
Urine protein ≤30 mg/dl, %	41.7	46.7	50	35.6
Black, %	93.8	96.7	95	92.9

Values are means ± SD. * p = 0.008 vs. <30% ↑; + p = 0.044 vs. <30% ↑.

Hirsch, S et.al. *Am.J.Nephrol. 36 (5):430-437, 2012.*

Decline in Kidney Function Over Time in Total Cohort.





Hirsch, S et.al. *Am.J.Nephrol. 36 (5):430-437, 2012.*

Staging of AKI for adults

AKI stage	Serum Creatinine: KDIGO	Serum Creatinine: AKIN	Criteria: RIFLE	Urine volume criteria: KDIGO/AKIN/RIFLE
1 (R)	1.5–1.9 times baseline or *≥0.3 mg/dl (≥26 µmol/l)* *Increase within 48h*	*Increase≥0.3 mg/dl (26.5 µmol/l)* or≥1.5- to 2-fold from baseline	Increase×1.5 baseline or GFR decrease >25%	<0.5ml/kg/h for 6–12 h
2 (I)	2.0–2.9 times baseline	Increase >2- to 3-fold from baseline	Increase×2 from baseline or GFR decreased >50%	<0.5ml/kg/h for 12 h
3 (F)	3.0 times baseline or increase in serum creatinine to≥4.0 mg/dl (354 µmol/l) or initiation of renal replacement therapy or, in patients <18 years, decrease in eGFR to <35ml/min per 1.73 m^2	Increased >300% (>3-fold) from baseline, or ≥4.0 mg/dl (354mmol/l) with an acute increase of ≥0.5 mg/dl (44 µmol/l) or on renal replacement therapy	Increase × 3 from baseline, or serum creatinine >4mg/dl (>354 µmol/l) with an acute rise >0.5mg/dl (>44 µmol/l) or GFR decreased >75%	<0.3ml/kg/h for 24 h or anuria for 12 h

Okusa, M. D. and A. Davenport Kidney Int 2014;85(1): 39-48

The story of worsening renal function
(i.e. change in serum creatinine ≥ 0.3mg/dl)

Correlates and Impact on Outcomes of Worsening Renal Function in Patients ≥65 Years of Age With Heart Failure*

Harlan M. Krumholz, MD, Ya-Ting Chen, PhD, Viola Vaccarino, MD, PhD, Yun Wang, MS, Martha J. Radford, MD, W. David Bradford, PhD, and Ralph I. Horwitz, MD

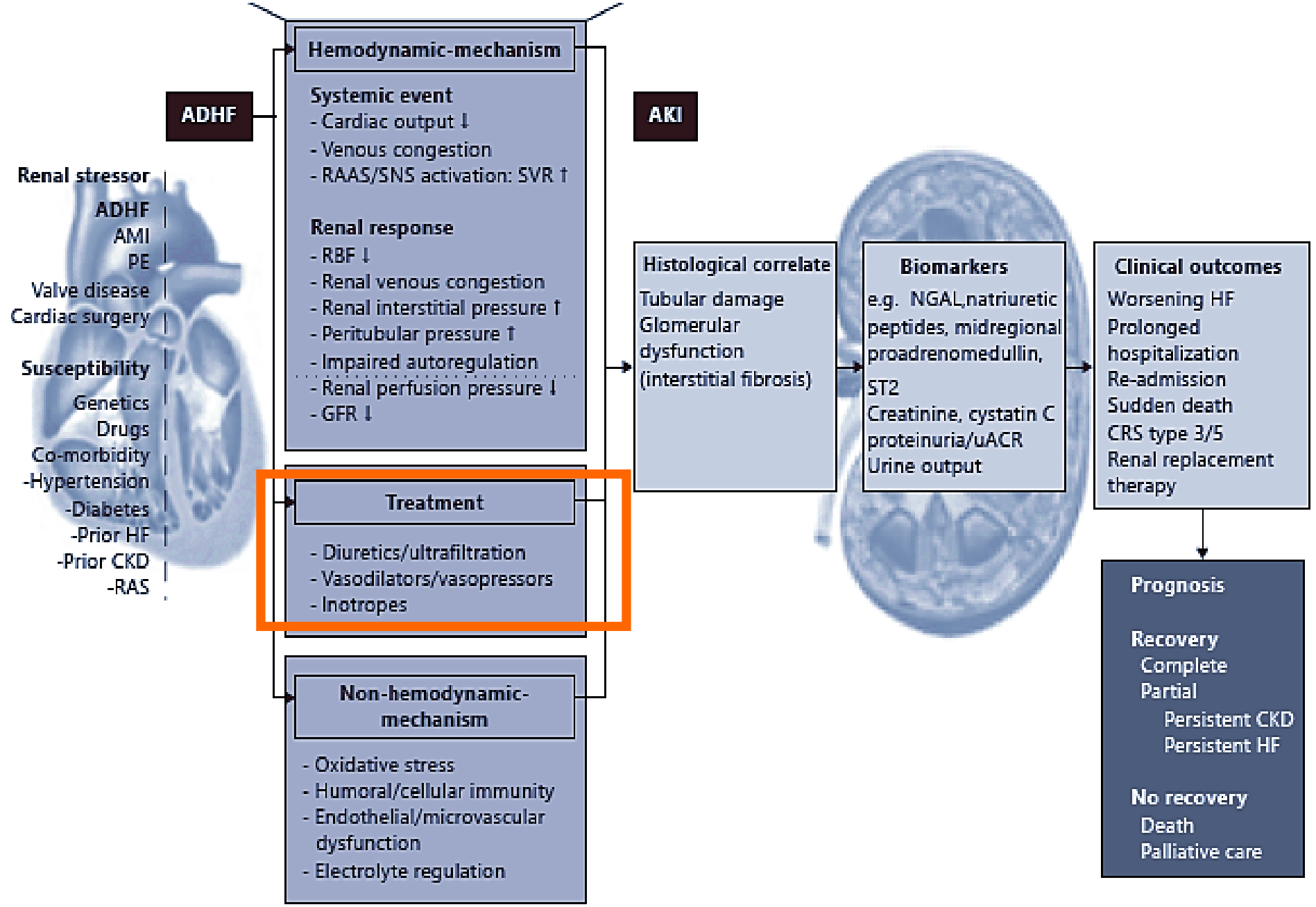
TABLE III Impact of Worsening Renal Function (WRF) on Patient Clinical Outcomes and Resource Consumption

Outcomes	Total	WRF Absent	WRF Present	Adjusted Estimate*
In-hospital mortality	68 (4%)	36 (3%)	32 (7%)	2.72 (1.62–4.58)
30-d mortality	123 (7%)	76 (6%)	47 (10%)	1.87 (1.25–2.80)
30-d readmission, all-cause	296 (18%)	201 (17%)	95 (20%)	1.29 (0.98–1.71)
30-d readmission, heart failure related	118 (7%)	80 (7%)	38 (8%)	1.17 (0.77–1.77)
6-month mortality	354 (21%)	235 (19%)	119 (25%)	1.56 (1.19–2.05)
6-month readmission, all-cause	790 (47%)	555 (46%)	235 (50%)	1.16 (0.93–1.44)
6-month readmission, heart failure related	380 (23%)	264 (22%)	116 (25%)	1.07 (0.82–1.39)
Length of hospital stay, mean (SD) (d)	7.55 (4.70)	6.93 (3.92)	9.14 (6.01)	2.28 (0.25)†
Hospital cost, mean (SD)	$6,823 ($5,175)	$6,327 ($4,874)	$8,085 ($5,665)	$1,758 ($287.2)†

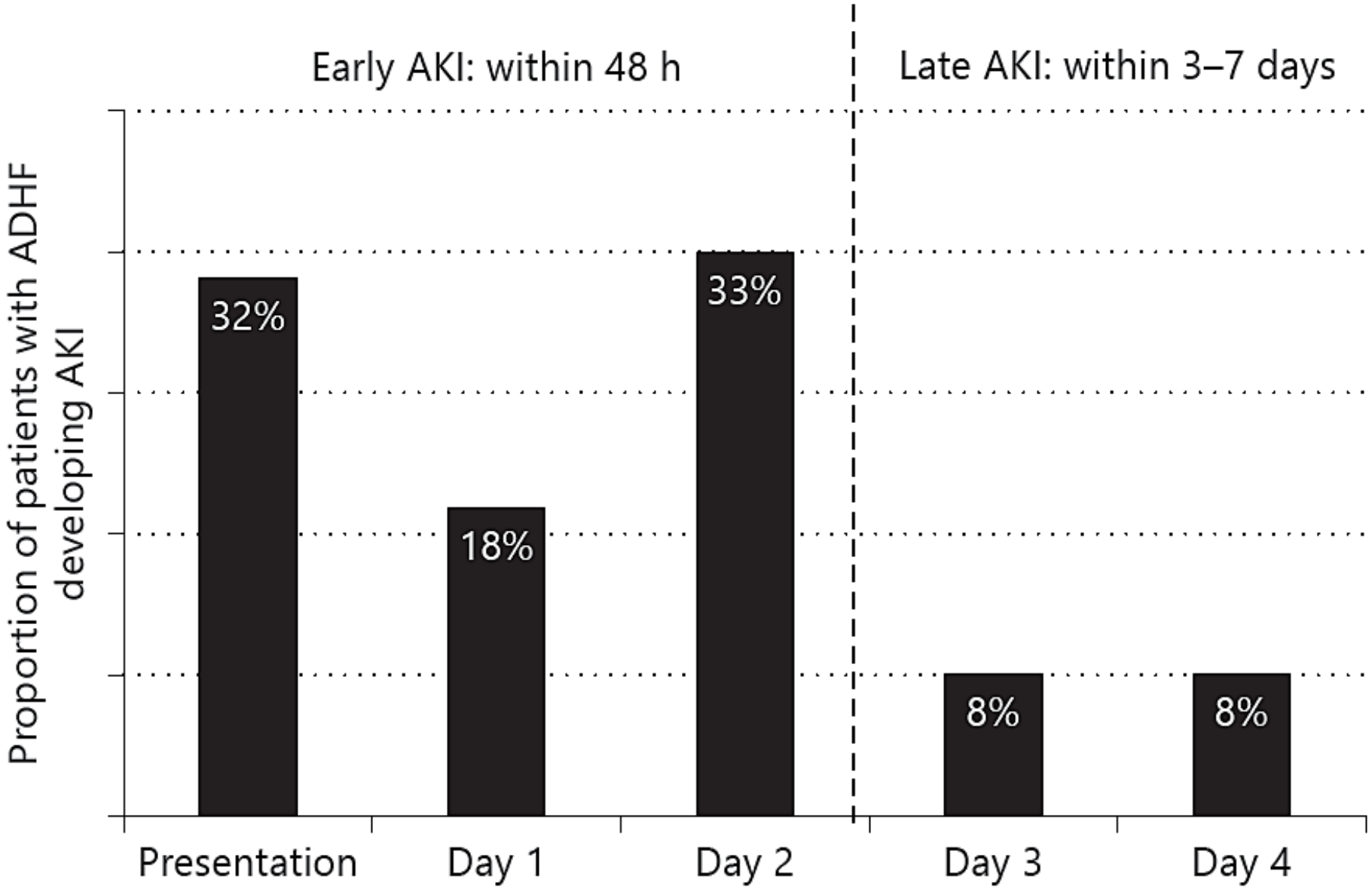
*Estimates were odds ratios and 95% confidence intervals for mortality and readmission outcomes, and regression coefficients and their standard errors for length of hospital stay and hospital cost outcomes; estimates adjusted for sex, age, diabetes, hypertension, rales, pulse, baseline creatinine, systolic blood pressure, and left ventricular ejection fraction.

†$p < 0.0001$.

Type I CRS: Acute Cardiac Dysfunction Leading to AKI



When does AKI occur in CRS Type I?



Breidthardt et al . *Crit Care* 2012 and Haase M et al. *Contrib Nephrol* 2013

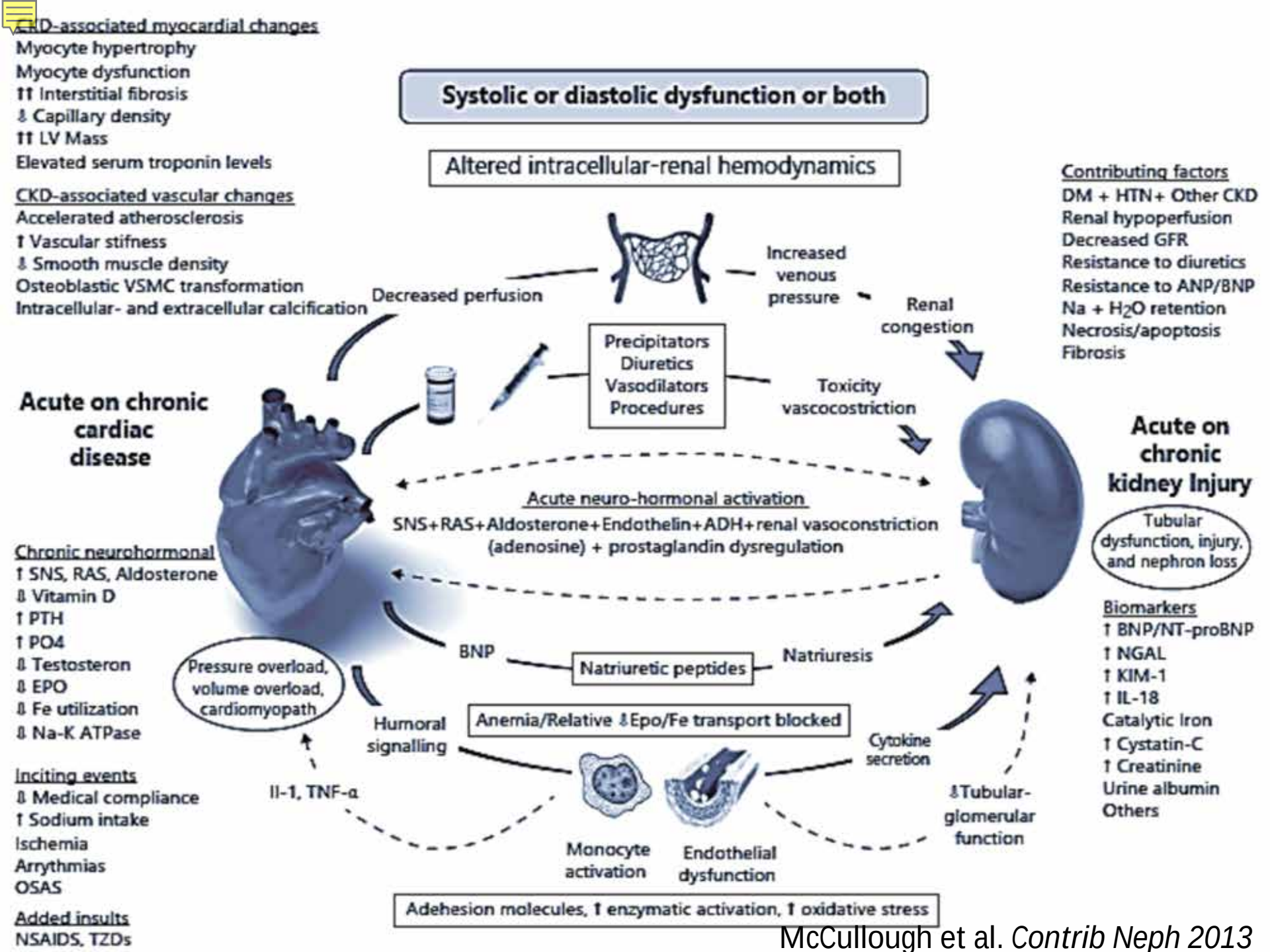
CRS I: Outcomes Meta-Analysis

	Risk/stage1	Studies/ Patients	Injury/stage2	Studies/ Patients	Loss/stage 3	Studies/ Patients
Mortality	3.45 (2.25–5.31)	16/53,066	9.57 (6.31–14.50)	13/39,644	20.37 (13.19–31.48)	12/38,575
LOS_{ICU}	0.99 (0.65–1.33)	8/16,348	2.22 (0.89–3.55)	7/12,479	8.32(3.39–13.24)	7/12,479
LOS_{hosp}	3.51 (2.63–4.39)	10/17,713	8.32 (5.87–10.78)	9/13,844	18.41 (14.74–22.09)	9/13,844

Data are presented as risk ratio (95% CI) for mortality and weighted mean difference (95% CI) for LOS. AKI = AKI defined by the RIFLE, AKIN or KDIGO classifications; WRF = AKI defined as worsening of renal function; RRT = AKI defined as the use of renal replacement therapy; CI = confidence interval.

Risk Ratios across stages
Weighted Mean Differences for LOS

Cardiorenal Med 2016;6:116–128



McCullough et al. *Contrib Neph 2013*

Table 1 Characteristics of patients included in the study by group

	Intervention group		Control group		
	n	Mean ± SD	n	Mean ± SD	p
Age (years)	30	78.2 ± 7.8	17	74.2 ± 5.9	0.079
BMI (weight/height^2)	28	27.5 ± 4.9	15	29.1 ± 4.5	0.316
Haemoglobin (g/dl)	30	10.6 ± 0.87	17	10.7 ± 1.02	0.735
Haematocrit (%)	30	31.7 ± 2.65	17	32.16 ± 2.85	0.547
Plasmatic creatinine (mg/dl)	30	1.97 ± 0.73	17	1.61 ± 0.36	0.068
Creatinine clearance (24-h) (ml/min/1.73 m^2)	30	31.97 ± 13.34	17	47.5 ± 8.74	<0.001
Albuminury (mg/24 h)	28	0.39 ± 0.58	16	0.86 ± 1.23	0.130
Ejection fraction (%)	29	48.20 ± 16.28	17	47.41 ± 11.7	0.862
Time of heart failure diagnosis (years)	30	5.03 ± 3.95	17	4.29 ± 3.98	0.542
Angiotensin inhibitors treatment at admission					
Angiotensin-converting-enzyme inhibitor (mg) (Enalapril)	18	8.3 ± 5.7	6	5.8 ± 2.0	0.494
Angiotensin receptor antagonists (mg) (Losartan)	12	56.2 ± 35.6	11	52.3 ± 26.1	0.928
	n	%	n	%	p
Gender					
Male	16	59.3%	11	40.7%	0.449
Female	14	70.0%	6	30.0%	
NYHA Classification					
I	5	62.5%	3	37.5%	0.736
II	19	67.9%	9	32.1%	
III	6	54.5%	5	45.5%	
IV	–	–	–	–	
Diabetes					
No	18	69.2%	8	30.8%	0.391
Yes	12	57.1%	9	42.9%	

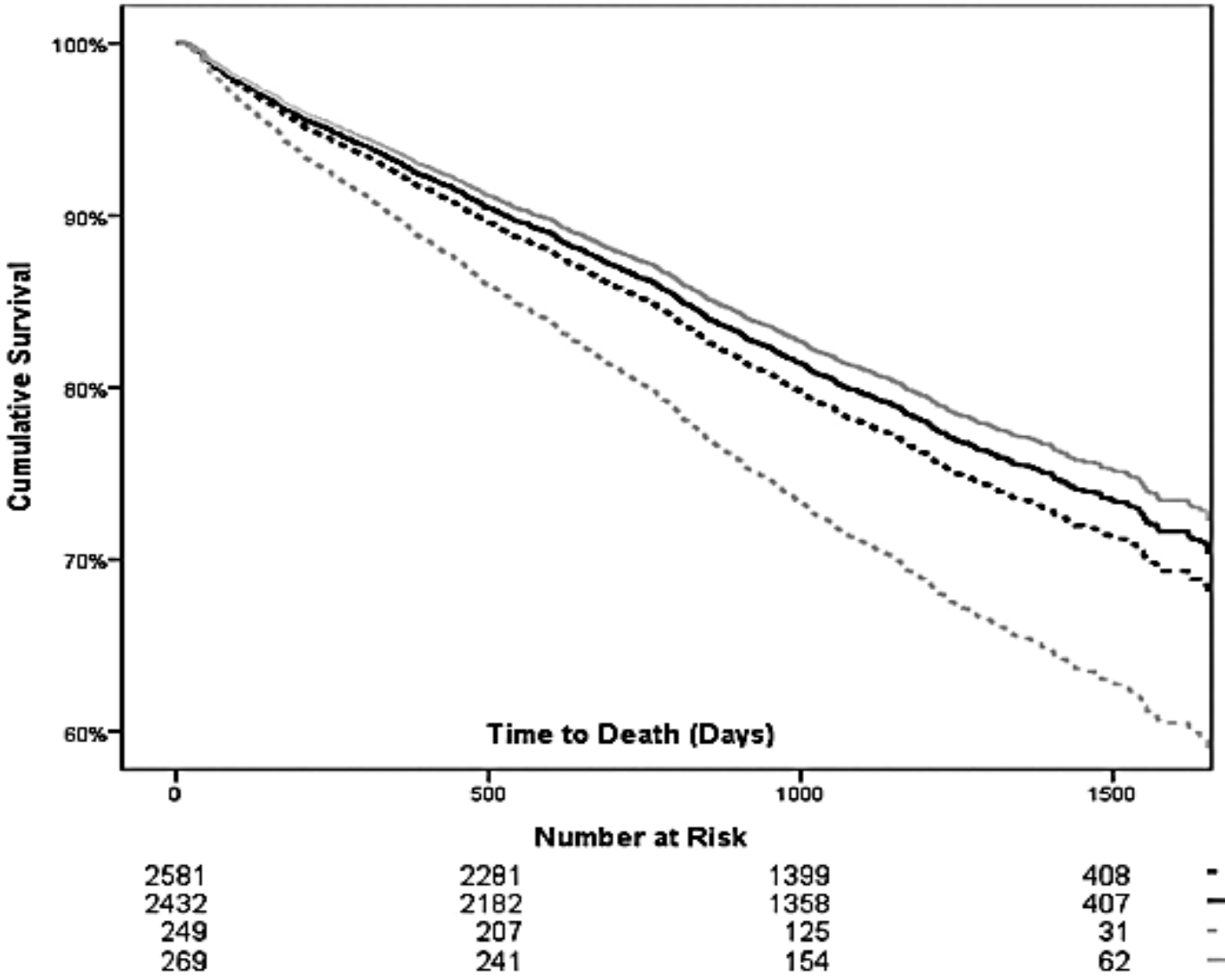
Table 2 Changes in the parameters studied during follow-up in the treatment and control groups

	Intervention group				Control group			
	Admission Mean ± SD	1–3 months after discharge Mean ± SD	p	Relative change (%)	Admission Mean ± SD	1–3 months after discharge Mean ± SD	p	Relative change (%)
Haemoglobin (g/dl)	10.6 ± 0.9	11.5 ± 1.1	< 0.001	8%	10.6 ± 1.0	10.1 ± 1.6	0.198	−4.9%
Haematocrit (%)	31.7 ± 2.8	34.4 ± 3.1	< 0.001	8.6%	32.0 ± 2.9	30.4 ± 4.7	0.212	−4.9%
Plasmatic creatinine (mg/dl)	1.9 ± 0.7	1.7 ± 0.4	0.004	−15.1%	1.6 ± 0.4	1.5 ± 0.4	0.269	−6.3%
Creatinine clearance (24-h) (ml/min/1.73 m^2)	32.5 ± 13.9	42.9 ± 20.7	0.001	32%	48.3 ± 8.8	41.7 ± 11.9	0.056	−13.5%
C-reactive protein (mg/dl)	3.2 ± 2.9	1.4 ± 1.9	0.008	−57.5%	1.9 ± 2.9	3.1 ± 5.9	0.560	6.2%
Homocysteine (mmol/L)	23.4 ± 9.0	25.1 ± 17.7	0.454	7.6%	22.2 ± 5.4	17.9 ± 8.6	0.208	−19.20%
Albuminury (mg/24 h)	0.43 ± 0.6	0.7 ± 1.2	0.231	5.9%	0.6 ± 0.9	0.7 ± 1.2	0.537	9.40%
Insulin (mcU/ml)	13.4 ± 18.4	9.5 ± 3.9	0.286	−29%	12.3 ± 8.7	10.0 ± 10.8	0.132	18.40%
	Admission	After randomization	p		Admission	After randomization	p	
Angiotensin-converting-enzyme inhibitor (mg) (Enalapril)	8.3 ± 5.7	4.2 ± 2.8	0.047		5.8 ± 2.0	5.8 ± 2.0	0.999	
Angiotensin receptor antagonists (mg) (Losartan)	56.2 ± 35.6	28.1 ± 17.8	0.008		52.3 ± 26.1	52.3 ± 26.1	0.999	

SD, standard deviation.

Pita-Fernandez, S et.al. Int J Clin Pract. 2014;68:1231-1240

SOLVD Revisited: Δ SCr Response to ACE-I and Survival



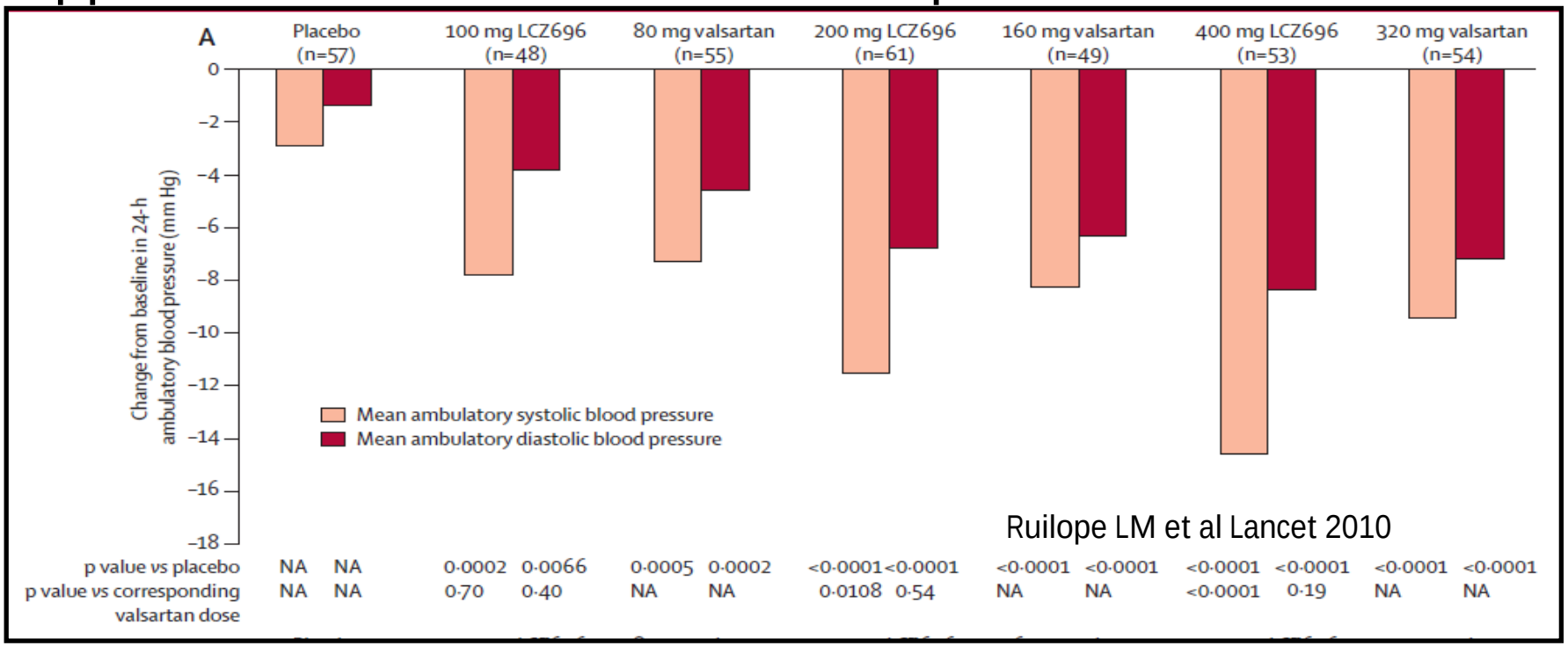
WRF defined as 20% drop in GFR in 14 days after starting ACE / placebo

Figure 2. Adjusted curves grouped by randomization to enalapril or placebo and subsequent early worsening renal function (WRF) status in patients who did not discontinue or dose reduce the study drug in proximity to WRF. Early WRF was defined as a 20% reduction in glomerular filtration rate (GFR) from baseline to 14 days after randomization. Covariates were adjusted for the following: age; race; ejection fraction; heart rate; diastolic blood pressure; New York Heart Association class; serum sodium level; estimated GFR; history of diabetes, hypertension, stroke, or myocardial infarction; loop diuretic; potassium-sparing diuretic; digoxin; and β-blocker use.

Testani, Coca et al *Circ Heart Fail* 2011

Neprilysin:

- *Entresto* : Neutral Endopeptidase - Prevents degradation of vaso-active peptides (e.g. natri-uretics, bradykinin, adrenomedullin)
  - Neprilysin-inhibition + ACE-I = lots of Angioedema
  - Neprilysin-inhibition leads to less vaso-constriction, less sodium retention and less maladaptive cardiac remodeling
- Supplies nice reduction of MAP – compared to ARB alone



Neprilysin Inhibition (PARADIGM)

8,442 subject with Class II, III and IV HF (EF < 40%)

Randomized, Double-blind, International (Neprilysin+ARB vs. ACE)

Primary endpoint: CV death or CHF hospitalization

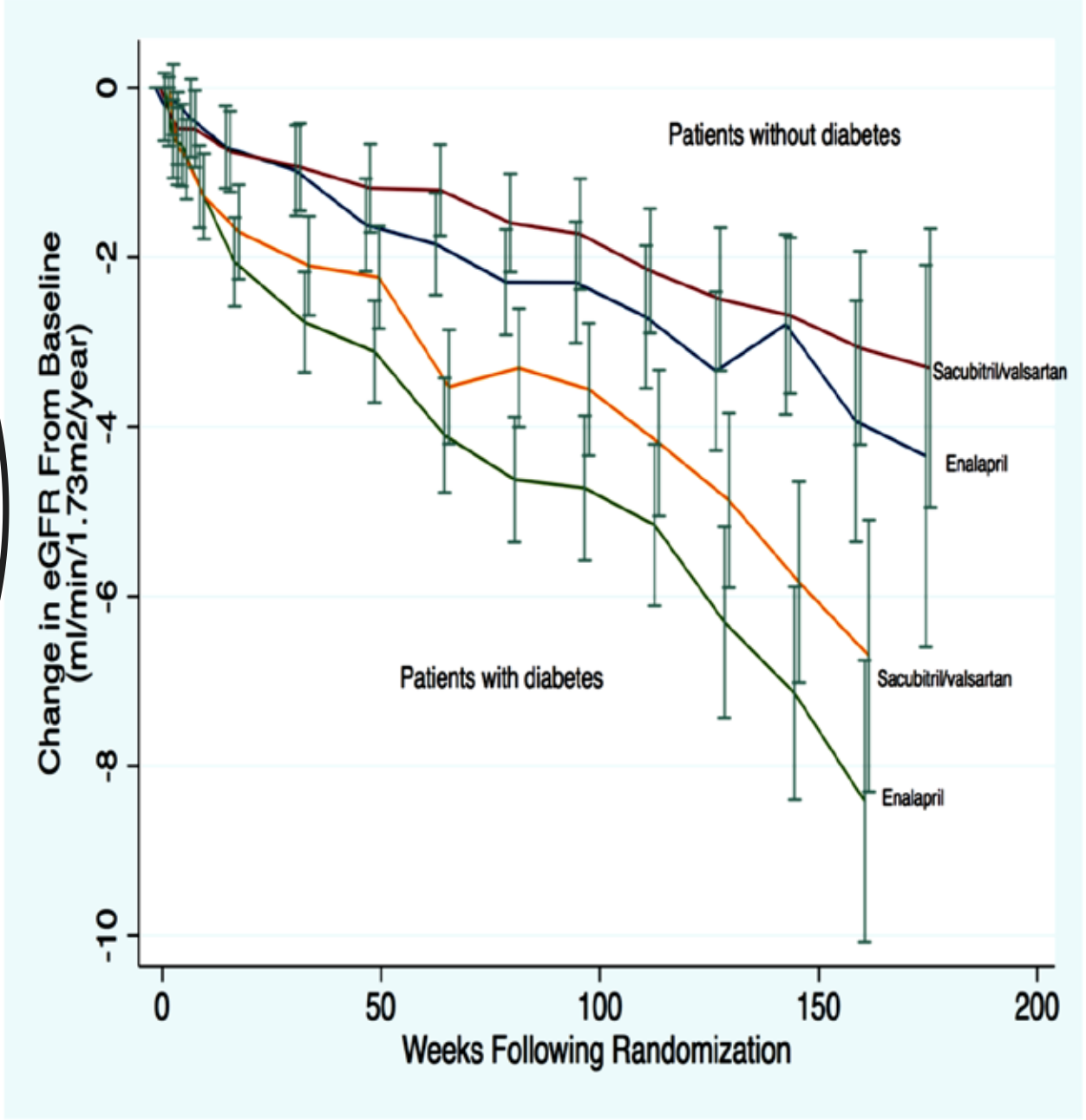
Stopped Early due to overwhelming benefit ….less adverse renal outcomes (p=NS for drop in eGFR or new ESRD/RRT)

Number needed to treat 35 – to prevent all cause mortality

Table 2. Primary and Secondary Outcomes.*

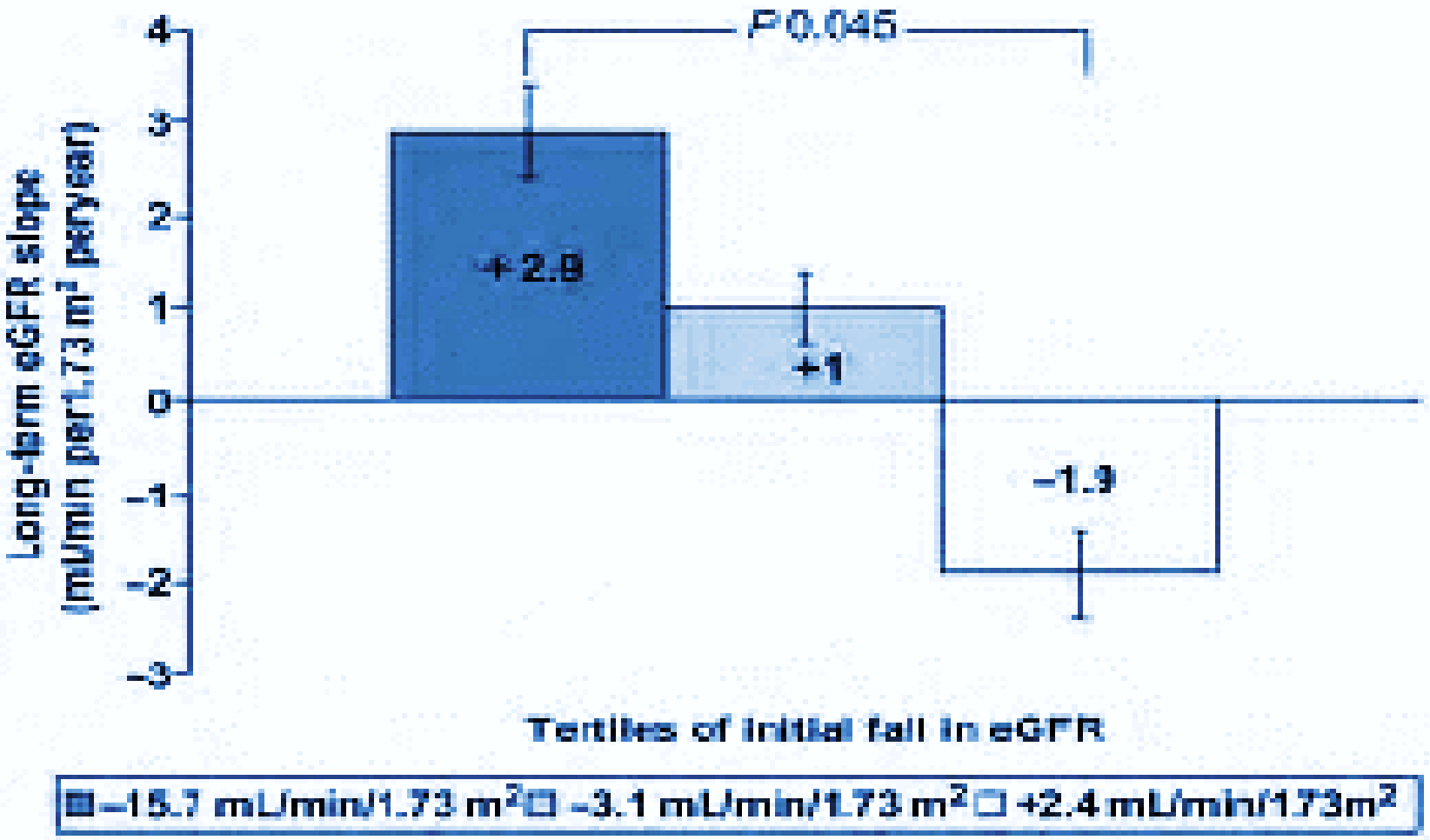
Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	−2.99±0.36	−4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

Rate of Change of Estimated GFR in Patients With and Without Diabetes Based on Treatment Assignment in PARADIGM



Packer M et.al. Lancet Diabetes and Endo In Press 2018

Spironolactone: Similar Effect



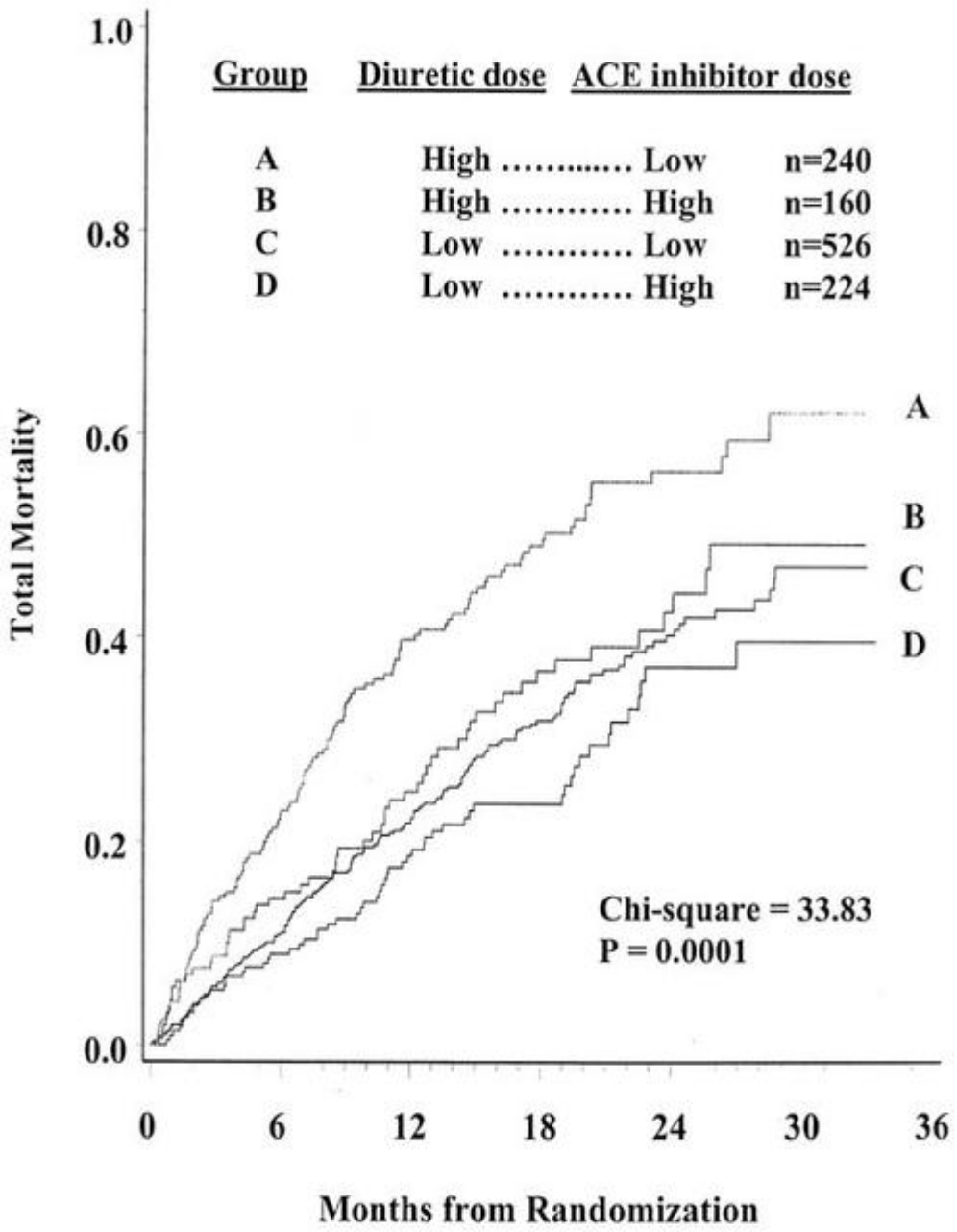
- Those with the biggest initial drop in eGFR post-spiro had the best 1 yr eGFRs

Nephrol Dial Transplant (2013) 28: 405–412
doi: 10.1093/ndt/gfs429
Advance Access publication 4 December 2012

MAJOR SUMMARY POINTS

- The kidney's response to RAAS blockade serves as a stress test of its hemodynamic integrity
- Injured and failing kidneys are less likely to be able to mount the appropriate physiologic response
- Larger increases in SCr (>30%) due to RAAS are a signal for morbidity / mortality
- Novel way to ascertain renal reserve capacity

Dose of Diuretics and ACE and Mortality



- 1153 pts advanced CHF
- Post-Hoc
- PRAISE – Amlodipine trial
  - Furosemide (mg) 170 vs 60
  - Bumetanide (mg) 4.7 vs 1.3
  - Metolazone (%-use) 25 vs 11
  - Captopril (mg) 153 vs 46
  - Enalapril (mg) 27 vs 7
  - Lisinopril (mg) 26 vs. 7.8
- High dose diuretics and use of metolazone were independently associated with mortality

Neuberg et al *Amer Heart J* – 2002

Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial

Alberto Palazzuoli[1*], Marco Pellegrini[1], Gaetano Ruocco[1], Giuseppe Martini[1], Beatrice Franci[1], Maria Stella Campagna[1], Marilyn Gilleman[1], Ranuccio Nuti[1], Peter A McCullough[2] and Claudio Ronco[3]

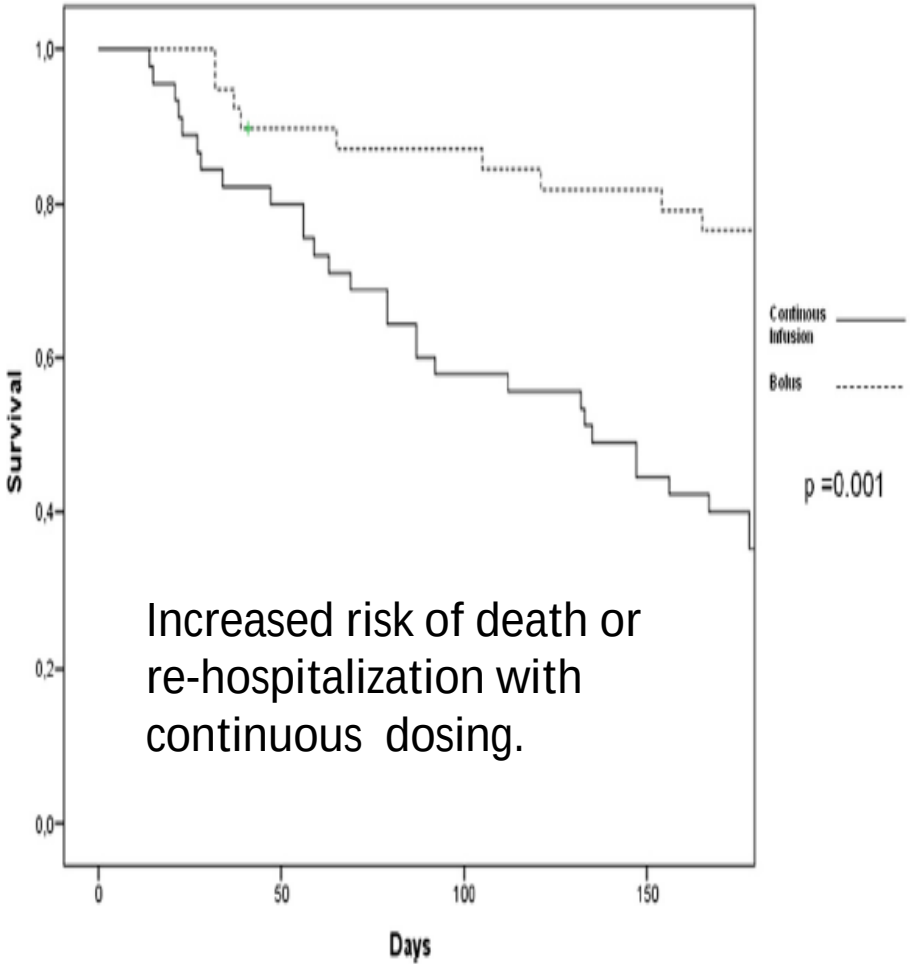
Table 2 Comparison of biochemical measures and urine output after the randomized treatment period of approximately 120 h

	Continuous infusion	Bolus	*P*-value
Urine output/24 h (mL)	2295 ± 775	2090 ± 421	<0.002
Serum creatinine (mg/dl)	1.78 ± 0.6	1.34 ± 0.3	<0.0001
eGFR (mL/min/1.73 m^2)	40.6 ± 10.5	50.4 ± 11.4	<0.01
BUN (mg/dl)	100 ± 60	69 ± 31	<0.02
BNP (pg/mL)	723 ± 497	822 ± 548	<0.05
Serum sodium (mEq/L)	138 ± 4	135 ± 16	NS
Serum potassium (mEq/L)	3.6 ± 0.8	4.0 ± 0.7	<0.04

Results are presented as mean ± SD. eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; NS, not significant.

Table 4 Secondary endpoints in the continuous infusion versus bolus arm

	Continuous infusion	Bolus	*P*-value
Acute kidney injury	22%	15%	0.30
Hypertonic saline solution	33%	18%	0.01
Inotropes infusion	35%	23%	0.02
Length of hospital stay (days), mean ± SD	14 ± 5	11 ± 5	<0.03
Death or rehospitalization	58%	23%	0.001
Weight loss (kg), mean ± SD	-4.1 ± 1,9	-3.5 ± 2.4	0.23

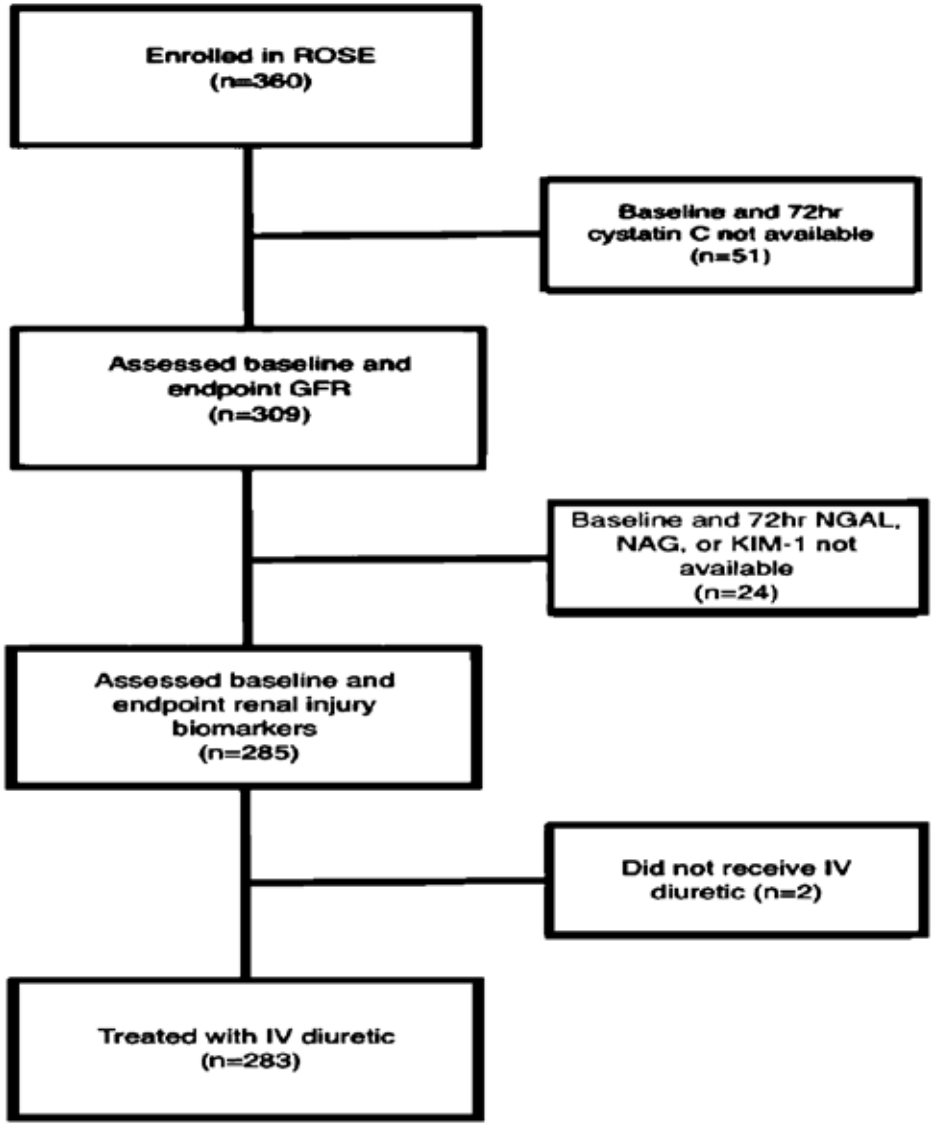


Increased risk of death or re-hospitalization with continuous dosing.

Palazzuoli *et al. Critical Care* 2014, **18**:R134

Worsening Renal Function in Acute Heart Failure Patients Undergoing Aggressive Diuresis NOT Associated with Tubular Injury

Consort Design and Flow of Study

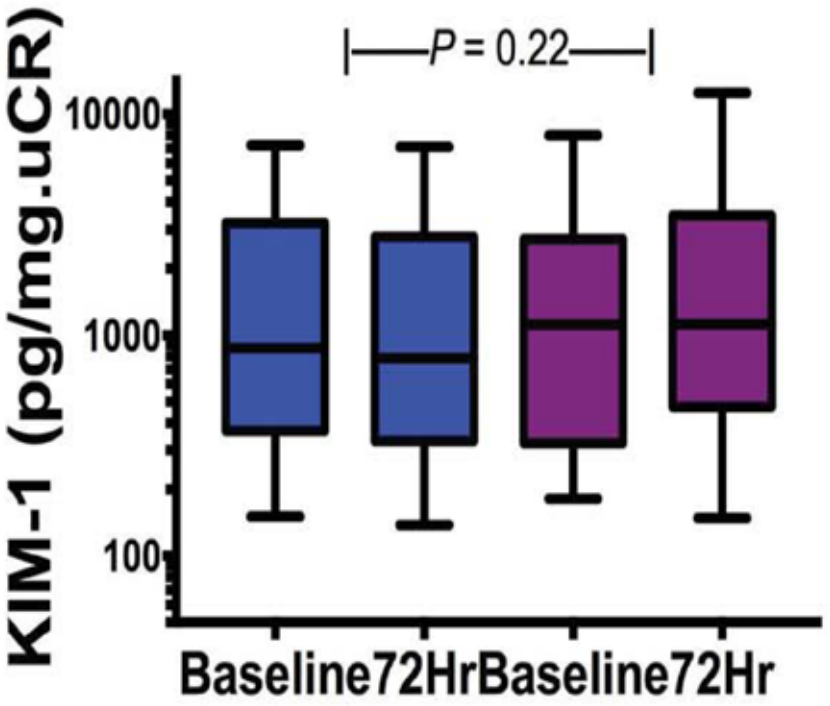


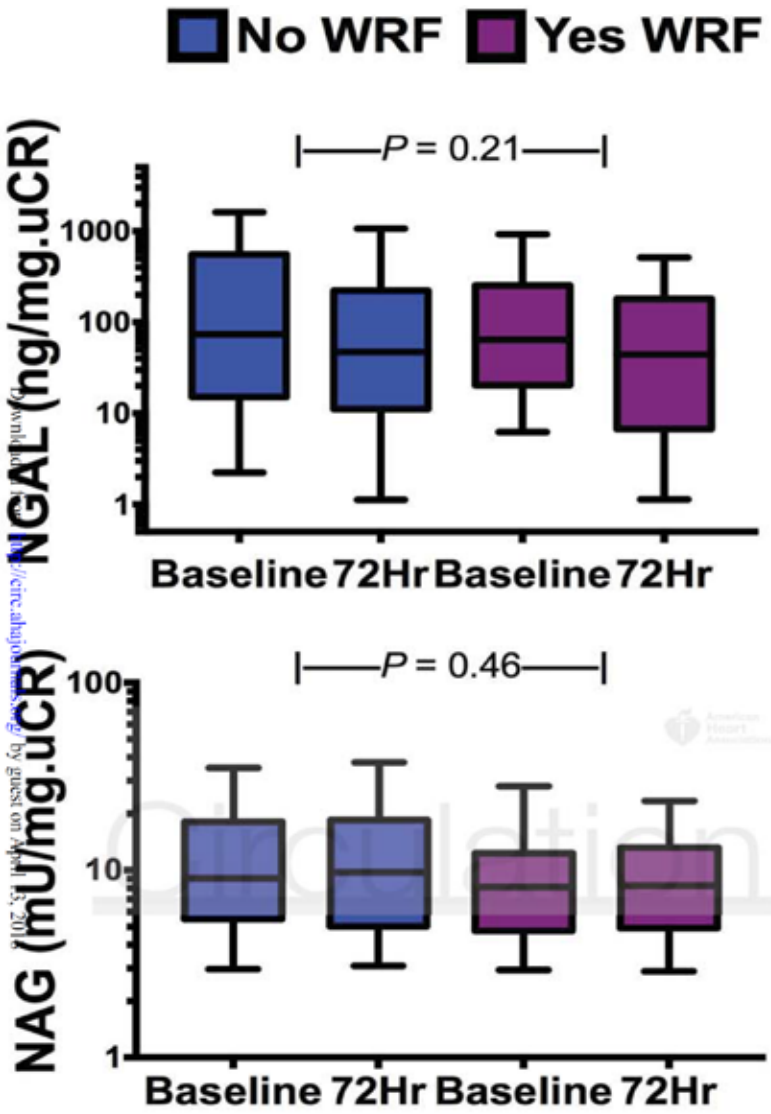
Baseline Characteristics of the Study Population

Characteristics	Study Cohort (*N*=283)	WRF (*N*=60)	No WRF (*N*=223)	*P*
Demographics				
Age, years	70 (62,79)	73 (63,82)	69 (62,79)	0.14
Male sex, %	75	73	75	0.81
White, %	76	83	74	0.13
Clinical Variables				
SBP, mmHg	114 (103,126)	119 (109,134)	113 (102,125)	0.02*
Edema ≥2+, %	71	77	69	0.26
Orthopnea, %	89	95	88	0.13
JVP ≥8 cm H_2O, %	96	97	95	0.68
Rales, %	55	60	54	0.38
HF Hospitalization, %	67	61	69	0.25
LVEF %	33 (20,51)	34 (25,53)	30 (20,51)	0.40
LVEF <50%, %	71	75	70	0.43
IHD, %	58	65	57	0.24
DM II, %	55	58	54	0.57
AF/AFL, %	58	63	57	0.34
ICD, %	45	37	47	0.15

Ahmad T et.al. Circulation Jan 2018 10.1161/CIRCULATIONAHA.117.030112

Baseline and 72 hour Biomarkers of Kidney Tubular Injury According to Cystatin-C based WRF Status





Ahmad T et.al. Circulation Jan 2018 10.1161/CIRCULATIONAHA.117.030112

CONSENSUS ON DIURETICS

- Comparisons between intravenous bolus and continuous infusion revealed no clear differences in outcomes such as weight loss, urine output, or change in renal function.
- Perhaps a signal for more harm with continuous but hard to decipher a true difference
- Combination of diuretics may lead to increased UOP but also increased risk of hypoNa+

CONCLUSIONS

- Cardio-Renal Interactions are Complex
- Response to RAAS may predict outcomes in the setting of CHF.
- Large increases >0.3 mg/dl in creatinine acutely are associated with higher mortality in HefRef **hospitalized** patients but **not** in other settings. The increased creatinine is a marker of underlying poor renal reserve.
- The Role Diuretic Dosing and RAS use in CRS 1 is increasingly clearer-*better to protocolized intermittent diuretic dosing*
- Clear benefits of ARB/Neprilysin combo over RAS blockade.