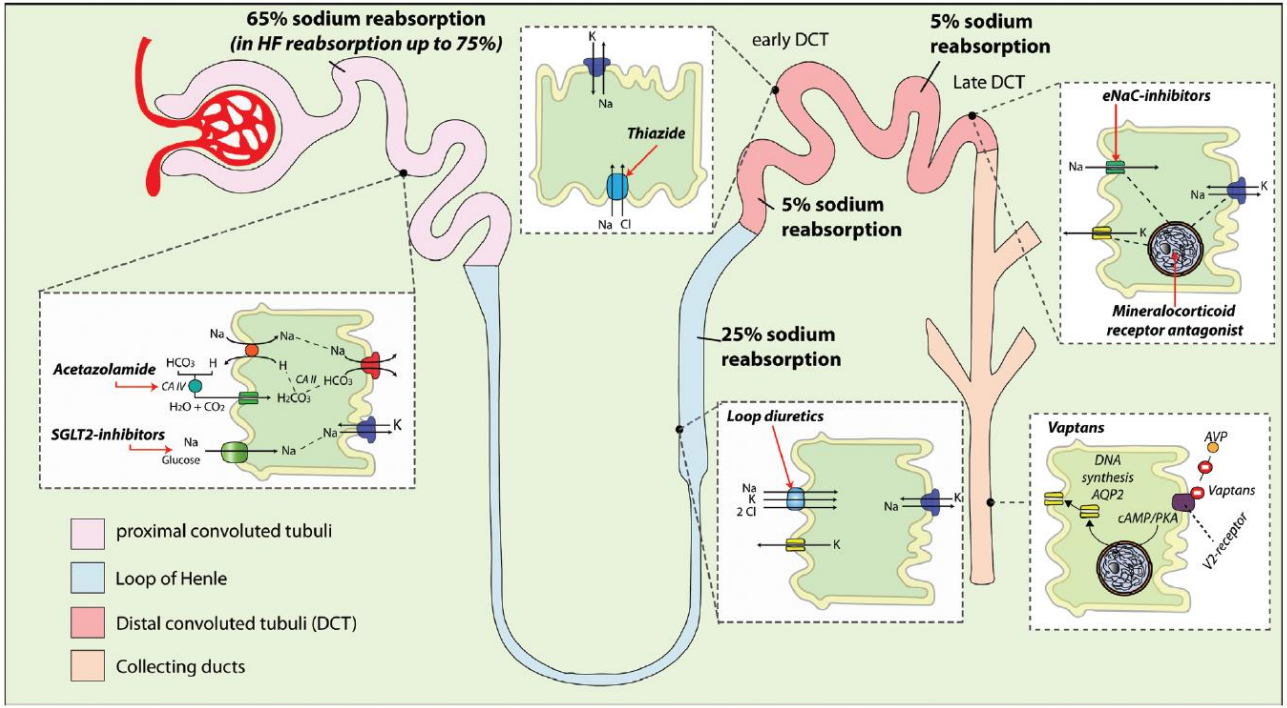
The ADVOR trial: update on renal interactions

Jeroen Dauw*, Evelyne Meekers*, Pieter Martens, Sebastiaan Dhont, Frederik H. Verbrugge, Petra Nijst, Jozine M. ter Maaten, Kevin Damman, Alexandre Mebazaa, Gerasimos Filippatos, Frank Ruschitzka, W.H. Wilson Tang, Matthias Dupont, Wilfried Mullens

Friday 25 August 2023

@JeroenDauw

Background



Acetazolamide blocks sodium reabsorption in the proximal tubule where the majority of sodium is reabsorbed

Mullens W et al. Eur J Heart Fail. 2019; 21:137-155

The NEW ENGLAND JOURNAL of MEDICINE

ADVOR

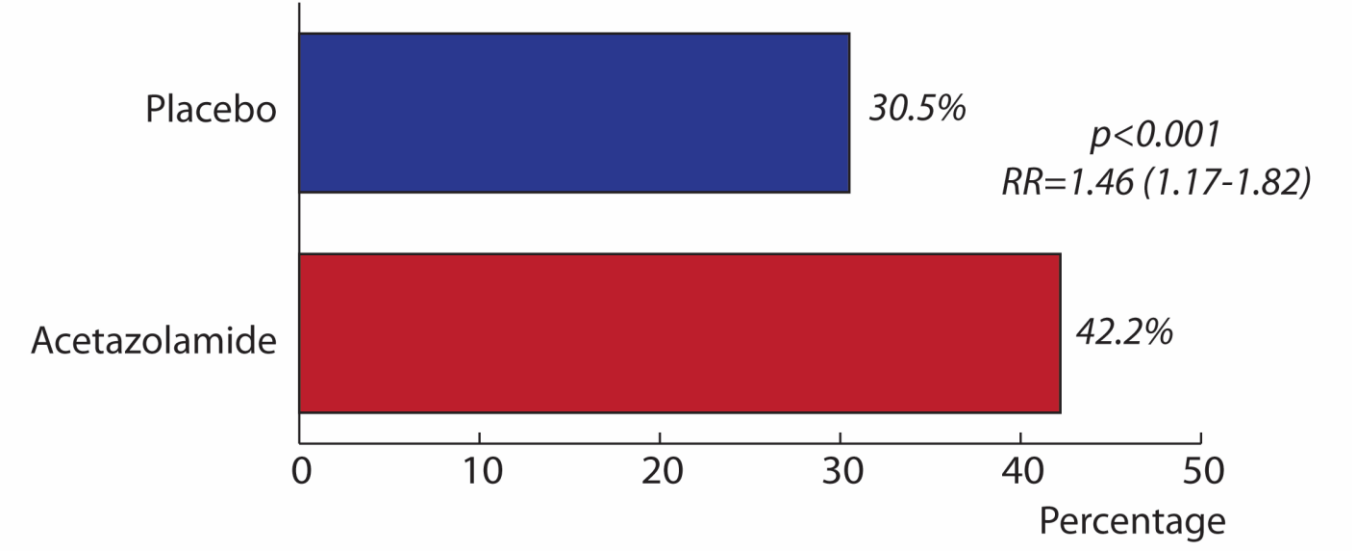
ORIGINAL ARTICLE

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

W. Mullens, J. Dauw, P. Martens, F.H. Verbrugge, P. Nijst, E. Meekers, K. Tartaglia, F. Chenot, S. Moubayed, R. Dierckx, P. Blouard, P. Troisfontaines, D. Derthoo, W. Smolders, L. Bruckers, W. Droogne, J.M. Ter Maaten, K. Damman, J. Lassus, A. Mebazaa, G. Filippatos, F. Ruschitzka, and M. Dupont, for the ADVOR Study Group*

Mullens W, Dauw J et al. N Engl J Med. 2022;387:1185-1195

Background



Acetazolamide + loop diuretics vs. loop diuretics alone associated with more successfull decongestion after 3 days

Mullens W, Dauw J et al. N Engl J Med. 2022;387:1185-1195

Aims

1. To evaluate the treatment effect of acetazolamide according to baseline renal function

2. To evaluate the effect of acetazolamide on renal function and its relation with outcomes

Methods

ADVOR
A multicenter, randomized, double-blind, placebo-controlled, trial

519 acute decompensated heart failure patients

500 mg acetazolamide IV + loop diuretics IV (*oral home dose bid*)
vs.
placebo + loop diuretics IV (*oral home dose bid*)

Primary endpoint: successful decongestion after 3 days without need for diuretic therapy escalation

Mullens W, Dauw J et al. N Engl J Med. 2022;387:1185-1195

Methods: patient selection

Main inclusion criteria

- Admitted with ADHF
- At least 1 sign of volume overload (edema, pleural effusion*, ascites°)

  To be confirmed with radiography or ultrasonography of the chest or ultrasonography of the abdomen°*
- At least 1 month maintenance dose of oral loop diuretics (≥ 40 mg furosemide)
- NT-proBNP > 1000 pg/ml or BNP > 250 pg/ml

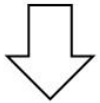
Main exclusion criteria

- Acetazolamide maintenance therapy
- Treatment with SGLT2i
- Systolic blood pressure < 90 mmHg
- eGFR < 20 ml/min

Mullens W, Dauw J et al. N Engl J Med. 2022;387:1185-1195

Methods: congestion score

EDEMA	No edema (score 0)	Trace edema (pitting disappear immediately) (score 1)	Clear pitting edema (score 2)	Visual deformation above ankle (score 3)	Visual deformation above knee (score 4)
PLEURAL EFFUSION (to be confirmed by chest X-ray or ultrasound on admission if suspected)	No pleural effusion (score 0)	Minor (non-amenable for punction) pleural effusion (score 2)		Major (amenable for punction) pleural effusion (score 3)	
ASCITES (to be confirmed by ultrasound on admission if suspected)	No ascites (score 0)	Minor ascites, only detected by echography (score 2)		Significant ascites (score 3)	



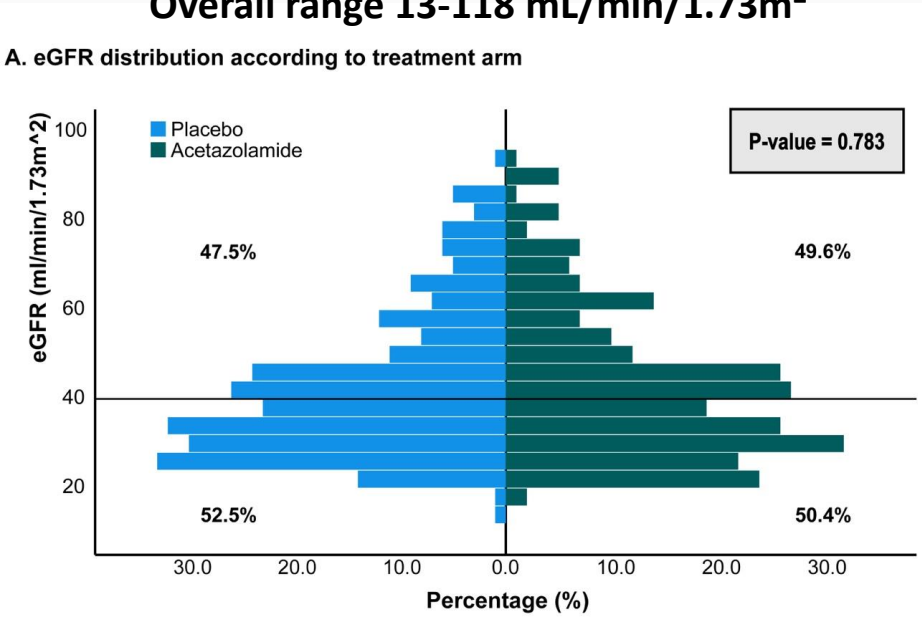
Successful decongestion

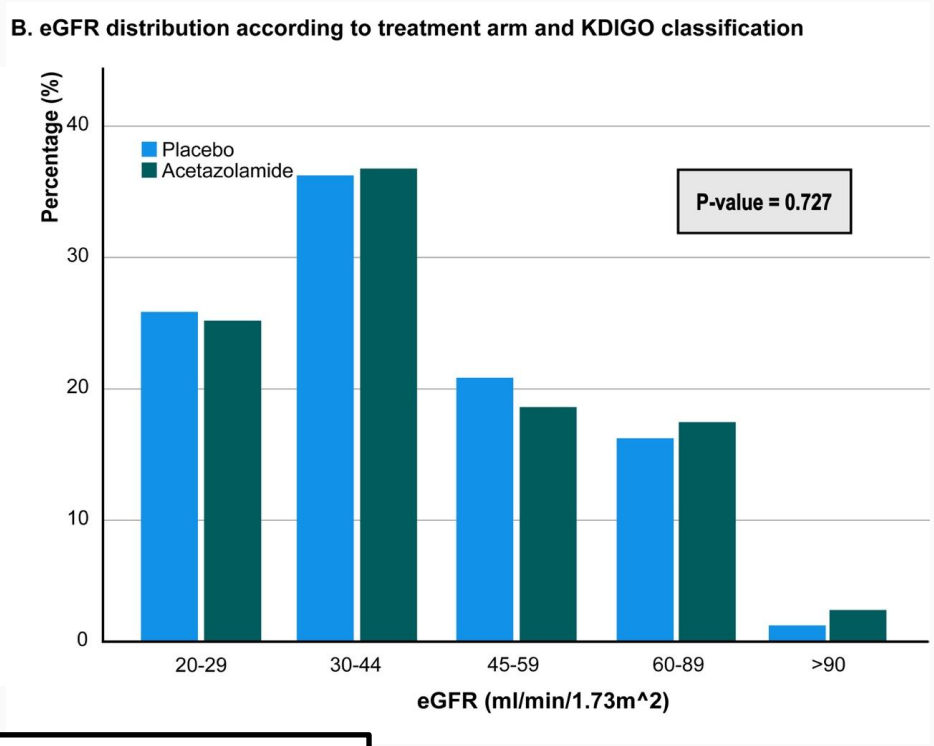
Continue IV diuretic therapy

Mullens W, Dauw J et al. N Engl J Med. 2022;387:1185-1195

Results: eGFR distribution

Overall range 13-118 mL/min/1.73m²





eGFR culculated with CKD-EPI

Results: baseline characteristics according to eGFR

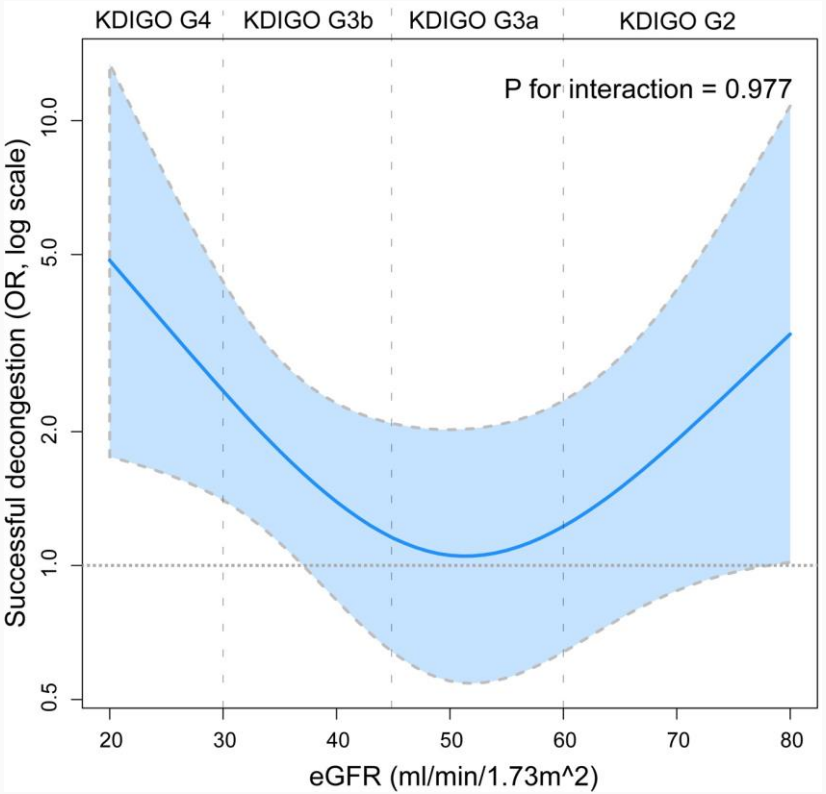
All analyses were adjusted for baseline differences

	eGFR ≤ 40 ml/min/1.73m² (n=265)	eGFR > 40 ml/min/1.73m² (n=254)	P-value
Acetazolamide	129 (48.7%)	130 (51.2%)	0.599
Age (years)	80 ± 8	77 ± 10	<0.001
Female	109 (41.1%)	85 (33.5%)	0.085
Congestion score	4 (3-6)	4 (3-6)	0.630
Home maintenance dose of furosemide (mg)	80 (40-132.2)	40 (40-100)	<0.001
LVEF (%)	42 ± 17	44 ±15	0.129
NT-proBNP (pg/mL)	7386 (3883-14417)	4435 (2517-8907)	<0.001
Ischemic cause	123 (46.4%)	109 (42.9%)	0.428
Hemoglobin (g/dL)	11.7 ± 1.9	12.1 ± 2.1	0.015
Sodium (mmol/L)	139.7 ± 4.0	139.2 ± 4.6	0.265
Serum creatinine (mg/dL)	1.92 (1.64-2.215)	1.17 (1.00-1.40)	<0.001
eGFR (mL/min/1.73m²)	30 (25-34)	54 (45-67)	<0.001
Treatment			
ACEi/ARB/ARNI	136 (51.3%)	133 (52.4%)	0.861
Beta blocker	221 (83.4%)	198 (78.0%)	0.121
MRA	115 (43.4%)	101 (39.8%)	0.423

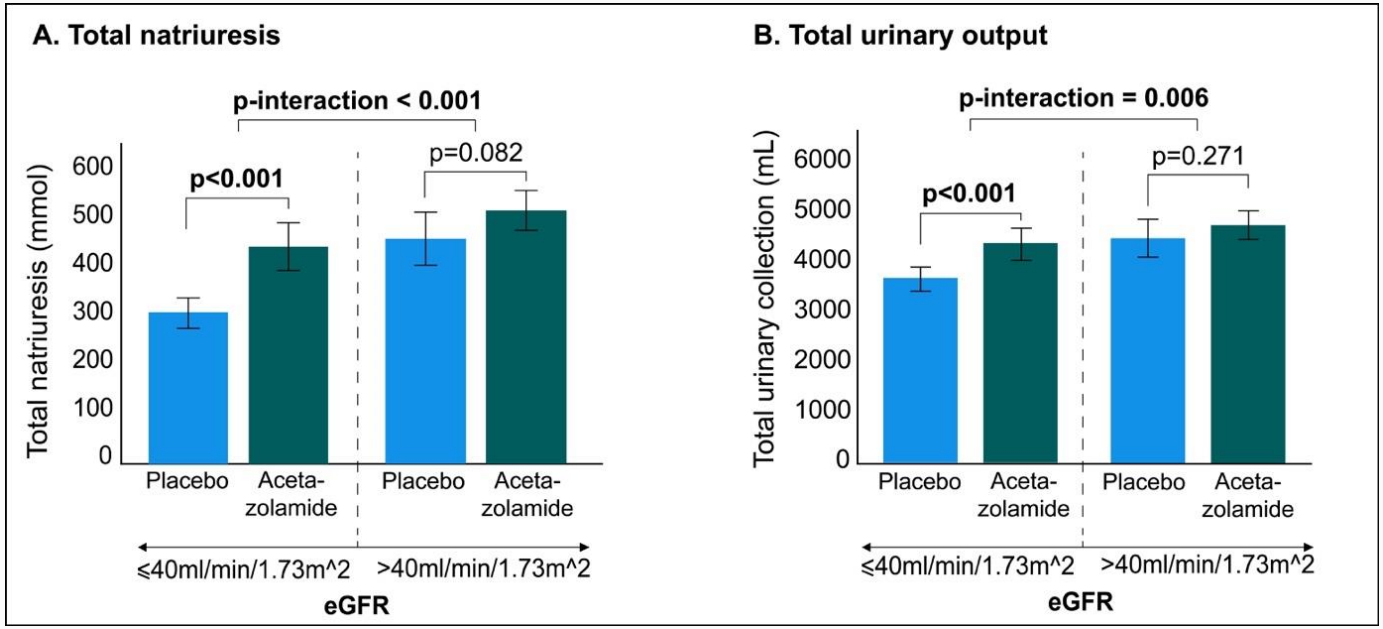
Results: acetazolamide treatment effect according to median eGFR

Parameter	Placebo	Acetazolamide	Adjusted OR/HR	P-value	*P-interaction
Primary endpoint (OR)					
Overall	79/259 (30.5%)	108/256 (42.2%)	1.97 (1.29-3.02)	0.002	
eGFR ≤40 ml/min/1.73m^2	34/136 (25.0%)	54/129 (41.9%)	2.32 (1.27-4.24)		0.672
eGFR >40 ml/min/1.73m^2	45/123 (36.6%)	54/127 (42.5%)	1.79 (0.97-3.30)		
Complete decongestion at discharge (OR)					
Overall	145/250 (58.0%)	190/252 (75.4%)	2.37 (1.54-3.65)	<0.001	
eGFR ≤40 ml/min/1.73m^2	77/132 (58.3%)	91/127 (71.7%)	1.88 (1.02-3.45)		0.467
eGFR > 40 ml/min/1.73m^2	68/118 (57.6%)	99/125 (79.2%)	3.00 (1.56-5.77)		
All-cause mortality and heart failure hospitalization (HR)					
Overall	72/259 (27.8%)	76/256 (29.7%)	1.09 (0.78-1.54)	0.618	
eGFR ≤40 ml/min/1.73m^2	43/136 (31.6%)	47/129 (36.4%)	1.17 (0.75-1.83)		0.636
eGFR >40 ml/min/1.73m^2	29/123 (23.6%)	29/127 (22.8%)	0.99 (0.96-1.02)		

Results: acetazolamide treatment effect across eGFR range

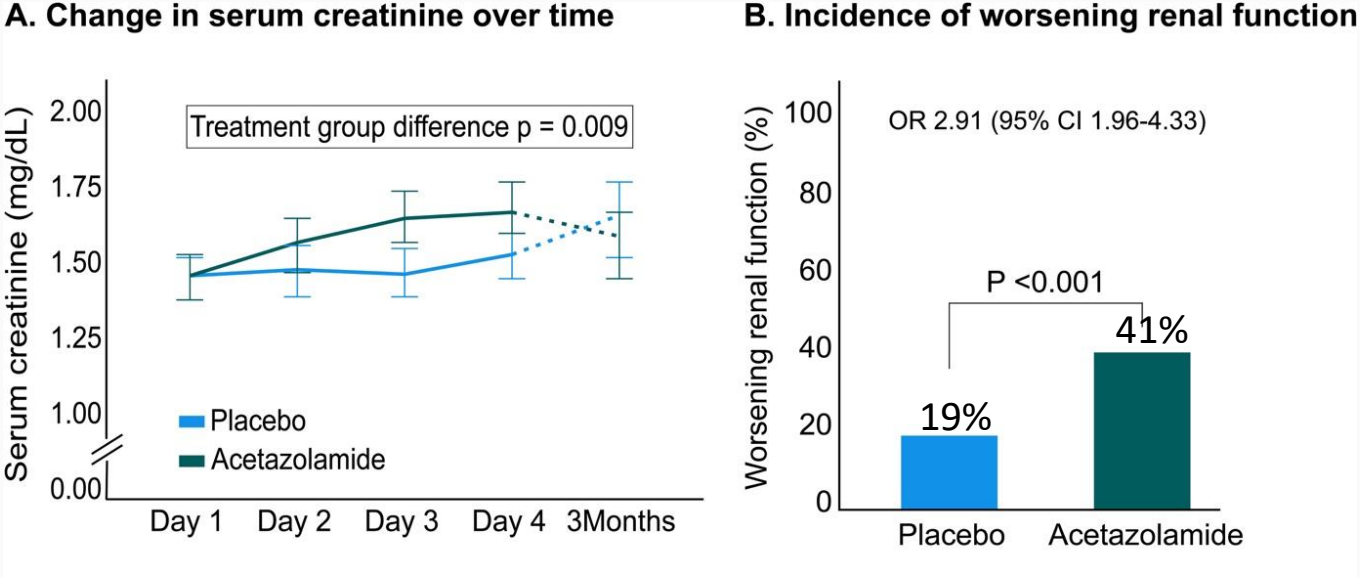


Results: renal function and diuretic response

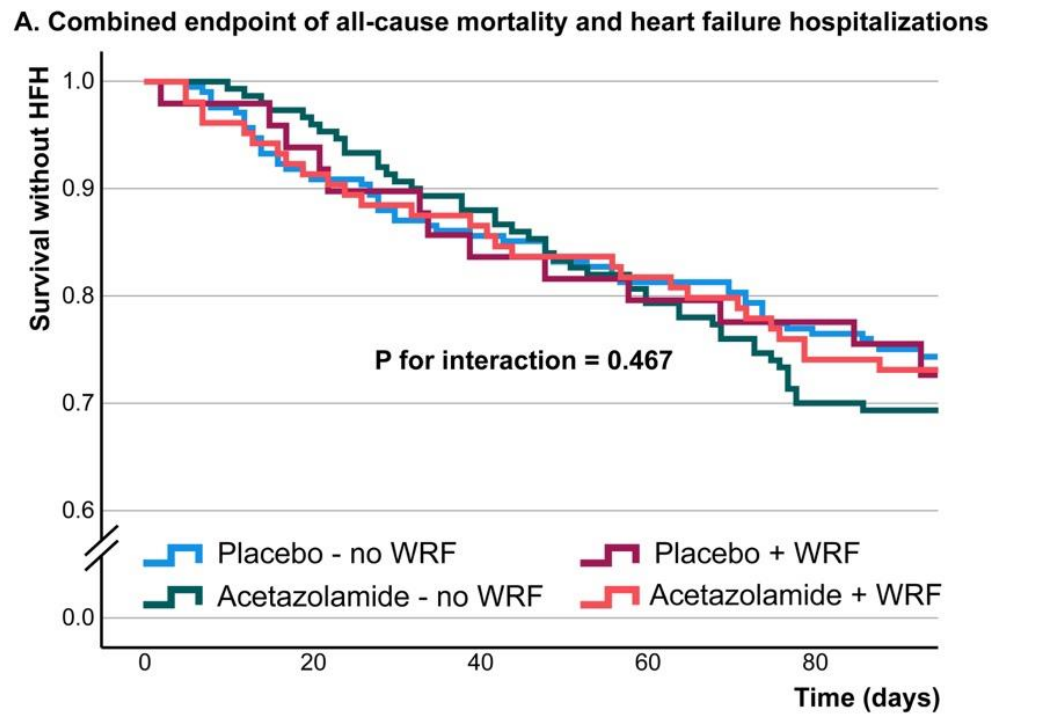


Results: worsening renal function

Worsening renal function = creatinine increase ≥ 0.3 mg/dL

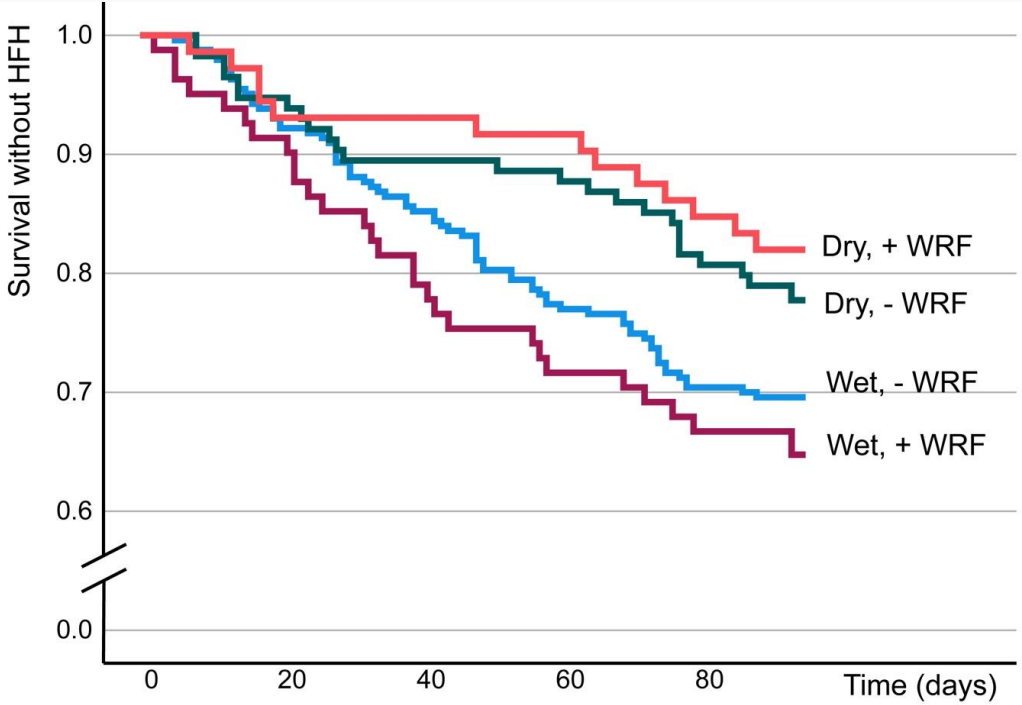


Results: occurrence of WRF and outcomes



No interaction between treatment effect and WRF on outomes

Results: succesful decongestion and outcomes



WRF +

HR 0.51

95% CI [0.27-0.94]

p=0.032

WRF -

HR 0.51

95% CI [0.27-0.94]

p=0.032

P for interaction 0.805

Conclusion

- The addition of acetazolamide to standardized loop diuretics in patients with acute decompensated heart failure is associated with a higher incidence of successful decongestion **across the full (≥20) eGFR range**
- All acetazolamide treated patients had higher natriuresis and diuresis, but the effect was even higher in patients with lower eGFR
- Acetazolamide was associated with more worsening renal function, but no difference in serum creatinine after 3 months
- No benefit on combined endpoint heart failure hospitalization or mortality
- Worsening renal function was only associated with worse outcomes in patients with persistent congestion

Simultaneously published

Renal Function and Decongestion With Acetazolamide in Acute Decompensated Heart Failure: The ADVOR Trial

ESC European Society of Cardiology

European Heart Journal