Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR)

On behalf of the ADVOR Study Group
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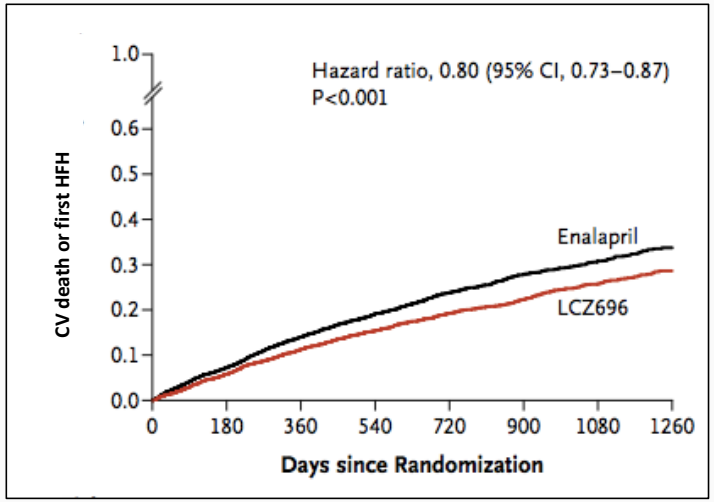
Disclosures

- The ADVOR trial was an independent academic clinical trial without industry involvement funded by the Belgian Health Care Knowledge Center under the KCE Trials Program.

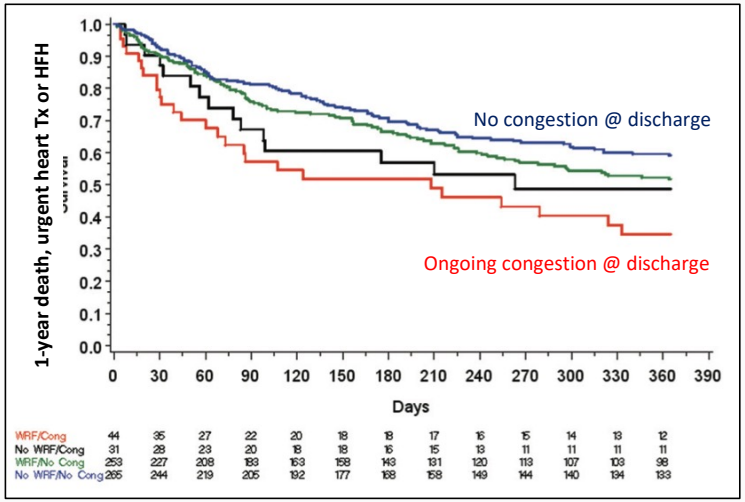
Background

Underappreciated risk linked to residual congestion in heart failure

Ambulatory: 20% risk at 2 years



Recently Hospitalized: 60% risk at 1 year



Mc Murray J. NEJM 2014
Metra M et al. Circ Heart Fail. 2012

Background

Recommendations	Class[a]	Level[b]
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.[427,472]	I	C

McDonagh T et al. Eur Heart J 2021

Background

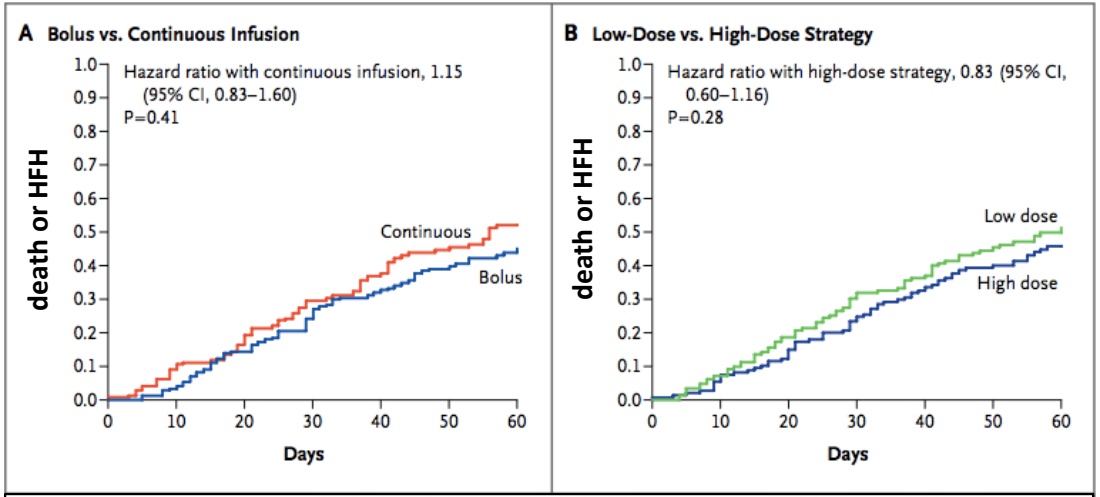
Loop diuretics *only* class I therapy for congestion in *all* HF subgroups

Loop diuretics		
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.[137]	I	C
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.[137]	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

McDonagh T et al. Eur Heart J 2021

Background

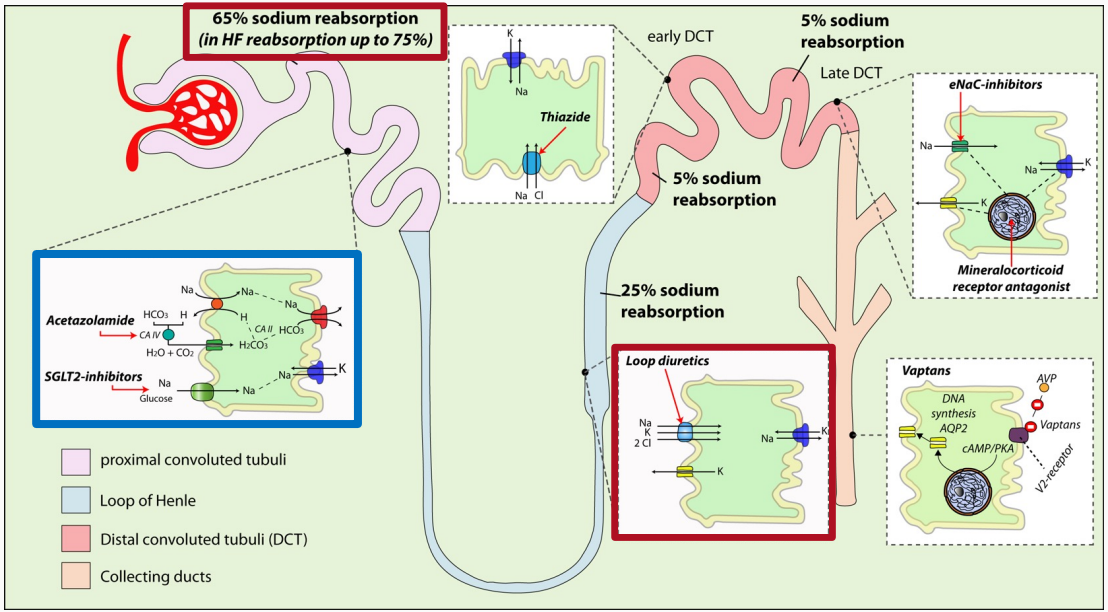
DOSE trial = largest RCT with loop diuretic



End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01

Felker M et al. NEJM 2011

Background

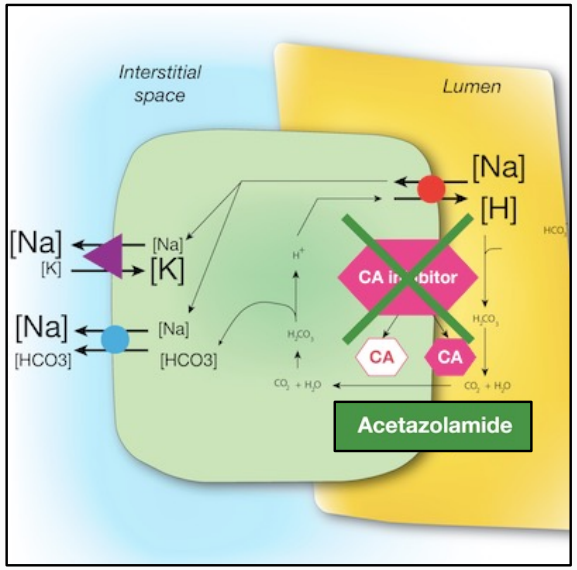


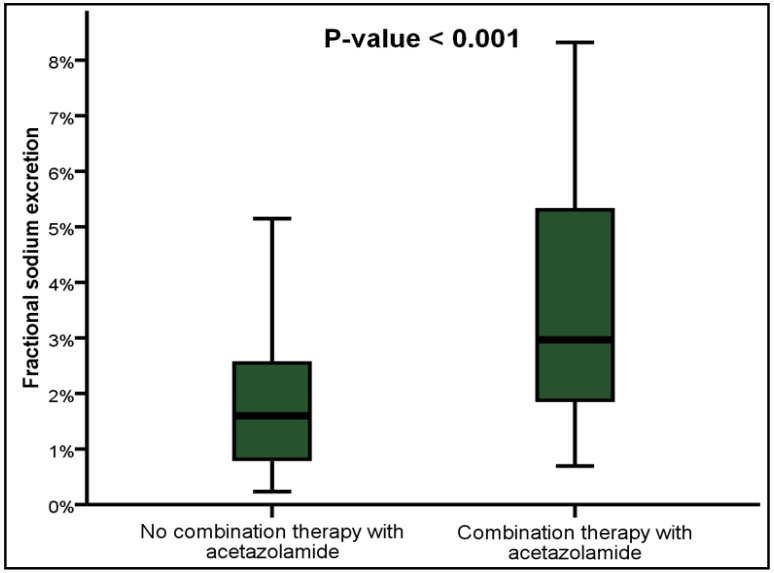
HF induces a state of increased proximal renal sodium reabsorption, but loop diuretics work distal at loop of Henle

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

Background

Acetazolamide might improve loop diuretic efficiency





Mullens W et al. Eur Heart J 2017
Verbrugge F et al. Acta Cardiol 2015 + Eur J Heart Fail 2019

Methods: trial design

- Prospective, multicenter, randomized, double-blind, placebo-controlled
- Academic trial without industry involvement
- Funding: Belgian Health Care Knowledge Center
- Sponsor: Ziekenhuis Oost Limburg, Genk Belgium (Clinical Trial Unit)
- Independent academic statistical center: CenStat, University Hasselt

Mullens W et al. Eur J Heart Fail. 2018;20:1591-1600

Methods: patients

Main inclusion criteria

- Admitted with ADHF
- At least 1 sign of volume overload (oedema, 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

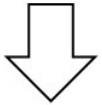
Main exclusion criteria

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

Mullens W et al. Eur J Heart Fail. 2018;20:1591-1600

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)	

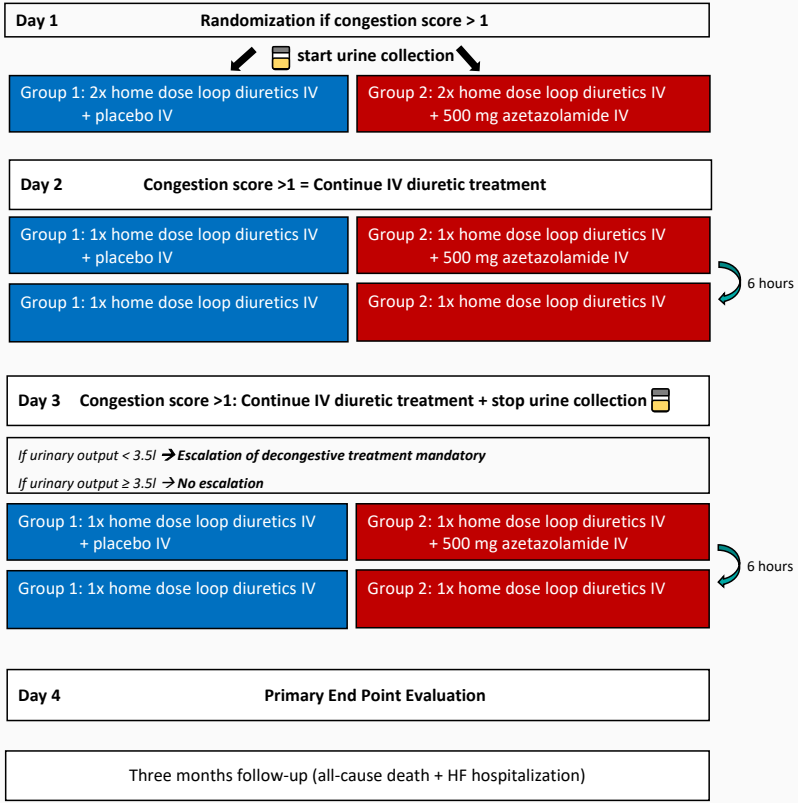


Successful decongestion

Continue IV diuretic therapy

Mullens W et al. Eur J Heart Fail. 2018;20:1591-1600

Methods: trial procedures



Mullens W et al. Eur J Heart Fail. 2018;20:1591-1600

Methods: end points

Primary end point:

Successful decongestion defined as congestion score ≤1 within 3 days after randomization without an indication for escalation of decongestive therapy

Secondary end points:

- Duration of the index hospital admission
- Death from any cause and rehospitalization for heart failure during 3 months follow-up

Safety end points: severe metabolic acidosis, renal events, hypokalemia, and hypotension

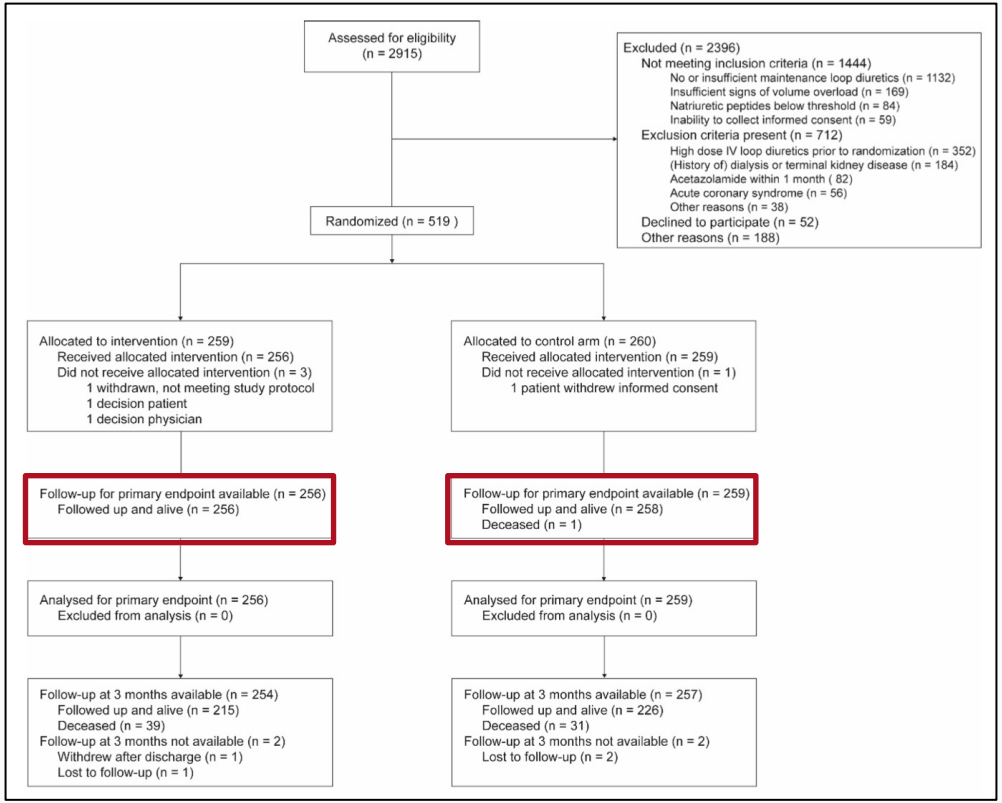
Mullens W et al. Eur J Heart Fail. 2018;20:1591-1600

Methods: statistical considerations

- **Sample size:**
  - DOSE trial (comparable with placebo in ADVOR) 15% successful decongestion
  - We estimated 25% in acetazolamide group (= clinically meaningfull absolute difference of 10%)
  - Assuming α=0.05 and power of 80%, sample size of 519 patients (including 5% potential withdrawal)
- **Randomization** stratified according to center + LVEF ≤40% or >40%
- **ITT analysis** in all patients who received at least 1 dose of IMP
- **Prespecified subgroup analysis** for primary end point
- Statistical analyses performed by an **independent academic statistician**

Statistical Analysis Plan ADVOR
Mullens W et al. Eur J Heart Fail. 2018;20:1591-1600

Results: flow diagram of patient inclusion



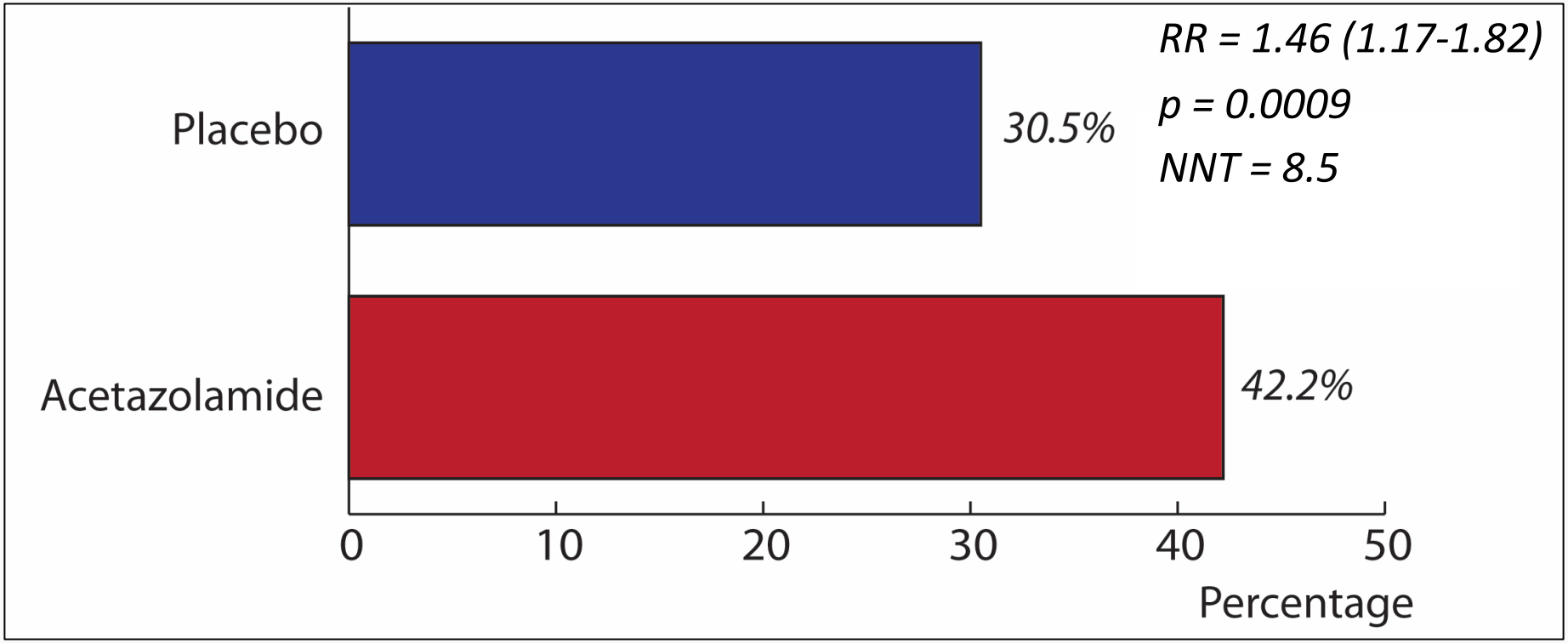
Results: baseline characteristics (1/2)

Parameter	Placebo (N=260)	Acetazolamide (N=259)
Age (years)	78.5 ± 8.8	77.9 ±9.0
Male sex	155 (60%)	170 (66%)
White race	256 (98.5%)	258 (99.6%)
Heart rate (beats/min)	77 ± 18	79 ± 19
Systolic blood pressure (mmHg)	127 ± 22	126 ± 20
Diastolic blood pressure (mmHg)	73 ± 13	72 ± 13
Weight (kg)	84.4 ± 19.7	85.3 ± 23.0
Congestion score at baseline°	4 (3-6)	4 (3-5)
Composite of volume assessment score° • Oedema (>1+) • Pleural effusion • Ascites	 241 (93%) 143 (55%) 25 (10%)	 237 (92%) 130 (50%) 21 (8%)
Maintenance dose - furosemide equivalents (mg)	60 (40-100)	80 (40-120)
LVEF (%)	43 ± 15	43 ± 15
Proportion LVEF<40%	111 (43%)	113 (44%)
NT-proBNP (pg/mL)	6,483 (3,262 – 11,839)	5,600 (3,034 – 10,100)

Results: baseline characteristics (2/2)

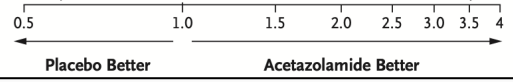
Parameter	Placebo (N=260)	Acetazolamide (N=259)
NYHA		
II	35 (13%)	31 (12%)
III	148 (57%)	148 (57%)
IV	77 (30%)	80 (31%)
Ischemic etiology	113 (43%)	119 (46%)
Serum hemoglobin (g/dL)	11.9 ± 2.0	11.9 ± 2.0
Sodium (mmol/L)	140 ± 4	139 ± 4
Serum creatinine (mg/dL)	1.5 (1.2 - 1.9)	1.5 (1.2 - 2.0)
eGFR (ml/min/1,73m²)	38 (29 - 51)	40 (30 – 52)
eGFR <60ml/min/1.73m²	215 (83%)	209 (81%)
COMORBIDITIES		
History of atrial fibrillation	189 (73%)	187 (72%)
history	133 (51%)	112 (43%)
Diabetes	207 (80%)	182 (70%)
Hypertension		
ACEi/ARB/ARNI	140 (54%)	130 (50%)
Beta-blocker	212 (82%)	207 (80%)
MRA	103 (40%)	113 (44%)
Loop Diuretic	260 (100%)	259 (100%)
ICD	41 (16%)	38 (15%)
CRT	25 (10%)	36 (14%)

Results: primary end point (successful decongestion within 3 days)

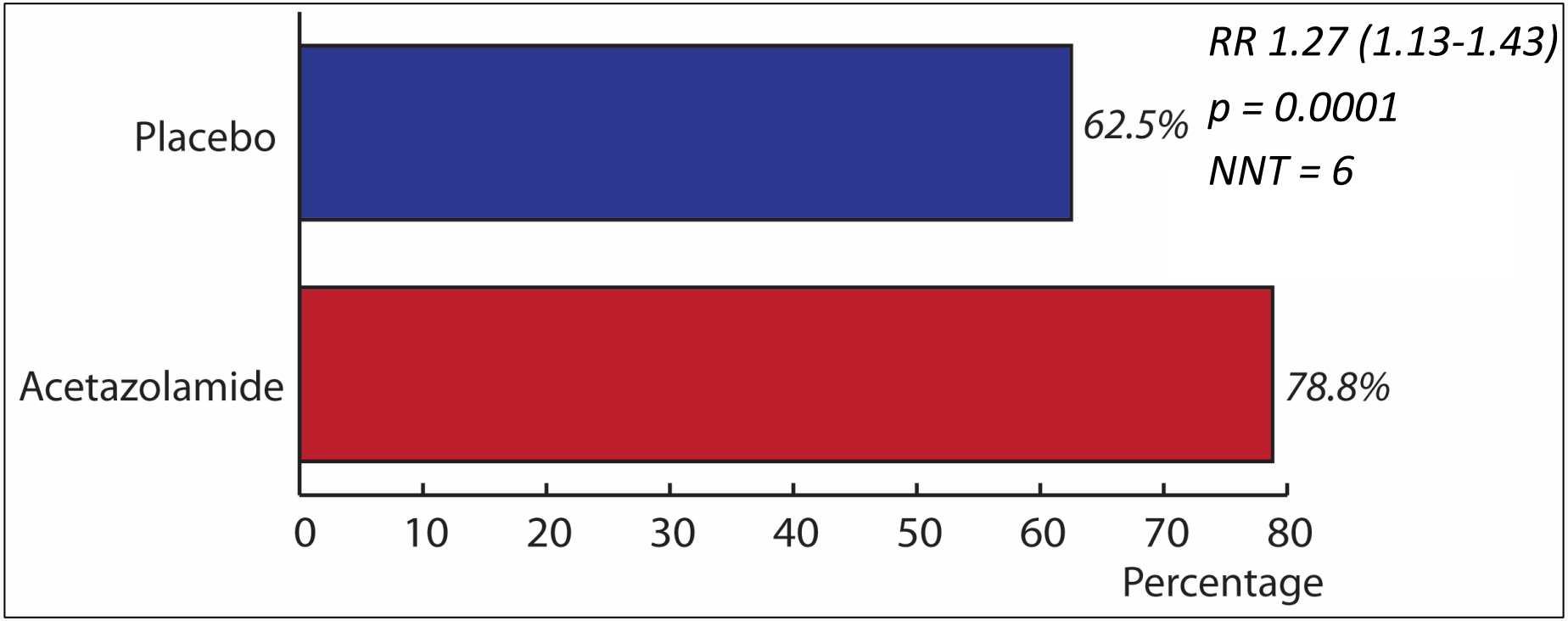


Results: primary end point (predefined subgroup analysis)

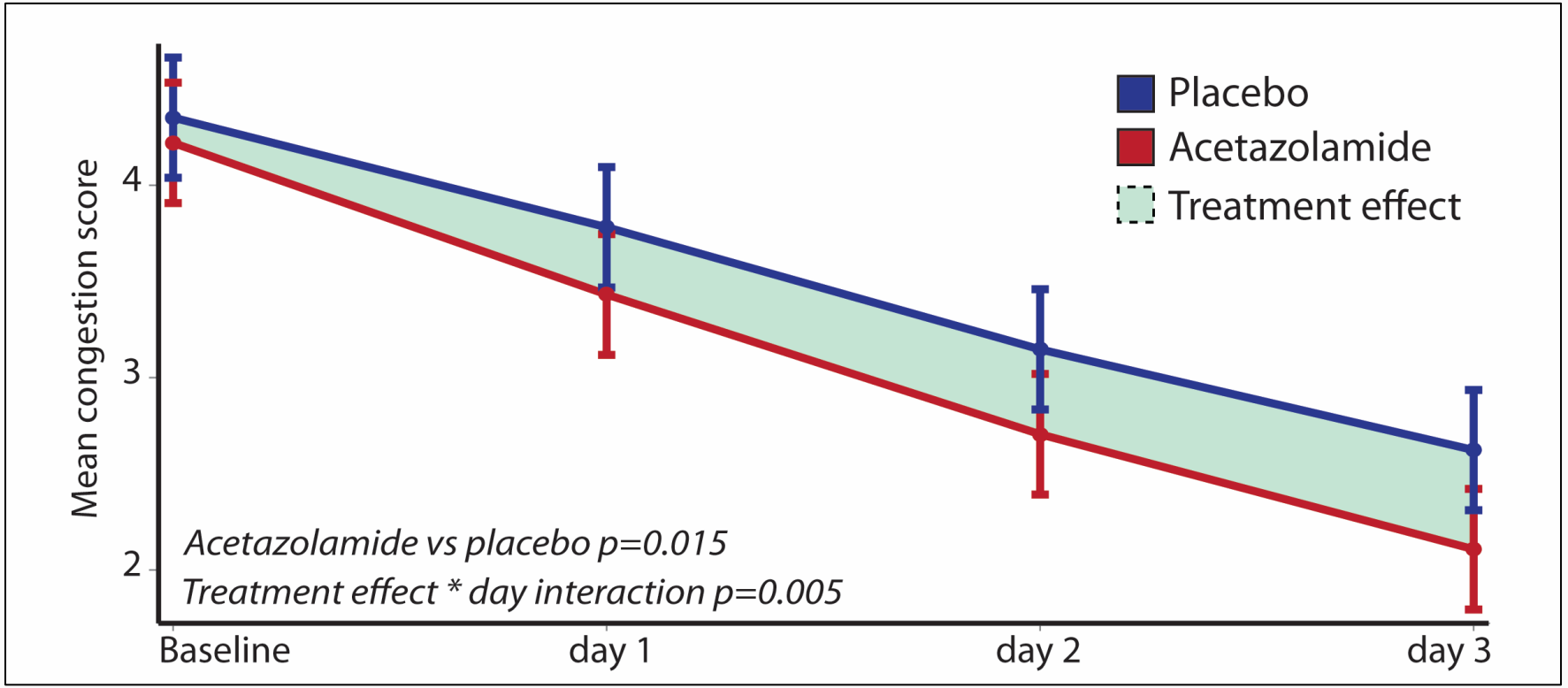
Subgroup	Placebo	Acetazolamide	Risk Ratio (95% CI)
	no. of patients/total no.		
Overall	79/259	108/256	1.46 (1.17–1.82)
Age			
≤79 yr	43/130	59/132	1.36 (1.02–1.82)
>79 yr	36/129	49/124	1.56 (1.11–2.21)
Left ventricular ejection fraction			
≤40%	36/111	43/111	1.24 (0.88–1.75)
>40%	43/148	65/145	1.63 (1.22–2.19)
NT-proBNP			
≤6173 pg/ml	51/122	68/132	1.35 (1.06–1.74)
>6173 pg/ml	27/135	38/120	1.61 (1.06–2.44)
Sex			
Female	37/104	36/88	1.21 (0.86–1.71)
Male	42/155	72/168	1.67 (1.24–2.25)
Estimated GFR			
<39 ml/min/1.73m^2	33/135	53/125	1.77 (1.25–2.5)
≥39 ml/min/1.73m^2	46/124	55/131	1.23 (0.92–1.65)
Cause of heart failure			
Ischemic	37/113	48/118	1.35 (0.97–1.87)
Nonischemic	42/146	60/138	1.57 (1.16–2.12)
Home maintenance loop diuretic dose			
≤60 mg furosemide equivalent	42/136	67/127	1.78 (1.33–2.36)
>60 mg furosemide equivalent	37/123	41/129	1.08 (0.76–1.55)
Baseline congestion score			
≤4	60/145	82/155	1.38 (1.1–1.74)
>4	19/114	26/101	1.62 (0.96–2.73)
Atrial fibrillation			
No	20/71	31/71	1.76 (1.14–2.72)
Yes	59/188	77/185	1.35 (1.04–1.75)



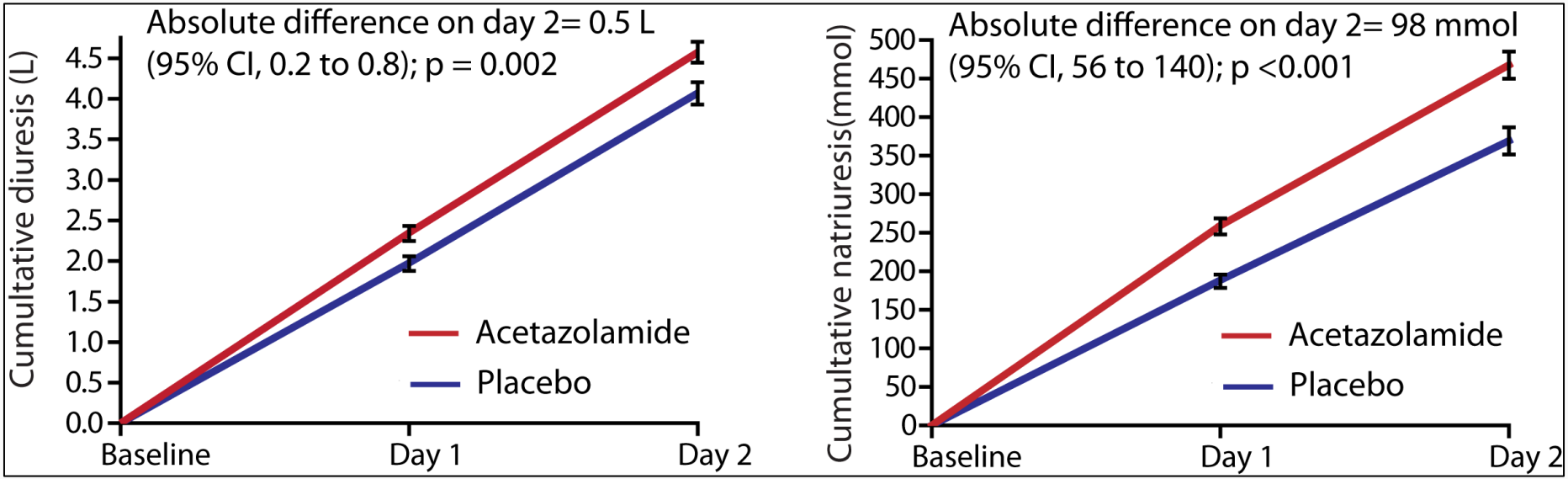
Results: successful decongestion at discharge



Results: effect of acetazolamide on congestion score



Results: effect of acetazolamide on diuresis and natriuresis



Results: secondary end points

Outcomes	Placebo	Acetazolamide	Risk Ratio, Geometric Mean or Hazard Ratio [95%CI]	p-value
Secondary endpoint				
Length of stay (days)	9.9 (9.1-10.8)	8.8 (8.0-9.5)	GM 0.89 (0.81 to 0.98)	0.016
All-cause mortality and hospitalization for heart failure at 3months	72 (27.8%)	76 (29.7%)	HR 1.07 (0.78 to 1.48)	ns
All-cause mortality at 3 months	31 (12.0%)	39 (15.2%)	HR 1.28 (0.78 to 2.05)	ns
Hospitalization for heart failure at 3 months	45 (17.4%)	47 (18.4%)	HR 1.07 (0.71 to 1.59)	ns
Sensitivity analysis of primary endpoint				
Successful decongestion within 3 days, irrespective of escalation	86 (33.2%)	115 (44.9%)	RR 1.42 (1.15 to 1.76)	0.001

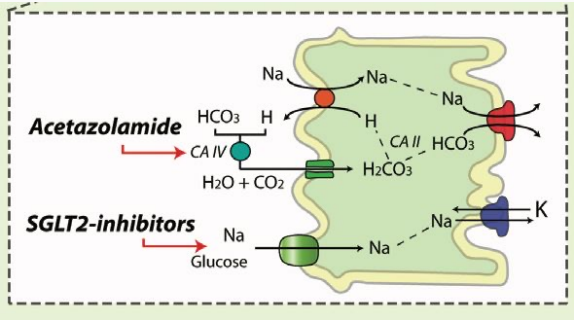
Results: safety end points

Outcome	Placebo	Acetazolamide	p-value
Adverse events during treatment phase			
Combined renal endpoint	2 (0.8%)	7 (2.8%)	0.10
Doubling of serum creatinine compared to baseline	0 (0%)	2 (0.8%)	0.24
≥50% sustained decrease in eGFR	1 (0.4%)	4 (1.6%)	0.21
Need for renal replacement therapy during index hospitalization	1 (0.4%)	4 (1.6%)	0.21
Severe metabolic acidosis bicarbonate <12 mmol/L	0 (0%)	0 (0%)	
Hypokalemia ≤3 mmol/L	10 (3.9%)	14 (5.5%)	0.39
Hypotension <85 mmHg	9 (3.5%)	17 (6.6%)	0.11
Adverse events during 3 months follow-up			
SAE overall	124 (47.9%)	123 (48.1%)	1.00
AE related to study drug	3 (1.2%)	8 (3.1%)	0.14
AE cardiovascular	122 (47.1%)	113 (44.1%)	0.53

(Acetazolamide has been used > 70 years)

Limitations

- Trial recruited exclusively in Belgium
- History of chronic HF with at least 40 mg furosemide
- SGLT2i not allowed to avoid imbalance between study groups
  - Not indicated / approved during most of study period
  - Different effect on proximal sodium uptake
    - 5% mediated by SGLT2i
    - 60% mediated by apical Na/H exchanger which is inhibited by Acetazolamide



Conclusions (1/2)

- ADVOR was the largest diuretic trial in ADHF ever performed with a very important clinical end point of decongestion (= Class I recommendation).
- In this multicenter, placebo-controlled trial in ADHF with volume overload, the addition of 500 mg IV acetazolamide to standardized intravenous loop diuretic was associated with 46% higher incidence of successful decongestion after 3 days.
- The benefit was generally consistent across all prespecified subgroups.
- Patients treated with acetazolamide:
  - more diuresis and natriuresis
  - shorter hospital stay
  - more likely to be discharged without residual volume overload (NNT 6)

Conclusions (2/2)

- There was no reduction in all-cause death / HFH but trial was underpowered AND rates were considerably lower (28% vs > 50% in DOSE) potentially related to more decongestion.

- There was no higher incidence of adverse events with acetazolamide treatment.

- The results of ADVOR highlight the importance of targeting congestion both early and aggressively and support the use of natriuresis as an indicator of diuretic response.

- ADVOR supports utilization of acetazolamide as it is a cheap, off-patent, easy-to-use, safe and very effective drug to improve decongestion.

Acknowledgements

- Participating sites, principal investigators, study nurses, patients
- Belgian Health Care Knowledge Center
- Trial steering committee
- Clinical Trial Unit, Ziekenhuis Oost Limburg Genk, Belgium
- My former and current Phd Students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Objective of research = treating patients you'll never meet…

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ADVOR

ORIGINAL ARTICLE

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

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