

4th KCE Trials Symposium

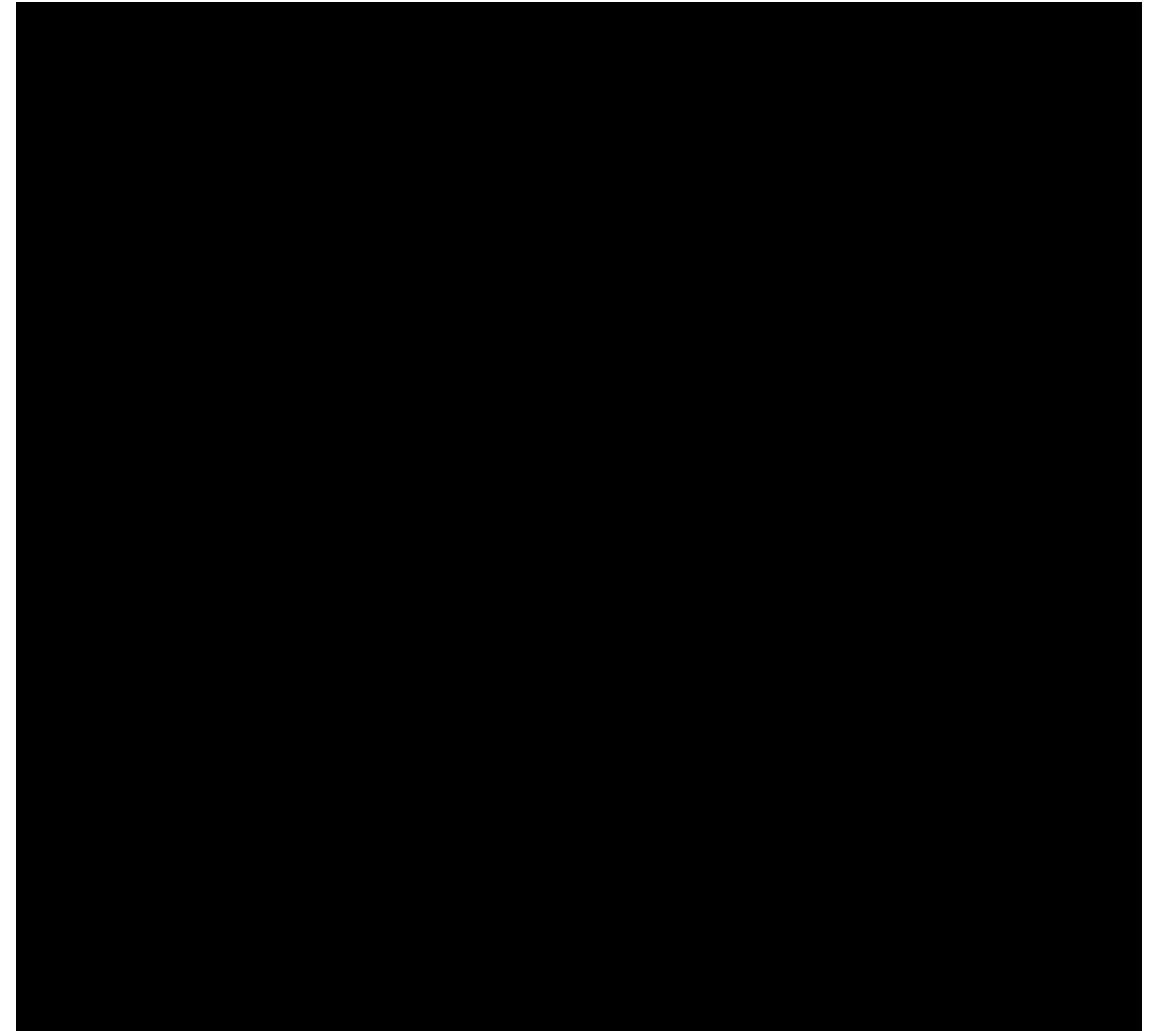
– May 25, 2023, Brussels

AD♥OR trial results: Acetazolamide in patients with Decompensated
heart failure and Volume oveRload

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Ziekenhuis Oost-Limburg, Genk
University Hasselt, Belgium
Fellow and Board Member of Heart Failure Association

Heart Failure

- Chronic uncurable disease
- 2-3% of population (Belgium > 250.000)
 - 15.000 new pnts / year
 - Incremental risk with aging (> 10% once 70 y)
- Very costly, 3% of health care budget
- Poor prognosis (25% vs 50% mortality 1-5 years)
- Poor QOL
- Hospitalizations problematic
 - 1/3 of cardiac hospitalizations
 - hospital admission 9 days
 - extreme discomfort for patients

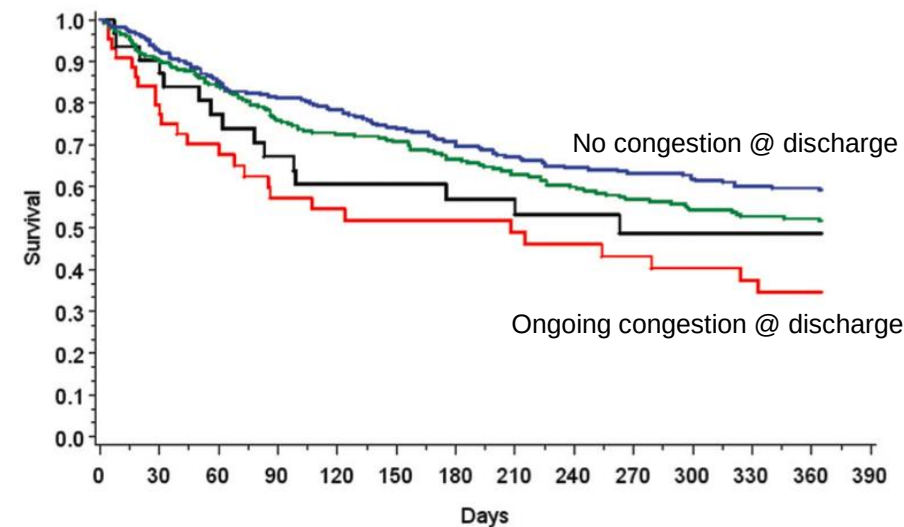
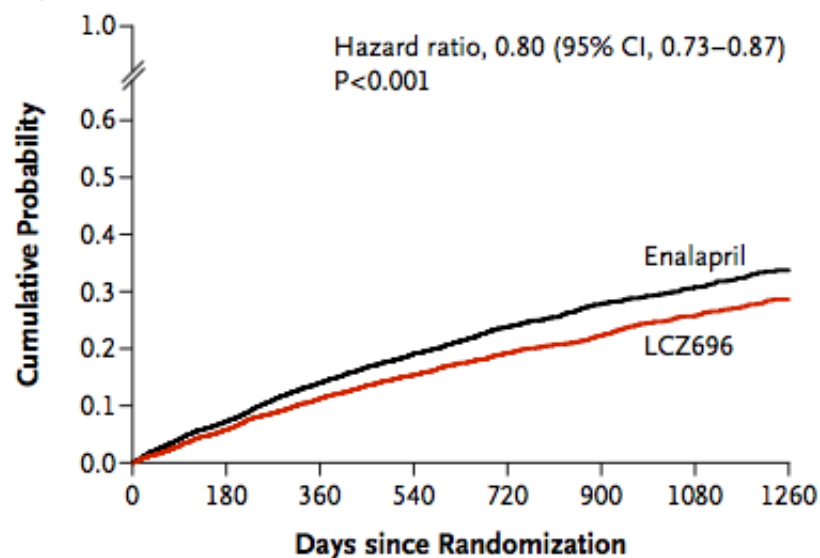


Underappreciated risk for hospitalization / death linked to residual congestion in HFpnts

Ambulatory: 20% risk at 2 years

Recently Hospitalized: 60% risk at 1 year

Primary End Point



WRF/Cong	44	35	27	22	20	18	18	17	16	15	14	13	12
No WRF/Cong	31	28	23	20	18	18	16	15	13	11	11	11	11
WRF/No Cong	253	227	208	193	163	158	143	131	120	113	107	103	98
No WRF/No Cong	265	244	219	205	192	177	168	158	149	144	140	134	133

Diuretics

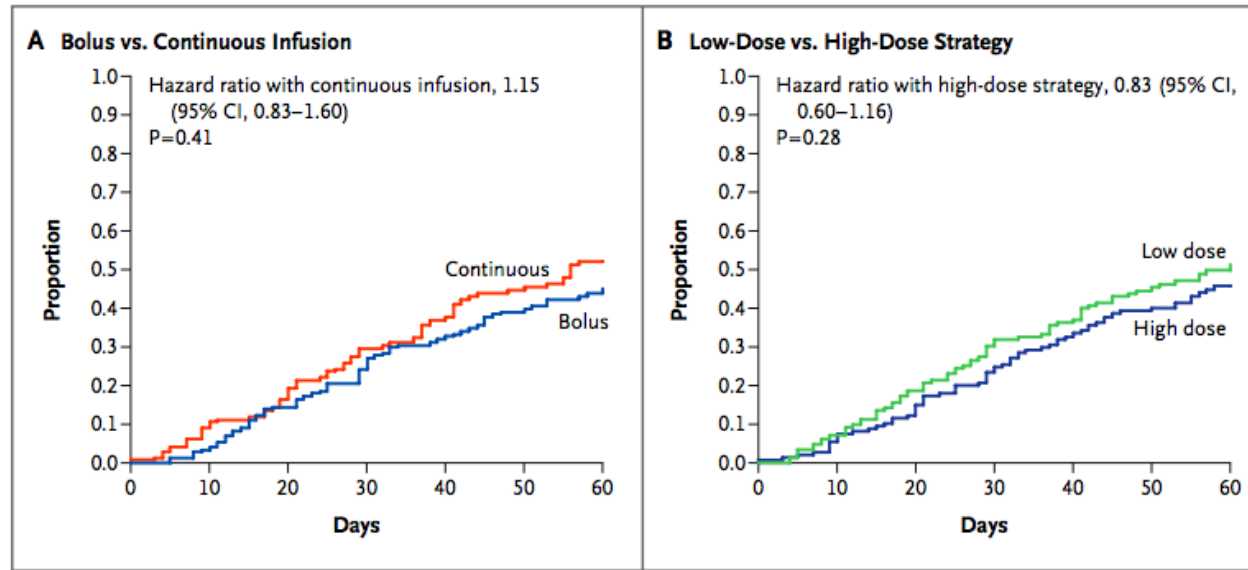
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.¹⁴⁵

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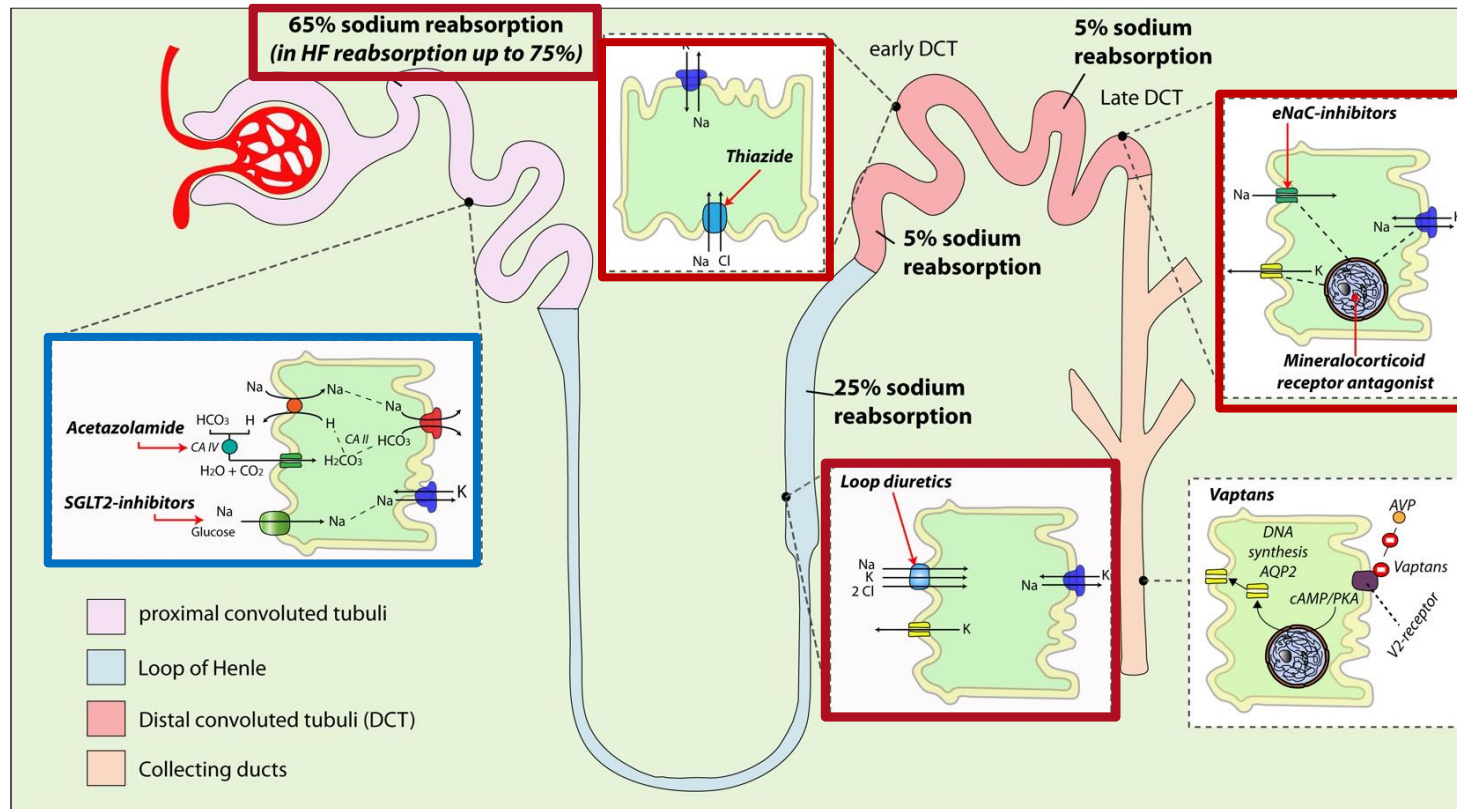
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The Diuretic Optimization Strategies Evaluation Study (DOSE)

Low (=home dose) vs high (x2.5 home dose) - continuous vs bolus every 12 h

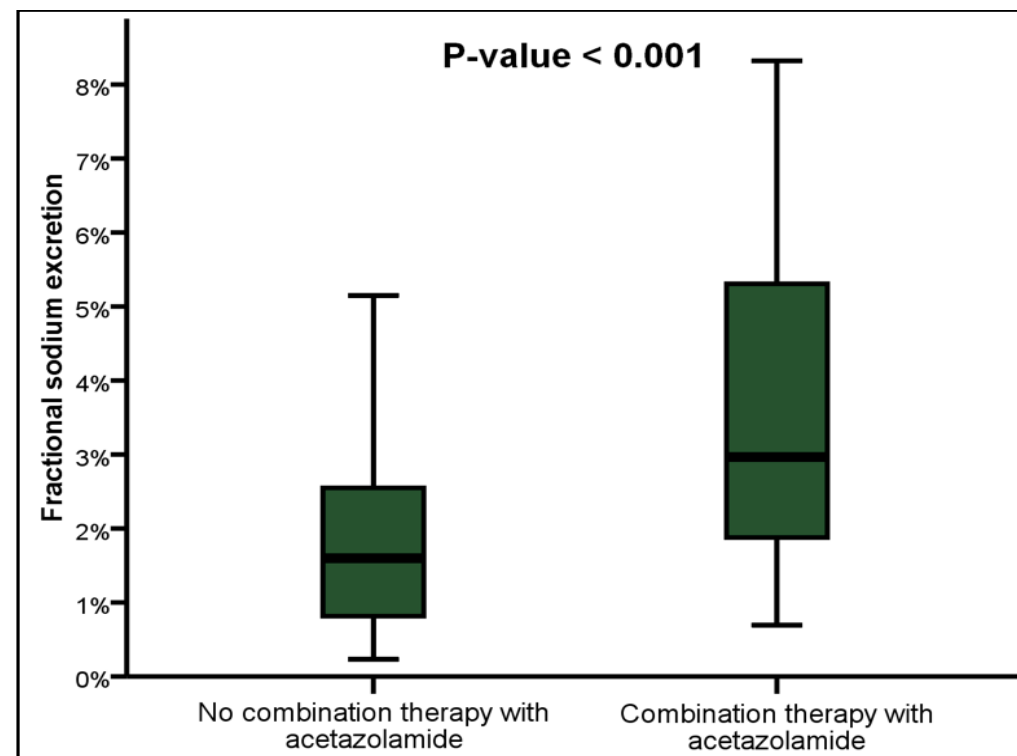
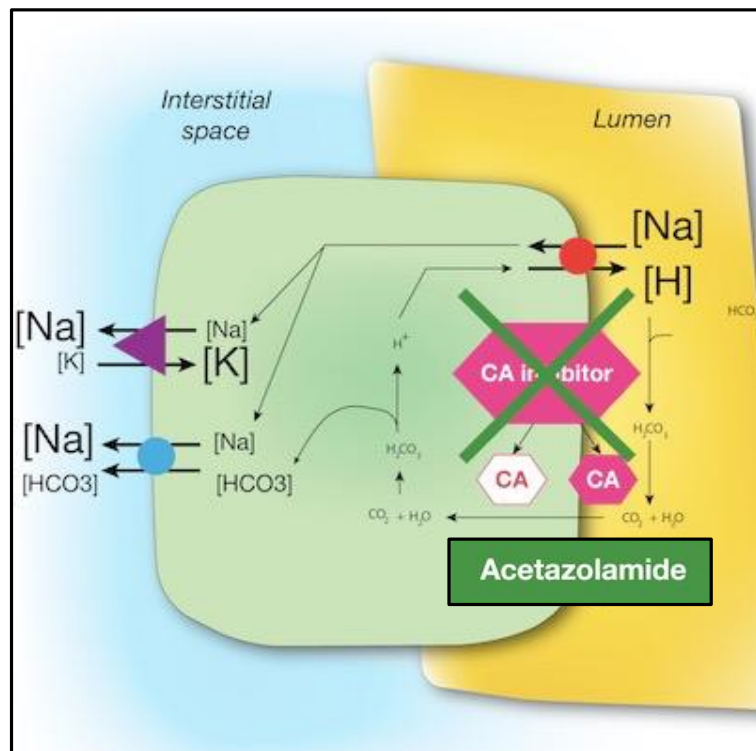


End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09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



HF induces a state of increased proximal renal sodium reabsorption, but loop diuretics, thiazides, MRA work too distal

Acetazolamide should improve loop diuretic efficacy





Acetazolamide in **D**ecompensated Heart Failure With **V**olume **O**ve**R**load

www.advor.be

Timelines

2016

Design of ADVOR



HFA
Heart Failure
Association



2017

KCE clinical trial program - grant application (January 2017)

Clinical Trial Unit development (March 22, 2017)

KCE grant approval (December 2017)

2018

Contract KCE – CTU-ZOL signed (April 9, 2018)

Preparation by CTU (Staff, IMP, shipment, randomiz, database, legal, sites, contracts....)

Methods manuscript Eur J Heart Fail (August 2, 2018)

EC/CA approval (August 3, 2018)

First site initiation visit (October 25, 2018)

First patient enrolled (November 11, 2018)

2019

COVID-19 (multiple lockdowns)

2020

Weekly tuesday meetings with CTU

Monthly newsletters

2021

Several Investigators Meetings (in-person, on-site, remote)

2022

Last patient enrolled (January 17, 2022)

Presubmission inquiry + SAP submitted to NEJM (February 24, 2022)

Last patient last visit (April 27, 2022)

Baseline characteristics manuscript EJHF (May 13, 2022)

Database lock (May 16, 2022)

Results presented to TSC (May 25, 2022)

Submission NEJM (June 15, 2022)

Acceptance NEJM (July 15, 2022)

LBCT @ ESC 2022 + simultaneous publication NEJM (August 27, 2022)

Clinical Trial Unit



Ziekenhuis
Oost-Limburg



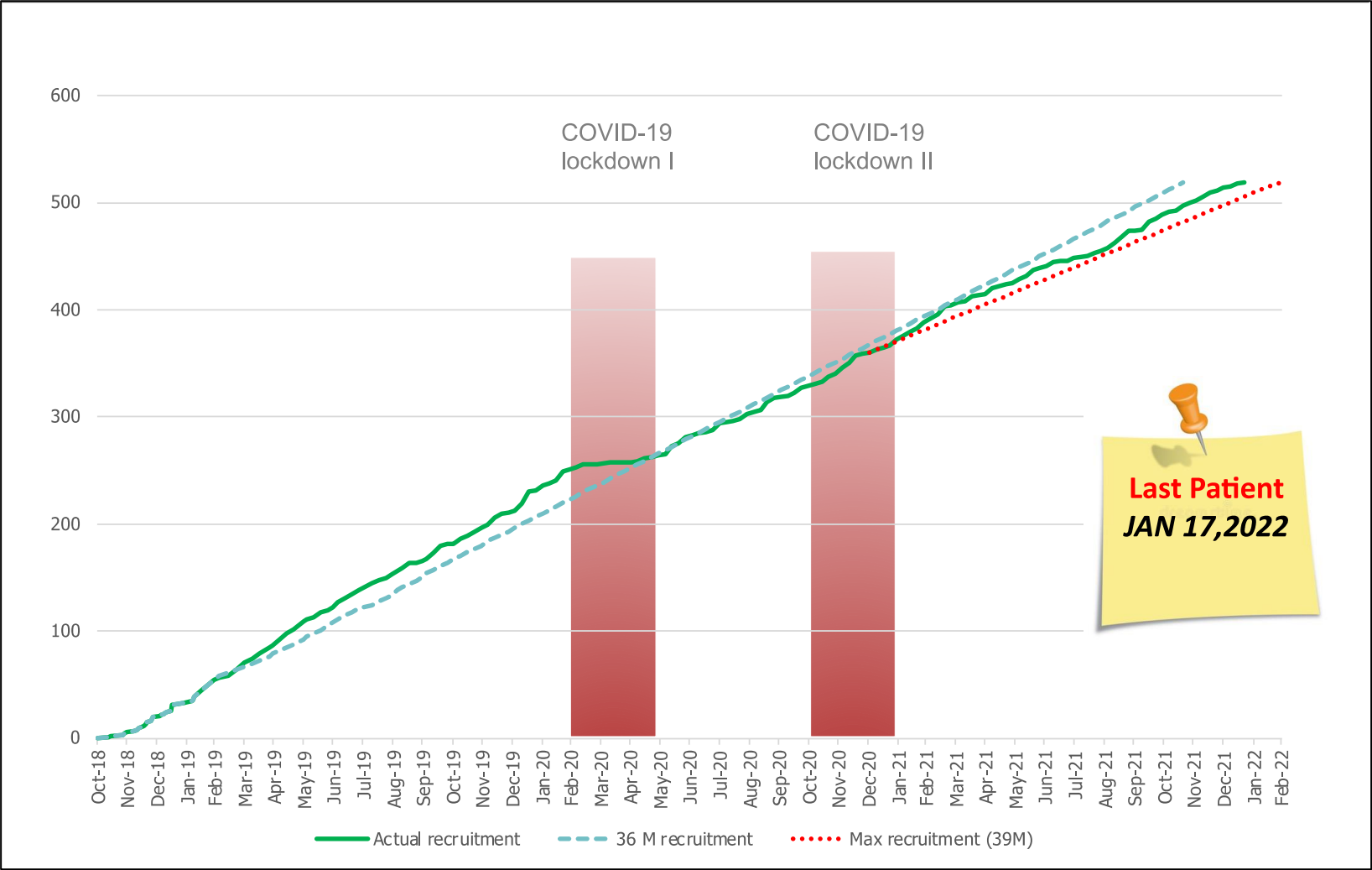
29 participating sites

Hospital	Principal Investigator
AZ Delta Roeselare-Menen	M. Deceunick
AZ Glorieux, Ronse	F. Van Durme
AZ Groeninge, Kortrijk	D. Derthoo
AZ klina, Antwerpen	W. Smolders
AZ Maria Middelaes Gent	D. Vervloet
AZ Mol	H. Striekwold
AZ Nikolaas, St-Niklaas	K. Goossens
AZ Sint-Lucas, Gent	H. Vandekerckhove
AZ Turnhout	P.J. Hofkens
CHR de la Citadelle, Luik	P. Troisfontaines
CHU Charleroi	S. Moubayed
CHU UCL Namur	L. Gabriel
Clinique Saint-Luc Bouge	P. Blouard
Grand Hôpital de Charleroi	F. Chenot
GZA, sint-Vincentius, Wilrijk	D. Raes

Hospital	Principal Investigator
Hôpital Erasme, Brussel	J.L. Vachier
Imeldaziekenhuis, Bonheiden	B. Ector
Jan Yperman	E. Viaene
Jessa Ziekenhuis, Hasselt	P. Timmermans
OLV Ziekenhuis Aalst-Asse-Ninove	R. Dierckx
Sint Maarten, Mechelen	G. Vervoort
UZ Antwerpen	E. Van Craenenbroeck
UZ Brussel	S. Lochy
UZ Gent	M. Depauw
UZ Leuven	W. Droogne
UZ Saint-Luc, Brussel	A.C. Pouleur
Ziekenhuis Maas en Kempen	M. Hulselmans
Ziekenhuis Oost Limburg AV	W. Mullens
ZNA Middelheim	E. Prihadi

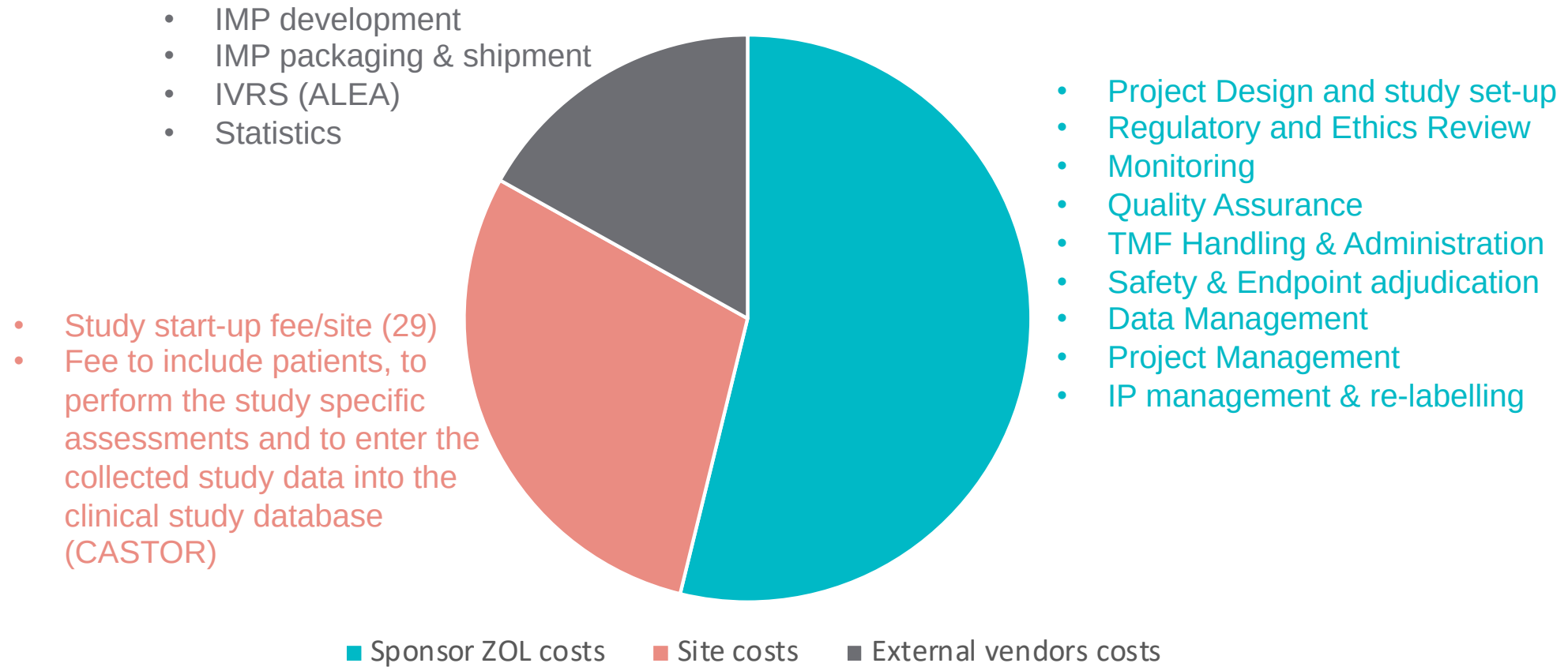


Patient recruitment



Budget

Total budget of 2,2 million euro (or 2,6 million euro (incl. VAT))



Prospective, multicenter, randomized, double-blind, placebo-controlled, academic trial

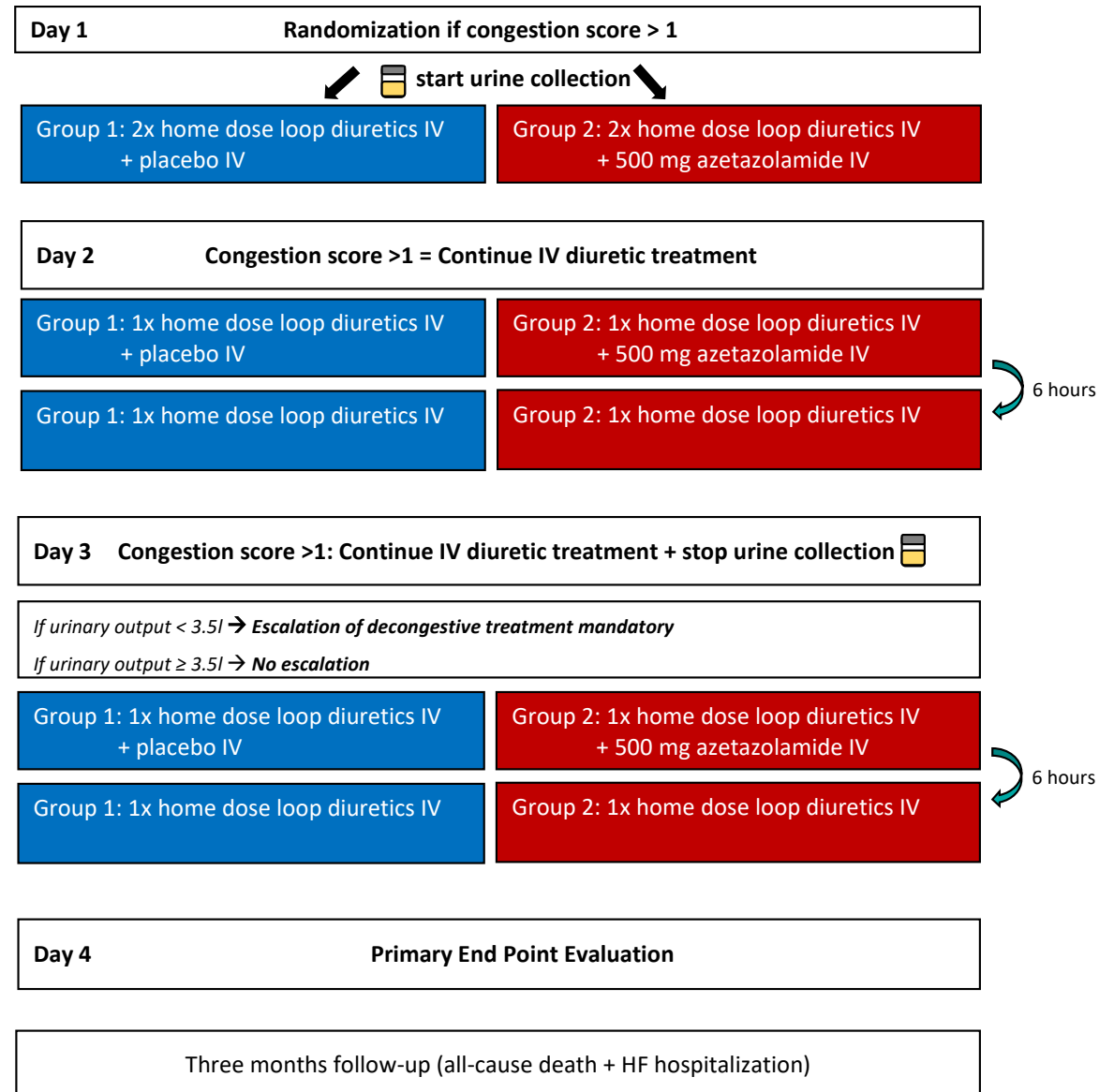
Main inclusion criteria

- 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

Statistics:

- Sample size n 519 to detect absolute RR of 10% (25 vs 15 %) based upon DOSE
- ITT analysis in all patients who received at least 1 dose of IMP

Methods: trial procedures



Methods: primary end point

Primary end point:

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

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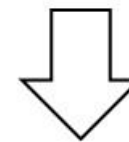
Recommendations	Class ^a	Level ^b
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment. ^{427,472}	I	C

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 puncture) pleural effusion (score 2)		Major (amenable for puncture) 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**



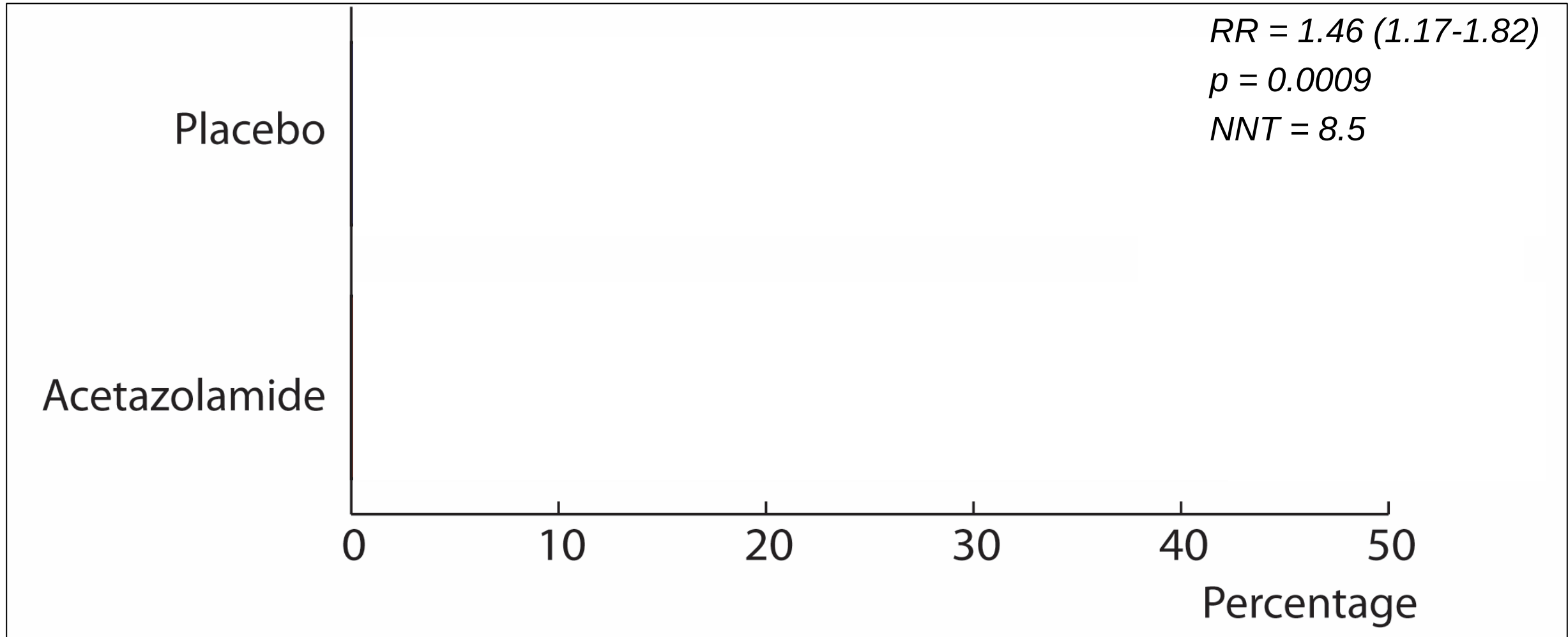
Continue IV diuretic therapy

Comparison with other diuretic RCT

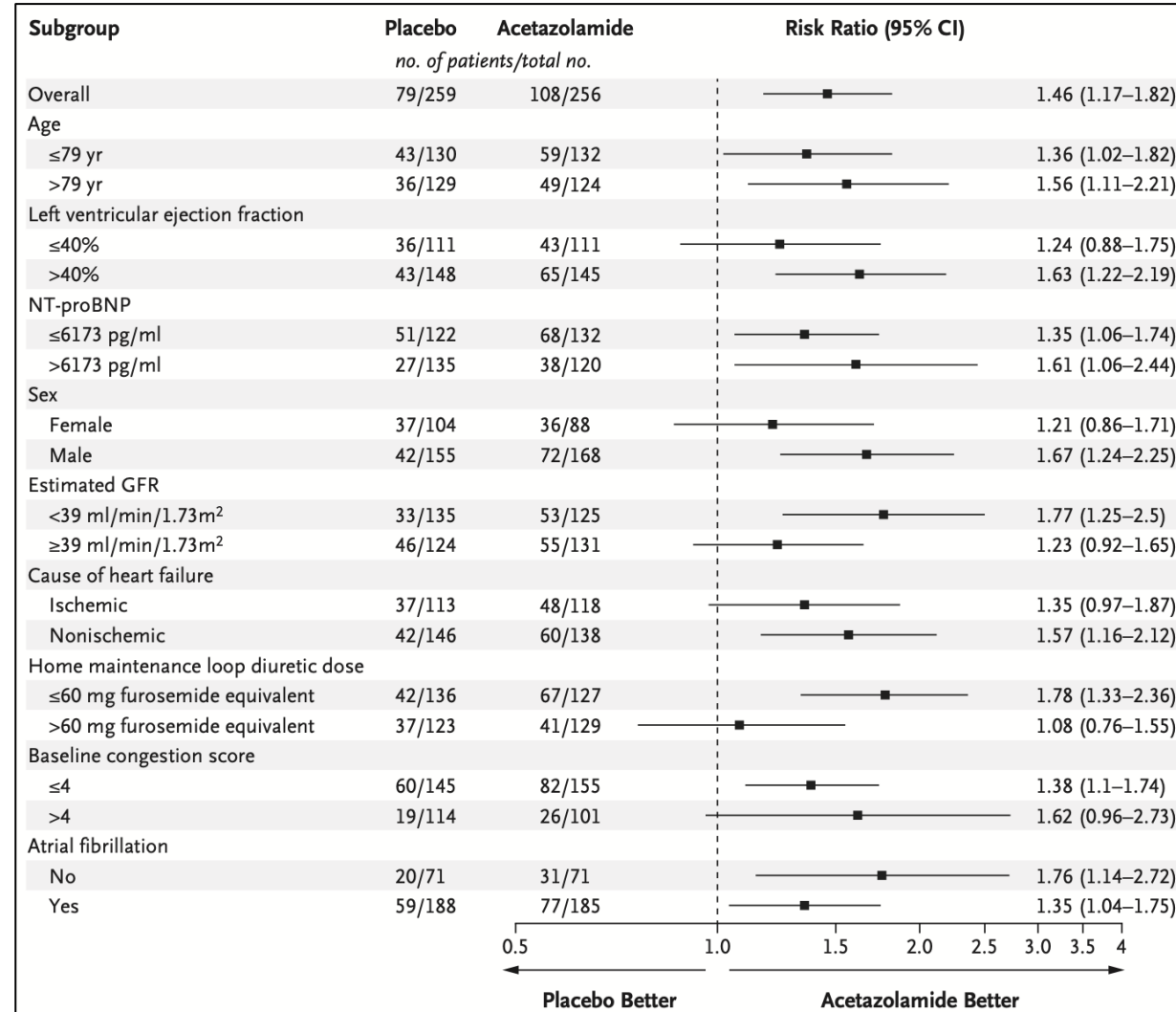
Table 3 Comparison of baseline characteristics in diuretic trials in acute heart failure

	ADVOR (n = 519)	DOSE (n = 308)	ATHENA-HF (n = 360)	CARRESS-HF (n = 188)
Intervention	Acetazolamide or matched placebo on top of high-dose loop diuretics	IV furosemide: - high vs. low-dose - continuous vs. intermittent bolus	High-dose spironolactone (100 mg) vs. placebo or 25 mg spironolactone	Stepped pharmacological therapy vs. ultrafiltration
Primary endpoint	Successful decongestion (score <2)	AUC VAS (wellbeing) and change in serum creatinine	Change in log NT-proBNP levels	Change in serum creatinine level and change in weight
Age (years)	78 ± 9	66	65	68
Male sex	63%	73%	64%	75%
EF (%)	43 ± 15	35 ± 18	34	37 ± 18
Proportion EF	>40%: 57%	≥50%: 27%	>45%: 27%	—
Ischemic aetiology	45%	57%	63%	61%
History of AF or AFI	72%	53%	48%	54%
Diabetes mellitus	47%	51%	41%	66%
ICD	15%	39%	16%	—
CRT	12%	—	16%	—
Loop diuretics	100%	100%	96%	94%
Dose of oral furosemide or equivalents (mg/day)	60 (40–100)	131 ± 51.4	80 (40–160)	120 (80–160) vs. 120 (80–240)
ACEi/ARB/ARNI	52%	64%	60%	54%
Beta-blocker	81%	83%	74%	78%
MRA	42%	28%	11%	20%
Systolic blood pressure (mmHg)	127 ± 21	119.5 ± 20.0	122	—
Heart rate (bpm)	78 ± 18	78.5 ± 16.0	79	—
Sodium (mmol/L)	139 ± 4	138 ± 4	140 (138–142)	137 ± 4
Creatinine (mg/dl)	1.5 (1.2–1.9)	1.5 ± 0.5	1.2	2.09 (1.71–2.65) vs. 1.90 (1.57–2.37)
eGFR (ml/min/1.73 m ²)	39 (29–52)	—	55 (46–71) vs. 58 (45–75)	—
NT-proBNP (pg/ml)	6173 (3068–10 896)	3790 (1890–8781)	4176 (1936–7456) vs. 4028 (2472–10 048)	4007 (1128–8534) vs. 5013 (2310–10 381)

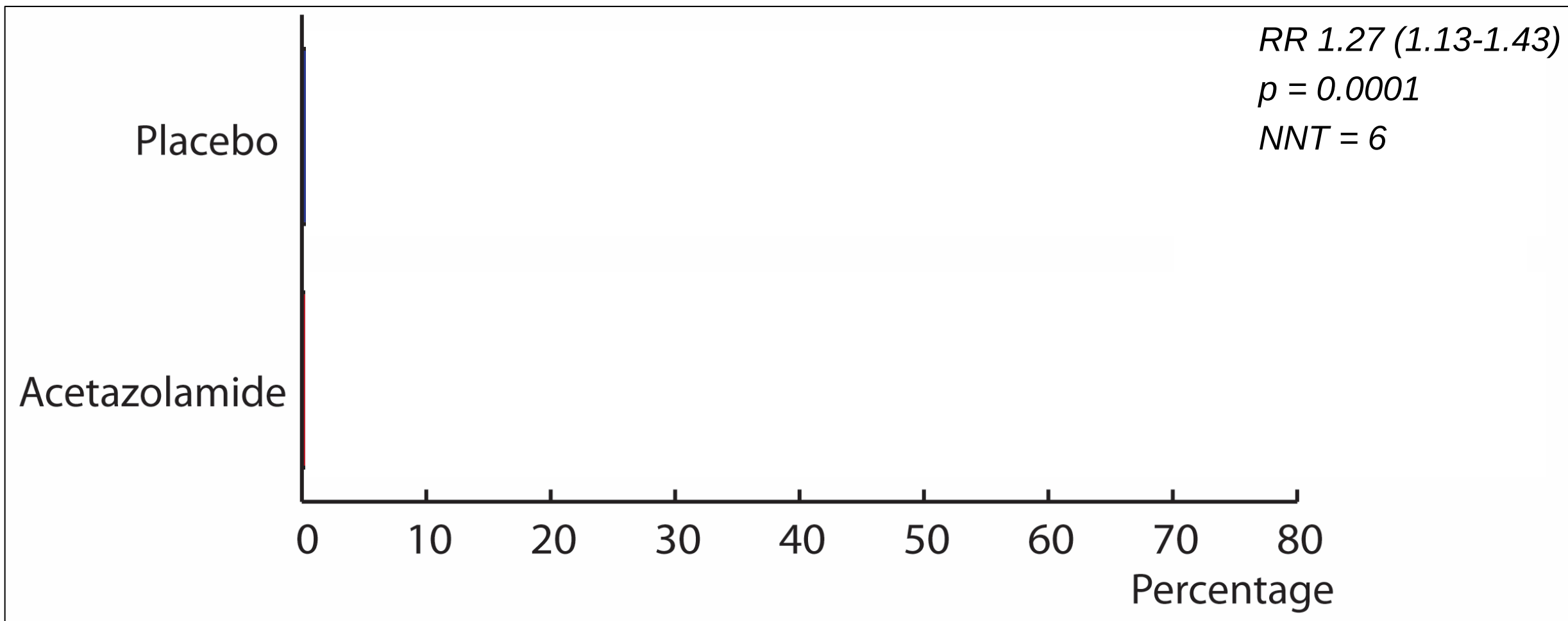
Results: primary end point (successful decongestion within 3 days)



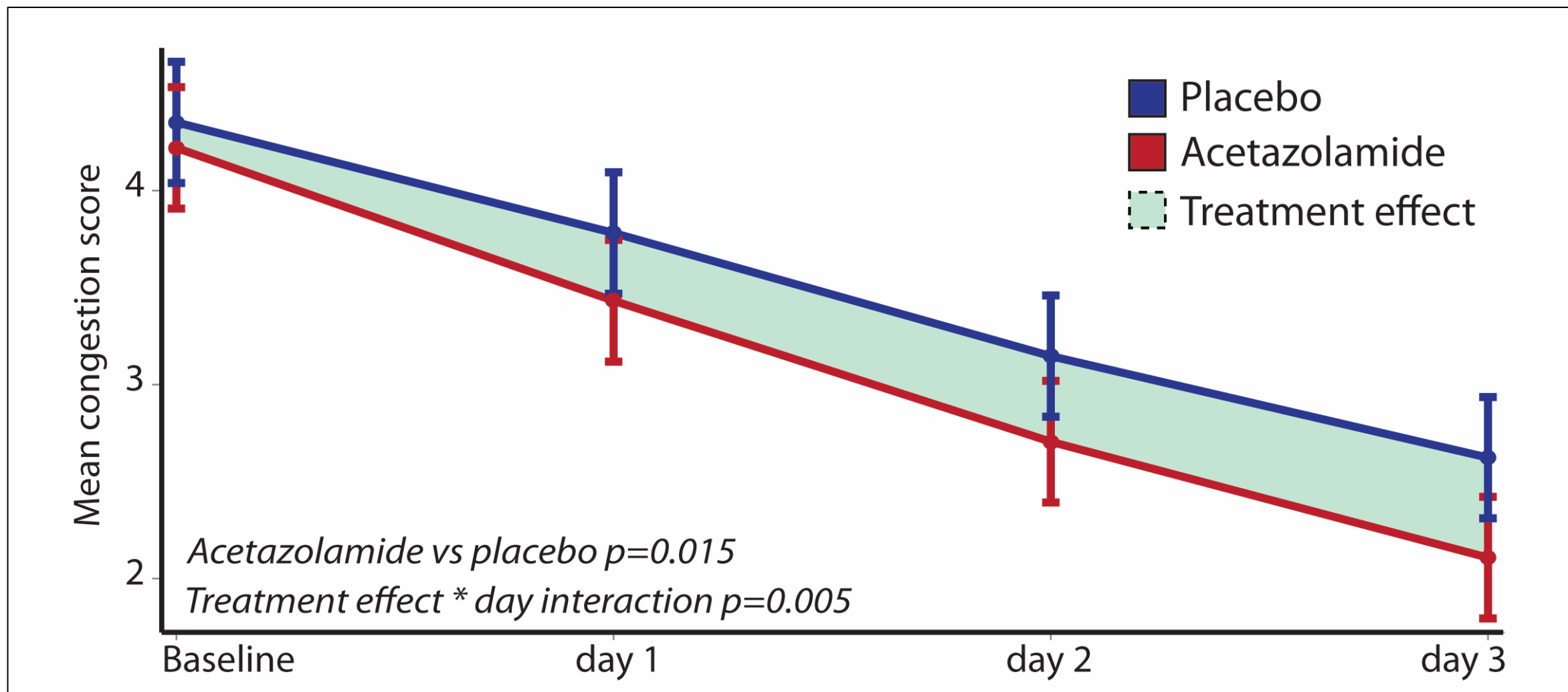
Results: primary end point (predefined subgroup analysis)



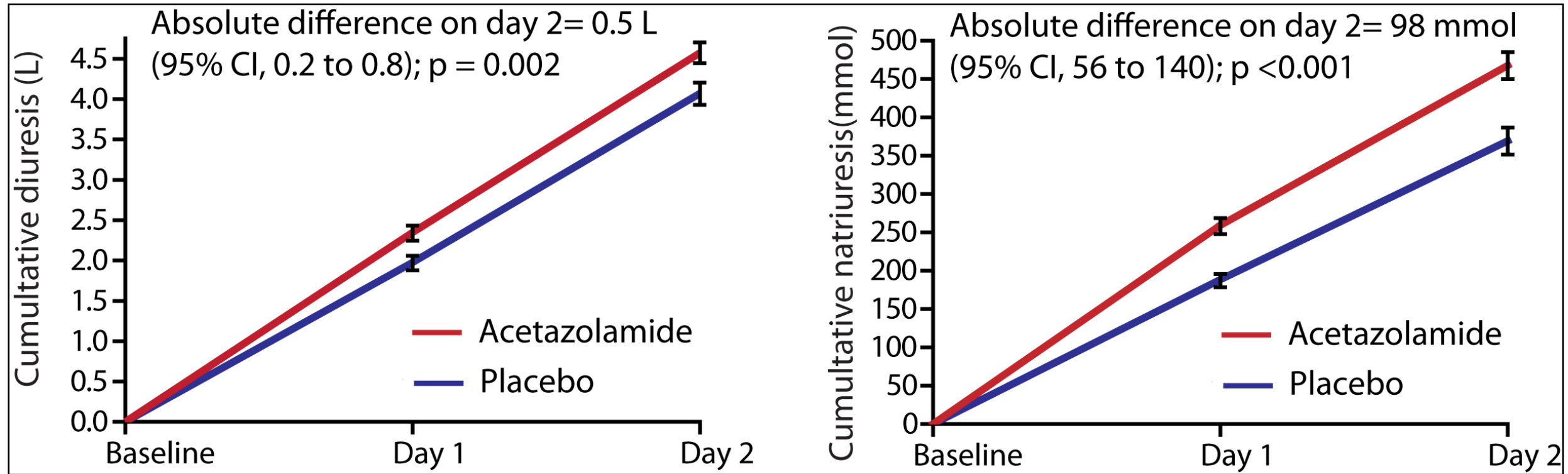
Results: successful decongestion at discharge



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)

AD[♥]OR

“door to combo-diuretic time”

ESC CONGRESS 2022
Barcelona & Online





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*

Scientific output...impact factor > 400

 **ESC**
European Society
of Cardiology

European Journal of Heart Failure (2018)
doi:10.1002/ehf.1307

STUDY DESIGN

Rationale and design of the **ADVOR** (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial

 **ESC**
European Society
of Cardiology

European Journal of Heart Failure (2022)
doi:10.1002/ehf.2587

RESEARCH ARTICLE

Acetazolamide in Decompensated Heart Failure with Volume Overload trial (**ADVOR**): baseline characteristics

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

Circulation

ORIGINAL RESEARCH ARTICLE

Decongestion With Acetazolamide in Acute Decompensated Heart Failure Across the Spectrum of Left Ventricular Ejection Fraction: A Prespecified Analysis From the ADVOR Trial

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PUBLISHED BY ELSEVIER

Natriuretic Response to Acetazolamide in Patients With Acute Heart Failure and Volume Overload

 **ESC**
European Society
of Cardiology

European Heart Journal (2023) **00**, 1–11
<https://doi.org/10.1093/eurheartj/ehad236>

FASTTRACK CLINICAL RESEARCH
Heart failure and cardiomyopathies

Pre-treatment bicarbonate levels and decongestion by acetazolamide: the **ADVOR** trial

Impact on guidelines ?

Diuretics

Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.¹⁴⁵

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Intravenous acetazolamide on top of loop diuretics is recommended for all patients with AHF admitted with signs/symptoms of fluid overload who were previously treated with oral loop diuretics to improve the incidence of decongestion

Ila

B

New in 2026 guidelines ???

Is there impact on patients in Belgium ?

Beste,

Hierbij melden we u dat Diamox inj 500 mg wereldwijd zeer beperkt beschikbaar is bij de firma en alle buitenlandse leveranciers.

Om te vermijden dat er helemaal geen Diamox IV meer kan toegediend worden, vragen we u om zoveel mogelijk de orale vorm Diamox 250 mg tabletten voor te schrijven.

Zo kan de Diamox IV gereserveerd worden voor kritische patiënten.

Tijdelijk vervangproduct: Diamox 250 mg tablet

Met vriendelijke groeten,

Secretariaat Apotheek



Ziekenhuis Oost-Limburg
Schiepse bos 6
3600 Genk
Tel. 089/32.14.14 – Fax. 089/32.79.21 Website: www.zol.be

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



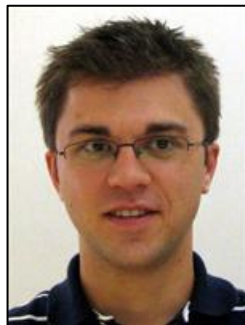
Matthias Dupont



Frank Ruschitzka



Diana Clemente, Liesbeth
Van Brussel, Marlies Dictus,
Charlotte Claes, Katrien Tartaglia



Frederik Verbrugge



Petra Nijst



Pieter Martens



Jeroen Dauw



Evelyne Meekers

Objective of research = treating patients you'll never meet via easy, safe, effective, cheap manner