University of Groningen

Acetazolamide in Decompensated Heart Failure with Volume Overload trial (ADVOR)

Mullens, Wilfried; Dauw, Jeroen; Martens, Pieter; Meekers, Evelyne; Nijst, Petra; Verbrugge, Frederik H.; Chenot, Fabien; Moubayed, Samer; Dierckx, Riet; Blouard, Philippe

Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.2587

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Mullens, W., Dauw, J., Martens, P., Meekers, E., Nijst, P., Verbrugge, F. H., Chenot, F., Moubayed, S., Dierckx, R., Blouard, P., Derthoo, D., Smolders, W., Ector, B., Hulselmans, M., Lochy, S., Raes, D., Van Craenenbroeck, E., Vandekerckhove, H., Hofkens, P. J., ... Dupont, M. (2022). Acetazolamide in Decompensated Heart Failure with Volume Overload trial (ADVOR): baseline characteristics. *European Journal of Heart Failure*, *24*(9), 1601-1610. Advance online publication. https://doi.org/10.1002/ejhf.2587

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 24-09-2023

Check for updates

ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 1601–1610
doi:10.1002/ejhf.2587

RESEARCH ARTICLE

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

Wilfried Mullens[1,2]*, Jeroen Dauw[1,2], Pieter Martens[1], Evelyne Meekers[1,2], Petra Nijst[1], Frederik H. Verbrugge[3,4], Fabien Chenot[5], Samer Moubayed[6], Riet Dierckx[7], Philippe Blouard[8], David Derthoo[9], Walter Smolders[10], Bavo Ector[11], Michaël Hulselmans[12], Stijn Lochy[3], David Raes[13], Emeline Van Craenenbroeck[14,15], Hans Vandekerckhove[16], Pieter-Jan Hofkens[17], Kathleen Goossens[18], Anne-Catherine Pouleur[19], Michel De Ceuninck[20], Laurence Gabriel[21], Philippe Timmermans[22], Edgard A. Prihadi[23], Frederik Van Durme[24], Michel Depauw[25], Delphine Vervloet[26], Els Viaene[27], Jean-Luc Vachiery[28], Katrien Tartaglia[1], Jozine M. ter Maaten[29], Liesbeth Bruckers[2], Walter Droogne[30], Pierre Troisfontaines[31], Kevin Damman[29], Johan Lassus[32], Alexandre Mebazaa[33], Gerasimos Filippatos[34], Frank Ruschitzka[35], and Matthias Dupont[1]

[1]Ziekenhuis Oost-Limburg, Genk, Belgium; [2]Hasselt University, Diepenbeek/Hasselt, Belgium; [3]Universitair Ziekenhuis Brussel, Jette, Belgium; [4]Vrije Universiteit Brussel, Jette, Belgium; [5]Grand Hôpital de Charleroi, Charleroi, Belgium; [6]CHU Charleroi, Charleroi, Belgium; [7]OLV Hospital, Aalst, Belgium; [8]Clinic Saint-Luc, Bouge, Belgium; [9]AZ Groeninge, Kortrijk, Belgium; [10]AZ Klina, Brasschaat, Belgium; [11]Imelda Hospital, Bonheiden, Belgium; [12]Ziekenhuis Maas en Kempen, Maaseik, Belgium; [13]GZA Sint-Augustinus, Wilrijk, Belgium; [14]Department of Cardiology, Antwerp University Hospital, Edegem, Belgium; [15]Research Group Cardiovascular Diseases, GENCOR, University of Antwerp, Antwerp, Belgium; [16]AZ Sint-Lucas, Ghent, Belgium; [17]AZ Turnhout, Turnhout, Belgium; [18]AZ Nikolaas, Sint-Niklaas, Belgium; [19]Cardiovascular Department, Cliniques Universitaires St Luc, Brussels, Belgium; [20]AZ Delta, Roeselare, Belgium; [21]CHU UCL Namur, Yvoir, Belgium; [22]Jessa Hospital, Hasselt, Belgium; [23]ZNA Hartcentrum, Antwerpen, Belgium; [24]AZ Glorieux, Ronse, Belgium; [25]Universitair Ziekenhuis Gent, Ghent, Belgium; [26]AZ Maria Middelares, Ghent, Belgium; [27]Jan Yperman Hospital, Ieper, Belgium; [28]Ziekenhuis Erasme, Brussels, Belgium; [29]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [30]University Hospitals Leuven, Leuven, Belgium; [31]CHR Citadelle Hospital, Liege, Belgium; [32]Helsinki University Central Hospital, Heart and Lung Center and Helsinki University Hospital, Helsinki, Finland; [33]Université de Paris Cité, Paris, France; [34]National and Kapodistrian University of Athens, Athens, Greece and [35]UniversitätsSpital Zürich, Zürich, Switzerland

Received 13 May 2022; revised 16 June 2022; accepted 19 June 2022; online publish-ahead-of-print 12 July 2022

Aims

To describe the baseline characteristics of participants in the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial and compare these with other contemporary diuretic trials in acute heart failure (AHF).

Methods and results

ADVOR recruited 519 patients with AHF, clinically evident volume overload, elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) and maintenance loop diuretic therapy prior to admission. All participants received standardized loop diuretics and were randomized towards once daily intravenous acetazolamide (500 mg) versus placebo, stratified according to study centre and left ventricular ejection fraction (LVEF) (≤40% vs. >40%). The primary endpoint was successful decongestion assessed by a dedicated score indicating no more than trace oedema and no other signs of congestion after three consecutive days of treatment without need for escalating treatment. Mean age was 78 years, 63% were men, mean LVEF was 43%, and median NT-proBNP 6173 pg/ml. The median clinical congestion score was 4 with an EuroQol-5 dimensions health utility index of 0.6. Patients with LVEF ≤40% were more often male, had more ischaemic heart disease, higher levels of NT-proBNP and less atrial fibrillation. Compared with diuretic trials in AHF, patients enrolled in ADVOR were considerably older with higher NT-proBNP levels, reflecting the real-world clinical situation.

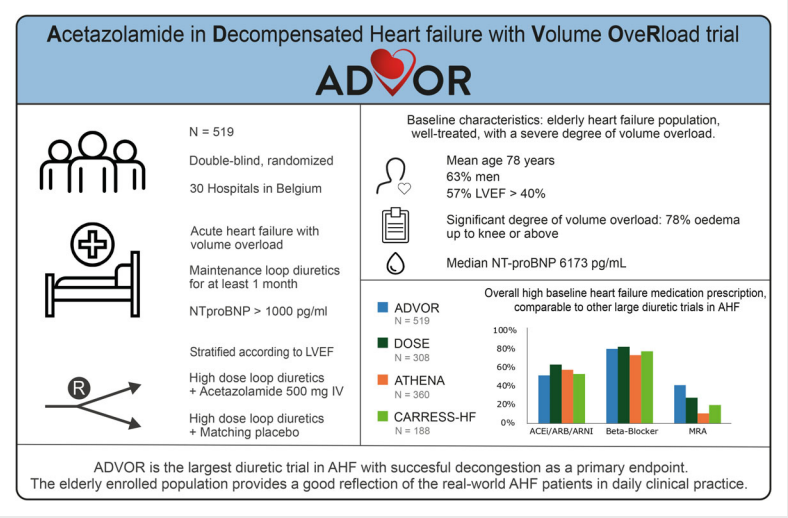
*Corresponding author. Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium. Tel: +32 89 327087, Fax: +32 89 327918, Email: wilfried.mullens@zol.be

© 2022 European Society of Cardiology

18790844, 2022, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2587 by University Of Groningen, Wiley Online Library on [07/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusion ADVOR is the largest randomized diuretic trial in AHF, investigating acetazolamide to improve decongestion on top of standardized loop diuretics. The elderly enrolled population with poor quality of life provides a good representation of the real-world AHF population. The pragmatic design will provide novel insights in the diuretic treatment of patients with AHF.

Graphical Abstract



Baseline characteristics of ADVOR trial participants. ACEi, angiotensin-converting enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin receptor blocker; IV, intravenous; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Keywords Acute heart failure • Diuretics • Randomized controlled trial • Acetazolamide • Congestion • Volume overload

Introduction

A high proportion of heart failure (HF) patients experience an episode of acute HF (AHF) during their disease course, often characterized by signs and symptoms of congestion. These episodes are associated with increased morbidity and mortality and are accompanied with a high burden on healthcare-related costs.[1] Current guidelines recommend the use of intravenous loop diuretics to improve symptoms, as a first-line treatment option for all patients with AHF and volume overload, independent of left ventricular ejection fraction (LVEF).[2] Although a recent consensus document on the use of diuretics supports a combinational diuretic therapy as a potential strategy to offset diuretic resistance with accompanying persistent congestion,[2,3] many patients are discharged with residual clinical congestion, which is a strong predictor of poor outcome.[4] In the Diuretic Optimization Strategies Evaluation (DOSE) study, only 15% of the patients were free from clinical congestion after 72 h of treatment.[5] In the Acute Decompensated Heart Failure National Registry (ADHERE), approximately 20% of the patients were discharged with an increase in body weight.[6]

Acetazolamide inhibits sodium reabsorption in the proximal tubules of the nephron and may boost diuretic efficacy when added to loop diuretics thereby facilitating decongestion.[7] Both an observational as well as a prospective randomized study demonstrated that the addition of acetazolamide (500 mg intravenous) to loop diuretics in patients with AHF enhanced urinary sodium excretion with approximately 40–100 mmol sodium per 40 mg furosemide or equivalents.[8,9] In addition, through a ceasing effect on neurohumoral activation, proximal diuretics might effectively reduce plasma volume.[10–12] The Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial investigates whether the addition of acetazolamide on top of standardized (twice home dose) loop diuretics improves decongestion in patients with AHF and clinical signs of volume overload. In this article, we describe the baseline characteristics of patients enrolled in the ADVOR trial and compare them with other contemporary diuretic trials in AHF.

© 2022 European Society of Cardiology

18790844, 2022, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2587 by University Of Groningen, Wiley Online Library on [07/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods

Study design

ADVOR is a pragmatic multicentre, randomized, double-blind, placebo-controlled trial, evaluating the addition of acetazolamide on top of standardized (twice home dose) intravenous loop diuretic therapy in patients with AHF.[7] Adults with an elective or emergency hospital admission due to AHF were eligible for enrolment if they had an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) >1000 pg/ml or B-type natriuretic peptide (BNP) level >250 ng/ml, had at least one clinical sign of volume overload (ascites, pleural effusion, or oedema) and were on maintenance therapy with at least 40 mg furosemide or equivalents for at least 1 month (conversion factor 20 mg torsemide = 40 mg furosemide = 1 mg bumetanide).[7] Patients were excluded if they were on acetazolamide maintenance therapy or another proximal nephron acting agent such as a sodium–glucose cotransporter 2 inhibitor, had a systolic blood pressure <90 mmHg or an estimated glomerular filtration rate <20 ml/min/1.73 m^2. Patients were randomized in a 1:1 fashion to loop diuretics in combination with either an intravenous bolus of acetazolamide 500 mg once daily or matching placebo for three consecutive days. Intravenous loop diuretic administration was protocolized as twice the oral home dose, given as a single bolus on the first day and split in two doses on the next two consecutive days. An automated web-based system was used to randomize patients stratified by LVEF (≤40% or >40%) and study centre. The primary endpoint of the ADVOR trial was defined as the rate of successful decongestion on the third morning after randomization (i.e. day 4) without the need for escalating decongestive therapies for poor loop diuretic efficacy on the morning of day 3. The study was done in accordance with the Declaration of Helsinki and approved by the institutional review board and ethics committees at individual study sites. All patients needed to sign written informed consent prior to inclusion. The details of the study design have been published and the trial is registered at ClinicalTrials.gov (Identifier: NCT03505788).[7]

Clinical congestion score and successful decongestion

The trained investigator had to assess all signs of volume overload and to complete a clinical congestion score every day (*Figure 1*). This clinical congestion score was based upon the presence or absence and severity of oedema, pleural effusion (to be confirmed by chest X-ray or ultrasound) and ascites (to be confirmed by ultrasound). Any patient with a clinical congestion score of ≥2, which meant more than trace oedema or the presence of residual pleural effusion or ascites, was considered volume overloaded and diuretic therapy needed to be continued. If the total cumulative urinary output from baseline to the morning of day 3 was less than 3.5 L and persistent clinical congestion was present (congestion score ≥2), escalation of decongestive treatment was mandatory. Successful decongestion

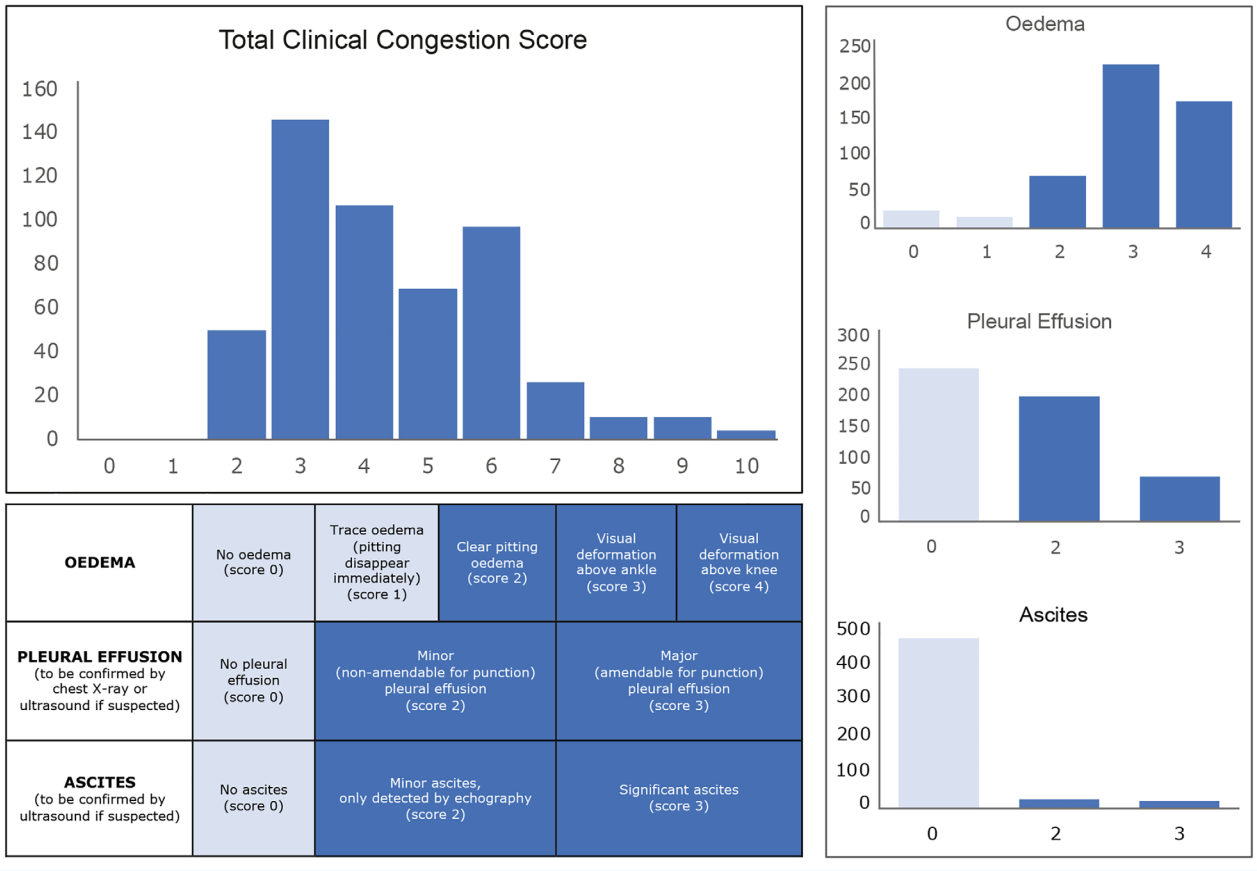


Figure 1 Clinical congestion score.

© 2022 European Society of Cardiology

18790844, 2022, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2587 by University Of Groningen, Wiley Online Library on [07/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

was defined as a congestion score ≤1 on the third morning after randomization, without need for escalating treatment because of poor loop diuretic efficacy.[7]

Quality of life

ADVOR also collected EuroQol-5 dimensions (EQ-5D) questionnaires, which is a self-assessed, health-related, quality-of-life questionnaire. The EQ-5D measures quality of life on a five-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D health utility index ranges from −0.532 (worst health state) to 1 (most optimal health state).[13] EuroQol-Visual Analogue Scale (EQ-VAS) records the patients' self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' (score 100) and 'The worst health you can imagine' (score 0).

Comparison with other acute heart failure trials

The baseline characteristics of the ADVOR trial were compared with the other large randomized diuretic trials enrolling patients with AHF, including DOSE, ATHENA-HF (Aldosterone Targeted Neurohormonal Combined with Natriuresis therapy in Heart Failure), and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure).[5,14,15]

Statistical analysis

ADVOR randomized 519 patients. Sample size was calculated based on the results of the DOSE trial, estimating an occurrence of 15% of the primary endpoint in the control group. No reliable data were available for the acetazolamide arm, but a clear meaningful benefit of 10% more congestion was chosen. Considering a type I error rate $\alpha = 0.05$ and a type II error rate $\beta = 0.20$, the target sample size was calculated at 494. A 5% drop-out rate was anticipated, which brings the total sample size to 519. To describe the baseline characteristics, numbers (%) or means ± standard deviation and medians (25th–75th percentile) are given as appropriate. All statistical analyses were done with Statistical Analysis System (SAS) software for Windows, Version 9.4, Copyright ©2016.

Results

Between 11 November 2018 and 17 January 2022, patients were screened for inclusion in 30 sites in Belgium. The first consecutive 519 patients who met in- and exclusion criteria and provided written informed consent were randomized towards acetazolamide or matched placebo.

Baseline characteristics

The ADVOR trial included an elderly population with a mean age of 78 ± 9 years. Most patients were male (63%) with mean LVEF of 43 ± 15%. The aetiology was ischaemic in 45%. Most patients had New York Heart Association functional class III or IV symptoms (87%). Cardiovascular comorbidities were very prevalent. Importantly, the median baseline estimated glomerular filtration rate (eGFR) was 39 ml/min/1.73 m^2 (29–52 ml/min/1.73 m^2) and 82% had stage 3 chronic kidney disease or worse (eGFR <60 ml/min/1.73 m^2). A cardiac resynchronization therapy and/or implantable cardioverter-defibrillator device was previously implanted in 19% of all patients and in 36% of the patients with HF with reduced ejection fraction (HFrEF). The mean heart rate was 78 ± 18 bpm, the mean systolic blood pressure 127 ± 21 mmHg and mean diastolic blood pressure 72 ± 13 mmHg. Patients had significant congestion with median NT-proBNP of 6173 (3068–10 896) pg/ml and a clinical congestion score of 4 (3–6), which was independent of LVEF (*Table 1* and online supplementary *Figure 1*). Oedema was the most important sign of volume overload, with 78% of the patients exhibiting oedema up to the knee or above (score ≥3), and 53% had pleural effusion with only 9% having ascites (*Figure 1*). The degree of oedema, pleural effusion and ascites at presentation with AHF did not differ between patients with an LVEF ≤40% or >40% (online supplementary *Figure 1*). At baseline, a urinary catheter was used in 51% of the patients.

Table 1 describes the baseline characteristics after stratification for LVEF ≤40% or >40% (strata used in randomization). Patients with an ejection fraction ≤40% were younger, more frequently male, were less likely to have atrial fibrillation or flutter and had more frequently an ischaemic aetiology. The NT-proBNP was clearly higher in patients with a reduced ejection fraction (9137 [5108–18 714] vs. 4393 [2414–8124] pg/ml), yet clinical congestion scores were similar (*Table 1*).

Maintenance therapy of enrolled patients is described in *Table 2*. As required for inclusion, all patients were treated with loop diuretics at home, with the majority receiving bumetanide (84%). The median dose of maintenance therapy was 60 mg furosemide or equivalents. Most patients (81%) were treated with beta-blockers. Despite the high frailty and degree of chronic kidney disease, 52% were taking an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB) or sacubitril/valsartan and 42% were prescribed a mineralocorticoid receptor antagonist (MRA). In line with the current guidelines for HF, the prescription of neurohormonal inhibitors (ACEi/ARB/ARNI), MRA and beta-blockers was higher in patients with a lower ejection fraction (online supplementary *Figure S2*).

Overall, the median EQ-5D health utility index was 0.6. Activities of daily living and mobility were mostly impaired and fewer self-reported impairments were noted with regard to anxiety/depression (*Figure 2*). Patients in the ADVOR trial reported a mean health score of 52 (40–65) out of 100 on the VAS.

Comparison with other acute heart failure trials

ADVOR is the largest randomized diuretic trial performed in patients with AHF. Similar to ADVOR, all the other large diuretic trials included patients across the full range of LVEF. The primary endpoint of ADVOR is focused on effective decongestion, assessed by trained HF physicians who were blinded for treatment allocation and confirmed with technical exam (in case of pleural effusion/ascites). In contrast, the primary endpoints of DOSE,

© 2022 European Society of Cardiology

18790844, 2022, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2587 by University Of Groningen, Wiley Online Library on [07/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1 Baseline characteristics

	Overall (n = 519)	EF ≤40% (n = 225)	EF >40% (n = 294)
Age (years)	78.2 ± 8.9	76.2 ± 9.5	79.8 ± 8.1
Male sex	325 (63%)	176 (78%)	149 (51%)
LVEF (%)	43 ± 15	29 ± 8	54 ± 8
Ischaemic aetiology	232 (45%)	136 (60%)	96 (33%)
Comorbidities			
Previous CABG	123 (24%)	66 (29%)	57 (19%)
Previous valve surgery	91 (18%)	36 (16%)	55 (19%)
Previous PTCA	125 (24%)	82 (36%)	43 (15%)
History of atrial fibrillation or flutter	376 (72%)	145 (64%)	231 (79%)
Stroke	62 (12%)	29 (13%)	33 (11%)
Diabetes	245 (47%)	110 (49%)	135 (46%)
Hypertension	389 (75%)	157 (70%)	232 (79%)
Peripheral arterial disease	101 (19%)	48 (21%)	53 (18%)
Current smoker	48 (9%)	29 (13%)	19 (6%)
COPD	101 (19%)	42 (19%)	59 (20%)
Malignancy	58 (11%)	24 (11%)	34 (12%)
NYHA class			
II	66 (13%)	34 (15%)	32 (11%)
III	296 (57%)	127 (57%)	169 (57%)
IV	157 (30%)	64 (28%)	93 (32%)
ICD	79 (15%)	70 (31%)	9 (3%)
CRT	61 (12%)	46 (20%)	15 (5%)
Weight (kg)	84.8 ± 21.4	85.0 ± 20.2	84.7 ± 22.4
Heart rate (bpm)	78 ± 18	77 ± 17	79 ± 19
Systolic blood pressure (mmHg)	127 ± 21	123 ± 19	130 ± 22
Clinical congestion score	4 (3–6)	4 (3–6)	4 (3–6)
Serum haemoglobin (g/dl)	11.9 ± 2.0	12.4 ± 1.9	11.5 ± 1.9
Haematocrit (%)	36.6 ± 5.9	38.2 ± 5.7	35.4 ± 5.7
Sodium (mmol/L)	139 ± 4	140 ± 4	139 ± 5
Potassium (mmol/L)	4.2 ± 0.6	4.3 ± 0.6	4.2 ± 0.6
Chloride (mmol/L)	100.6 ± 5.3	101.3 ± 4.8	100.0 ± 5.7
Bicarbonate (mmol/L)	26.3 ± 4.1	25.6 ± 3.9	26.8 ± 4.1
Serum urea (mg/dl)	72 (52–100)	80 (59–109)	65 (49–90)
Serum creatinine (mg/dl)	1.5 (1.2–1.9)	1.7 (1.3–2.1)	1.4 (1.1–1.7)
eGFR (ml/min/1.73 m^2)	39 (29–52)	36 (27–50)	42 (31–53)
eGFR <60 ml/min/1.73 m^2	424 (82%)	184 (82%)	240 (82%)
Ferritin (μg/dl)	115 (63–235)	126 (69–275)	101 (60–200)
Troponin (ng/L)	40 (25–63)	46 (31–72)	37 (22–59)
NT-proBNP (pg/ml)	6173 (3068–10 896)	9137.0 (5108–18 714)	4393 (2414–8124)

Values are mean ± standard deviation, or median (25th–75th percentile), unless otherwise indicated.
CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angioplasty.

ATHENA-HF and CARRESS-HF were more secondary derivatives of the elimination of residual congestion (change in NT-proBNP, change in weight or VAS of wellbeing) (online supplementary *Table S1*).

Patients enrolled in ADVOR were older than those in DOSE, ATHENA-HF and CARRESS-HF (*Table 3*). Most participants were male in all four trials. The ejection fraction was slightly higher in ADVOR with a lower rate of ischaemic HF compared to the others. Comorbidities were equally common with a higher history of atrial fibrillation/flutter in ADVOR. Only ADVOR and DOSE required maintenance therapy with loop diuretics for at least 1 month prior to enrolment. However, the rate of maintenance therapy with loop diuretics in patients enrolled in ATHENA-HF and CARRESS-HF was also very high (96% and 94%, respectively). In ADVOR 52% and 81% of the patients received an ACEi/ARB/ARNI and a beta-blocker, respectively, which is similar to the ACEi/ARB and beta-blocker use in the other trials. The prescription of MRA was higher in ADVOR (42%) than in DOSE and CARRESS-HF (28% and 20%, respectively) and obviously higher than ATHENA-HF (11%) as a result of the study design (*Figure 3*).

© 2022 European Society of Cardiology

18790844, 2022, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2587 by University Of Groningen, Wiley Online Library on [07/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2 Maintenance therapy

	Overall (n = 519)	EF ≤40% (n = 225)	EF >40% (n = 294)
Maintenance dose–furosemide equivalents (mg)[a]	60 (40–100)	70 (40–100)	60 (40–120)
Thiazides	34 (7%)	14 (6%)	20 (7%)
ACEi/ARB/ARNI	270 (52%)	137 (61%)	133 (45%)
ACEi	141 (27%)	57 (25%)	84 (29%)
ARB	53 (10%)	12 (5%)	41 (14%)
ARNI	76 (15%)	68 (30%)	8 (3%)
Beta-blocker	419 (81%)	194 (86%)	225 (77%)
MRA	216 (42%)	112 (50%)	104 (35%)
Ivabradine	10 (2%)	9 (4%)	1 (0.3%)
Hydralazine	9 (2%)	6 (3%)	3 (1%)
Nitrates	28 (5%)	11 (5%)	17 (6%)
Digoxin	34 (7%)	12 (5%)	22 (7%)
Antiplatelets	182 (35%)	91 (40%)	91 (31%)
Anticoagulation	337 (65%)	135 (60%)	202 (69%)
Statin	328 (63%)	155 (69%)	173 (59%)
Amiodarone	119 (23%)	60 (27%)	59 (20%)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; EF, ejection fraction; MRA, mineralocorticoid receptor antagonist.
[a]Median (25th–75th percentile).

Median NT-proBNP levels in ADVOR were considerably higher than in DOSE, ATHENA-HF and CARRESS-HF (*Table 3*). Overall, renal function assessed by serum creatinine did not differ between patients enrolled in ADVOR, DOSE and ATHENA-HF, but renal function in CARRESS-HF was worse.

Discussion

ADVOR is to date the largest randomized diuretic trial performed in patients with AHF. The pragmatic set-up of the ADVOR trial enabled an enrolment of patients representing daily clinical practice, which is evident by the high degree of congestion, the advanced age and frequent comorbidities, as well as the expected distribution of patients according to LVEF. Compared to other randomized diuretic trials, ADVOR enrolled a more elderly population with significant congestion as evidenced by high NT-proBNP levels (6173 pg/ml) and congestion score, which corresponds to the patient profile observed in clinical practice. Signs and symptoms of congestion could not distinguish patients with reduced and preserved ejection fraction (online supplementary *Figure S1*). ADVOR is designed to determine if the addition of acetazolamide, a proximal working diuretic agent, on top of standardized (twice home dose) loop diuretics will lead to more effective and efficient decongestion in those patients. Importantly, achieving decongestion has a class I recommendation of the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF.[2] As such, the results of ADVOR are extremely important because registry and clinical trial data report that only a minority of AHF patients are discharged without residual congestion.[5,6]

Compared to other diuretic trials, patients in ADVOR had higher levels of NT-proBNP.[14,15] Moreover, all patients had unequivocal clinical signs of severe volume overload, reflected in the clinical congestion score (78% of patients had >grade 2 oedema and 53% had pleural effusion) and the overall very high levels of NT-proBNP. The average age of 78 years is clearly older than the patients enrolled in DOSE, ATHENA-HF and CARRESS-HF, where the mean age was around 65 years and even older than in large AHF registries.[6,16–21] The most recent large registries, i.e. the ESC Heart Failure Long-Term Registry[20] and the GREAT registry,[21] had both a median age of 71 years. However, clinical trials and registries, mainly done in cardiology wards, do not always represent the real-world population encountered in daily clinical practice.[22] Patients in a recent cohort study in the Belgian primary care setting[23] and a large population-based study in the United Kingdom,[24] representing a less selected population, had a comparable age as the ADVOR trial. This was confirmed in the Swedish Heart Failure Registry[25] and in a retrospective observational study in the United States in which the mean age was approximately 77 years for patients with stable chronic HF and 78 years for patients with a worsening HF event.[26] A prospective observational trial, conducted in 4041 patients admitted with AHF in Japan without any exclusion criteria, demonstrated an even higher median age of 80 years.[27] Therefore, patients in ADVOR are very similar as those seen in real-world clinical practice. This makes ADVOR the largest and first diuretic trial in AHF for which the results will be more representative for the global HF population including all age categories.

While the presence of comorbidities was similar between all diuretic trials, the study design of CARRESS-HF required worsening renal function as inclusion criteria, which subsequently explains the worse kidney function observed in CARRESS-HF. However, 82% of patients included in ADVOR had chronic kidney disease defined as an eGFR <60 ml/min/1.73 m^2. The prognostic impact of any reduction in eGFR is well-established in HF and therefore

© 2022 European Society of Cardiology

18790844, 2022, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2587 by University Of Groningen, Wiley Online Library on [07/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

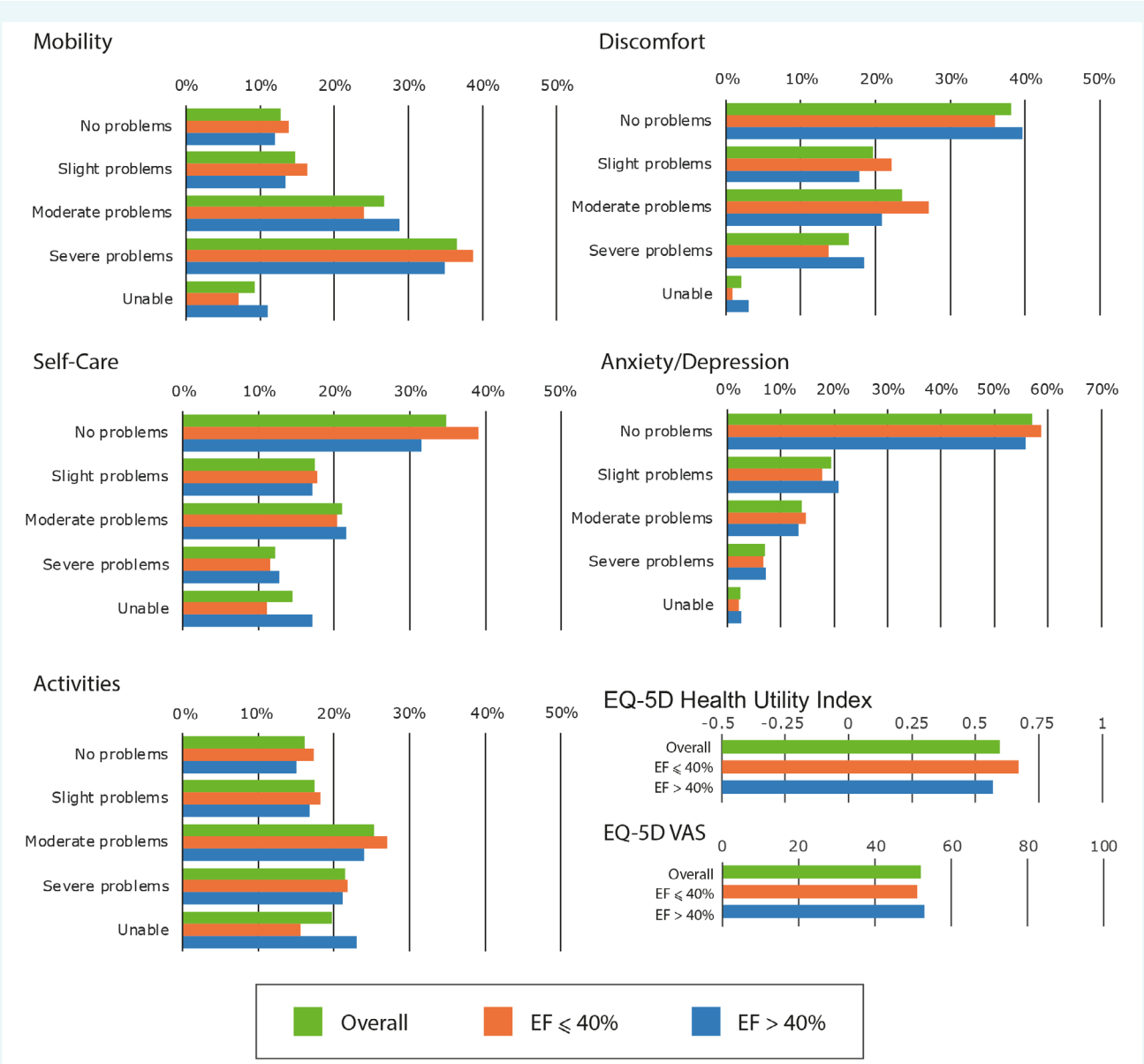


Figure 2 EuroQol-5 dimensions (EQ-5D) quality of life according to different domains. EF, ejection fraction; VAS, visual analogue scale.

the population included in ADVOR is at very high risk for adverse events.[28–30]

Additionally, on top of length of hospital stay, HF hospitalization and all-cause mortality, ADVOR will also report on a self-reported quality-of-life score as secondary endpoint. A consensus paper of the ESC emphasizes the importance of gaining insight into the patients' experience and perspective.[31] This is even more important in an elderly patient population with many comorbidities in which quality of life might be as important as longevity. Moreover, an inverse association between the self-assessed quality-of-life score and all-cause mortality and HF hospitalizations has been reported.[32] The EQ-5D of patients in the ADVOR trial was considerably lower than the average EQ-5D for the Belgian population.[13] As expected in patients with a high congestion score and in an elderly population, patients enrolled in ADVOR reported mostly problems with mobility and daily activities. However, the majority denied any moderate or major problems with self-care or anxiety/depression. In the ADVOR trial, the self-reported VAS scored a mean of only 52 out of 100, which was comparable between patients with an ejection fraction ≤40% and >40% but clearly lower than the average for the Belgian population of 77.1.[13]

Randomization towards acetazolamide or matched placebo was stratified based on ejection fraction ≤40% and >40%, which enables an equally representation of both groups in the intervention and placebo group. Overall, baseline clinical characteristics were similar between the two pre-specified groups of ejection fraction in ADVOR with the exception of a higher level of NT-proBNP and less history of atrial fibrillation or flutter in the

© 2022 European Society of Cardiology

18790844, 2022, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2587 by University Of Groningen, Wiley Online Library on [07/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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 AFl	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)

Values are mean ± standard deviation, or median (25th–75th percentile), unless otherwise indicated.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AF, atrial fibrillation; AFl, atrial flutter; ARNI, angiotensin receptor–neprilysin inhibitor; AUC, area under the curve; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter-defibrillator; IV, intravenous; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VAS, visual analogue scale.

LVEF ≤40% group, which is reflected in the slightly lower prescription of direct oral anticoagulants. This difference in natriuretic peptides between patients with HFrEF and HF with preserved ejection fraction (HFpEF) has been described in both AHF and chronic HF.[33–35] In patients with HFrEF, eccentric remodelling is associated with a higher increase in wall stress compared to concentric remodelling in patients with HFpEF. As the release of natriuretic peptides depends on the degree of wall stress, this will be higher in patients with HFrEF than with HFpEF.[36] As the clinical congestion score was similar between groups, the difference in NT-proBNP in our cohort probably reflects different pathophysiological processes rather than a difference in clinical volume overload.

A particularly important consideration in any HF trial is the adequacy of background treatment. Overall, there was a high prescription of medical HF therapy in ADVOR, in line with current HF guidelines with a higher degree in the group with the lower ejection fraction. The prescription of ACEi/ARB is lower in ADVOR than in other diuretic trials, but comparable when adjusted for ARNI use. The use of beta-blocker was comparable to DOSE, ATHENA-HF and CARRESS-HF, however the use of MRA was obviously higher. ADVOR represents a vulnerable patient population that despite baseline medical therapy is still at a very high risk for decompensation. ADVOR allowed a broad inclusion for all AHF patients with signs of volume overload and maintenance therapy with at least 40 mg furosemide or equivalents for at least 1 month.

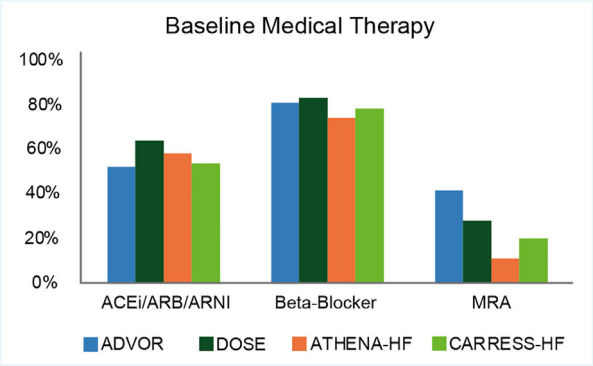


Figure 3 Baseline prescription of guideline-directed medical therapy in ADVOR and other diuretic trials. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

© 2022 European Society of Cardiology

18790844, 2022, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2587 by University Of Groningen, Wiley Online Library on [07/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusion

ADVOR is a multicentre, double-blind, placebo-controlled randomized trial and is the largest diuretic trial in AHF performed to date. The higher age of the study population is more reflective of a real-world HF population than previous diuretic trials in AHF. Furthermore, despite adequate maintenance therapy, patients were severely congested, with pronounced clinical signs of volume overload and elevated levels of natriuretic peptides. As such, the results of ADVOR will provide contemporary and novel insights in the diuretic treatment of patients with AHF and fluid overload.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

Belgian Health Care Knowledge Centre as independent reviewer of the study protocol.

Funding

This study (KCE-17001) is an independent research funded by Belgian Health Care Knowledge Centre under the KCE Trials Programme. The views expressed in this publication are those of the author and not necessarily those of Belgian Health Care Knowledge Centre.

Conflict of interest: none declared.

References

1. Arrigo M, Jessup M, Mullens W, Reza N, Shah AM, Sliwa K, et al. Acute heart failure. *Nat Rev Dis Primers*. 2020;**6**:16.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;**24**:4–131.
3. Mullens W, Damman K, Harjola V, Mebazaa A, Rocca HB, Martens P, et al. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;**21**:137–55.
4. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail*. 2012;**5**:54–62.
5. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al.; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;**364**:797–805.
6. Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2005;**149**:209–16.
7. Mullens W, Verbrugge FH, Nijst P, Martens P, Tartaglia K, Theunissen E, et al. Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial. *Eur J Heart Fail*. 2018;**20**:1591–600.
8. Verbrugge FH, Dupont M, Bertrand PB, Nijst P, Penders J, Dens J, et al. Determinants and impact of the natriuretic response to diuretic therapy in heart failure with reduced ejection fraction and volume overload. *Acta Cardiol*. 2015;**70**:265–73.
9. Verbrugge FH, Martens P, Ameloot K, Haemels V, Penders J, Dupont M, et al. Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance. *Eur J Heart Fail*. 2019;**21**:1415–22.
10. Griffin M, Rao VS, Ivey-Miranda J, Fleming J, Mahoney D, Maulion C, et al. Empagliflozin in heart failure: diuretic and cardio-renal effects. *Circulation*. 2020;**142**:1028–39.
11. Heerspink HJL, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab*. 2013;**15**:853–62.
12. Verbrugge FH, Dupont M, Steels P, Grieten L, Swennen Q, Tang WHW, et al. The kidney in congestive heart failure: 'are natriuresis, sodium and diuretics really the good, the bad and the ugly?'. *Eur J Heart Fail*. 2014;**16**:133–42.
13. Van Wilder L, Charafeddine R, Beutels P, Bruyndonckx R, Cleemput I, Demarest S, et al. Belgian population norms for the EQ-5D-5L, 2018. *Qual Life Res*. 2022;**31**:527–37.
14. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, et al.; National Heart Lung and Blood Institute Heart Failure Clinical Research Network. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. *JAMA Cardiol*. 2017;**2**:950–8.
15. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, et al.; Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;**367**:2296–304.
16. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail*. 2017;**19**:1624–34.
17. Mebazaa A, Parissis J, Porcher R, Gayat E, Nikolaou M, Boas FV, et al. Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. *Intensive Care Med*. 2011;**37**:290–301.
18. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al.; OPTIMIZE-HF Investigators and Hospitals. Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). *Am J Cardiol*. 2009;**104**:107–15.
19. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al.; EuroHeart Survey Investigators; Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J*. 2006;**27**:2725–36.
20. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al.; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail*. 2016;**18**:613–25.
21. Arrigo M, Gayat E, Parenica J, Ishihara S, Zhang J, Choi DJ, et al.; GREAT Network. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail*. 2017;**19**:201–8.
22. Niederseer D, Thaler CW, Niederseer M, Niebauer J. Mismatch between heart failure patients in clinical trials and the real world. *Int J Cardiol*. 2013;**168**:1859–65.
23. Smeets M, Vaes B, Mamouris P, Van Den Akker M, Van Pottelbergh G, Goderis G, et al. Burden of heart failure in Flemish general practices: a registry-based study in the Intego database. *BMJ Open*. 2019;**9**:1–9.
24. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet*. 2018;**391**:572–80.
25. Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson Å, Jernberg T, et al. Association between enrolment in a heart failure quality registry and subsequent mortality – a nationwide cohort study. *Eur J Heart Fail*. 2017;**19**:1107–16.
26. Mentz RJ, Pulungan Z, Kim S, Yang M, Teigland C, Hilkert R, et al. Quality outcomes, healthcare resource utilization and costs in Medicare patients with chronic heart failure with reduced ejection fraction with and without a worsening event. *J Med Econ*. 2021;**24**:698–705.
27. Yaku H, Ozasa N, Morimoto T, Inuzuka Y, Tamaki Y, Yamamoto E, et al.; KCHF Study Investigators. Demographics, management, and in-hospital outcome of hospitalized acute heart failure syndrome patients in contemporary real clinical practice in Japan: observations from the prospective, multicenter Kyoto Congestive Heart Failure (KCHF) registry. *Circ J*. 2018;**82**:2811–9.
28. Damman K, Valente MAE, Voors AA, O'Connor CM, Van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014;**35**:455–69.
29. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2000;**35**:681–9.
30. Givertz MM, Postmus D, Hillege HL, Mansoor GA, Massie BM, Davison BA, et al. Renal function trajectories and clinical outcomes in acute heart failure. *Circ Heart Fail*. 2014;**7**:59–67.

© 2022 European Society of Cardiology

18790844, 2022, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2587 by University Of Groningen, Wiley Online Library on [07/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

31. Zannad F, Stein K, Garcia AA, Anker SD, Armstrong PW, Calvo G, et al. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. *Eur J Heart Fail*. 2013;**15**: 1082–94.
32. Johansson I, Joseph P, Balasubramanian K, McMurray JJV, Lund LH, Ezekowitz JA, et al. Health-related quality of life and mortality in heart failure: the global congestive heart failure study of 23 000 patients from 40 countries. *Circulation*. 2021;**143**:2129–42.
33. Van Veldhuisen DJ, Linssen GCM, Jaarsma T, Van Gilst WH, Hoes AW, Tijssen JGP, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. *J Am Coll Cardiol*. 2013;**61**: 1498–506.
34. Sanders-Van Wijk S, Van Empel V, Davarzani N, Maeder MT, Handschin R, Pfisterer ME, et al. Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. *Eur J Heart Fail*. 2015;**17**:1006–14.
35. Maeder MT, Rickenbacher P, Rickli H, Abbühl H, Gutmann M, Erne P, et al.; TIME-CHF Investigators. N-terminal pro brain natriuretic peptide-guided management in patients with heart failure and preserved ejection fraction: findings from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). *Eur J Heart Fail*. 2013;**15**:1148–56.
36. Maeder MT, Mariani JA, Kaye DM. Hemodynamic determinants of myocardial B-type natriuretic peptide release: relative contributions of systolic and diastolic wall stress. *Hypertension*. 2010;**56**:682–9.

© 2022 European Society of Cardiology

18790844, 2022, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2587 by University Of Groningen, Wiley Online Library on [07/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License