

Medication adherence in patients with acutely decompensated heart failure: A cross-sectional study in the emergency department (ADHF-ED)

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Aims

Non-adherence to guideline-directed medical therapy may worsen outcomes in chronic heart failure (CHF). Objectively assessed adherence in patients presenting with acutely decompensated heart failure (ADHF) remains largely unexplored. This study evaluated adherence to medication in patients with ADHF presenting in the emergency department.

Methods and results

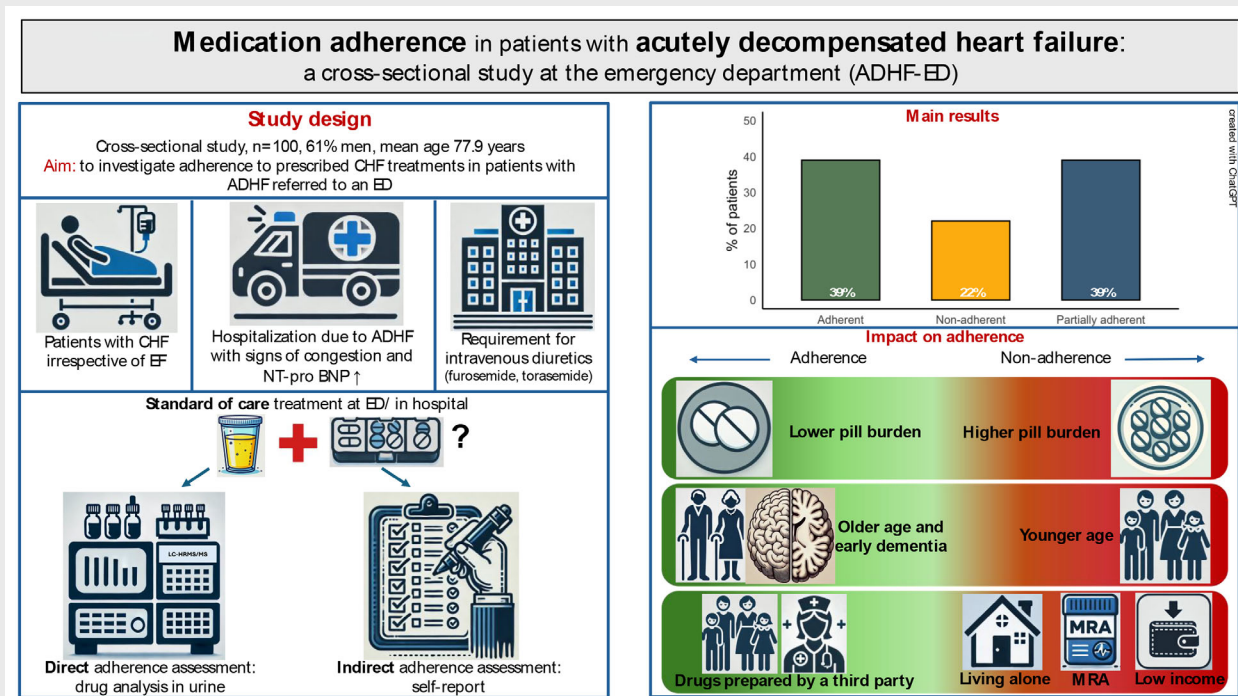
This cross-sectional study assessed medication adherence using both indirect (self-reported) and direct methods (qualitative toxicological analysis in urine). A total of 100 patients were included of whom 61% were men, with a mean age of 77.9 ± 10.1 years, and a median N-terminal pro-B-type natriuretic peptide level of 4846 pg/ml. In 39% of patients, all prescribed CHF medications were detected in urine, indicating full adherence. Partial adherence was observed in 39% of patients with one prescribed CHF medication not detected. Non-adherence, defined as the absence of ≥ 2 prescribed drugs, was observed in 22% of patients. Non-adherent patients had a significantly higher number of CHF medications prescribed compared with partially adherent ($p = 0.0047$) and adherent ($p = 0.0002$) patients and had a significantly higher pill burden than adherent patients ($p = 0.002$). Non-adherent patients were younger than partially adherent ($p = 0.0144$) and adherent ($p = 0.0054$) patients. Adherent patients were significantly more likely to have an abnormal DemTect cognitive screening test result ($p = 0.049$). Medication prepared by a third party, such as caregiver or pharmacist, reduced the likelihood of both non- and partial adherence. Self-reported adherence monitoring was found to be inaccurate.

Conclusions

Adherence to CHF medication in patients presenting with ADHF was low. Non-adherence represents a significant contributor to worsening CHF, potentially leading to ADHF hospitalization. Further research is needed to develop feasible and validated tools for assessing medication adherence in CHF and ADHF, using toxicological testing as reference standard.

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Graphical Abstract



The ADHF-ED trial. ADHF, acutely decompensated heart failure; CHF, chronic heart failure; ED, emergency department; EF, ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide. Created with the support of AI (ChatGPT).

Keywords

Heart failure hospitalization • Acutely decompensated heart failure • Adherence • Guideline-directed medical therapy • Toxicological analysis • Self-report

Introduction

Despite significant advancements in pharmacotherapy, chronic heart failure (CHF) remains a major health burden, with more than 50% of patients dying within 5 years after initial diagnosis.^{1,2} However, patients with CHF experience frequent hospitalizations for acutely decompensated heart failure (ADHF), often requiring intravenous diuretics at least once a year.³ Among older patients, ADHF is one of the most common reasons for emergency department (ED) visits⁴ and is associated with high rehospitalization rates and an in-hospital mortality rate of approximately 10%.⁵ Non-adherence and non-persistence to prescribed medications are common and challenge the management of patients with chronic diseases, especially those with polypharmacy – often defined as the use of ≥ 5 chronic medications.⁶ Adherence to medication is influenced by multiple factors, including patient characteristics, complexity of the treatment regimen, healthcare system barriers, and socioeconomic constraints.⁶ Previous studies assessing adherence to CHF medication have largely relied on indirect methods, such as self-reports or claims data⁷ with reported

non-adherence rates varying between 18% and 82%, depending on the medication class and duration of follow-up.^{8–15} However, adherence rates tend to decline over time.^{8,9} While a few studies have utilized direct measurements of drug or metabolite levels in body fluids^{13–15}, which is considered the gold standard for adherence assessment, most research has relied on indirect methods.^{8,9,11,12} Self-reported adherence is prone to overestimation of adherence¹⁶ and may not accurately reflect actual medication use.

This study aimed to (i) measure adherence to CHF medications in patients with ADHF admitted to the ED, (ii) identify patient-related risk factors for non-adherence, and (iii) assess the impact of adherence on in-hospital mortality (*Graphical Abstract*).

Methods

Between January 2023 and May 2024, patients presenting to the ED at Saarland University Medical Center (Homburg, Germany) with ADHF fulfilling the following criteria were included in the study “medication Adherence in patients with acutely Decompensated Heart Failure: a cross-sectional study at the Emergency Department (ADHF-ED Trial)”.

The main inclusion criteria were age ≥ 18 years, a diagnosis of CHF independent of left ventricular ejection fraction (LVEF) with stable CHF medication > 2 weeks, worsening of CHF (=acute on chronic heart failure), ≥ 1 clinical sign of congestion (peripheral oedema, pulmonary congestion on chest radiography, ascites, pleural effusions), N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 300 pg/ml, and the requirement of intravenous diuretics. Patients who were unable to provide informed consent and pregnant women were excluded. The study was approved by the local ethics committee, and all participants provided written informed consent. The trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT06459115) (NCT06459115).

Clinical assessment

All invasive examinations were performed as part of the standard clinical work-up for patients with ADHF. Data collection included medical history, best possible medication history (BPMH), educational background and social environment, physical examination, routine blood chemistry with NT-proBNP, echocardiography, chest radiography, electrocardiogram, and vital signs. The BPMH was established as the most accurate and comprehensive list of all prescribed medications a patient was actively taking at the time of admission. The BPMH was obtained through a structured, multi-step process conducted at the ED (online supplementary [Figure S2](#)):

- 1 Patient interview: upon admission, patients were asked whether their provided medication list was accurate and whether they were taking the medications as listed.
- 2 Systematic medication verification: each prescribed medication was reviewed with the patient to confirm adherence and to identify any omissions, additions, or modifications to the regimen.
- 3 Physician confirmation: to further ensure accuracy, the patient's general practitioner was contacted during hospitalization to obtain the most up-to-date medication list, which was then cross-checked with the patient's self-reported information.

Validated questionnaires (Hospital Anxiety and Depression Scale-German version [HADS-D]; Rief Adherence Index [RAI]; ENRICH Social Support Instrument [ESSI]; Soziale Unterstützung bei chronischen Erkrankungen (Scale to assess Social Support in Chronic Diseases)-4 Items [SUCE-4]; Beliefs about Medicines Questionnaire [BMQ]) were completed by the patients to assess various psychosocial factors. These are questionnaires to screen for anxiety and depression (HADS-D),¹⁷ non-adherence (RAI),¹⁸ and lacking social support (ESSI, SUCE-4).^{19,20} The BMQ assesses patients' beliefs about their individual prescribed medication as well as their beliefs about medicines in general.²¹ The DemTect questionnaire (Demenz-Detektions-Test), to detect a mild cognitive impairment or beginning dementia, was conducted by a trained student with the patient.²²

Patients were asked detailed questions about their medication intake habits, including the timing of their most recent dose (as recorded in the BPMH), whether they were currently taking all prescribed medications and, if not, which specific drugs had been discontinued. Additionally, patients were asked who was responsible for preparing their medications and whether they had experienced any side effects. An estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² was defined as chronic kidney disease. Heart failure classification was based on current guideline definitions: heart failure with reduced ejection fraction (HFrEF) as an LVEF $\leq 40\%$,

heart failure with mildly reduced ejection fraction (HFmrEF) as an LVEF 41–49%, and heart failure with preserved ejection fraction (HFpEF) as an LVEF $\geq 50\%$ in combination with signs of diastolic dysfunction, including elevated NT-proBNP levels.² Patients were categorized according to the LVEF measured during echocardiography performed in the ED. Guideline-directed medical therapy (GDMT) for patients with HFpEF includes an angiotensin-converting enzyme inhibitor (ACE-I), or angiotensin receptor blocker (ARB), or angiotensin receptor–neprilysin inhibitor (ARNI), and a beta-blocker (BB), a mineralocorticoid receptor antagonist (MRA), a sodium–glucose co-transporter 2 inhibitor (SGLT2-I), and a diuretic.² For patients with heart failure with mildly reduced or preserved ejection fraction, GDMT consists of an SGLT2-I and a diuretic, respectively.²³

Sampling of plasma and urine and drug analysis

Venous ethylenediaminetetraacetic acid (EDTA) blood and spot urine samples were obtained immediately upon study inclusion and as soon as possible after admission to the ED. The samples were protected from light and transported to the Department of Experimental and Clinical Toxicology and Pharmacology at Saarland University (Homburg, Germany) for analyses. Adherence was assessed using qualitative measurement of drugs and their metabolites by liquid chromatography coupled with high-resolution mass spectrometry (LC-HRMS/MS). Human plasma (100 μ l) or urine (100 μ l) was prepared according to Helfer *et al.*²⁴ by precipitation with 200 μ l of acetonitrile (0.1% formic acid). After shaking and centrifugation (15 000 \times g, 30 min), the supernatant was transferred into an LC vial and injected onto the LC-HRMS/MS system. The detailed analytical procedures of the used LC-HRMS/MS have been described elsewhere.^{24,25} In summary, gradient reversed-phase elution was performed on a Thermo Fisher Scientific (TF) Accucore Phenyl-Hexyl column (100 \times 2.1 mm, 2.6 μ m). A TF Dionex UltiMate 3000 RS pump consisting of a degasser, a quaternary pump, and an Ultimate autosampler, coupled with a TF Q Exactive Focus equipped with a heated electrospray ionization (HESI)-II source was used. The analysis of SGLT2-I was done using a Nucleodor 300-5C18 EC column (100 \times 3 mm, 5 μ m) on a TF Vanquish Duo ultra high-performance liquid chromatography (UHPLC) system, which consisted of a degasser, a binary pump, and a dual split sampler. This setup was coupled to a TF Orbitrap Exploris 120 system equipped with a HESI-II source.²⁵ Detailed information is provided in online supplementary [Text S1](#).

Definition of adherence

Adherence classification was based on previously published criteria.²⁶ Patients were categorized as 'adherent' if all prescribed drugs/metabolites for the treatment of CHF were detectable in urine. If only one prescribed CHF medication was not detectable, the patient was classified as 'partially adherent'. If two or more prescribed drugs were not detectable, the patient was classified as 'non-adherent'. For patients with single-pill combinations (SPC), adherence was evaluated differently: if at least one component of the SPC was detectable in urine, adherence to all components of the SPC was assumed.

For the overall population, acceptable to good adherence to a substance class was defined as an adherence rate of $\geq 60\%$, while low adherence to a substance class was defined as $< 60\%$.

Statistical analyses

The data are presented as mean \pm standard deviation, median and interquartile range (IQR), and frequencies (%). Normal distribution was tested using the Shapiro–Wilk test and visual evaluation via histogram. The Kruskal–Wallis test was used for comparisons between adherent, partially adherent, and non-adherent patients. If the Kruskal–Wallis test showed significance, the Bonferroni post-hoc method was applied for pairwise comparisons. For categorical variables, comparisons between adherence groups were performed using Pearson's Chi-squared or Fisher's exact test, as appropriate. *P*-values were adjusted using the Bonferroni post-hoc method. Multimodal logistic regression analyses were performed, with adherence as the dependent variable, incorporating predefined factors potentially influencing adherence (education level, vocational training, employment status, income, marital status, living alone/social support, method of medication preparation, and side effects) as well as different substance classes used in CHF treatment. Details are provided in online supplementary Table S5. A two-sided *p*-value <0.05 was considered statistically significant. All statistical analyses were conducted using R/RStudio (Posit PBC, Boston, MA, USA).

Results

A total of 105 patients were included in the study, of whom 5 patients were excluded from the final analysis due to not requiring intravenous diuretics ($n=4$) or not undergoing echocardiography ($n=1$) (online supplementary Figure S3). Among the 100 included patients, 61% were men, with a mean age of 77.9 ± 10.1 years, a mean LVEF of $44 \pm 13\%$, a mean body mass index of 29.3 ± 6.9 kg/m², and a median NT-proBNP of 4846 pg/ml (IQR 2091–9863). The cohort consisted of 35% patients with HFrEF, 22% with HFmrEF, and 43% with HFpEF. Most patients had multiple cardiovascular risk factors, including hypertension (78%), type 2 diabetes mellitus (43%), dyslipidaemia (41%), and obesity (38%). In addition, 49% had coronary artery disease, and 63% had atrial fibrillation, while 78% had an eGFR <60 ml/min/1.73 m². Table 1 summarizes patient characteristics. The primary reasons for ED presentation were dyspnoea in New York Heart Association class III–IV (92%) and/or peripheral oedema (92%). The in-hospital mortality rate was 5%, with all deaths attributed to cardiogenic shock and/or respiratory failure, as diuretics failed to achieve recompensation and dialysis was declined by the patients.

Adherence to heart failure medication and adherence influencing factors

A total of 39% of patients were adherent (all prescribed CHF substances or metabolites detectable in urine), 39% were partially adherent (one prescribed substance or metabolite not detectable in urine), and 22% were non-adherent (≥ 2 prescribed substances or metabolites not detectable in urine) (Figure 1). In two patients, none of the prescribed medications were detected in urine, although their BPMH suggested the intake of 14 and 20 different drugs, respectively. On the other hand, 41% of patients had at least one drug detected in urine that was not listed in their

BPMH and had not been administered in the ED. These unrecorded medications were primarily cardiovascular drugs, non-steroidal anti-inflammatory drugs, or other analgesics (online supplementary Table S6).

Non-adherent patients had significantly more CHF medications prescribed (4.45 ± 1.01) compared to partially adherent (3.54 ± 1.00 , $p=0.0047$) and adherent patients (3.26 ± 0.94 , $p=0.0002$). Daily pill burden for CHF treatment was also significantly higher in non-adherent patients (6.36 ± 2.76) compared to adherent patients (4.45 ± 1.55 , $p=0.022$) (Figure 2). Younger age was associated with lower adherence, as non-adherent patients were significantly younger than both partially adherent (72.0 ± 9.7 vs. 79.4 ± 9.2 , $p=0.0144$) and adherent (79.6 ± 10.3 , $p=0.0054$) patients. Non-adherent patients were also more likely to use SPCs (all types of SPCs, mainly antihypertensive, antidiabetic, and lipid-lowering SPC) than adherent patients (0.82 ± 0.39 vs. 0.46 ± 0.51 SPCs in the BPMH, $p=0.043$), though overall pill burden remained high across all patients. Adherent patients had a lower eGFR than non-adherent ($p=0.018$) and partially adherent patients ($p=0.010$) (Table 1). Patients with an eGFR <60 ml/min/1.73 m² were more likely to be adherent compared to non-adherent ($p=0.0028$) and partially adherent patients ($p=0.0382$). In-hospital mortality was not associated with adherence status ($p=0.63$).

Medication and adherence rates

Angiotensin-converting enzyme inhibitors were prescribed to 22% of patients, ARB to 31%, ARNI to 26%, BB to 91%, MRA to 41%, and SGLT2-I to 43% (Table 2). Nearly all patients were prescribed a diuretic, with 89% receiving a loop diuretic and 18% a thiazide/thiazide-like diuretic. Ertugliflozin ($n=1$) or indapamide ($n=2$) were prescribed to three patients, but these substances were not detectable in the analytical methods used, so these were excluded from adherence analysis. Only 29% of HFrEF patients were on GDMT, defined as the use of all five drug classes with a Class I recommendation. Among HFmrEF and HFpEF patients, 45% and 23% were receiving a combination of a diuretic and an SGLT2-I, respectively (Class I recommendation) (Figure 3). The total pill burden was high, with patients taking an average of 13.3 ± 5.2 pills/day and having 11.2 ± 4.0 different medications in their regimen. A total of 58% of patients were prescribed at least one SPC.

Adherence rates varied by drug class. Adherence to ACE-I (72.2%), ARB (67.7%), ARNI (84.6%), BB (90.1%), and loop diuretics (87.6%) were acceptable to good (Figure 4). In contrast, adherence to MRA (39%), SGLT2-I (58.1%), and thiazide or thiazide-like diuretics (44.4%) was low. The results of the SGLT2-I analysis were controlled by the presence or absence of glucosuria and corresponded well with the direct toxicological drug testing (online supplementary Table S7). Across all drug classes, the overall adherence was 74.2%. All included patients received intravenous diuretics in the ED, including furosemide (78%) and torsemide (27%).

The prescription of MRAs was associated with non-adherence, with an odds ratio (OR) for non-adherence of 8.3 (95% confidence

Table 1 Patient characteristics

Characteristic	All patients (n = 100)	Non-adherent patients (n = 22)	Partially adherent patients (n = 39)	Adherent patients (n = 39)	p-value
Age, years	77.9 ± 10.1	72.1 ± 9.7	79.4 ± 9.2	79.6 ± 10.3	0.004
Male sex, n (%)	61	18 (82)	22 (56)	21 (54)	0.075
BMI, kg/m ²	29.3 ± 6.9	30.5 ± 6.8	29.7 ± 6.9	28.2 ± 7.1	0.440
Total number of pills/day (all)	13.3 ± 5.2	15.1 ± 6.3	13.2 ± 4.9	12.3 ± 4.5	0.284
Total number of substances (all)	11.2 ± 4.0	12.2 ± 3.9	11.3 ± 4.3	10.6 ± 3.8	0.338
Number of pills/day for CHF	5.1 ± 2.1	6.4 ± 2.8	4.9 ± 2.0	4.5 ± 1.6	0.024
Number of substances for CHF	3.6 ± 1.1	4.5 ± 1.0	3.5 ± 1.0	3.3 ± 0.9	<0.0002
LVEF, %	43.6 ± 13.3	41.9 ± 12.1	45.8 ± 12.9	42.4 ± 14.3	0.351
HFrEF, n (%)	35	8 (36)	11 (28)	16 (41)	0.489
HFmrEF, n (%)	22	6 (27)	10 (26)	6 (15)	0.413 ^a
HFpEF, n (%)	43	8 (36)	18 (46)	17 (44)	0.756
LVEDD, mm	53.3 ± 9.1 (n = 95)	57.2 ± 10.9	52.2 ± 9.1 (n = 37)	52.1 ± 7.1 (n = 36)	0.221
E/E'	16.9 ± 8.4 (n = 77)	18.5 ± 10.8 (n = 21)	17.8 ± 8.7 (n = 26)	15.1 ± 5.7 (n = 30)	0.625
NT-proBNP, pg/ml	4846 [2091–9863]	5729 [2827–8822]	4134 [1858–7876]	4775 [2082–10 281]	0.577
hs-Troponin, pg/ml	42 [23–68] (n = 47)	66 [21–112] (n = 12)	26 [20–38] (n = 16)	51 [36–66] (n = 19)	0.136
eGFR, ml/min/1.73 m ²	42.5 ± 20.3	49.6 ± 22.2	47.3 ± 20.8	33.7 ± 15.4	0.0033
Potassium, mmol/L	4.3 ± 0.7	4.4 ± 0.6	4.3 ± 0.7	4.3 ± 0.7	0.814
CRP, mg/L	14.8 ± 16.6 (n = 98)	15.7 ± 20.2	16.1 ± 16.3 (n = 37)	13.1 ± 15.0	0.518
Heart rate, bpm	84 ± 21	95 ± 24	81 ± 18	82 ± 21	0.093
Systolic blood pressure, mmHg	137 ± 26 (n = 97)	135 ± 33 (n = 21)	132 ± 19 (n = 38)	142 ± 26 (n = 38)	0.203
Diastolic blood pressure, mmHg	82 ± 16 (n = 97)	82 ± 16 (n = 21)	81 ± 15 (n = 38)	82 ± 17 (n = 38)	0.863
In-hospital death, n (%)	5	0	3 (8)	2 (5)	0.631 ^a
NYHA class III–IV, n (%)	92	21 (95)	36 (92)	35 (90)	0.830 ^a
Peripheral oedema, n (%)	92	19 (86)	35 (90)	38 (97)	0.206 ^a
Jugular vein distention, n (%)	45	10 (46)	17 (44)	18 (46)	0.973
Ascites, n (%)	24	6 (27)	8 (21)	10 (26)	0.800
Obesity, n (%)	38	10 (46)	16 (41)	12 (31)	0.464
Type 2 diabetes, n (%)	43	6 (27)	19 (49)	18 (46)	0.235
Hypertension, n (%)	78	15 (68)	30 (77)	33 (85)	0.332 ^a
Chronic coronary syndrome, n (%)	49	11 (50)	17 (44)	21 (54)	0.660
Valve replacement/intervention, n (%)	21	8 (36)	5 (13)	8 (21)	0.157 ^a
Atrial fibrillation, n (%)	63	13 (59)	25 (64)	25 (64)	0.912
Stroke, n (%)	8	1 (5)	3 (8)	4 (10)	0.896
Chronic obstructive lung disease, n (%)	17	6 (27)	7 (18)	4 (10)	0.261
Reported chronic kidney disease, n (%)	49	10 (46)	18 (46)	21 (54)	0.740
eGFR <60 ml/min/1.73 m ² , n (%)	78	13 (59)	28 (72)	37 (95)	0.0013^a
Psychiatric disorder, n (%)	9	2 (9)	5 (13)	2 (5)	0.729

Values are mean ± standard deviation, n (%), or median [interquartile range].

BMI, body mass index; CHF, chronic heart failure; CRP, C-reactive protein; E/E', transmitral E velocity to early diastolic mitral annular velocity ratio; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs, high sensitivity; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Adherence rates were corrected for single-pill combinations.

P-values are given for between-group comparisons.

^aFisher's exact test.

interval [CI] 2.0–34.3), and 4.2 (95% CI 1.3–14.0) for partial adherence. Thiazide or thiazide-like diuretics were also linked to non-adherence (OR 12.3, 95% CI 1.8–83.1) and partial adherence (OR 6.7, 95% CI 1.3–34.6). The prescription of BBs or loop diuretics was associated with a higher risk of non-adherence but not partial adherence (online supplementary Table S5).

Indirect adherence monitoring and questionnaires

Self-reported adherence was found to be unreliable when compared with toxicological results. While 86% of patients stated they were taking all prescribed medications according to their BPMH,

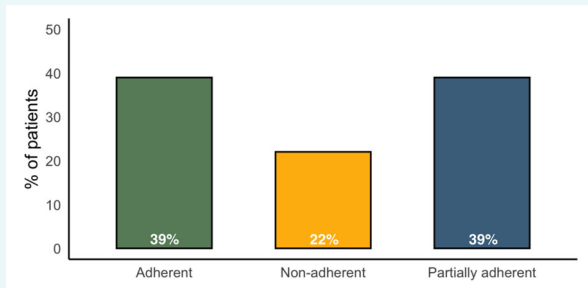


Figure 1 Adherence rates using liquid chromatography coupled to high-resolution mass spectrometry in urine. Patients were classified as 'adherent' if all prescribed drugs for chronic heart failure treatment were detected in urine. If one or at least two of the prescribed drugs for chronic heart failure treatment were not detectable in urine, the patient was considered to be 'partially adherent' or 'non-adherent', respectively. Adherence rates were corrected for single-pill combinations.

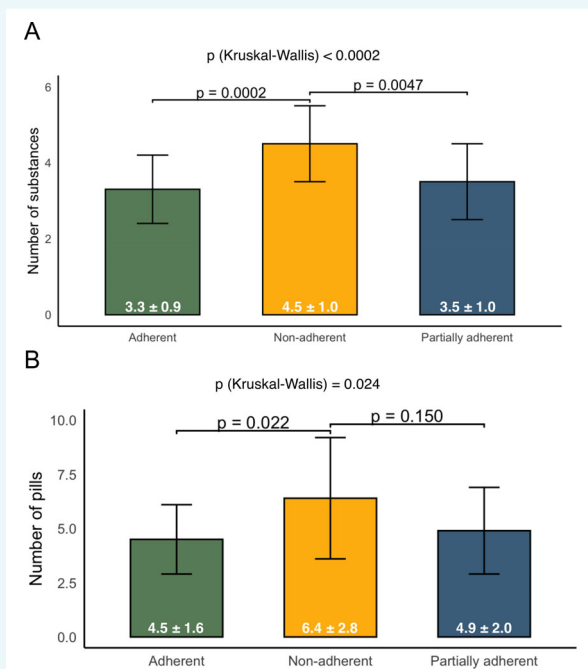


Figure 2 Impact of chronic heart failure therapy and dosing regimen on adherence. The impact of the total number of substances (A) and the total number of pills for chronic heart failure treatment (B) on adherence. Adherence rates were corrected for single-pill combinations. The Kruskal–Wallis test was used for comparisons between adherent, partially adherent, and non-adherent patients. *P*-values are given for between-group comparisons.

only 39% were confirmed as fully adherent based on toxicological testing in urine (online supplementary Table S8). Discrepancies between self-reported and actual adherence were found in 60% of cases.

Table 2 Patients' drug treatment

Substance class	Prescription rate (%)	Detection rate (%)
ACE-I	22	16
Ramipril	18	14
Lisinopril	2	1
Enalapril	2	1
ARB	31	21
Candesartan	14	8
Valsartan	10	9
Telmisartan	3	2
Olmесartan	2	0
Losartan	1	1
Irbesartan	1	1
ARNI	26	22
BB	91	82
Bisoprolol	61	58
Metoprolol	25	21
Carvedilol	2	1
Nebivolol	1	0
Atenolol	2	2
MRA	41	16
Spironolactone	25	12
Eplerenone	16	4
SGLT2-I ^a	43	25
Empagliflozin	23	17
Dapagliflozin	20	8
Loop diuretic	89	78
Torsemide	87	76
Furosemide	2	2
Thiazide diuretic ^a	18	8
HCT	8	2
Xipamide	8	6
Chlorthalidone	2	0
Concomitant drug treatment		
Single pill combination	58	
Antiplatelet therapy/anticoagulation		
Acetylsalicylic acid	33	
P2Y ₁₂ inhibitor	10	
Oral anticoagulation	60	
Other cardiac drugs		
Vericiguat	4	
Amiodarone	9	
Ivabradine	2	
Digoxin/digitoxin	5	
Other antihypertensive drugs		
Amlodipine	23	
Other drugs		
Statin	70	
GLP-1 agonist	6	
Antidepressant	14	
Antipsychotic	6	

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; GLP-1, glucagon like peptide-1; HCT, hydrochlorothiazide; MRA, mineralocorticoid receptor antagonist; SGLT2-I, sodium–glucose co-transporter 2 inhibitor. ^aOne patient was prescribed to ertugliflozin and two patients to indapamide, but these substances are not detectable in the toxicological analyses used, so these were excluded.

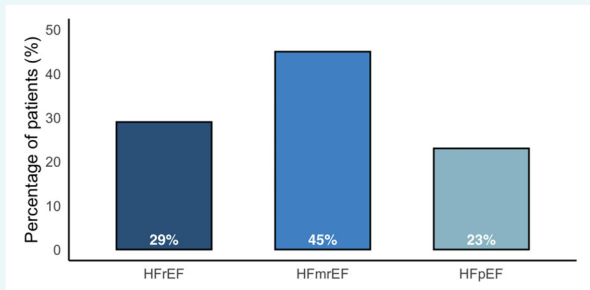


Figure 3 Percentage of patients on guideline-directed medical therapy. A guideline-directed medical therapy includes an angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker, or angiotensin receptor–neprilysin inhibitor, and a beta-blocker, a mineralocorticoid receptor antagonist, a sodium–glucose co-transporter 2 inhibitor, and a diuretic for patients with heart failure with reduced ejection fraction (HF_rEF). For patients with heart failure with mildly reduced (HF_{mr}EF) or preserved ejection fraction (HF_pEF), a guideline-directed medical therapy encompasses a sodium–glucose co-transporter 2 inhibitor and a diuretic, respectively.

According to the DemTect test, 41% of patients had cognitive performance appropriate for their age, 21% had mild cognitive impairment, and 27% suspected dementia, 11% of the patients declined to complete this test. Adherent patients were more likely to have an abnormal DemTect test result ($p = 0.049$), an indicator for beginning dementia if the result is ≤ 12 points, with a lower mean score compared to partially adherent patients (9.53 ± 4.80 vs. 12.27 ± 3.94 , $p = 0.031$).

Adherence questionnaires (RAI, BMQ) and assessments for adherence-influencing factors, such as depression and anxiety

(HADS-D) or lack of social support (ESSI, SUCCE-4), showed no significant correlation with adherence status. In the HADS-D-Anxiety screening, 58% of patients had normal results, 28% were borderline, 10% were conspicuous, and 3% had a very conspicuous test result. The HADS-D-Depression screening questionnaire found that 51% of the patients had normal results, 23% were borderline, 15% were conspicuous, and 10% had a very conspicuous test result. One patient declined participation in both the HADS-D-Anxiety and -Depression.

Most patients had at least a secondary school certificate or equivalent (74%), the majority were retired (86%), 27% had a net income of ≤ 1500 Euros, and 27% lived alone. Medication was self-prepared by 63% of patients. Multimodal logistic regression analysis showed that having medication prepared by a third party (e.g. family member or healthcare professional) reduced the risk of non-adherence ($p < 0.0001$) and partial adherence ($p < 0.0001$) (online supplementary Table S5 and Figure S4). In contrast, self-preparation of medication by the patient increased the risk of non-adherence ($p = 0.0004$) and partial adherence ($p < 0.0001$). Being retired was associated with a lower risk of non- and partial adherence (both $p < 0.0001$), while living alone was associated with a higher rate of non-adherence ($p < 0.0001$). Low income increased the risk of non-adherence ($p < 0.0001$) and partial adherence ($p = 0.0008$).

Discussion

This study aimed to investigate adherence to CHF medication in patients with ADHF presenting to the ED, to assess patient-related factors influencing adherence, and to evaluate the potential impact of adherence on in-hospital mortality. The results indicate a high pill burden among an elderly and comorbid population, and notably

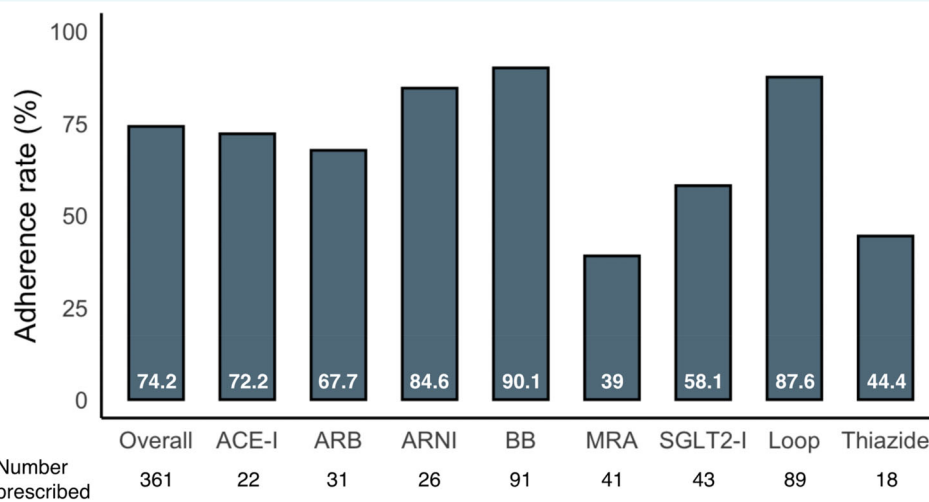


Figure 4 Adherence rates for different substance classes. Adherence rates were corrected for single-pill combinations. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; Loop, loop diuretic; MRA, mineralocorticoid receptor antagonist; SGLT2-I, sodium–glucose co-transporter 2 inhibitor; Thiazide, thiazide (-like) diuretic.

low adherence rates, with only 39% of patients being fully adherent to their prescribed CHF medications in the days before admission, as detected by urine analysis. Key factors associated with poor adherence included high pill burden, younger age, living alone, self-preparation of the medication, low income, and the prescription of MRAs or thiazide/thiazide-like diuretics. In contrast, medication preparation by a third party using a pill organizer and being retired were associated with improved adherence. Only 29% of the included HFrEF, 45% of the HFmrEF, and 23% of the HFpEF patients were on all Class I recommended medications per European Society of Cardiology guidelines.^{2,23} This suboptimal implementation of recommendations is concerning, as GDMT has been shown to lower hospitalization rates and mortality.

Most studies investigating adherence to medication in patients with CHF have relied on indirect methods, such as self-reports or claims data, which are known to overestimate adherence.^{10,27,28} In this trial, indirect adherence monitoring was inaccurate, underlining the limitations of self-reports for assessing adherence. In only 40% of the cases, the patient's self-reported medication intake correlated with the urine toxicology result and adherent patients were significantly more likely to provide 'accurate statements'. According to the World Health Organization, adherence to long-term therapy in chronic diseases is only 50%⁶, which aligns with previous CHF studies reporting non-adherence rates ranging from 18–82%, depending on the measurement method and duration of follow-up.^{8–14} In line with this, 61% of patients were either partially or non-adherent in this study, reinforcing the urgency of addressing medication adherence in CHF management.

Several studies have shown that better adherence to CHF medications is associated with lower mortality and hospitalization rates.^{29–31} For example, adherence to BB following acute myocardial infarction in 38 608 patients was linked to a 23% lower all-cause mortality risk and a 17% reduction in heart failure-related hospitalizations after 1 year.¹² Similarly, in a nationwide longitudinal cohort study, adherence to ARNI was associated with a 25% lower risk of all-cause mortality compared to traditional renin–angiotensin system blockade (ACE-I/ARB), emphasizing the importance of adherence in optimizing CHF outcomes.³² Direct measurement of adherence via LC-MS/MS in spot urine samples has been investigated in patients with HFrEF, confirming high rates of non-adherence (45.9%).¹⁴ These findings suggest that non-adherence is a key predictor of adverse clinical outcomes in CHF patients.

Adherence rates vary by drug, and non-adherence generally increases with longer treatment duration.^{8,9} MRA, diuretics, and BB, mainly due to the side effect profile, have been associated with high rates of non-adherence.^{26,33,34} The decreased adherence to MRA (39%) and thiazide or thiazide-like diuretics (44.4%) was confirmed herein. In contrast, loop diuretics (87.6%) and BB (90.1%) had high adherence rates in this study, likely due to their symptom-relieving effects in ADHF patients. In this study, adherence to SGLT2-I therapy was low (58.1%). The low adherence may be explained by high rates of urinary tract infections or indwelling urinary catheters in the study population, which might be

barriers to continuous SGLT2-I use in elderly and institutionalized patients. Furthermore, this study included a 'real-world' patient cohort with ADHF presenting to the ED unlike other studies, where patients 4–6 weeks after a hospitalization for ADHF were included.¹³ Adherence to medication may be improved after hospitalization due to heightened patient awareness of their condition following an acute event, which could lead to better adherence rates. This might explain the discrepancy between the adherence rates observed in the previous (82.4%) and our study (39%). In the aforementioned study, patients were unaware that their adherence was being tested, whereas in the ADHF-ED trial, patients were informed about the drug adherence testing before inclusion. However, a deterioration in adherence after an acute event is also possible due to a loss of trust in the effectiveness of the therapy.³⁵

The observed association between older age, abnormal DemTect test results, and better adherence is likely due to older patients with (early) dementia having their medications managed by caregivers or healthcare professionals. This finding is consistent with previous studies reporting better adherence in older populations³⁶, though diuretics were associated with lower adherence rates.³³ A substantial proportion of patients (41%) were found to have taken medications not listed on their BPMH, including cardiovascular drugs such as xipamide, metoprolol, amiodarone, ARNI, and ibuprofen. The unknown use of these medications may lead to drug–drug interactions, potentially impacting inpatient outcomes.

Improving medication adherence has the potential to reduce hospitalizations and mortality in CHF patients. Studies have shown that withdrawal of CHF medications in patients with 'recovered' HFrEF results in a 44% relapse rate within 6 months, and even a 48-h interruption in CHF medication can lead to marked increases in NT-proBNP levels, blood pressure, and left atrial volume.^{37,38} The PHARM-CHF randomized controlled trial assessed adherence using claims data and demonstrated that structured pharmacy-based interventions significantly improved adherence and quality of life over 2 years in elderly patients with CHF.²⁸ Another study evaluating medication reminder devices in 53 480 participants with suboptimal adherence to their long-term drug therapy, found that simple reminder systems, such as pill bottle strips, digital timer caps, or standard pillboxes, failed to improve long-term adherence.³⁹ These findings highlight the need for tailored, patient-specific adherence interventions beyond generic reminders.

In general, five categories of factors with an impact on adherence to medical therapy are known: sociodemographic, healthcare system, therapy, condition, and patient-related factors.⁴⁰ Known predictors of poor adherence include younger age, low income, lack of social support, high pill burden, side effects, depression, dementia, and poor quality of life.^{6,40} While some of these factors were confirmed in this study, others, such as depression and social support, were not significantly associated with adherence status. The most significant predictors of poor adherence in this study were high pill burden, younger age, living alone, self-preparation of the medication, and low income, while medication preparation by a third party and being retired were associated with improved adherence.

Limitations

This study has several limitations. The sample size was relatively small, without priori power calculation. As there is no benchmark study on direct toxicological adherence testing in ADHF, descriptive statistics had to be provided. Consequently, the results, especially the adherence-influencing factors, should be regarded as hypothesis-generating. Adherence was measured only at admission, providing a snapshot of short-term adherence rather than a longitudinal assessment of medication-taking behaviour. Urine analysis reflects recent medication intake, typically within the past 24 to 72 h, depending on elimination half-life of the drug, which is mainly determined by (renal) clearance and volume of distribution. This may lead to an overestimation of adherence for medications with long elimination half-lives and an underestimation for drugs with short half-lives that are taken regularly over extended periods. In the context of CHF pharmacotherapy, most guideline-directed drugs are long-acting agents with relatively long half-lives (e.g. ACE-I, ARB, ARNI, BB, MRA, SGLT2-I). For many of these agents, the urinary washout period exceeds multiple half-lives and typically spans more than 24 h making false-positive adherence findings more likely than false negatives. Consequently, non-detection of these agents in urine is unlikely to be solely due to delayed sampling and more plausibly reflects true non-intake. However, urine is less prone to analytical interactions compared to venous blood, making it a robust medium for adherence assessment. We did not account for potential changes in LVEF over time. Heart failure classification and the subsequent assessment of GDMT were based solely on the LVEF measured during the index admission. Previous echocardiographic data, if available, were not considered, therefore, patients who may have transitioned from HFpEF or HFmrEF to HFrfEF prior to admission were not reclassified accordingly. While adherence status was not associated with in-hospital mortality in our cohort, data on rehospitalization rates were not available. As such, it remains unclear whether non-adherence was the primary trigger for acute decompensation or represented a contributing factor among others. Finally, the ED setting is not optimal for completing detailed adherence questionnaires, and cognitive screening (DemTect test) was conducted by a single trained investigator, which could introduce variability in test administration.

Conclusions

Short-term adherence rates in patients with ADHF presenting to the ED were notably low, with more than half of the patients not taking all their prescribed CHF medications. Furthermore, only a small proportion of patients were on GDMT, and nearly half were found to be taking non-prescribed medications, raising concern about unknown drug–drug interactions. Non-adherence to medical therapy is a neglected but critical contributor to worsening of CHF, potentially leading to avoidable hospitalization due to ADHF. Future studies should focus on interventions to improve adherence, including medication simplification strategies, third-party medication management, and structured adherence programmes, which may help reduce CHF-related morbidity and

mortality. Further research should aim to develop cost-effective, validated methods for routine adherence assessment in patients with CHF and ADHF. Given its objectivity, toxicological adherence testing via LC-HRMS/MS may serve as a research gold standard.

Supplementary Information

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

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