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Non-adherence to heart failure medications predicts clinical outcomes: assessment in a single spot urine sample by liquid chromatography-tandem mass spectrometry (results of a prospective multicentre study)

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Aims

Liquid chromatography-mass spectrometry (LC-MS/MS) is an objective new technique to assess non-adherence to medications. We used this method to study the prevalence, predictors and outcomes of non-adherence in patients with heart failure with reduced left ventricular ejection fraction (HFrEF).

Methods and results

This study included 1296 patients with HFrEF from BIOSTAT-CHF, a study that aimed to optimise guideline-recommended therapies. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists, β -blockers and loop diuretics were measured in a single spot urine sample at 9 months using LC-MS/MS. The relationship between medication non-adherence and the composite endpoint of all-cause death or heart failure hospitalisation, over a median follow-up of 21 months, was evaluated. Non-adherence to at least one prescribed medication was observed in 45.9% of patients. The strongest predictor of non-adherence was non-adherence to any of the other medication classes ($P < 0.0005$). Regional differences within Europe were observed. On multivariable analyses, non-adherence to ACEi/ARBs and β -blockers was associated with an increased risk of the composite endpoint [hazard ratio (HR) 1.38, 95% confidence interval (CI) 1.09–1.95, $P = 0.008$ and HR 1.48, 95% CI 1.12–1.96, $P = 0.006$, respectively]. Non-adherence to β -blockers was also associated with an increased risk of death (HR 2.48, 95% CI 1.67–3.68, $P < 0.0005$). Patients who were non-adherent to loop diuretics were healthier and had a decreased risk of the composite endpoint (HR 0.69, 95% CI 0.51–0.93, $P = 0.014$). Non-adherence to mineralocorticoid receptor antagonists was not related to any clinical outcome.

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Conclusion

Non-adherence to medications, assessed by a single urine test, is common and predicts clinical outcomes in patients with HFrEF.

Keywords

Non-adherence • BIOSTAT-CHF • Heart failure • Biochemical adherence screening • All-cause mortality • β -blockers • Angiotensin-converting enzyme inhibitors • Angiotensin receptor blockers

Introduction

Non-adherence to guideline-directed medical therapies in patients with heart failure (HF) is associated with worsening symptoms, frequent hospitalisations and premature death.¹ Non-adherence also poses risks to patients through unnecessary treatment escalation, tests (e.g. imaging, laboratory) and invasive interventions (e.g. device therapy, cardiac transplantation, etc.), with significant cost to the economy through avoidable hospital admissions, resource waste and disease complications.^{2,3}

Current estimates of non-adherence to HF medications range from 55% to 60% across cohorts⁴ and, in these studies, non-adherence was associated with an increased risk of adverse clinical outcomes including death and/or hospital admissions due to HF.^{5–7} A major limitation of previous studies has been the unreliability, impracticality and lack of specificity of the methods used to assess non-adherence, such as pill counting, patient self-administered questionnaires, electronic-monitoring devices and review of prescription claim databases.^{8–10} The wide range of non-adherence rates reported in HF reflects the current lack of a reliable, standard test for non-adherence in these patients.⁴

Given the high rates of non-adherence in patients with HF, the difficulties in assessing non-adherence and the proven benefits of several classes of medicines in HF with reduced ejection fraction (HFrEF), there is a need for an objective tool to assess non-adherence in clinical practice that in turn could lead to an improvement in adherence and outcomes in this cohort of patients.¹¹

Recently, an objective and robust biochemical test for the presence of medication in a spot urine or blood sample has become available.^{12–16} In the present study, we used biochemical adherence testing in urine from a large group of well-characterised patients with HFrEF to describe prevalence, clinical characteristics and outcomes related to non-adherence of HF therapies.

Methods**Patients**

BIOSTAT-CHF (The BIOlogy Study to Tailored Treatment in Chronic Heart Failure)¹⁷ was a large, multicentre, prospective observational study that enrolled 2516 patients from 69 centres in 11 European countries. Its aim was to characterise biological pathways related to the response to or failure of guideline-recommended pharmacological therapy for HF. Patients were included if they had a clinical diagnosis of HF, were receiving loop diuretics and had a left ventricular ejection fraction of $\leq 40\%$ or plasma concentrations of B-type natriuretic peptide (BNP) >400 pg/mL or N-terminal pro B-type

Figure 1 Flow diagram of participants included in the study. LVEF, left ventricular ejection fraction.

natriuretic peptide (NT-proBNP) >2000 pg/mL. They also had either not to be prescribed, or prescribed $\leq 50\%$ of the optimal dose, of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs) or β -blockers. The treatment to HF was optimised in the initial 3 months of follow-up, as guided by the patient's medical team. Patients were assessed at 9 months, at which time symptoms and prescribed medications were documented and blood and urine tests taken. Patients were subsequently followed up by standard clinic visit or by telephone contact. The primary outcome measure was a composite of all-cause death and unplanned hospital admission due to HF.¹⁷

This study is a post-hoc, sub-group analysis of patients enrolled in BIOSTAT-CHF who had baseline left ventricular ejection fraction $\leq 40\%$ and who were alive and had urine samples available at their 9-month visit ($n = 1296$) by which time their medication should have been fully optimized (Figure 1). This population had 374 first events (151 deaths and 223 unplanned hospital admissions due to HF) during a median follow-up period of 21 months (interquartile range 15–27 months).

While there were no separate checks such as pill counts to assess adherence, the nature of the study meant that specific attention was focused on the use of HF medications. The medications were reported in detail in the case report form at 9 months and 6 months thereafter. All participants were contacted the same number of times and at similar time points. The comparison of the study population vs. the rest of the BIOSTAT-CHF cohort is shown in online supplementary Table S1.

Biochemical adherence testing

Testing was performed at the National Centre for Adherence Testing (NCAT), University Hospitals of Leicester¹⁸ as described previously.¹⁶ In brief, samples were kept frozen at -80°C until analysis and batch-analysed on the Agilent Technologies 1290 High Pressure Liquid Chromatograph interfaced with an Agilent Technologies 6460 Triple Quad Mass Spectrometer (Santa Clara, CA, USA) fitted with a jet-stream electrospray source. A medication and/or its metabolite was identified by its retention time and unique mass to charge (m/z) ratio (at least two m/z ratios for each). This method is highly sensitive and can detect analytes at concentrations in the nanomolar range. The methodology has high specificity and has been derived from techniques used in forensics and in sports medicine for detection of drug abuse in elite competitions.^{13,19,20} Further, it has been shown that half-lives of medications and other pharmacokinetic parameters such as bioavailability, volume of distribution and the amount of a medication or its metabolite excreted in urine do not have any impact on the ability to detect a medication, in urine by LC-MS/MS.²¹

For the present analysis, we focused on the following medication classes: (i) ACEi/ARBs; (ii) β -blockers; (iii) mineralocorticoid receptor antagonists (MRAs); and (iv) loop diuretics. The full list of medications analysed is provided in online supplementary Table S2. Non-adherence was defined as lack of detection of a prescribed medication and/or its metabolite.

Statistical analysis

All statistical analysis was undertaken using SPSS 25 (IBM, Chicago, IL, USA) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics are presented as count (percentages), mean (standard deviation). Comparison of demographics, clinical characteristics and laboratory parameters between groups (e.g. adherent vs. non-adherent) was conducted using Chi-square for nominal variables, Kendall's tau-B for ordinal variables and one-way ANOVA for continuous variables as appropriate. Post-hoc comparisons were performed using the Bonferroni correction for multiple testing. Modelling using binary logistic regression was undertaken for non-adherence to each medication using significant variables and factors on univariable comparisons. The c-statistic was calculated from the probability of non-adherence of each drug type. Univariable Cox proportional hazards survival analyses for non-adherence to each group of medications were undertaken for the primary composite endpoint (all-cause mortality and first HF hospitalisation) and for all-cause survival using the appropriate time to event. Multivariable modelling using Cox proportional hazard was also undertaken using the appropriate BIOSTAT-CHF risk scores for the primary composite endpoint and mortality.

The BIOSTAT-CHF risk scores are validated scores for mortality and the composite endpoint of mortality and hospitalisations due to HF.²² The variables included in the scores were age, history

of coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), smoking, hospitalisation due to HF in the last year, New York Heart Association (NYHA) class, peripheral oedema, systolic and diastolic blood pressure, estimated glomerular filtration rate (eGFR), log blood urea nitrogen, log NT-proBNP and haemoglobin, haematocrit, high-density lipoprotein, sodium, log total bilirubin, log alkaline phosphatase and β -blocker usage at baseline. The c-statistic for HFrEF was 0.70 for the composite endpoint.

Ethical approval

The study complies with the Declaration of Helsinki, medical ethics committee of participating centres approved the study, and all patients provided written informed consent before inclusion (EudraCT 2010-020808-29).

Results

Prevalence of non-adherence

Most patients (54.6%) were prescribed all four classes of medications while none was prescribed only an ACE/ARB, β -blocker or MRA (Figure 2A). Non-adherence to at least one of the screened medications occurred in 45.9% of patients, with 29.9% non-adherent to one class, 9.7% to two classes, 3.6% to three and 2.8% to all four classes of medication (online supplementary Figure S1). Non-adherence to loop diuretics was 23.4% (302/1293), to MRAs was 23.8% (182/765), to ACEi/ARBs was 21.5% (174/1261) and to β -blockers was 13.7% (166/1208) (Figure 2B).

Univariable and multivariable predictors of non-adherence

At baseline, the non-adherent population had higher systolic ($P = 0.002$) and diastolic ($P < 0.0005$) blood pressures and were less likely to have atrial fibrillation ($P = 0.024$) or device therapy ($P = 0.005$) (Table 1).

We observed significant regional variation in the prevalence of non-adherence ($P < 0.0005$; online supplementary Table S3 and Figure S2). Study participants from Serbia had the highest non-adherence to any of the four medication classes (60.4%, 174/288, $P < 0.0005$). Participants from Sweden (22.7%, 10/44, $P = 0.037$) and the Netherlands (36.1%, 78/216, $P = 0.034$) had the highest adherence.

Logistic regression analysis for prediction of non-adherence to each medication class was performed using the variables showing $P < 0.05$ on univariate analysis (Tables 2 and 3 and online supplementary Tables S4–S7). Non-adherence to β -blockers or MRAs was related to non-adherence for all of the remaining classes ($P \leq 0.002$ for all), whilst non-adherence to ACEi, ARBs and loop diuretics was related to non-adherence to β -blockers and MRAs ($P \leq 0.0005$). The c-statistic of the probability of non-adherence for each class of medicine ranged from 0.725 to 0.839.

Figure 2 Venn diagram of medication therapy (A) and non-adherence to medications (B). Hierarchical clustering for all medications. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Table 1 Baseline population characteristics (n = 1296)

Variable	Adherent (n = 819)	Non-adherent (n = 477)	P-value
Age, years	67.4 (12.0)	66.4 (12.0)	0.164
Women	177/701 (25.2)	154/595 (25.9)	0.799
Caucasian	694/701 (99.0)	587/595 (98.7)	0.562
Region (between 11 countries)	701/1296 (54.1)	595/1296 (45.9)	<0.0005
BMI, kg/m ² (n = 1285)	27.8 (5.2)	28.0 (5.4)	0.570
Current smoker (n = 1138)	85/609 (14.0)	81/529 (15.3)	0.556
Diabetes	213/701 (30.4)	176/595 (29.6)	0.761
Hypertension	419/701 (59.8)	377/595 (63.4)	0.188
COPD	125/701 (17.8)	93/595 (15.6)	0.298
Atrial fibrillation	306/701 (43.7)	223/595 (37.5)	0.024
Coronary artery disease	389/701 (55.5)	324/595 (54.5)	0.737
Stroke	60/701 (8.6)	47/595 (7.9)	0.667
Peripheral arterial disease	70/701 (10.0)	47/595 (7.9)	0.207
Device therapy	186/701 (26.5)	118/595 (19.8)	0.005
NYHA class (n = 1275)			
I	10/686 (1.5)	20/589 (3.4)	0.158
II	276/686 (40.2)	240/589 (40.7)	
III	319/686 (46.5)	272/589 (46.2)	
IV	81/686 (11.8)	57/589 (9.7)	
Quality of life (VAS) (n = 1250)	55.0 (20.8)	55.4 (21.5)	0.718
Systolic blood pressure, mmHg (n = 1185)	123.1 (20.2)	126.8 (20.2)	0.002
Diastolic blood pressure, mmHg (n = 1184)	73.9 (11.5)	76.6 (12.3)	<0.0005
BNP, pg/mL (n = 1226)	334.0 (367.4)	325.3 (382.6)	0.685
eGFR, mL/min (n = 1284)	67.2 (27.4)	68.1 (26.9)	0.231

N = 1296 for each parameter unless stated otherwise. Numbers are in counts (%) or mean (± standard deviation).

BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; VAS, visual analogue scale.

Any P-value ≤0.05 considered as significant are in bold.

Table 2 Multivariable analysis of non-adherence to medication

Variables	ACEi/ARB non-adherence		β-blocker non-adherence		Loop diuretic non-adherence		MRA non-adherence	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age	0.996 (0.977–1.015)	0.667	1.020 (0.996–1.045)	0.107	0.969 (0.949–0.991)	0.005		
NYHA class								
Hypertension							1.510 (0.999–2.283)	0.05
Diabetes					0.564 (0.334–0.951)	0.032		0.051
COPD					0.432 (0.198–0.942)	0.035		
IHD			1.183 (0.696–2.010)	0.534	1.007 (0.997–1.016)	0.161		
eGFR	0.987 (0.978–0.997)	0.008			1.038 (1.004–1.073)	0.029		
LVEF					1.006 (0.995–1.018)	0.286		
Systolic blood pressure			0.993 (0.981–1.007)	0.324	0.862 (0.548–1.356)	0.522		
Log BNP					0.676 (0.412–1.107)	0.12		
Atrial fibrillation					0.934 (0.515–1.694)	0.821	0.764 (0.472–1.236)	0.764
Device therapy			0.736 (0.372–1.457)	0.376		0.015		
Country								
ACEi/ARB non-adherence	4.775 (2.879–7.918)	<0.0005	5.272 (3.094–8.982)	<0.0005	1.008 (0.552–1.84)	0.98	2.703 (1.702–4.295)	<0.0005
β-blocker non-adherence	1.162 (0.700–1.928)	0.562	3.674 (2.066–6.533)	<0.0005	4.93 (2.549–9.532)	<0.0005	2.106 (1.231–3.604)	0.007
Loop diuretic non-adherence	2.640 (1.678–4.154)	<0.0005	2.390 (1.366–4.182)	0.002	4.917 (2.976–8.122)	<0.0005	4.207 (2.724–6.496)	<0.0005
MRA non-adherence	0.725 (0.676–0.773)	<0.0005	0.840 (0.795–0.884)	<0.0005	0.830 (0.792–0.867)	<0.0005	0.757 (0.713–0.801)	<0.0005
C-statistic*								

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MRA, mineralocorticoid receptor antagonist.

*P-values for difference to c-statistic of 0.5.

Table 3 Risk of death or heart failure hospitalisation related to non-adherence to medications

	ACEi/ARB non-adherence		β -blocker non-adherence		Loop diuretic non-adherence		MRA non-adherence	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Univariable	1.53 (1.21–1.93)	<0.0005	1.51 (1.14–1.98)	0.003	0.51 (0.38–0.68)	0.001	0.87 (0.62–1.21)	0.405
Model 1	1.38 (1.09–1.75)	0.008	1.48 (1.12–1.96)	0.006	0.69 (0.51–0.93)	0.014	0.90 (0.64–1.23)	0.546
Model 2	1.25 (0.99–1.58)	0.060	1.38 (1.05–1.81)	0.022	0.77 (0.57–1.04)	0.083	0.96 (0.68–1.34)	0.804

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist. Model 1: adjusted for age, gender, past history of hypertension, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, ischaemic heart disease, estimated glomerular filtration rate, New York Heart Association class.

Model 2: adjusted for BIOSTAT-CHF risk score for all-cause death and/or heart failure hospitalisation.

Non-adherence and outcomes

Table 3 summarizes the composite risk of death and hospital admissions due to HF.

On univariate analysis, non-adherence to β -blockers and ACEi/ARB were each associated with increased risk of this composite endpoint. These associations remained significant following adjustment for clinical variables such as age, gender, past history of hypertension, COPD, diabetes, peripheral arterial disease, ischaemic heart disease, eGFR and NYHA class (model 1). The impact of non-adherence to β -blockers or ACEi/ARBs is illustrated in the Kaplan–Meier plots (Figure 3A and 3B). A second model adjusted for the BIOSTAT-CHF risk score for death and/or hospitalisation showed β -blocker non-adherence remained significant for this composite outcome (HR 1.38, 95% CI 1.05–1.81, $P = 0.022$) and ACEi/ARB non-adherence also trended towards statistical significance (HR 1.25, 95% CI 0.99–1.58, $P = 0.06$). Non-adherence to ACEi alone was related to death and/or HF on univariable analysis (HR 1.68, 95% CI 1.28–2.20, $P < 0.0005$) and on adjustment for variables in model 1 (HR 1.54, 95% CI 1.17–2.03, $P = 0.002$) or the BIOSTAT-CHF score (model 2, HR 1.35, 95% CI 1.03–1.77, $P = 0.031$).

Non-adherence to loop diuretics was associated with a lower risk of the composite endpoint on univariable analysis (HR 0.51, 95% CI 0.38–0.68, $P < 0.0005$) largely due to their lower overall risk profile (online supplementary Table S5). The association with the composite outcome remained significant following adjustment for clinical variables (model 1, Table 3), but not after adjustment for the BIOSTAT-CHF risk score (model 2, Table 3). Non-adherence to MRAs was not related to the primary composite endpoint.

Non-adherence to β -blockers was associated with increased risk of death on univariable analysis (HR 2.48, 95% CI 1.67–3.68, $P < 0.0005$), which remained significant after adjusting for clinical variables (model 1, HR 2.46, 95% CI 1.64–3.69, $P < 0.0005$) or the BIOSTAT-CHF risk score for all-cause death (HR 2.32, 95% CI 1.56–3.44, $P < 0.0005$) (Table 4 and Figure 3C). Non-adherence to ACEi/ARBs and loop diuretics was related to all-cause death on univariable analysis (HR 1.55, 95% CI 1.07–2.25, $P = 0.021$, and HR 0.41, 95% CI 0.25–0.68, $P = 0.001$, respectively), although these associations were not significant following adjustments (model 1 and 2, Table 4). Non-adherence to MRAs was not associated with death.

Discussion

In this first of its kind study that used biochemical screening of non-adherence in a large, international cohort of patients with HFrEF, nearly 46% were non-adherent to at least one of their HF medications with more than 10% being non-adherent to two medications and more than 6% non-adherent to at least three groups of medications. Non-adherence to each class of medications exceeded 20% except for β -blockers which was 13.7%. We are aware of only two previous studies that used biochemical screening to study the prevalence of non-adherence in HF. A small single-centre study of 81 patients with stable chronic HF showed the prevalence of non-adherence was ~25%.²³ In our study of 331 hospitalised patients with HF, conducted across three centres, the non-adherence rate was 18% with the highest non-adherence rate to diuretics.²⁴

The present study has shown that non-adherence to any given class of medication is strongly associated with non-adherence to the other three groups of medications – for example non-adherence to ACEi/ARBs increased the risk of non-adherence to β -blockers more than fivefold.

Further, there appears to be a regional variation in non-adherence, although the interpretation of the results of the regional variation in non-adherence rates is limited by relative sample numbers from each country.

In the present study, those non-adherent to ACEi/ARBs or β -blockers had around a 40–50% higher risk of death and admissions due to HF. Non-adherence to β -blockers was associated with around two and a half times the risk of death in this cohort of patients with HFrEF. These results are in keeping with the well proven benefits of ACEi/ARBs and β -blockers in randomised trials of HFrEF.^{25,26} Previous studies of the risk of non-adherence in HF and outcomes were mainly retrospective.^{1,5} A small prospective study of 135 patients used electronic monitoring (where the opening of a bottle containing pills is recorded) to assess adherence to β -blockers and ACEi/ARBs. It found that the risk of events increased twofold in those who were non-adherent to either of the two medication classes.⁶

Medications are eliminated from blood after 4–6 half-lives. Therefore if a medication is not detected, the conclusion that can be drawn is that the medication was not ingested for at least its previous 4–6 half-lives.⁹ This period varies for and

Figure 3 Survival curves (derived after multivariate analysis, Table 2). (A) Non-adherence to angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) and all-cause mortality and hospital admissions due to heart failure (HF). (B) Non-adherence to β -blockers and all-cause mortality and hospital admissions due to HF. (C) Non-adherence to β -blockers and all-cause mortality.

is relatively short from around 8–10 h to 7–10 days for HF medications.⁹

Biochemical adherence testing provides a snapshot of adherence status and the question that was not answered, prior to this study, was whether this single measure of short-term non-adherence can relate to long-term outcomes. Previously, it has been demonstrated that biochemical non-adherence correlates with clinical surrogates, i.e. high blood pressure, high glycated haemoglobin and high lipid levels in non-adherent patients on antihypertensive medications, oral hypoglycaemic agents and lipid-lowering therapy.^{27,28} This study demonstrates that a single assessment of non-adherence in HF predicts adverse long-term outcomes. The implication of this finding is that a person with HF who was detected to be non-adherent at a one time point by testing in urine with LC-MS/MS is likely to have been consistently non-adherent and hence have poor outcomes.

Database records are often inaccurate and electronic pill monitoring for adherence testing is expensive, cumbersome and can only be used for some medications. These methods have limited usefulness in the clinical setting.⁹ The objective confirmation of medication adherence is a neglected issue in patients with HF. Enhancing adherence is an important component of

the multi-disciplinary management of patients with HF as better adherence is associated with reduction in hospital admissions and mortality.^{29–31} One of the best interventions to enhance medication adherence in HF is to improve health care providers' skills in assessing non-adherence,³¹ and robustly diagnosing non-adherence thus helps achieve this.

Further, non-adherence with medical advice is strongly affected by patient knowledge and beliefs about their condition.³² Biochemical adherence testing helps in this aspect by providing the ability to initiate conversation with patients, provides them with an understanding of the role of medications in their body and helps to identify simple ways to correct reasons of non-adherence such as forgetfulness and complex dosing.^{9,33}

Biochemical screening for adherence has mainly been used in hypertension where it has been shown to improve adherence and blood pressure control in observational studies.^{27,34} One study shows that systolic blood pressure had dropped by ~20 mmHg with most patients becoming adherent on follow-up while the number of antihypertensive medications remained the same.²⁷ Clinically, the NCAT service, run by our department as a routine NHS service, receives around 1500 samples a year from approximately 35 hypertension centres across the UK.¹⁸ Similar services have

Table 4 Risk of death related to non-adherence to medications

	ACEi/ARB non-adherence		β -blocker non-adherence		Loop diuretic non-adherence		MRA non-adherence	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Univariable	1.55 (1.07–2.25)	0.021	2.48 (1.67–3.68)	<0.0005	0.41 (0.25–0.68)	0.001	0.67 (0.36–1.25)	0.205
Model 1	1.31 (0.89–1.92)	0.178	2.46 (1.64–3.69)	<0.0005	0.62 (0.37–1.03)	0.065	0.70 (0.37–1.32)	0.273
Model 2	1.28 (0.88–1.87)	0.189	2.32 (1.56–3.44)	<0.0005	0.70 (0.42–1.16)	0.165	0.73 (0.39–1.36)	0.324

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist. Model 1: adjusted for age, gender, past history of hypertension, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, ischemic heart disease estimated glomerular filtration rate, New York Heart Association class. Model 2: adjusted for BIOSTAT-CHF risk score for all-cause death.

been set up in mainland Europe. The European Societies of Cardiology and Hypertension suggest that biochemical detection by LC-MS/MS is the preferred method to detect non-adherence.³⁵ The benefit of biochemical adherence testing in improving adherence and blood pressure control in hypertension indicates that similar analogous benefit in adherence and outcomes could be possible in patients with HF. It remains difficult to predict non-adherence to individual drugs, as the main predictors are non-adherence to other medications. This implies that all patients should be tested. Since the findings suggest an association between non-adherence and poor outcome, it remains to be demonstrated that an intervention directed to alter non-adherence may lead to an improvement in outcome. However, a randomised clinical trial would be the best route to test this hypothesis.

Biochemical screening thus may be useful in a routine clinical setting, but how easy is it? The equipment for LC-MS/MS is expensive (~£150 000) and setting up the method and its interpretation requires specialist knowledge, but these are available in most large hospitals.⁹ The urine sample can be transported in ordinary post, with samples being stable for at least 3 days at room temperature.³⁶ The test has been used in the primary care setting, supporting management of HF in the community.²⁸ Therefore, it is possible that a central laboratory can provide testing service for a region as run by the NCAT service.

This study has several strengths. The population studied is a large well-characterised multicentre, multinational HF cohort with long-term follow-up data, and careful assessment of medication throughout the study. However, this was a post-hoc analysis. Patients were excluded if they did not have urine samples at 9 months; these patients might have had poorer adherence as may those who died before 9 months. Also, we did not assess baseline adherence and compare it with analysis at 9 months. The design of the BIOSTAT-CHF trial would make it difficult to undertake such an analysis as all participants needed to be on loop diuretics at baseline and the other medications were at suboptimal dosing. Further, we did not collect data on the reasons for the medications being stopped. This could be related to factors such as adverse reactions to medications, but nevertheless it would be expected that this was discussed or disclosed to their doctors at the 9-month visit. Other limitations of this study are the lack of comparison of biochemical adherence with an alternative method of adherence assessment such as pharmacy refill rate and lack of data on reasons

that may influence adherence such as socio-economic status and education levels. Further, it is possible that patients used loop diuretics in a symptom-driven way, which may explain the findings that those who were non-adherent to this group of medications were patients with less severe disease. Also, there is lack of robust data on the change in pharmacokinetics of medications in HF and this could in theory affect the excretion of medications and hence their detection in HF patients. Further data are needed to validate these results in a different cohort of HF patients and collation of real-world data from centres. In addition, the non-adherence rates detected in this cohort may be affected by a selection bias of patients and the non-adherence rates in the general HF population could be higher.

In conclusion, non-adherence is common in patients with HFrEF. This is the first study to demonstrate that a single biochemical screening test to detect non-adherence predicts clinical outcomes in patients with HFrEF. This test could be used in the clinical setting to detect and manage non-adherence, thereby guiding treatment decisions and potentially improving outcomes.

Supplementary Information

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

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