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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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 cohorts [4] 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 heart failure, the difficulties in assessing non-adherence and the proven benefits of several classes of medicines in heart failure with reduced left ventricular 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, 13 14-16] In the present study, we used biochemical adherence testing in urine from a large group of well-characterized 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, multicenter, prospective observational study that enrolled 2,516 patients from 69 centers 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 (LVEF) of ≤ 40% or plasma concentrations of brain natriuretic peptide (BNP) > 400pg/mL or N terminal pro B type natriuretic peptide (NT-proBNP) > 2000pg/mL. They also had either not to be prescribed, or prescribed ≤ 50% of the optimal dose, of angiotensin converting enzyme inhibitors (ACEi), angiotensin-2 receptor blockers (ARBs) or β-blockers. The treatment to HF was optimised in the initial three 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 LVEF ≤ 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 (IQR: 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 CRF 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 Table S1.

Biochemical adherence testing

Testing was performed at the National Centre for Adherence Testing (NCAT), University Hospitals of Leicester [18] as described previously.[16] In brief, samples were kept frozen at -80^0 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, California, 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: 1) ACEi/ ARBs; 2) β-blockers; 3) mineralocorticoid receptor antagonists (MRA); 4) loop diuretics. The full list of medications analyzed is provided in 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 two groups (e.g.: adherent vs. non adherent) was conducted using chi^2 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. Modeling 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 end point (all-cause mortality and first HF hospitalization) and for all-cause survival using the appropriate time to event. Multivariable modeling 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, COPD, smoking, hospitalisation due to HF in the last year, NYHA class, peripheral oedema, systolic and diastolic blood pressure, eGFR, log blood urea nitrogen (BUN) log NT-pro-BNP and haemoglobin, haematocrit, HDL, sodium, log total bilirubin, log alkaline phosphatase and beta 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 (Figures 2 and S1)

Most patients (54.6%) were prescribed all four classes of medications while none was prescribed only an ACE/ARBi, β-blocker or an 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 (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 (Tables 1-3, S4-7)

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).

We observed significant regional variation in the prevalence of non-adherence (P <0.0005, Table S3, 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 (Table 2). Non-adherence to β-blockers or MRAs was related to non-adherence for all of the remaining classes (P ≤0.002 for all), whilst non-adherence to ACEi, ARBs and loop diuretics was related to non-adherence to β-blockers and MRAs (P ≤0.0005). The C-

statistic of the probability of non-adherence for each class of medicine ranged from 0.725 to 0.839.

Non-adherence and outcomes (Tables 3,4 and Figure 3)

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, ischemic 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 (Figures 3a and 3b). A second model adjusted for the BIOSTAT-CHF risk score for death and/or hospitalization 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/ARBs 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 (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 / 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 heart failure 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 have used biochemical screening to study the prevalence of non- adherence in HF. A small single center study of 81 patients with stable chronic HF showed the prevalence of non-adherence was ~25%.[23] In our study of 331 hospitalized with HF, conducted across three centers, 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 five-fold.

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 randomized 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 beta- 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 is relatively short from around 8-10 hours 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 HbA1c and high lipids levels in non-adherent patients on antihypertensive medications, oral hypoglycemic 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 30, 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 ~20mmHg with most patients becoming adherent on follow-up while the number of antihypertensive medications remained the same.[27] Clinically, the National Center for Adherence testing (NCAT) service, run by our department as a routine NHS service, receives around 1500 samples a year from approximately 35 hypertension centers across the UK.[18] Similar services have 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 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 to an intervention directed to alter non-adherence should 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 characterized multicenter, 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 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 is needed to validate these results in a different cohort of HF patients and collation of real-world data from centers. In addition, the non-adherence rates detected in this cohort maybe 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.

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Figure Legends

Figure 3: Derived after multivariate analysis (Table 5).

Figure 1: Flow diagram of participants included in the study

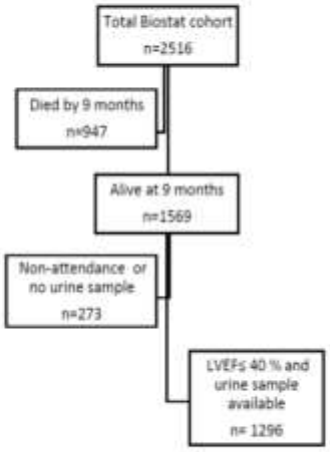
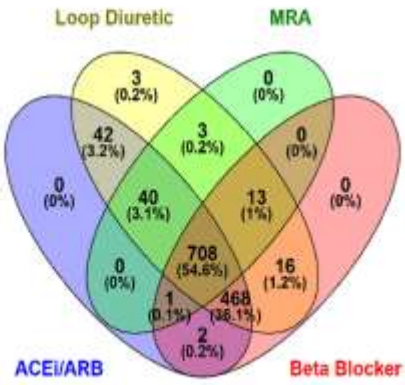


Figure 2 Venn diagram of medication therapy (a) and non-adherence to medications (b). Hierarchical clustering for all medications

a



b

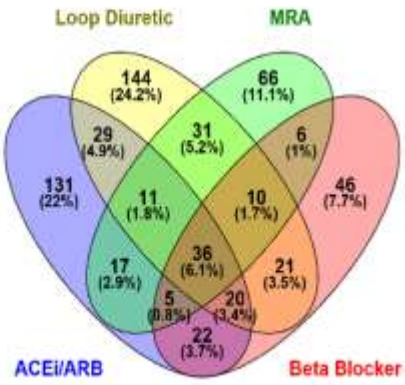
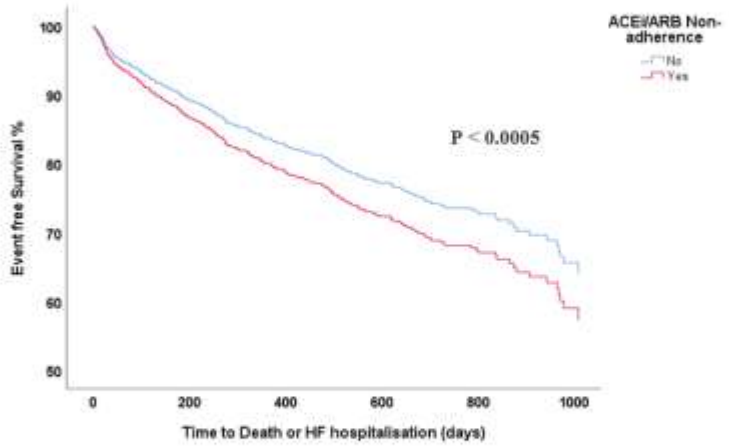
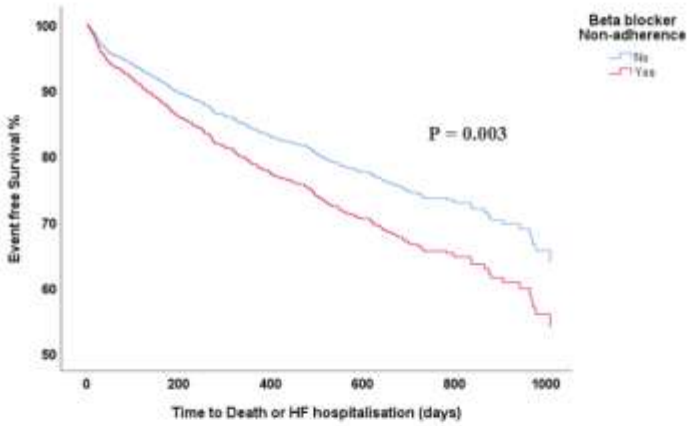


Figure 3: Survival curves

a) Non-adherence to ACEi/ARBS and all-cause mortality and hospital admissions due to heart failure



b) Non-adherence to β-blockers and all-cause mortality and hospital admissions due to heart failure



c) Non-adherence to betablockers and all-cause mortality

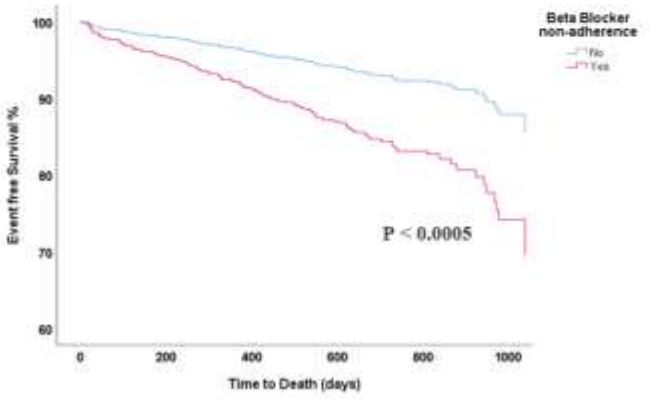


Table 1: Baseline population characteristics (N=1296)

Variable	Adherent (n=819)	Non- Adherent (n=477)	P value
Age yr	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/m2 (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)			
Class I	10/686 (1.5)	20/589 (3.4)	0.158
Class II	276/686 (40.2)	240/589 (40.7)	
Class III	319/686 (46.5)	272/589 (46.2)	
Class 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. Numbers are in counts (%) or mean (± standard deviation). Any P value ≤ 0.05 considered as significant and are in italics

Table 2: Multivariable analysis of non-adherence to medication

	ACEi/ARB non-adherence		Beta Blocker non-adherence		Loop Diuretic non-adherence		MRA non-adherence	
Variables	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						0.003		0.05
Hypertension							1.510 (0.999-2.283)	0.051
Diabetes					0.564 (0.334-0.951)	0.032		
COPD					0.432 (0.198-0.942)	0.035		
IHD			1.183 (0.696-2.010)	0.534				
eGFR	0.987 (0.978-0.997)	0.008			1.007 (0.997-1.016)	0.161		
LVEF %					1.038 (1.004-1.073)	0.029		
Systolic BP			0.993 (0.981-1.007)	0.324	1.006 (0.995-1.018)	0.286		
Log BNP					0.862 (0.548-1.356)	0.522		
Atrial Fibrillation					0.676 (0.412-1.107)	0.12		
Device Therapy			0.736 (0.372-1.457)	0.376	0.934 (0.515-1.694)	0.821	0.764 (0.472-1.236)	0.764

Country				0.009		0.015		
ACEi/ARB non-adherence			5.272 (3.094-8.982)	<0.0005	1.008 (0.552-1.84)	0.98	2.703 (1.702-4.295)	<0.0005
Beta Blocker non-adherence	4.775 (2.879-7.918)	<0.0005			4.93 (2.549-9.532)	<0.0005	2.106 (1.231-3.604)	0.007
Loop Diuretic non-adherence	1.162 (0.700-1.928)	0.562	3.674 (2.066-6.533)	<0.0005			4.207 (2.724-6.496)	<0.0005
Aldosterone blocker 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		
C statistic*	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

MRA: Mineralocorticoid receptor blockers * P values for difference to C statistic of 0.5

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

	HR ACEi/ARB non-adherence	P value	HR β-blocker non-adherence	P value	HR loop diuretic non-adherence	P value	HR MRAs non-adherence	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)	0.000	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

Data are HR (95% Cl), HR: Hazards ratio. ACEi: Angiotensin-converting-enzyme inhibitors. ARB: angiotensin-receptor blocker. MRA: Mineralcorticoid receptor

Model 1: adjusted for age, gender, past history of hypertension, diabetes, COPD, peripheral arterial disease, ischemic heart disease, eGFR, NYHA class.

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

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

	HR ACEi/ARB non-adherence	P value	HR β-blocker non-adherence	P value	HR loop diuretic non-adherence	P value	HR MRAs non-adherence	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

Data are HR (95% Cl), HR: Hazard ratio. ACEi: Angiotensin-converting-enzyme inhibitors. ARB: angiotensin-receptor blocker. MRA: Mineralocorticoid receptor antagonist

Model 1: adjusted for age, gender, past history of hypertension, diabetes, COPD, peripheral arterial disease, ischemic heart disease, eGFR, NYHA class.

Model 2: adjusted for BIOSTAT-CHF risk score for all cause death