




# Adherence to prescribed medications in patients with heart failure: insights from liquid chromatography–tandem mass spectrometry-based urine analysis

Joanne Simpson<sup>1\*</sup>, Colette E. Jackson<sup>1</sup>, Caroline Haig<sup>2</sup>, Pardeep S. Jhund <sup>1</sup>, Maciej Tomaszewski <sup>3,4</sup>, Roy S. Gardner<sup>1</sup>, Yannis Tsorlalis<sup>1</sup>, Mark C. Petrie <sup>1</sup>, John J. V. McMurray<sup>1</sup>, Iain B. Squire<sup>5,6</sup>, and Pankaj Gupta<sup>5,7</sup>

<sup>1</sup>Institute of Cardiovascular and Medical Sciences, University of Glasgow, British Heart Foundation Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow G12 8TA, UK; <sup>2</sup>Robertson Centre for Biostatistics, Boyd Orr Building, University of Glasgow, Glasgow G12 8QQ, UK; <sup>3</sup>Division of Cardiovascular Sciences, Faculty of Biology, Medicine and Health, University of Manchester, AV Hill Building, Upper Brook Street, Manchester M13 9PT, UK; <sup>4</sup>Division of Medicine, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK; <sup>5</sup>Department of Cardiovascular Sciences, University of Leicester, NIHR Biomedical Research Centre, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK; <sup>6</sup>National Institute of Health Research Leicester Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK; and <sup>7</sup>Department of Chemical Pathology, University Hospitals of Leicester NHS Trust, Sandringham Building, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW, UK

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<b>Aims</b>	None of the existing studies on adherence have directly measured levels of all medications (or their metabolites) in patients with heart failure (HF).
<b>Methods and results</b>	We used liquid chromatography–tandem mass spectrometry to measure the presence of prescribed drugs (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists) in the urine of patients reviewed 4–6 weeks after hospitalization with HF. Patients were unaware that adherence was being assessed. Of the 341 patients studied, 281 (82.4%) were adherent, i.e. had all prescribed drugs of interest detectable in their urine. Conversely, 60 patients (17.6%) were partially or completely non-adherent. Notably, 24 of the 60 were non-adherent to only diuretic therapy and only seven out of all 341 patients studied (2.1%) were completely non-adherent to all prescribed HF drugs. There were no major differences in baseline characteristics between adherent and non-adherent patients.
<b>Conclusion</b>	Non-adherence, assessed using a single spot urine measurement of drug levels, was confirmed in one of five patients evaluated 4–6 weeks after hospitalization with HF.
<b>Keywords</b>	Adherence • Heart failure • Mass spectrometry • Urine

## Introduction

Adherence is a foundation of successful pharmacological therapy. In heart failure (HF), higher adherence is associated with lower mortality and less frequent HF hospitalization and better adherence may reduce the need for costly advanced device therapies and even cardiac transplantation.<sup>1</sup> Conversely, non-adherence is an independent

predictor of a higher risk of hospitalization for HF and poorer survival.<sup>1,2</sup> It is suggested that non-adherence rates range from 5% to 60% in some cohorts with HF, but the true prevalence is not known.<sup>3</sup> Many patient factors associated with poor adherence such as higher number of comorbid conditions, complexity of medical regimens, and depression, are all prevalent amongst patients with HF.<sup>4</sup> However, the rates of non-adherence reported in patients with HF

\* Corresponding author. Tel: 00447834534244, Email: [joannesimpson1@nhs.net](mailto:joannesimpson1@nhs.net)

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vary widely in existing studies. This may in part reflect the different ways in which adherence was measured in these studies, including by pill counting, questionnaires, electronic-monitoring devices, and review of prescription claim databases.<sup>5–9</sup> None of these methods are considered entirely reliable as they depend, variously, on patient reporting or return of pill boxes, accuracy of electronic records and patients taking the treatment which they have been dispensed, among others. Indeed, each of these methods is thought to overestimate true adherence.<sup>10</sup> Direct measurement of drug levels provides objective evidence of adherence. Assays for most drugs prescribed in HF are available and have been used to examine adherence in other health conditions.<sup>11</sup> This has seldom been performed in contemporary cohorts of patients with HF, although adherence to digoxin therapy using serum concentrations in patients with HF is well described.<sup>12</sup> We have used liquid chromatography–tandem mass spectrometry assays to directly measure the presence of prescribed drugs in the urine of patients with HF.

## Methods

### Patients studied

In this *post hoc* exploratory analysis, we used a previously reported cohort of near consecutive patients hospitalized with HF who were enrolled in a prospective observational study of the association between microvolt T-wave alternans and mortality.<sup>13,14</sup> Patients were recruited from three hospitals in Glasgow from December 2006 to January 2009. Heart failure was defined according to European Society of Cardiology guidelines and brain natriuretic peptide >100 pg/mL was required for enrolment in the study.<sup>15</sup> Urine samples were obtained at the study visit, 4–6 weeks after hospital discharge and stored at -70°C.

### Adherence measure

Urine samples were batched analysed after purification by solvent extraction and dilution. The analysis took place on an Agilent Technologies 1290 series High Pressure Liquid Chromatograph interfaced with an Agilent Technologies 6460 Triple Quad Mass Spectrometer fitted with a Jetstream electrospray source. The techniques used have been described previously.<sup>11</sup> Each urine sample was analysed twice, in positive and negative ion mode. A potential of 40 medications was measured as listed in our previous work.<sup>11</sup> The assay is a qualitative yes/no assay. Compounds were identified by using 2 or 3 unique *m/z* ratios and most of the compounds have a detection limit of 5–10 nanogram per mL. Non-detection implies that the medication of interest was not ingested for at least four half-lives prior to sample collection; this is generally more than 24 h except for loop diuretics such as furosemide where it is between 4 and 12 h.<sup>16</sup> Further details of the technique used are described in the [Supplementary material online, Appendix](#). As these analyses were conducted retrospectively, patients were not aware that their adherence to prescribed therapies was being assessed. Patients provided written consent for storage of samples of urine for future biomarker analyses.

### Definition of adherence

Full (complete) adherence was defined as detection of *all* prescribed HF medications in a patient's urine. Two categories of non-adherence were considered; non-adherence to diuretic therapy alone, and non-adherence to disease-modifying drugs. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists were classed as 'disease-modifying therapy'. The term

partial non-adherence is used to refer to patients who were non-adherent to one or more of their prescribed HF medications, irrespective of class of medication. We looked specifically at non-adherence to diuretic therapy, as patients may choose to (or be advised to) withhold diuretics when travelling to attend hospital appointments or when undertaking other journeys or social outings.

### Statistical analyses

Categorical data are presented as numbers and percentages. For continuous data, normally distributed data are summarized as the mean and standard deviation. Medians and interquartile ranges are used where data were not normally distributed.

When comparing parameters between patients who were adherent and those who were not, a *P*-value of <0.05 was considered statistically significant. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.1.2.

The study was approved by the Local Ethical Committee and complied with the Declaration of Helsinki. As collection of urine was only commenced after a protocol amendment, consent for storing and further testing of urine samples was provided by a subset of patients in the original study. The data underlying this article are available in the article and its online supplementary material.

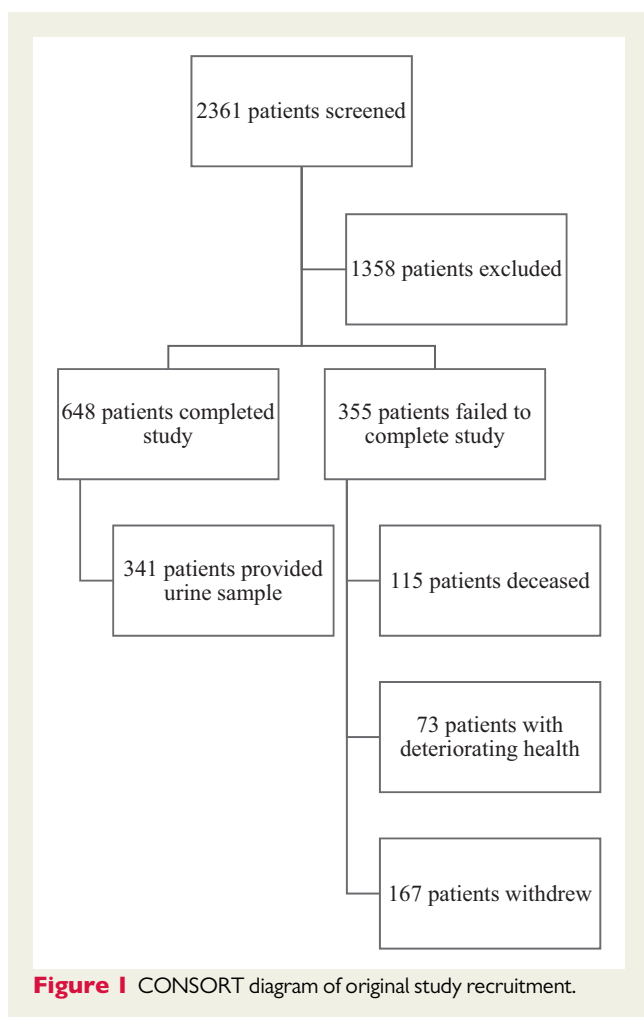
## Results

A total of 1003 patients were enrolled during a hospital admission. Of these, 648 patients returned for the 4- to 6-week study visit. A CONSORT diagram of original study recruitment is shown in [Figure 1](#). Once ethical approval for obtaining a urine sample was in place, 341 of 342 consecutive patients attending the study visit provided a sample. All 341 samples were analysed. The mean left ventricular ejection fraction (LVEF) was 40% (SD 11.6%). A total of 77% of patients had reduced ejection fraction, defined at time of recruitment as an ejection fraction <50%. One patient in the cohort had an implantable cardioverter-defibrillator.

Considering assays of all drugs prescribed for HF, 281 of these 341 patients (82.4%) were fully adherent, i.e. had all the prescribed drugs of interest for HF detectable in their urine sample. Conversely, 60 of the 341 patients (17.6%) were partially or completely non-adherent with prescribed HF treatments. Of note, 24 of the 60 (7% of the study population, 40.0% of non-adherent patients), were non-adherent to *only* diuretic therapy. Of all 341 patients, 7 (2.1%) were completely non-adherent to their prescribed HF medications. Of the 60 patients with partial or complete non-adherence, non-adherence was evident for 22 of 47 prescribed an angiotensin converting enzyme inhibitor (ACE-I) [9.1% of all patients prescribed ACE-I (*n* = 242)]. The equivalent numbers for other drugs were: angiotensin receptor blocker (ARB) 7/12 (18.9% of 37), beta-blocker 9/36 (3.9% of 232), mineralocorticoid receptor antagonist 2/7 (3.9% of 51), and diuretic 33/60 (9.7% of 339) (categories are not mutually exclusive). The clinical characteristics of the patients according to adherence subgroup are shown in [Table 1](#).

### Comparison of adherent and non-adherent patients

There were few statistically significant differences between patients adherent and those non-adherent to their prescribed medications. In



terms of medical history, non-adherent patients were more likely to be anaemic ( $P = 0.03$ ) and there were higher proportions of non-adherent patients with urinary incontinence (16.7% vs. 8.5%;  $P = 0.09$ ) although this difference was not statistically significant. Systolic and diastolic blood pressures (BPs) were higher (systolic BP: 137 mmHg vs. 130 mmHg;  $P = 0.05$  and diastolic BP: 72 mmHg vs. 67 mmHg;  $P = 0.006$ ) and LVEF tended to be lower (37.7 vs. 40.7%;  $P = 0.07$ ) in non-adherent patients. Potassium levels tended to be higher in patients found to be non-adherent to any medication and highest in those non-adherent to disease-modifying therapy (although this difference was not statistically significant). A higher proportion of patients in lower deprivation categories were non-adherent to prescribed HF medications when compared with those in higher deprivation categories (49.2% vs. 8.5%) when categorized according to the Scottish Index of Multiple Deprivation. The number of prescribed cardiac and non-cardiac medications was the same for patients adherent and those non-adherent to their prescribed medications.

### Patients non-adherent to diuretics only

There were few statistically significant differences between patients non-adherent to diuretics only compared with other HF treatments. In comparison to patients non-adherent to disease-modifying therapies, those non-adherent to diuretic therapy tended to have higher

serum potassium levels (4.30 mmol/L vs. 4.10 mmol/L;  $P = 0.08$ ) and were less likely to be prescribed an ACE-I or ARB (100.0 vs. 83.3%). A higher proportion of patients non-adherent to diuretics reported urinary incontinence compared with those non-adherent to disease-modifying therapies, and patients who were adherent (25% vs. 16.7% vs. 8.5%).

## Discussion

Adherence to prescribed medications can be assessed in a variety of ways. This is the largest report of the use of liquid chromatography–tandem mass spectrometry to assess the presence, or absence, of multiple prescribed medications in the urine of patients with HF. Using this objective approach, approximately 18% of patients in our cohort were observed to be non-adherent to one or more of their prescribed HF treatments. Both patients and investigators were unaware at the time of urine collection that treatment adherence would be investigated.

Comparison of our observed rate of non-adherence to those reported in previous studies in patients with HF is difficult in the context of the differing methods of assessment utilized in previous reports. Indeed, only one previous study has assessed directly the presence or absence of prescribed medications in biological samples from patients with HF.<sup>17</sup> Pelouch *et al.*<sup>17</sup> used serum drug levels to show that 25% patients with chronic HF were non-adherent to one or more prescribed drugs. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Programme non-adherence (defined as presumed consumption of less than 80% of prescribed study-drug as estimated by pill count over the whole duration of the trial), the non-adherence rate was 11%.<sup>1</sup> In the Systolic Heart failure treatment with the If-inhibitor ivabradine Trial (SHIFT), non-adherence was defined very differently as premature and permanent discontinuation of study-drug (i.e. before the final study visit or death); the non-adherence rate in SHIFT was 19.8%.<sup>18</sup> Both of these reports are from clinical trials, which included frequent monitoring and patient-prescriber contact, which might have led to higher adherence rates than in routine practice. Moreover, only adherence to study-drug was assessed. On the other hand, both of those reports considered persistence of tablet taking over time whereas we used a single spot urine sample. Another approach considered to give reliable data on adherence is the electronic medication event monitoring system (MEMS). Viana *et al.*<sup>19</sup> used MEMS to measure adherence to 3 different drugs over a median of 96 (range 49–180) days in patients attending an HF clinic in Portugal. Patients were categorized as adherent when they took  $\geq 88\%$  of doses prescribed. Of the 63 patients studied, 22% were classified as non-adherent to ACE-Is, 30% to beta-blockers, and 30% to loop diuretics. These reported rates of non-adherence are higher than those found in our study where of 341 patients studied, 9.1% were non-adherent to ACE-Is, 3.9% to beta-blockers, and 9.7% to loop diuretics. The influence of the 'spot-check' nature of our study rather than a cumulative percentage measure of adherence on different visits may partly explain the observed differences. However, the MEMS method of measuring adherence relies on patient participation and patients are aware their medications are being monitored, which may improve medication adherence rates. Despite our study patients

**Table 1** Baseline characteristics according to adherence category

	Adherent to all medication (A)	Non-adherent to at least one medication (B)	P-value A/B	Non-adherent to one or more disease-modifying therapy (C)	Non-adherent to diuretic only (D)	P-value C/D
	281 <sup>a</sup>	60 <sup>a</sup>		36 <sup>a</sup>	24 <sup>a</sup>	
<b>Demographics</b>						
Age (years)	72.1 (10.3)	69.7 (12.1)	0.42	71.6 (12.6)	67.0 (11.0)	0.14
Male	170 (60.5)	40 (66.7)	0.47	26 (72.2)	14 (58.3)	0.28
SIMD quintile			0.93			0.20
Total	267	59		35	24	
1	133 (49.8)	29 (49.2)		16 (45.7)	13 (54.2)	
2	46 (17.2)	13 (22.0)		8 (22.9)	5 (20.8)	
3	32 (12.0)	7 (11.9)		6 (17.1)	1 (4.2)	
4	27 (10.1)	5 (8.5)		4 (11.4)	1 (4.2)	
5	29 (10.9)	5 (8.5)		1 (2.9)	4 (16.7)	
<b>Heart failure status</b>						
LVEF (%)	40.7 (11.7)	37.7 (10.7)	0.07	36.8 (10.6)	39.0 (10.8)	0.45
NYHA classification			0.62			0.26
I	4 (1.4)	2 (3.3)		0 (0.0)	2 (8.3)	
II	181 (64.4)	37 (61.7)		23 (63.9)	14 (58.3)	
III	94 (33.5)	21 (35.0)		13 (36.1)	8 (33.3)	
IV	2 (0.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Duration of diagnosis >2 years	89 (31.7)	20 (33.3)	0.94	11 (30.6)	9 (37.5)	0.20
Ischaemic aetiology	250 (89.0)	50 (83.3)	0.27	30 (83.3)	20 (83.3)	1.00
<b>Clinical signs and symptoms</b>						
Heart rate (b.p.m.)	74.6 (14.9)	78.3 (16.9)	0.14	78.0 (19.2)	78.8 (13.0)	0.86
Systolic blood pressure (mmHg)	129.8 (22.3)	137.3 (24.1)	0.05	135.5 (22.0)	140.1 (27.2)	0.49
Diastolic blood pressure (mmHg)	67.0 (13.1)	71.8 (12.1)	0.006	70.0 (12.7)	74.5 (10.9)	0.16
Orthopnoea	90 (32.0)	14 (23.3)	0.22	8 (22.2)	6 (25.0)	1.00
PND	44 (15.7)	6 (10.0)	0.32	4 (11.1)	2 (8.3)	1.00
Ankle swelling	85 (30.2)	15 (25.0)	0.53	7 (19.4)	8 (33.3)	0.24
<b>Laboratory results</b>						
Estimated GFR (mL/min)	58.0 (42.0–61.0)	61.0 (49.5–61.0)	0.10	61.0 (47.3–61.0)	61.0 (58.0–61.0)	0.47
Potassium (mmol/L)	4.0 (3.7–4.3)	4.2 (3.8–4.4)	0.09	4.1 (3.7–4.3)	4.3 (4.1–4.7)	0.08
BNP (pg/mL)	391.0 (202.0–870.0)	430.5 (221.8–744.3)	0.77	470.5 (261.8–799.8)	393.0 (212.5–613.0)	0.36
<b>Medical history</b>						
Hypertension	188 (66.9)	34 (56.7)	0.14	19 (52.8)	15 (62.5)	0.60
Valvular heart disease	130 (46.3)	28 (46.7)	1.0	16 (44.4)	12 (50.0)	0.79
Atrial fibrillation	150 (53.4)	33 (55.0)	0.9	21 (58.3)	12 (50.0)	0.60
Diabetes mellitus	98 (34.9)	17 (28.3)	0.37	11 (30.6)	6 (25.0)	0.77
COPD	82 (29.2)	15 (25.0)	0.64	10 (27.8)	2 (20.8)	0.76
Anaemia	114 (40.7)	34 (56.7)	0.03	23 (63.9)	11 (45.8)	0.19
Urinary incontinence	24 (8.5)	10 (16.7)	0.09	4 (11.1)	6 (25.0)	0.18
Previous MI	116 (41.3)	30 (50.0)	0.25	18 (50.0)	12 (50.0)	1.00
Previous PCI	37 (13.2)	11 (18.3)	0.31	4 (11.1)	7 (29.2)	0.10
Previous CABG	50 (17.8)	10 (16.7)	1.0	5 (13.9)	5 (20.8)	0.50
Depression	68 (24.2)	12 (20.0)	0.62	5 (13.9)	7 (29.2)	0.19
Smoking	198 (70.5)	42 (70.0)	1.0	26 (72.2)	16 (66.7)	0.78
Alcohol	199 (70.8)	46 (76.7)	0.43	28 (77.8)	18 (75.0)	1.00
Number of comorbidities (max 18)	5 (0–9)	5 (0–10)	0.69	4 (1–10)	5 (0–9)	0.61
<b>Medications</b>						
ACE-I	194 (69.0)	48 (80.0)	0.116	29 (80.6)	19 (79.2)	1.00
ARB	25 (8.9)	12 (20.0)	0.020	10 (27.8)	2 (8.3)	0.10

Continued

**Table 1** Continued

	Adherent to all medication (A)	Non-adherent to at least one medication (B)	P-value A/B	Non-adherent to one or more disease-modifying therapy (C)	Non-adherent to diuretic only (D)	P-value C/D
	281 <sup>a</sup>	60 <sup>a</sup>		36 <sup>a</sup>	24 <sup>a</sup>	
ACE-I or ARB	212 (75.4)	56 (93.3)	0.002	36 (100.0)	20 (83.3)	0.02
Beta-blocker	196 (69.9)	36 (60.0)	0.170	23 (63.9)	13 (54.2)	0.59
Spironolactone	44 (15.7)	7 (11.7)	0.551	4 (11.1)	3 (12.5)	1.00
Digoxin	47 (16.7)	13 (21.7)	0.355	9 (25.0)	4 (16.7)	0.53
Loop diuretic	272 (96.8)	60 (100.0)	0.370	36 (100.0)	24 (100.0)	—
Thiazide diuretic	5 (1.8)	2 (1.7)	1.000	0 (0.0)	1 (4.2)	0.40
Number of cardiovascular medications prescribed	4 (1–8)	4 (1–7)	0.359	3.5 (1–6)	4 (1–7)	0.48
Number of non-cardiovascular medications prescribed	3 (1–10)	3 (1–6)	0.339	3 (1–6)	2 (1–5)	0.09

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

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; COPD, chronic obstructive airways disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PND, paroxysmal nocturnal dyspnoea; SIMD, Scottish Index of Multiple Deprivation.

<sup>a</sup>The total number of patients studied was 341; of these, 333 were prescribed a diuretic and 311 disease-modifying drugs.

being unaware that their pill taking was being monitored, the measured adherence rates were higher than previously observed. Other observational studies in HF have reported non-adherence rates which varied from 17% to 44%, with one meta-analysis estimating a mean non-adherence rate of 27%.<sup>20</sup>

Perhaps the most appropriate and direct comparison of non-adherence rates is with a prior study, using the same analytical technique applied to a spot urine sample, in 208 patients with hypertension attending a tertiary care clinic.<sup>11</sup> In that study, 10% of patients were totally non-adherent (defined as the absence of all prescribed anti-hypertensive medications in the urine) and a further 15% partially non-adherent (the absence of one or more, but not all, prescribed medications). The highest rates of any non-adherence were observed in patients with inadequate BP control (28.8%) and in patients referred for consideration of renal denervation (23.5%). In a larger study of 676 patients with hypertension, partial non-adherence was observed in 41.6%.<sup>21</sup> In a further study of patients with resistant hypertension referred for renal denervation, median non-adherence was 26.2% and adherence patterns of individuals fluctuated over a 17-month period.<sup>22</sup>

High non-adherence rates have also been reported in other studies in hypertension and in studies of primary and secondary prevention, assessed using a variety of methods.<sup>23,24</sup>

It was also notable in these analyses patients who were non-adherent to diuretic therapy were more likely to report urinary incontinence. In clinical practice, patients are often advised to adjust their diuretic dose according to need and told it is permissible to delay or omit dosing if they must make a journey, for example to a hospital clinic. High rates of urinary incontinence have previously been reported in patients with HF. Hwang et al.<sup>25</sup> surveyed a group of 89 patients with chronic HF and found 49% of patients described urinary incontinence. Higher doses of diuretics were noted in

patients who described themselves as incontinent and, when compared to continent patients, reported missing or altering a diuretic dose more frequently.

Adherence in HF might be better than in these other conditions because HF is a highly symptomatic condition and HF therapies improve symptoms and quality of life and reduce the risk of HF hospitalization and premature death. These may be powerful motivational determinants of adherence, especially in patients recently hospitalized with worsening HF. Use of liquid chromatography–tandem mass spectrometry as a direct and objective measure of prescription medications has several potential applications in clinical practice. Most obviously, non-adherent patients might be targeted for intensive education and counselling in relation to the importance of taking prescribed therapy. Patients hospitalized with worsening HF, especially those with frequent admissions, might be particularly appropriate candidates for this investigation and intervention. Further work using this technique is required to examine the effects of non-adherence on long term outcomes.

## Limitations

This was a *post hoc* analysis of a prospective observational study and is subject to limitations inherent to this type of analysis. The patients we studied had recently been hospitalized with HF and were participating in a clinical research study. These features may have resulted in better adherence when compared to ‘real world’ ambulatory patients with HF in the community. Although our initial cohort consisted of consecutive, unselected, patients recruited in hospital, only 648 of 1003 (64.6%) of patients returned for a follow-up visit. However, 341 of 342 (99.7%) consecutive patients invited to provide a urine sample were able to.

All prescription medications are supplied free of charge to patients in the Scottish National Health Service and payment or co-payment



might reduce adherence in other healthcare systems. Marital status, a factor well-recognized to be associated with medication adherence, was not collected for this cohort of patients.

Liquid chromatography–tandem mass spectrometry provides a snap-shot, rather than a longitudinal, assessment only of adherence to medication. While this direct measure is one of the strengths of the study, an impending clinic appointment has been shown to influence adherence behaviour although patients in this study were not aware that their adherence to medication was being assessed.

## Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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