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

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Abstract

Aims: None of the existing studies on adherence have directly measured levels of medications (or their metabolites) in patients with heart failure.

Methods and Results: 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 to 6 weeks after hospitalisation with heart failure. 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 7 out of all 341 patients studied (2.1%) were completely non-adherent to all prescribed heart failure drugs. There were no major differences in baseline characteristics between adherent and non-adherent patients.

Conclusion: Non-adherence, assessed using a single spot urine measurement of drug levels, was confirmed in 1 of 5 patients evaluated 4 to 6 weeks after hospitalisation with heart failure.

Key words

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 hospitalisation and better adherence may reduce the need for costly advanced device therapies and even cardiac transplantation.[1] Conversely, non-adherence is an independent predictor of a higher risk of hospitalisation for heart failure and poorer survival.[1,2] It is suggested that non- adherence rates range from 5-60% in some cohorts with HF, but the true prevalence is not known.[3] Many patient factors associated with poor adherence such as higher number of co-morbid conditions, complexity of medical regimens, and depression, are all prevalent amongst patients with heart failure.[4] However, the rates of non-adherence reported in patients with heart failure 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.[5-9] 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.[10] Direct measurement of drug levels provides objective evidence of adherence. Assays for most drugs prescribed in heart failure are available and have been used to examine adherence in other health conditions. [11] This has seldom been performed in contemporary cohorts of patients with heart failure, although adherence to digoxin therapy using serum concentrations in patients with heart failure is well described.[12]We have used liquid chromatography-tandem mass spectrometry assays to directly measure the presence of prescribed drugs in the urine of patients with heart failure.

Methods

Patients studied

In this post hoc exploratory analysis, we used a previously reported cohort of near consecutive patients hospitalised with HF who were enrolled in a prospective observational study of the association between microvolt T wave alternans and mortality.[13,14] Patients were recruited from three hospitals from December 2006 to January 2009. HF was defined according to European Society of Cardiology guidelines and BNP >100 pg/mL was required for enrollment in the study.[15] Urine samples were obtained at the study visit, 4 to 6 weeks after hospital discharge and stored at -70^{o} 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.[11] Each urine sample was analysed twice, in positive and negative ion mode. A potential of 40 medications were measured as listed in our previous work.[11] The assay is a qualitative yes/no assay. Compounds are 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 hours except for loop diuretics such as furosemide where it is between 4-12hrs.[16] Further details of the technique used are described in the supplementary 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/social outings.

Statistical Analyses

Categorical data are presented as numbers and percentages. For continuous data, normally distributed data are summarised 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, North Carolina) and R version 3.1.2.

The study was approved by the Local Ethics 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.

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%). 77% of patients had reduced ejection fraction, defined at time of recruitment as an EF<50%. One patient in the cohort had an implantable cardioverter defibrillator.

Considering assays of all drugs prescribed for heart failure, 281 of these 341 patients (82.4%) were fully adherent i.e. had all the prescribed drugs of interest for heart failure detectable in their urine sample. Conversely, 60 of the 341 patients (17.6%) were partially or completely non-adherent with prescribed heart failure 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 heart failure medications Of the 60 patients with partial or complete non-adherence, non-adherence was evident for 22 of 47 prescribed an ACE-I (9.1% of all patients prescribed ACE inhibitor (n=242)). The equivalent numbers for other drugs were: ARB 7/12 (18.9% of 37); beta-blocker 9/36 (3.9% of 232), MRA 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 (BP) 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 heart failure medications when compared to those in higher deprivation categories (49.2% vs. 8.5%) when categorised 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 heart failure treatments. In comparison to patients non-adherent to disease-modifying therapies, those non-adherent to diuretic therapy tended to have higher serum potassium levels (4.30mmol/L vs 4.10mmol/L; P=0.08) and were less likely to be prescribed an ACE inhibitor 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 heart failure. Using this objective approach, approximately 18% of patients in our cohort were observed to be non-adherent to one or more of their prescribed heart failure 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 utilised in previous reports. Indeed, only one previous study has assessed directly the presence or absence of prescribed medications in biological samples from patients with heart failure.[17] Pelouch et al used serum drug levels to show that 25% patients with chronic heart failure 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%.[1] In the Systolic Heart failure treatment with the I*f*-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%.[18] 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 and colleagues used MEMS to measure adherence to 3 different drugs over a median of 96 (range 49 to 180) days in patients attending a HF clinic in Portugal.[19] Patients were categorised as adherent when they took ≥88% of doses prescribed. Of the 63 patients studied, 22% were classified as non-adherent to ACEIs, 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 ACEIs, 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 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%.[20]

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.[11] 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 blood pressure 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%.[21] 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.[22]

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.[23,24]

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 heart failure. Hwang et al surveyed a group of 89 patients with chronic heart failure and found 49% of patients described urinary incontinence.[25] 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 heart failure might be better than in these other conditions because heart failure is a highly symptomatic condition and heart failure therapies improve symptoms and quality of life and reduce the risk of heart failure hospitalisation and premature death. These may be powerful motivational determinants of adherence, especially in patients recently hospitalized with worsening heart failure. 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 hospitalised with worsening heart failure, 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 hospitalised 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 health-care systems. Marital status, a factor well recognised 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.

Conflicts of Interest

JS, CEJ, PG, CH, PSJ, MT, YT and MCP have nothing to disclose. RSG reports grants from British Heart Foundation, grants, personal fees and non-financial support from Abbott, personal fees and non-financial support from Boston Scientific, personal fees and non-financial support from Novartis, personal fees from Vifor. JMcM reports other from Roche Pharmaceuticals, during the conduct of the study; other from Novartis, other from

Cardiorentis, other from Amgen, other from Oxford University/Bayer, other from GlaxoSmithKline, other from Theracos, other from Abbvie, other from DalCor, other from Pfizer, other from Merck, other from AstraZeneca, other from Bristol Myers Squibb (BMS), other from Kidney Research UK (KRUK)/Kings College Hospital, London/Vifor-Fresenius Pharma, outside the submitted work. IS reports grants and personal fees from Novartis.

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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*	**60***		**36***	**24***	
Demographics						
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)	
Heart failure status						
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		20 (33.3)		11 (30.6)	9 (37.5)	

>2 years	89 (31.7)		0.94			0.20
Ischaemic aetiology	250 (89.0)	50 (83.3)	0.27	30 (83.3)	20 (83.3)	1.00
Clinical signs and symptoms						
Heart rate (bpm)	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
Laboratory results						
Estimated GFR	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	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	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
Medical history						
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 co-morbidities (max 18) (med, range)	5 [0-9]	5 [0-10]	0.69	4 [1-10]	5 [0-9]	0.61
Medications						
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
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

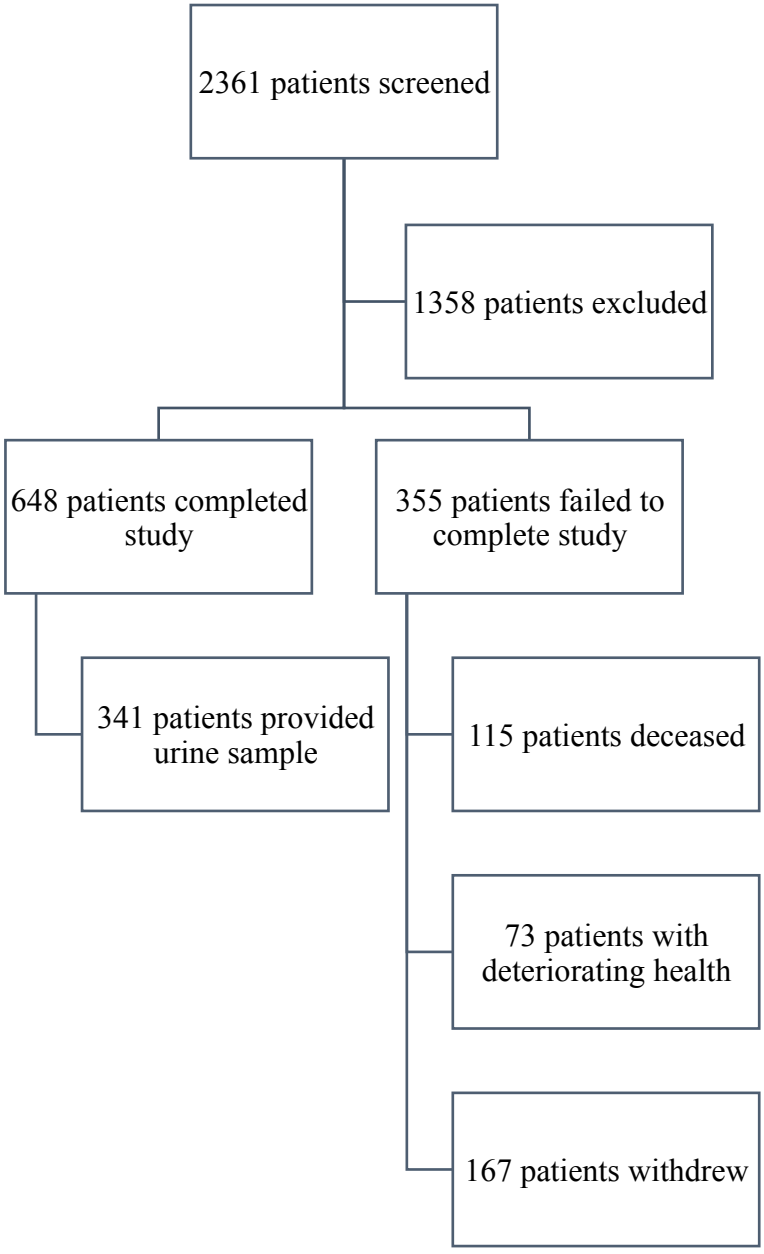
Values are mean ± SD, n (%), or median [interquartile range].

*The total number of patients studied was 341; of these, 333 were prescribed a diuretic and 311 disease modifying drugs.

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

blocker.

Figure 1. CONSORT diagram of original study recruitment



Appendix

Details of the LC-MS/MS technique for biochemical adherence testing

LC-MS/MS consists of a high- pressure liquid chromatography column (HPLC) which is sequentially linked to two mass spectrometers. The initial purification of analytes in matrices such as urine or blood is obtained by filtering the sample through the HPLC. The purified analytes are then volatised and presented in sequence to two mass spectrometers. Each mass spectrometer consists of quadruple magnets that select analytes (and fragments) by their unique mass (m) to charge (z) ratios. Therefore analytes can be identified with great prescision.[1]

It is considered to be the gold standard for measurement of various analytes including Vitamin D , metanephrines, steroids which have been traditionally difficult to measure.[2] The sensitivity and specificity of LC-MS/MS has led to its use in forensic analysis and in the detection of drug abuse in elite sport competitions.[3-5] This technique has recently been adapted for adherence testing.[6-8] It now recommended as the preferred method for adherence testing in hypertension by the European Society of Cardiology.[9]

We and others have confirmed the accuracy and sensitivity (detection ability in the nmoles per litre range) of the method for adherence testing to cardiovascular medications including those used in the treatment of chronic heart failure.[7, 10] Further, in a sensitivity analysis of 27 of the most commonly used cardiovascular medications in 463 patient samples (prescribed a total of 1709 medications), we have demonstrated that there is no link between the pharmacokinetic parameters, such as half-life, volume of distribution bioavailability, and adherence result of a medication.[11]. In our laboratory, biochemical adherence testing by LC-

MS/MS method is certified by UKAS, UK's national accreditation body and the test is provided as a routine clinical service

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