Medication Adherence to Specific Drug Classes in Chronic Heart Failure

Marta Viana, MSc; Olga Laszczynska, MSc; Sandra Mendes, MSc; Fernando Friões, MD; Patrícia Lourenço, MD; Paulo Bettencourt, MD, PhD; Nuno Lunet, MPH, PhD; and Ana Azevedo, MD, PhD

ABSTRACT

BACKGROUND: Adherence to medication is crucial to improve clinical outcomes in patients with heart failure (HF). However, at least 1 out of 4 patients is nonadherent to his or her medication. Several studies have quantified medication adherence in HF patients, monitoring only 1 drug with the Medication Event Monitoring System (MEMS). Some authors have argued that monitoring 1 drug reflects the whole adherence behavior, although there is some evidence of important differences in adherence to distinct drug classes. Furthermore, medication characteristics could be a relevant predictor of adherence, and different drugs could pose different barriers to patients.

OBJECTIVES: To (a) quantify medication adherence to angiotensin-converting enzyme inhibitors (ACEI), beta blockers, and loop diuretics and (b) compare the agreement in adherence among drug classes in chronic HF.

METHODS: Medication adherence to 3 different drugs was monitored using MEMS in 63 patients (81% male, mean age 63.5 years). Medication adherence was measured as the percentage of prescribed doses effectively taken. Patients were considered to be adherent when at least 88% of prescribed doses were taken. Adherence agreement between drug classes was analyzed with Bland-Altman plots and Kappa coefficients.

RESULTS: The mean adherence was 97.3% for ACEI, 97.2% for beta blockers, and 96.0% for loop diuretics. Individual patients did not adhere equally to all drug classes, with differences within the same patient ranging from -35% to 33%. The proportion of patients classified as adherent was 77.8% to ACEI, 69.8% to beta blockers, and 69.8% to loop diuretics. The agreement between each of 2 drugs regarding adherence was substantial (beta blocker vs. ACEI: K=0.72; beta blocker vs. diuretic: K=0.62; ACEI vs. diuretic: K=0.72). If patients were classified as adherent and nonadherent based only on 1 drug, 20% of patients would be misclassified regarding the other drugs.

CONCLUSIONS: Patients can adhere differently to medication used in HF treatment, with lowest adherence to loop diuretic and beta blockers and highest adherence to ACEI. Studies measuring medication adherence should always specify the drug class being analyzed and should not mix different drug classes to generalize about adherence behavior.

J Manag Care Pharm. 2014;20(10):1018-26

What is already known about this subject

- Adherence to medication in heart failure (HF) remains suboptimal, contributing to lower treatment effectiveness.
- Several studies have quantified medication adherence in HF patients, monitoring only 1 drug with the Medication Event Monitoring System (MEMS).
- Some authors have argued that monitoring 1 drug reflects the whole adherence behavior, although there is some evidence of important differences in adherence to distinct drug classes.

What this study adds

- This study quantifies medication adherence to 3 different drug classes and analyzes the agreement in adherence among them.
- One-fifth to one-third of the patients were nonadherent to medication, with lowest adherence to beta blockers and loop diuretics and highest to angiotensin-converting enzyme inhibitors (ACEI).
- About 20% of the patients were adherent to 1 drug and nonadherent to another, indicating that adherence can be variable according to drug classes.
- Studies measuring medication adherence should always specify the drug class being analyzed and should not mix different drug classes to generalize about adherence behavior.

Heart failure (HF) is a syndrome caused by cardiac dysfunction, affecting 1%-2% of the adult population, with an incidence of 5-10 per 1,000 persons per year.[1] Its prevalence and incidence rise progressively with age in persons older than aged 50 years.[1] Patients with HF require long-term pharmacological therapy in order to improve disease prognosis. The cornerstone of HF treatment includes the use of angiotensin-converting enzyme inhibitors (ACEI; or angiotensin receptor blockers (ARB) if ACEI is not tolerated), beta blockers, mineralocorticoid receptor antagonists (MRA), and diuretics.[2,3] While diuretics are important to relieve symptoms, ACEIs, ARBs, MRAs, and beta blockers change the natural course of disease and are crucial to prevent hospitalizations and improve survival.[2,3]

Despite the proven efficacy of recommended pharmacological therapy for patients with HF, adherence to treatments remains suboptimal, contributing to lower treatment effectiveness. It is estimated that at least 1 out of 4 patients with HF is nonadherent to his or her medication.[4-6] Medication adherence is a complex phenomenon, influenced by a multitude of factors related to patients, diseases, therapies, health care systems, and socioeconomic conditions.[7] Among these, patient-related predictors have been extensively described in the literature, but age, gender, marital status, and education have failed to fully explain the variation in patient adherence.[8] Some authors have argued that

there is no clear profile for nonadherent patients.[9] Furthermore, several studies show that medication characteristics, such as adverse side effects,[10] dosing frequency,[5,11,12] and timing of administration,[12] could be relevant predictors of adherence.

Several studies have quantified medication adherence in patients with HF using electronic-monitoring devices, such as the Medication Event Monitoring System (MEMS).[4,11,13-15] MEMS has been reported as a valid, reliable, and precise instrument,[16] providing detailed information about the medication-taking behavior that is not possible with other methods. Most previous studies of patients with HF have monitored only 1 drug with MEMS, arguing that monitoring 1 drug reflects the whole adherence behavior.[4,11,13-15] However, this argument is not evidence based, and recent studies using different methods to measure adherence in patients with HF have reported differences in adherence depending on the drug class analyzed.[10,17] We, therefore, conducted this study of patients with HF to quantify medication adherence to ACEI, beta blockers, and loop diuretics using MEMS and to assess the degree of agreement in adherence to different drug classes. In addition, we identified the patient and medication characteristics associated with adherence to all 3 of these drug classes.

Methods

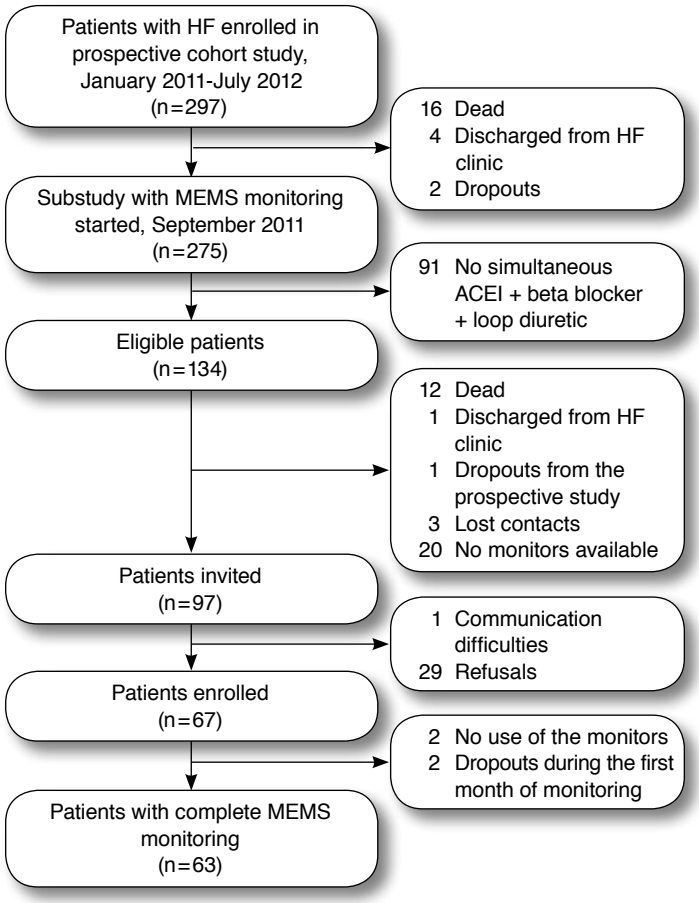
Study Design and Sample Selection

This observational study is based on a cohort of patients with chronic HF assembled with the main objective of analyzing the prognostic effect of drug therapy as used in routine. Between January 2011 and July 2012, we recruited patients followed at an outpatient clinic dedicated to HF patients—Hospital de São João, a tertiary-level teaching hospital located in the urban area of Porto, in the northern region of Portugal. The criteria to be enrolled in the study were a confirmed diagnosis of chronic HF according to the European Society of Cardiology criteria,[2] with a history of systolic dysfunction and no hospitalizations for HF in the previous 3 months (n = 297). Patients were prospectively followed for 2 years, during which monthly contacts were established, either by telephone or face to face at scheduled clinical appointments. The study was approved by the Ethics Committee of Hospital de São João, and all participants provided written informed consent.

A subsample of patients from this cohort was consecutively selected to be monitored for 3 months with MEMS if they were aged 18 years or above; had a prescribed therapy from the HF outpatient clinic that included the simultaneous use of an ACEI, a beta blocker, and a loop diuretic; and who managed their own medications.

A total of 97 patients were invited to be monitored, and 67 accepted to participate. Among the latter, 2 patients did not use the monitors at all, and another 2 quit at some point during the first month, leaving 63 for analysis (Figure 1). Compared with participants, nonparticipants (n = 34) were older (mean age: 73.2 vs. 63.5 years, $P < 0.001$) and more likely to be women (35.3% vs. 19.1%, $P = 0.077$) and not married (47.1% vs. 20.6%, $P < 0.007$) with lower income (87.5% vs. 74.6, $P = 0.148$) and lower education (85.3% vs. 82.5%, $P = 0.727$).

FIGURE 1 Sample Selection Flowchart



ACEI = angiotensin-converting enzyme inhibitor; HF = heart failure; MEMS = Medication Event Monitoring System.

Procedures

On the day of the scheduled medical appointment in the HF clinic, participants were invited to a meeting with a trained researcher in order to be provided with a set of monitors and instructions. The participants were asked to bring all of their ACEI, beta blocker, and loop diuretic medications. Those who agreed to participate signed a specific written informed consent for this substudy, and each received 3 monitors: 1 for the ACEI, 1 for the beta blocker, and 1 for the loop diuretic.

The MEMS caps have a microchip that records real-time data on the openings of the monitor. Each monitor had a label with the name of the corresponding medicine to allow patients

to distinguish them. In addition, each monitor was tagged with 2 colored dots—one on the container and one on the cap—to avoid unintended swapping of caps. Patients were given verbal and written instructions on the use and refilling of monitors. Patients were instructed to open the monitors only to take their medications and afterwards to close them, making sure that each monitor was properly closed and that each cap was on the correct container. If patients had to take half a pill, they were instructed to open the monitor, remove a pill and break it in half, take a half, and put the other half back in the container. We also asked patients to write down all extra openings, for refills or by mistake, in the log provided for this purpose. During the appointment, the researcher demonstrated how to use the monitors and asked the patients to repeat the procedure and explain back. The researcher filled the monitors for the first time; afterwards monitors were refilled by patients at home.

During the monthly interviews of the prospective study, the researcher queried patients about the ongoing monitoring and asked if there were any questions that needed to be clarified. Participants were monitored for 3 months.

Data Collection and Definition of Variables

At the baseline of the prospective cohort study, clinical data were abstracted from the medical files using a standardized form comprising information on age, sex, disease etiology, and comorbidities. Left ventricular systolic dysfunction in the first appointment at the outpatient clinic was also collected, based on the measurement of left ventricular ejection fraction. Education, income, and marital status were updated by questionnaire upon entrance to the substudy. Income was assessed in comparison to the national minimum wage, which was at the time 485 euros per month.

At the beginning of MEMS utilization, a trained researcher collected data from the patients' medical records regarding current clinical data, including New York Heart Association (NYHA) functional class, duration of follow-up at the outpatient clinic, and the total number of drugs prescribed. We converted ramipril to the lisinopril equivalent using the dose ratio of 5:20, and similarly, we converted bisoprolol and nebivolol doses to the carvedilol equivalent using the dose ratio of 1:5. Data about patients' hospitalizations during the monitoring period were also collected.

Adherence data were downloaded to a computer and analyzed by AARDEX software (AARDEX Group, Ltd., Sion, Switzerland), which generated adherence indicators. We computed the percentage of prescribed doses taken during the monitoring period (dose-count) and classified the patients as adherent to each of the medicines monitored when they took ≥88% of the doses prescribed, based on previous research that demonstrated that this adherence rate is associated with better clinical outcomes in HF.[4] All extra openings of the MEMS and periods in which patients were hospitalized were not considered in data analysis.

Data Analysis

Descriptive data are presented as percentages for categorical variables. Continuous variables are presented using mean with standard deviation or median with 25th-75th percentiles (P25-P75), as appropriate. The chi-square test was used to compare proportions between groups. A P value of <0.05 was considered to be statistically significant.

To assess the level of agreement between adherence to ACEIs, beta blockers, and loop diuretics, we used Bland-Altman plots and Kappa coefficients. Bland Altman plots were used when considering adherence as a continuous variable, while Kappa coefficients and their 95% confidence intervals (CI) were used when adherence was defined as a dichotomous variable.

Data analysis was carried out using STATA version 11 for Windows (StataCorp LP, College Station, TX).

Results

The characteristics of the 63 patients are presented in Table 1. The mean age was 63.5 years. Most patients were male (81.0%), married (79.4%), with less than 9 years of education (82.5%) and income lower than the national minimum wage (74.6%). The disease etiology was nonischemic for 57.1% of the patients, and among these, the main cause of HF was alcohol abuse (30.5%). Most patients had moderate-to-severe left ventricular systolic dysfunction (92.1%) at the time of diagnosis. The prevalence of important comorbidities ranged between 17.5% for chronic renal failure and 61.9% for dyslipidemia.

At the beginning of MEMS monitoring, patients had been followed in the outpatient clinic for 2.7 years, and most were in NYHA class I (54.0%) or II (38.1%). The median daily doses of ACEIs, beta blockers, and loop diuretics were 10 milligrams (mg) of lisinopril-equivalent, 25 mg of carvedilol-equivalent, and 40 mg of furosemide, respectively. Almost all patients had the ACEI prescribed once a day (98.4%), while a large proportion of patients had the beta blocker (60.3%), as well as the loop diuretic (44.6%) prescribed twice daily. Regarding the 3 drugs being monitored, most patients (61.9%) had at least 2 different daily administrations, while only 8 (12.7%) took all the drugs at a single time. The mean number of all drugs taken per patient was 7.8.

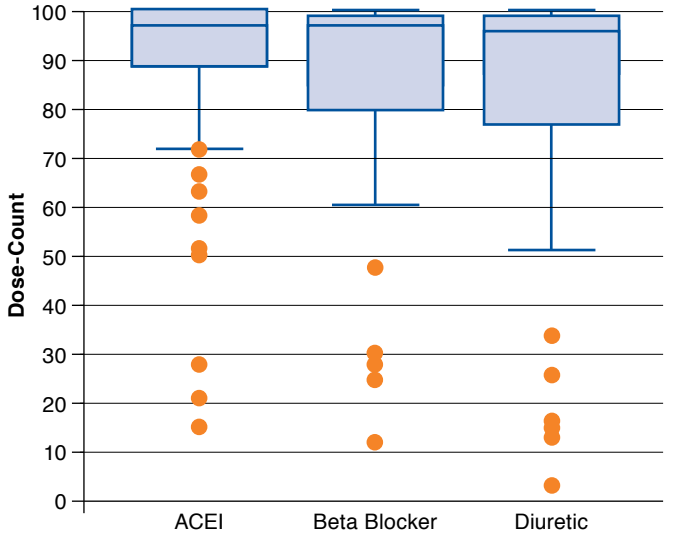
Patients were monitored with MEMS for a median of 96 (P25-P75: 89-105) days, with a minimum and a maximum of 49 and 180 days, respectively. The median proportion of doses taken was 97.3% (P25-P75: 88.7-100.0) for ACEIs, 97.2% (P25-P75: 79.6-99.1) for beta blockers, and 96.0% (P25-P75: 76.6-98.9) for loop diuretics (Figure 2). On average, the difference in adherence to each of the drugs was small (beta blocker vs. ACEI: -3.4%; beta blocker vs. diuretic: -1.0%; ACEI vs. diuretic: -4.4%), but in individual patients, it ranged from -35% of doses to 33% of doses for specific drug classes, indicating that patients who failed drug doses were often not the same among the 3 drug classes (Figure 3).

TABLE 1 Sociodemographic and Clinical Characteristics of the Study Sample

Sociodemographic characteristics		
Age (years), mean [SD]	63.5	[13.2]
Male sex, n (%)	51	(81.0)
Education (years), n (%)		
≤9	52	(82.5)
>9	11	(17.5)
Income, n (%)[a]		
≤National minimum wage	44	(74.6)
>National minimum wage	15	(25.4)
Marital status, n (%)		
Married	50	(79.4)
Single/divorced/widowed	13	(20.6)
Clinical characteristics		
Moderate-severe LVSD, n (%)[b]	58	(92.1)
NYHA functional class, n (%)		
Class I	34	(54.0)
Class II	24	(38.1)
Class III	5	(7.9)
HF etiology, n (%)		
Ischemic	27	(42.9)
Nonischemic	36	(57.1)
Comorbidities, n (%)		
Dyslipidemia	39	(61.9)
Hypertension	31	(49.2)
Diabetes mellitus	21	(33.3)
Chronic obstructive pulmonary disease	17	(27.0)
Chronic renal failure	11	(17.5)
Length of follow-up in the HF clinic (years), median (P25-P75)	2.7	(1.2-4.8)
Prescribed medication		
Daily dose of ACEI (mg), median (P25-P75)[c]	10	(5-20)
Frequency of ACEI (times/day), n (%)		
Once daily	62	(98.4)
Twice daily	1	(1.6)
Daily dose of beta blocker (mg), median (P25-P75)[d]	25	(25-50)
Frequency of beta blocker (times/day), n (%)		
Once daily	25	(39.7)
Twice daily	38	(60.3)
Daily dose of diuretic (mg), median (P25-P75)	40	(40-100)
Frequency of diuretic (times/day), n (%)		
Once daily	35	(55.6)
Twice daily	28	(44.4)
Schedules with HF medication: (ACEI, beta blocker, and diuretic), n (%)		
Once daily	8	(12.7)
Twice daily	31	(49.2)
Three times daily	24	(38.1)
Total number of drugs, mean [SD]	7.8	[2.5]

[a]*n = 59.*
[b]*Ejection fraction < 40%.*
[c]*Lisinopril-equivalent.*
[d]*Carvedilol-equivalent.*
ACEI = angiotensin-converting enzyme inhibitor; HF = heart failure; LVSD = left ventricular systolic dysfunction; mg = milligram; NYHA = New York Heart Association; P25-P75 = 25th-75th percentiles; SD = standard deviation.

FIGURE 2 Adherence to Specific Drugs for Heart Failure

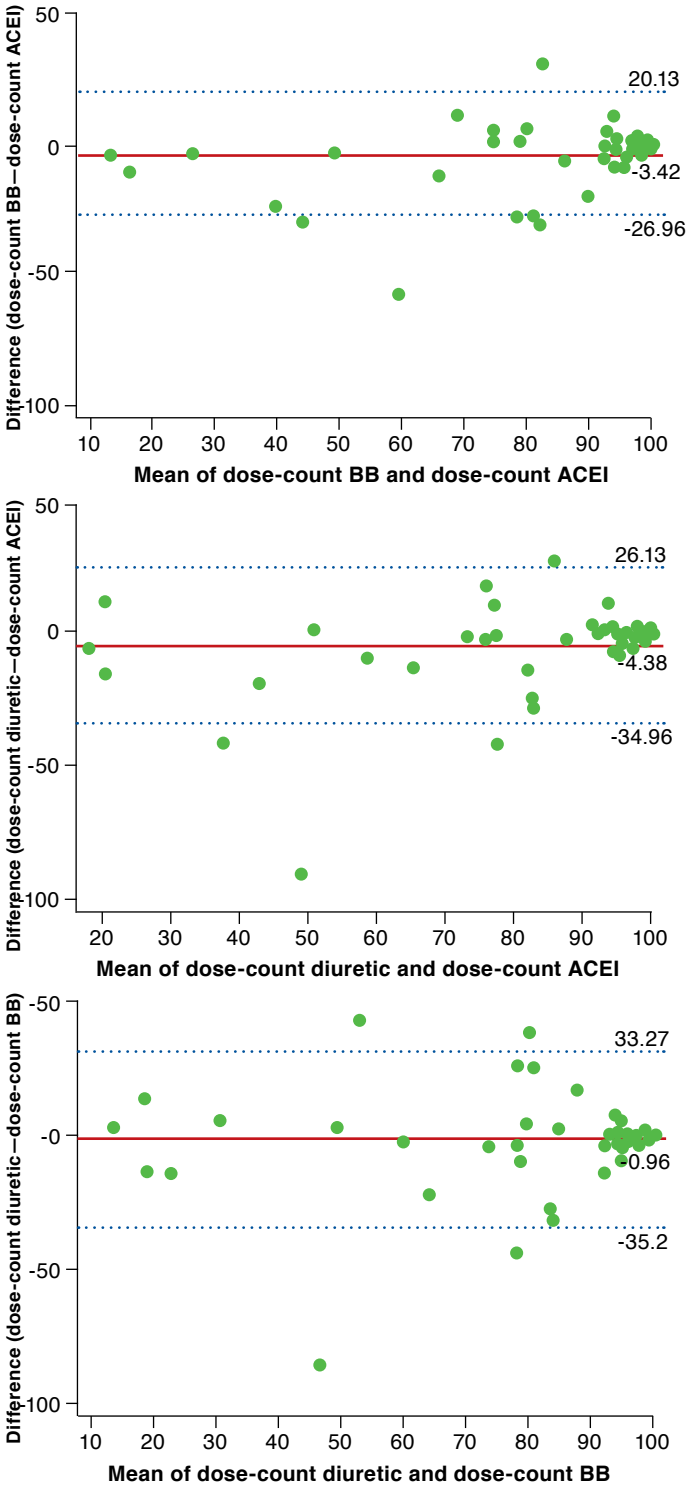


[a]*Dose-count is the percentage of prescribed doses taken.*
ACEI = angiotensin-converting enzyme inhibitor.

Among the 63 patients, 49 (77.8%) were classified as adherent to ACEIs, 44 (69.8%) to beta blockers, and 44 (69.8%) to loop diuretics. Our results show that 81% of the patients were concordant, either adherent or nonadherent to the 3 drugs, while 19% of the patients were classified either as adherent or nonadherent, depending on the specific drug analyzed. Among the patients with a discordant classification, 4 (33.3%) patients were adherent to ACEIs and beta blockers and nonadherent to loop diuretics; 4 (33.3%) patients were adherent to ACEIs and loop diuretics and nonadherent to beta blockers; 2 (16.7%) patients were adherent to ACEIs and nonadherent to loop diuretics and beta blockers; and the other 2 (16.7%) patients were nonadherent to ACEIs and to 1 of the other drugs classes. Agreement in patient classification regarding adherence in each pair of drug classes was substantial (beta blocker vs. ACEI: K = 0.72; beta blocker vs. diuretic: K = 0.62; ACEI vs. diuretic: K = 0.72; Table 2).[18]

The characteristics of patients and therapeutic regimen according to the classification as adherent to all drugs, nonadherent to all drugs, and nonadherent to 1 or 2 drugs are presented in Table 3. Unspecific nonadherence to all drugs was associated with younger age, while adherence to all drugs was associated with higher education and income, but the differences were not statistically significant. Higher doses of ACEIs and beta blockers and more complex regimens were associated with unspecific nonadherence, while dose and frequency of

FIGURE 3 Agreement in Adherence to Different Drugs for Heart Failure



[a]*Dose-count is the percentage of prescribed doses taken.*
ACEI = angiotensin-converting enzyme inhibitor; BB = beta blocker.

diuretics had a gradual inverse association with adherence (highest in unspecific nonadherents, intermediate in partial adherents, and lowest in adherents to all drugs).

Discussion

The present study provides evidence on medication adherence simultaneously to 3 different drug classes—ACEIs, beta blockers, and loop diuretics—in HF patients. Overall, one-fifth to one-third of the patients took less than 88% of prescribed doses of each drug class and were thus classified as nonadherent. The proportion of nonadherent patients was larger for beta blockers and loop diuretics than for ACEIs. Furthermore, although most patients were classified as adherent or nonadherent to all 3 drugs, about 20% of the patients were adherent to 1 drug and nonadherent to another, indicating that adherence can be variable according to drug classes.

In previous studies, medication adherence rates in patients with HF have been highly variable, ranging from 10% to 100%, which can be explained, at least partially, by the diversity of methods used to assess adherence.[5,12,14,15,19-24] Medication adherence can be assessed using direct and indirect methods, but no gold standard is widely accepted. Direct methods include the measurement of serum or urine drug levels and biologic markers,[25] providing information about the recent use of a drug; however, these depend on the variability in metabolism and have shortcomings to quantify adherence in the long term.[16] Medication adherence has been assessed indirectly in patients with HF using self-report,[26] pill counts,[27] prescription refill records,[10,17] and electronic-monitoring devices.[5,14,15,28,29] In our study, the adherence estimated using MEMS was consistent with other studies that measured medication adherence with the same method, among patients with HF.[5,14,15,28,29]

Our data suggest that adherence between drug classes could be different in the same subject, indicating intrasubject disagreement in adherence. Previous studies have monitored only 1 drug with MEMS, assuming that adherence reflects an individual behavior.[4,11,13-15] However, our results do not support this approach, and some recent studies using pharmacy refill data also suggested that it is not enough to monitor 1 drug to understand patient behavior. Gislason et al. (2007) have reported different adherence estimates for inhibitors of the renin angiotensin system (RAS; 79%), beta blockers (65%), and spironolactone (56%).[10] In a study with patients followed in an HF clinic, adherence was 93% for RAS inhibitors, 92% for beta blockers, and 86% for spironolactone after 1 year and 90% for RAS inhibitors, 88% for beta blockers, and 74% for spironolactone after 3 years.[17] These data support our results that patients can adhere differently to specific drug classes. and the assumption might be made that different drugs pose different barriers to adherence.

TABLE 2 Agreement in Patient Classification Regarding Adherence to Different Drugs

		Patient Classification, n (%)[a]			Agreement	
		ACEI				
		Adherent	Nonadherent	Total	K	95% CI
Beta blocker	Adherent	43 (68.3)	1 (1.6)	44 (69.9)	0.72	0.52-0.91
	Nonadherent	6 (9.5)	13 (20.6)	19 (30.1)		
	Total	49 (77.8)	14 (22.2)	63 (100.0)		
		Diuretic				
		Adherent	Nonadherent	Total	K	95% CI
Beta blocker	Adherent	39 (61.9)	5 (7.9)	44 (69.8)	0.62	0.41-0.84
	Nonadherent	5 (7.9)	14 (22.2)	19 (30.1)		
	Total	44 (69.8)	19 (30.1)	63 (100.0)		
		Diuretic				
		Adherent	Nonadherent	Total	K	95% CI
ACEI	Adherent	43 (68.3)	6 (9.5)	49 (77.8)	0.72	0.52-0.91
	Nonadherent	1 (1.6)	13 (20.6)	14 (22.2)		
	Total	44 (69.9)	19 (30.1)	63 (100.0)		

[a]*Patients were classified as adherent when the prescribed number of doses taken exceeded 88%.*
ACEI = angiotensin-converting-enzyme inhibitor; CI = confidence interval; K = kappa coefficient.

The most common method to analyze adherence data has been to classify patients as adherent or nonadherent. However, the cutpoints that have been chosen are commonly arbitrary.[4,30] In order to provide a clinically relevant cutpoint in patients with HF, Wu et al. (2009) have demonstrated that medication adherence rates below 88% were associated with worse clinical outcomes, namely emergency room visits, hospitalizations, and mortality.[4] Using this evidence-based cutpoint, our results have demonstrated a considerable proportion of patients that were nonadherent to ACEIs (22%), to beta blockers (30%), and to loop diuretics (30%). Two studies using the same cutpoint have reported proportions of nonadherent patients that differ from those observed in our sample. One study that measured adherence to 1 drug—which could be either an ACEI, beta blocker, digoxin, or diuretic—reported that 44% were classified as nonadherent.[4] Another study measuring adherence either to an ACEI or an ARB has described a proportion of nonadherent patients of 24%.[5] The Heart Failure Adherence and Retention Trial (HART) found that 37% of the patients took less than 80% of the prescribed medication.[6] The differences observed in the proportions of nonadherent patients can be explained not only by the cutpoint being used, but also by the differences in the criteria to select the drug to be monitored. In these studies, patients were monitored for only 1 drug, which could be different between studies and within the same study.[4-6]

In our study, patients had better adherence to ACEIs than to beta blockers or loop diuretics. A meta-analysis that quantified the association between antihypertensive drug classes and adherence in clinical settings has also concluded that adherence to ACEIs was superior to adherence to beta blockers and loop diuretics.[31] This pattern by drug class can be related to several factors. First, loop diuretics and beta blockers were more frequently prescribed twice daily compared with ACEIs, and frequency of doses is a well-recognized predictor to nonadherence.[11,19,32-36] Second, patients that had beta blockers or loop diuretics prescribed twice daily had the second dose often prescribed in the middle of the day, which can represent a barrier to adherence, since it can interfere with the patients' daily activities. Also, each of the drug classes is associated with different side effects, which can represent an important barrier to adherence.[8] Patients on diuretics can experience an increase in urinary frequency, erectile dysfunction, and muscle cramps.[37] Beta blockers can also cause erectile dysfunction, as well as dizziness, hyperglycaemia, claudication, and bradycardia.[38] These important side effects can make the management of these specific drug classes more difficult.

Adherence is influenced by a multitude of factors such as age, gender, marital status, socioeconomic status, education, comorbidities, disease severity, and regimen complexity. Several studies have investigated the predictors of nonadherence; however, the results are still inconsistent, demonstrating that there is no clear profile for nonadherent HF patients.[9] The complexity of the medication regimen and experienced side effects seem to be particularly important in explaining medication adherence. Our results indicate that patients with lower doses of ACEIs, beta blockers, and loop diuretics were more likely to be adherent to all drugs, corroborating previous research.[11,19,32-36] Also, patients taking loop diuretics once daily were more likely to be adherent to all the drugs. The frequency of loop diuretics is inseparable from its dose, since patients taking higher doses have more frequent daily dosing. Therefore,

TABLE 3 Patient and Medication Characteristics According to Agreement in Patient Classification Regarding Adherence to Different Drugs

	Nonadherent to All Drugs		Nonadherent to 1 or 2 Drugs		Adherent to All Drugs		*P* Value
	n (%)		n (%)		n (%)		
Total	12	(19.1)	12	(19.1)	39	(61.9)	
Patient characteristics							
Aged ≤ 65 years	9	(75.0)	6	(50.0)	16	(41.0)	0.120
Male sex	9	(75.0)	9	(75.0)	33	(84.6)	0.641
Education ≤ 9 years	12	(100.0)	11	(91.7)	29	(74.4)	0.080
Income ≤ national minimum wage	11	(91.7)	10	(83.3)	23	(65.7)	0.151
Married	9	(75.0)	8	(66.7)	33	(84.6)	0.372
Moderate or severe LVSD	11	(91.7)	11	(91.7)	36	(92.3)	0.996
NYHA class I (vs. II-III)	6	(50.0)	6	(50.0)	22	(56.4)	0.884
Ischemic etiology	4	(33.3)	4	(33.3)	19	(48.7)	0.488
Hypertension	7	(58.3)	3	(25.0)	21	(53.9)	0.170
Diabetes mellitus	4	(33.3)	3	(25.0)	14	(35.9)	0.783
Dyslipidemia	9	(75.0)	6	(50.0)	24	(61.5)	0.450
Chronic obstructive pulmonary disease	3	(25.0)	3	(25.0)	11	(28.2)	0.962
Chronic renal failure	3	(25.0)	3	(25.0)	5	(12.8)	0.466
≤ 1 year of follow-up at the HF clinic	1	(8.33)	3	(25.0)	7	(18.0)	0.556
Medication characteristics							
ACEI > 10 mg/day[a]	8	(66.7)	0	(0.0)	14	(35.9)	0.003
Beta blocker >25 mg/day[b]	9	(75.0)	1	(8.3)	17	(43.6)	0.004
Diuretic > 40 mg/day	10	(83.3)	7	(58.3)	14	(35.9)	0.013
ACEI 2 times/day	1	(8.33)	0	(0.0)	0	(0.0)	0.115
Beta blocker 2 times/day	7	(58.3)	6	(50.0)	25	(64.1)	0.675
Diuretic 2 times/day	10	(83.3)	6	(50.0)	12	(30.7)	0.005
3 times/day for HF medication[c] (vs. 1-2)	8	(66.7)	3	(25.0)	13	(33.3)	0.067
> 8 different drugs prescribed	10	(83.3)	9	(75.0)	29	(74.4)	0.811

[a]*Lisinopril-equivalent.*
[b]*Carvedilol-equivalent.*
[c]*Angiotensin-converting enzyme inhibitors, beta blocker, and diuretics.*
ACEI = angiotensin-converting enzyme inhibitor; HF = heart failure; LVSD = left ventricular systolic dysfunction; mg/day = milligrams per day; NYHA = New York Heart Association.

we cannot disentangle if adherence to loop diuretics is related to the frequency or to the dose. Furthermore, this relationship can be explained, to some extent, by reverse causality, since nonadherent patients may have had more severe symptoms and, consequently, higher doses of prescribed loop diuretics.

Limitations

The design of this study offered the opportunity to measure simultaneously medication adherence to 3 different drugs classes using MEMS. However, there are some important limitations of this study that need to be acknowledged.

High adherence rates observed might be explained by patients' selection criteria, since patients who were selected by doctors for the study and who agreed to participate might be more motivated to adhere to medication. Moreover, lower participation was associated with older age and not being married. Although some studies found older age to have a positive effect on adherence, the results are still inconsistent.[9]

This study applies to a Portuguese setting, where the medication reimbursement scheme is embedded in the National Health Service, which is funded by general taxation and provides health coverage for the whole population. The costs of medication are partially supported by the government and partially by the patients. The reimbursement scheme is divided into 4 tiers, according to the essentiality of the drug.[39] ACEIs, beta blockers, and loop diuretics are included in the second tier, which includes essential drugs for chronic diseases that are reimbursed for 69% of the drug price. Furthermore, an extra reimbursement of 15% can be applied to low-income patients. Thus, patients in our sample had costs with medication, and the level of reimbursement was uniform within the study sample.

Due to the selection procedures and the participants' characteristics, as well as the characteristics of the Portuguese health care system, the generalizability of the results to the whole HF population should be done with caution.

Conclusions

We demonstrated that a considerable proportion of patients were nonadherent to ACEIs, beta blockers, and loop diuretics. Furthermore, there are differences in adherence to different drug classes with lower adherence rates associated with loop diuretics and beta blockers and higher adherence rates associated with ACEIs. Also, patients could be adherent to 1 drug and nonadherent to another. Our findings indicate that studies measuring medication adherence should always specify the drug class being analyzed and should not mix different drug classes to generalize about adherence behavior.

Authors

MARTA VIANA, MSc, is a Graduate Student; ANA AZEVEDO, MD, PhD, is Assistant Professor of Epidemiology; and NUNO LUNET, MPH, PhD, is Assistant Professor of Epidemiology, Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, and Institute of Public Health of the University of Porto, Portugal. OLGA LASZCZYNSKA, MSc, and SANDRA MENDES, MSc, are Research Fellows, Institute of Public Health of the University of Porto, Portugal. FERNANDO FRIÕES, MD, and PATRÍCIA LOURENÇO, MD, are Attending Internists, Department of Internal Medicine, and PAULO BETTENCOURT, MD, PhD, is Head, Department of Internal Medicine, Centro Hospitalar de São João, Porto, Portugal.

AUTHOR CORRESPONDENCE: Marta Viana, MSc, Instituto de Saúde Pública da Universidade do Porto, Rua das Taipas nº 135, 4050-600 Porto, Portugal. Tel.: +351.222.061.820; Fax: +351.222.061.821; E-mail: marta.viana@ispup.up.pt.

DISCLOSURES

This study was supported by Fundação para a Ciência e a Tecnologia (PTDC/SAU-ESA/107940/2008). The authors declare no conflicts of interest.

Viana collaborated in the analysis and interpretation of the data and wrote the first draft of the article. Laszczynska and Mendes collaborated in the acquisition of the data and revision of the manuscript. Friões, Lourenço, and Bettencourt recruited patients and reviewed the article critically for important intellectual content. Azevedo and Lunet designed the study, analyzed and interpreted the data, and reviewed the article critically for important intellectual content. All authors read and approved the final manuscript.

REFERENCES

1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93(9):1137-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17699180. Accessed July 30, 2014.

2. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33(14):1787-847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22611136. Accessed July 30, 2014.

3. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):1810-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23741057. Accessed July 30, 2014.

4. Wu J, Moser D, Lennie T, et al. Defining an evidence-based cutpoint for medication adherence in heart failure. *Am Heart J*. 2009;157(2):285-91. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19185635. Accessed July 30, 2014.

5. Nieuwenhuis MM, Jaarsma T, van Veldhuisen DJ, van der Wal MH. Self-reported versus 'true' adherence in heart failure patients: a study using the Medication Event Monitoring System. *Neth Heart J*. 2012;20(7-8):313-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22527915. Accessed July 30, 2014.

6. Calvin JE, Shanbhag S, Avery E, Kane J, Richardson D, Powell L. Adherence to evidence-based guidelines for heart failure in physicians and their patients: lessons from the Heart Failure Adherence Retention Trial (HART). *Congest Heart Fail*. 2012;18(2):73-78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22432552. Accessed July 30, 2014.

7. Sabaté E. Adherence to long-term therapies: evidence for action. World Health Organization. 2003. Available at: http://whqlibdoc.who.int/publications/2003/9241545992.pdf. Accessed July 30, 2014.

8. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. *Front Pharmacol*. 2013;4:91. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23898295. Accessed July 30, 2014.

9. Oosterom-Calo R, van Ballegooijen AJ, Terwee CB, et al. Determinants of adherence to heart failure medication: a systematic literature review. *Heart Fail Rev*. 2013;18(4):409-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22723048. Accessed July 30, 2014.

10. Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Persistent use of evidence-based pharmacotherapy in heart failure is associated with improved outcomes. *Circulation*. 2007;116(7):737-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17646585. Accessed July 30, 2014.

11. Riegel B, Lee CS, Ratcliffe SJ, et al. Predictors of objectively measured medication nonadherence in adults with heart failure. *Circ Heart Fail*. 2012;5(4):430-36. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22647773. Accessed July 30, 2014.

12. George J, Shalansky SJ. Predictors of refill non-adherence in patients with heart failure. *Br J Clin Pharmacol*. 2007;63(4):488-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17076693. Accessed July 30, 2014.

13. Wu JR, Lennie TA, De Jong MJ, et al. Medication adherence is a mediator of the relationship between ethnicity and event-free survival in patients with heart failure. *J Card Fail*. 2010;16(2):142-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20142026. Accessed July 30, 2014.

14. Wu JR, Moser DK, Chung ML, Lennie TA. Predictors of medication adherence using a multidimensional adherence model in patients with heart failure. *J Card Fail*. 2008;14(7):603-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18722327. Accessed July 30, 2014.

15. Wu JR, Moser DK, Chung ML, Lennie TA. Objectively measured, but not self-reported, medication adherence independently predicts event-free survival in patients with heart failure. *J Card Fail*. 2008;14(3):203-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18381183. Accessed July 30, 2014.

16. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther*. 1999;21(6):1074-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10440628. Accessed July 30, 2014.

17. Gjesing A, Schou M, Torp-Pedersen C, et al. Patient adherence to evidence-based pharmacotherapy in systolic heart failure and the transition of follow-up from specialized heart failure outpatient clinics to primary care. *Eur J Heart Fail*. 2013;15(6):671-78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Gjesing+A%2C+Schou+M%2C+Torp-Pedersen+C. Accessed July 30, 2014.

18. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159-74. Available at: http://www.ncbi.nlm.nih.gov/pubmed/843571. Accessed July 30, 2014.

19. van der Wal MH, Jaarsma T, van Veldhuisen DJ. Non-compliance in patients with heart failure; how can we manage it? *Eur J Heart Fail*. 2005;7(1):5-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15642526. Accessed July 30, 2014.

20. Dunlay SM, Eveleth JM, Shah ND, McNallan SM, Roger VL. Medication adherence among community-dwelling patients with heart failure. *Mayo Clin Proc*. 2011;86(4):273-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21389248. Accessed July 30, 2014.

21. Murray MD, Young J, Hoke S, et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. *Ann Intern Med*. 2007;146(10):714-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17502632. Accessed July 30, 2014.

22. Bagchi AD, Esposito D, Kim M, Verdier J, Bencio D. Utilization of, and adherence to, drug therapy among Medicaid beneficiaries with congestive heart failure. *Clin Ther*. 2007;29(8):1771-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17919558. Accessed July 30, 2014.

23. Bohachick P, Burke LE, Sereika S, Murali S, Dunbar-Jacob J. Adherence to angiotensin-converting enzyme inhibitor therapy for heart failure. *Prog Cardiovasc Nurs*. 2002;17(4):160-66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12417831. Accessed July 30, 2014.

24. Evangelista LS, Berg J, Dracup K. Relationship between psychosocial variables and compliance in patients with heart failure. *Heart Lung*. 2001;30(4):294-301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11449216. Accessed July 30, 2014.

25. MacFadyen RJ, Gorski JC, Brater DC, Struthers AD. Furosemide responsiveness, non-adherence and resistance during the chronic treatment of heart failure: a longitudinal study. *Br J Clin Pharmacol*. 2004;57(5):622-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15089816. Accessed July 30, 2014.

26. Muzzarelli S, Brunner-La Rocca H, Pfister O, et al. Adherence to the medical regime in patients with heart failure. *Eur J Heart Fail*. 2010;12(4):389-96. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20172940. Accessed July 30, 2014.

27. Granger BB, Swedberg K, Ekman I, et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. *Lancet*. 2005;366(9502):2005-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16338449. Accessed July 30, 2014.

28. Wu JR, Corley DJ, Lennie TA, Moser DK. Effect of a medication-taking behavior feedback theory-based intervention on outcomes in patients with heart failure. *J Card Fail*. 2012;18(1):1-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22196835. Accessed July 30, 2014.

29. Udelson JE, Pressler SJ, Sackner-Bernstein J, et al. Adherence with once daily versus twice daily carvedilol in patients with heart failure: the Compliance And Quality of Life Study Comparing Once-Daily Controlled-Release Carvedilol CR and Twice-Daily Immediate-Release Carvedilol IR in Patients with Heart Failure (CASPER) Trial. *J Card Fail*. 2009;15(5):385-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19477398. Accessed July 30, 2014.

30. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009;119(23):3028-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19528344. Accessed July 30, 2014.

31. Kronish IM, Woodward M, Sergie Z, Ogedegbe G, Falzon L, Mann DM. Meta-analysis: impact of drug class on adherence to antihypertensives. *Circulation*. 2011;123(15):1611-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21464050. Accessed July 30, 2014.

32. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23(8):1296-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11558866. Accessed July 30, 2014.

33. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther*. 2001;26(5):331-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11679023. Accessed July 30, 2014.

34. Mills EJ, Nachega JB, Bangsberg DR, et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. *PLoS Med*. 2006;3(11):e438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17121449. Accessed July 30, 2014.

35. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm*. 2012;18(7):527-39. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=15582.

36. Bae JP, Dobesh PP, Klepser DG, et al. Adherence and dosing frequency of common medications for cardiovascular patients. *Am J Manag Care*. 2012;18(3):139-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22435907. Accessed July 30, 2014.

37. Weinberger MH. Diuretics and their side effects. Dilemma in the treatment of hypertension. *Hypertension*. 1988;11(3 Pt 2):II16-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3280487. Accessed July 30, 2014.

38. Barron AJ, Zaman N, Cole GD, Wensel R, Okonko DO, Francis DP. Systematic review of genuine versus spurious side-effects of beta-blockers in heart failure using placebo control: recommendations for patient information. *Int J Cardiol*. 2013;168(4):3572-79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23796325. Accessed July 30, 2014.

39. Teixeira I, Vieira I. Pharmaceutical pricing and reimbursement information: Portugal. October 2008. Available at: https://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO_DO_MERCADO/OBSERVATORIO/Projectos_Internacionais/Portugal_PPRI_2008.pdf. Accessed July 30, 2014.