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Electronic measurement of medication adherence in patients with heart failure

Elektroniczny pomiar regularności przyjmowania leków u pacjentów z niewydolnością serca

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Abstract

Introduction. Heart failure (HF) is a significant clinical and socioeconomic problem both in Poland and around the world. However, objective data on the level of adherence in the era of improved medical therapy is lacking. Therefore, the aim of the study was to investigate the level of medication adherence and its association with demographical and clinical variables in patients with HF.

Material and methods. We have conducted a prospective cohort study of 25 patients with diagnosed HF. Medication adherence was measured for 30 consecutive days using the Medication Event Monitoring System (MEMS) — an electronic cap attached to the medication container, allows to record the exact moment of taking the measured medicine. Based on the acquired data, patients were classified as adherent or non-adherent using an evidence-based cut-point. In addition to adherence measurement, patients' demographic and clinical information was collected.

Results. Twenty-two patients provided full results from the MEMS devices. The median age of the patients was 70 years (interquartile range =14), and the mean left ventricular ejection fraction was 33% ± 12. The mean percentage of correct doses was 89% ± 17. Twenty-seven percent of patients (n = 6) were classified as non-adherent. Patients classified as non-adherent were significantly younger (54 vs. 71 years; p = 0.015), had a lower left ventricular ejection

fraction (24 vs. 36%; p = 0.04), and were more frequently enrolled after HF hospitalization (83 vs. 19%; p = 0.011).

Conclusions. In the short-term observation, a significant proportion of patients with HF were found to be non-adherent. In our study, we identified a population with an increased risk of non-adherence. Those patients require the implementation of more intensive and targeted healthcare system-based interventions in order to improve their prognosis.

Key words: heart failure, medication adherence, telemedicine

Introduction

Heart failure (HF) is a significant clinical and socioeconomic problem both in Poland and around the world. It is estimated that the prevalence of HF in the general population of adult patients is about 1–2% [1]. In Poland, there are around 1,240,000 patients with heart failure, and according to the statistics of the National Health Fund and the Central Statistical Office from 2021, it was the primary cause of over 120,000 deaths per year [2, 3]. Patients diagnosed with HF are hospitalized on average once a year, and the financial burden associated with this diagnosis is very high — it is estimated that expenditure related to HF accounts for approximately 0.6% of Poland's gross domestic product [1, 2]. Recently, new drugs have been registered in the treatment of HF, like angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i), which were proven to reduce mortality and the number of hospitalizations for cardiovascular reasons [4, 5]. However, as the patient's pill burden is gradually increasing, so are concerns about non-adherence to guideline-directed medical therapy, which may lead to deterioration of treatment results [6, 7]. It has been previously shown that non-adherence can be the cause of 20–64% of HF readmissions [8]. However, objective data on the level of adherence in the era of improved medical therapy is lacking. Therefore,the aim of the study was to investigate the level of medication adherence and its association with demographical and clinical variables in patients with HF.

Materials and methods

Study design and population

We have conducted a prospective cohort study of patients with diagnosed HF. Twenty-five participants were enrolled in the period from April 2021 to March 2022, both directly after HF-related hospitalization in the Cardiology Department of the Central Clinical Hospital in Lodz, as well as in the cardiology outpatient clinic. Eligible patients were aged 18 years or older, with the diagnosis of HF according to the European Society of Cardiology Guidelines [1], with symptoms in I–III New York Heart Association (NYHA) class and N-terminal pro-B-type natriuretic peptide concentration greater than or equal to 125 pg/mL in patients with sinus rhythm or 365 pg/mL in patients with atrial fibrillation. Exclusion criteria were defined as life expectancy < 1 year, acute coronary syndrome or stroke within the last 3 months, and presence of cognitive impairment that, in the investigator's opinion, prevents the proper use of the monitoring device in accordance with the instructions. The study complied with the Declaration of Helsinki and was approved by the local medical ethics committee. Written informed consent was provided by all patients prior to their participation in the study.

Measurements of adherence

Medication adherence was continuously measured using the Medication Event Monitoring System (MEMS, Aardex Group, Belgium). MEMS is an electronic cap attached to the medication container, allowing one to record the exact moment of taking the measured medicine. The recorded data can then be transferred with a dedicated electronic reader, as shown in Figure 1. Devices of this type have been vastly used in studies evaluating adherence of patients treated for chronic conditions like ischemic heart disease, hypertension, and HF [9–11]. The information stored on the device was transferred to the Study Site during the follow-up visit, which took place at least 30 days after the enrollment. If such a visit was delayed, only the data from 30 days after the beginning of monitoring was analyzed. The choice of the monitored drug was made at the beginning of the study after consultation with the patient. Preferentially it was a HF drug (for example, angiotensin-converting-enzyme inhibitor, angiotensin II receptor blocker, ARNI, beta-blocker, mineralocorticoid receptor antagonist or SGLT-2i) with priority for the substance with twice-daily dosing. Using diuretics as a monitored drug was avoided. It was possible to change the monitored drug under special circumstances after consultation with the Site, provided that the new drug was dosed in the same way.

A missed dose was defined as the device not being opened for 24 hours for once-daily drugs and 12 hours from midnight to noon and noon to midnight for twice-daily drugs.

Satisfactory dose intake (dosing adherence) was defined as at least 88% of doses taken out of all planned doses, and patients with this percentage were classified as adherent. Conversely, patients with lower dosing adherence were classified as non-adherent. The above cut-off point was selected based on an earlier study in patients with HF, where it was shown that the percentage of doses taken equal to or greater than 88% is associated with a significant reduction in cardiovascular events [12]. This cut-off point was also subsequently used in other studies of patients with HF [11, 13].

Subjects' demographic and clinical data

Before handing over the measuring device, patient characteristics were collected, such as age, gender, years of education, marital status, presence of cohabitants, place of residence (village, city), number of years since the diagnosis of HF, the overall number of drugs taken, number of hospitalizations due to HF in the previous 12 months. Clinical information such as left ventricular ejection fraction (LVEF, %), NYHA functional class, and level of N-terminal pro-B-type natriuretic peptide was also acquired from the medical record.

Data analysis

All the data from the study were analyzed using STATISTICA 13.3 software (TIBCO, Palo Alto, CA, USA). Descriptive statistics were used to characterize the study population and assess medication adherence. The normality of data was assessed with the Shapiro–Wilk test. Categorical variables are presented as percentages, while continuous variables are presented using means with standard deviation or median with interquartile range. Differences between adherent and non-adherent patients were tested using Fisher's exact test for dichotomous variables and Student's T test or Mann–Whitney test for normally and non-normally distributed continuous variables respectively. The p-value < 0.05 was considered statistically significant.

Results

Twenty-five patients were enrolled in the study, of whom 22 provided full results from the MEMS devices. One patient lost the device during another HF hospitalization and 2 patients

refused to use the device during the follow-up. The characteristics of the patients with full data acquired are presented in Table 1.

The mean percentage of correctly taken doses was 89% and 73% of patients (n = 16) were classified as adherent. Examples of readings from devices used by adherent and non-adherent patients are presented in Figure 2. Patients classified as non-adherent (27%; n = 6) were significantly younger (54 vs. 71; p = 0.015), had a lower LVEF (24 vs. 36%; p = 0.04), and were more frequently enrolled after HF hospitalization (83 vs. 19%; p = 0.011). There were no statistically significant differences in other parameters.

Discussion

The presented study provides insight into the objectively measured level of adherence in a prospective cohort of contemporary patients with HF. Although the mean dosing adherence of the studied population is 89%, the percentage of patients meeting the evidence-based criteria for satisfactory adherence is only 73%. Previous research conducted on patients with HF showed different levels of medication non-adherence ranging from 11% to 61% [14–16]. Those significant discrepancies may be caused by varying adherence assessment methods (questionnaires, electronic monitoring devices, prescription databases), as well as diverse populations and different healthcare systems in which participants were recruited. However, one study based on a similar methodology estimated the percentage of adherent ambulatory HF patients to be 76% [13].

In our study, the non-adherent patients were significantly younger. The results of previous studies evaluating the effect of age on adherence in patients with cardiovascular disease are ambiguous [17–20]. One of the studies on hypertensive patients showed that there is a U-shaped relationship — both older and younger patients are less adherent, with most adherent patients at the age of 60 to 69 years [21]. However, a systematic literature review of several studies measuring adherence specifically in patients with HF showed that older age alone is not related to poorer medication adherence and in fact, there might be a positive correlation of age and adherence, which is consistent with the results of our study [22].

Furthermore, the non-adherent patients had significantly lower ejection fraction. Similar results have been reported previously in a study using a questionnaire method of assessing medication adherence [23]. Moreover, this relationship may be also related to the fact that the non-adherent patients were more frequently enrolled after HF hospitalization as

opposed to the adherent patients. We did not find any previous research on such a relationship in the literature, however, it may reflect the established fact that non-adherence is a major cause of failure exacerbation, resulting in a greater number of non-adherent patients in the hospital population [8]. For that reason, future interventions aimed at increasing adherence should consider focusing on patients after recent HF hospitalization.

Interestingly, we have not detected any association between adherence and the complexity of the monitored drug regimen (once daily vs. twice daily). Such association has been previously reported in several studies using MEMS [9, 13]. This difference may stem from the fact that the overall number of patients with twice-daily medication regimens was relatively low. Also, the mean total number of medications did not differ between adherent and non-adherent patients, supporting the results of an earlier study in hypertensive patients in which the complexity of the medication regimen, not the number of medications alone, was a predictor of non-adherence [24].

Limitations

There are several limitations to our study. First, the study sample was relatively small, hence we have not performed multivariate analysis. In addition, adherence for only one medication was measured and only the act of opening the device was assessed, therefore, there remains a level of uncertainty about whether patients actually ingested the medicine. Additionally, we can assume that patients who agreed to participate in the study and received the monitoring device are more motivated and may have higher adherence. Nonetheless, apart from repeated measurements of serum drug concentration, electronic measurement of medication adherence is considered to be a gold standard in studies assessing adherence [25].

Conclusions

In the short-term observation, a significant proportion of patients with HF were found to be non-adherent. In our study, we identified a population with an increased risk of non-adherence. Those patients require the implementation of more intensive and targeted healthcare system-based interventions in order to improve their prognosis. Further research conducted on a larger population is needed to confirm the aforementioned observations and to develop effective interventions to increase the level of medication adherence.

Conflict of interest

None declared

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Table 1. Characteristics of the study population with differences between the adherent and non-adherent patients

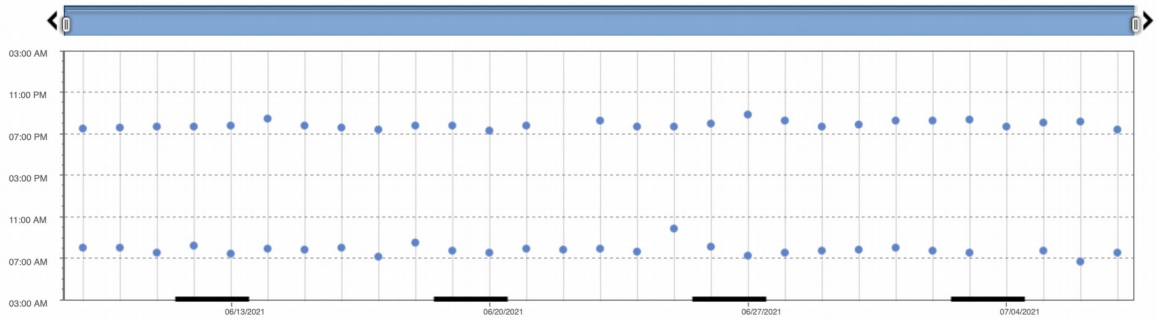
	All patients (n = 22)	Adherent patients (n = 16)	Non-adherent patients (n = 6)	P-value
Age (years) median, (IQR)	70 (14)	71 (5)	54 (11)	**0.015**
Female, % (n)	27% (6)	31% (5)	17% (1)	0.634
Not living alone (%) (n)	86% (19)	81% (13)	100% (6)	0.532
Married % (n)	59% (13)	50% (8)	83% (5)	0.333
Living in a city with population > 20,000	86% (19)	88 % (14)	83% (5)	> 0.999
Higher education % (n)	23% (5)	19 %(3)	33% (2)	0.585
> 1 year since diagnosis of HF % (n)	50% (11)	50% (8)	50% (3)	> 0.999
Inclusion in the study directly after HF hospitalization % (n)	36% (8)	19% (3)	83% (5)	**0.011**
NYHA class % (n)				> 0.999
— I	5% (1)	6% (1)	0% (0)	
— II	82% (18)	81% (13)	83% (5)	
— III	14% (3)	13% (2)	17% (1)	
NT-proBNP pg/mL, median (IQR)	1571 (1856)	1519 (1682)	1711 (4492)	0.971
LVEF (%), mean ± SD	33 (12)	36 (13)	24 (7)	**0.04**
Total number of medications, mean ± SD	10 (3)	10 (3)	10 (4)	0.884
Dosage twice a day % (n)	23% (5)	25% (4)	17% (1)	> 0.999
Dosing adherence(%), mean, ±SD	89 (17)	98 (3)	67 (20)	

HF — heart failure; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association

Figure 1. The medication Adherence Monitoring System (MEMS), consisted of an electronic cap, medication container, and a reader, enabling the programing of the device as well as transferring the adherence data

Figure 2. Data from a MEMS device was acquired from two patients. Blue dots indicate the precise moment of opening the device: **A.** Patient with twice-daily dosing of a monitored drug. The patient omitted 2 of 60 doses of the drug, hence his dosing adherence is 97%. This patient is considered adherent (dosing adherence ≥ 88%); **B.** Patient with once-daily dosing of a monitored drug. The patient omitted 8 of 30 doses of the drug (dosing adherence 73%). This patient is considered non-adherent

a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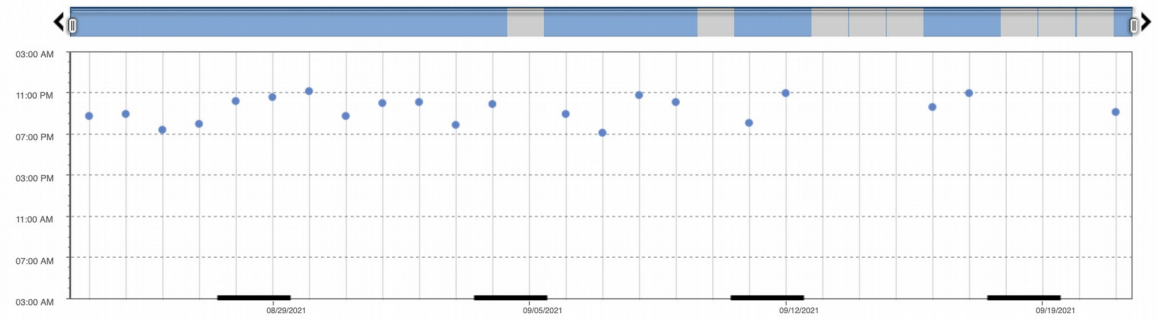
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