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Adherence to Pharmacotherapy in Post-Menopausal Women with Hypertension or Metabolic Syndrome: Real World Experience

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Abstract

Background: Adherence to medications is dependent upon a variety of factors, including individual characteristics of the patient, interactions with health care providers, and medication complexity. Even though several studies were conducted to test intervention strategies, results are uncertain. **Aim:** The aim of the study is to assess if a tailored combined intervention strategy improves medication adherence in a large population of post-menopausal women affected by hypertension or metabolic syndrome. **Methods:** We enrolled 6833 patients aged 50 to 69 years, 85.7% with hypertension, and 14.3% with metabolic syndrome. A network between patients, general practitioners, and cardiologists was established. Interventions included education, adequate information to patients, a simplified scheme of treatment, and periodic adherence assessment. These were either delivered as healthcare provider supports or using modern technology. Medication adherence was estimated by the proportion of days covered for all classes of drugs after the index date. **Results**: Non-adherent hypertensive women were 297 (5%), and those with metabolic syndrome were 73 (7.4%) ($p < 0.02$). Considering only patients with cardiomyopathy non-adherent were 234 (5.4%), while without cardiomyopathy 136 (5.3%); non-adherent hypertensive postmenopausal women with cardiomyopathy were 194 (5.2%), non-adherent postmenopausal women with metabolic syndrome and cardiomyopathy were 40 (7.2%) ($p < 0.04$). Non-adherent hypertensive postmenopausal women without cardiomyopathy were 103 (4.9%), and non-adherent postmenopausal women with metabolic syndrome and without cardiomyopathy were 33 (7.7%) ($p < 0.01$). **Conclusions:** The rate of non-adherence in both settings of postmenopausal women was 7.7%, much lower than that described in the literature. This rate

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was increased in patients with metabolic syndrome; probably it is related to the complexity of the therapeutic scheme or to a poor consciousness of the disease. Therefore, implementing a tailored combined intervention can improve significantly patients' adherence to medical therapy.

Keywords

Adherence, Cardiovascular Prevention, Postmenopausal Women, Hypertensive, Metabolic Syndrome

1. Introduction

The risk of CVD increases markedly after menopause [1]. Menopause is characterized by a decrease in the endogenous production of estrogen, which is associated with vascular dysfunction, increased blood pressure, redistribution of body fat toward abdominal areas, and hyperlipidemia, all of which increases CVD risk [1]. The typical age range for menopausal transition is between 45 and 55 years; menopause onset at an age younger than 45 years is considered early menopause [1]. Early menopause may be more detrimental to women's cardiovascular health because of the early cessation of estrogen's cardiovascular protection [1]. Early menopause has been associated with an increased risk of coronary heart disease (CHD) [2] and heart failure (HF) and less consistently with stroke [3]. Midlife women with underlying metabolic disorders face a higher risk of CVD [2]. Although effective medications that control risk factors and reduce the risk of cardiovascular disease are available, low adherence to drugs, especially to the polypill approach, persists as major public health and clinical challenge. Interventions to promote medication adherence may target a number of identified patient specific-barriers: lack of symptoms [4], depression [5], low health literacy, medication complexity, cost, and concerns, use of alternative medicine, poor health care system perceptions; poor communication or provider-patient interaction, medication side effects; forgetfulness; inadequate social support or coping, caring for dependents, and lack of motivation for self-care [6] [7] [8]. Interventions that target these factors can be classified as informational, behavioral, social, or combined [9]. Informational interventions use didactic or interactive approaches to educate and motivate patients and to increase their understanding of their condition and its treatment [10]. Behavioral interventions move beyond the cognitive approaches of informational interventions to influence patient behaviors by shaping, reminding, or rewarding desired behaviors, whereas social interventions enlist family members or others in supporting medication adherence [10]. Finally, combined interventions include elements of more than one informational, behavioral, or social strategy. Strategies may vary in intensity, setting as an individual or group, mechanism of delivery as face-to-face or technology-mediated, and required personnel as a physician, allied health professional, or lay individual [11]. When evaluating the effectiveness of interven-

tions to improve adherence, consideration should be given to the adherence measure used. Validated objective as pharmacy fill or electronic monitoring [12] [13] [14] and subjective as self-report [15] [16] measures for assessing medication-taking behavior are available. However, notwithstanding a large number of studies previously conducted, the effectiveness of the interventions tested is controversial. In this study combined interventions to promote pharmacological adherence were tested. Pharmacy fill was used to assess medication-taking in a postmenopausal woman with a high risk of cardiovascular events.

2. Methods

2.1. Study Design

This is a retrospective observational study. Ethical approval has been obtained from institutional review boards at the study sites.

2.2. Study Population

We included in our study women in menopause, only after, at least, twelve consecutive months of amenorrhea. The mean age of the patients was 59.9 ± 12 years. None of them was on hormone replacement therapy because estrogen can interfere with arterial stiffness. 5857 of them had a diagnosis of arterial hypertension according to the 2018 European Hypertension Guidelines [17]; moreover, 976 menopausal patients were diagnosed with metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III [18] (**Table 1**). TTE was performed with the patient in left lateral decubitus, after 10 minutes of resting, with the exam table elevated by 30˚. The exam was carried out with 3.5 MHz probe, with ECG trigger. We used echo-Doppler system equipped with a multifrequency transducer, Philips, Epiq 7, Utrasound System for Cardiology, Healthcare, viale Sarca 235, Milan (Italy). We assessed: intraventricular septum thickness in diastole (IVSd) and in systole (IVSs), left ventricular diastolic end-systolic diameter (LVDD), left ventricular posterior wall thickness during in diastole (LVPWd) and in systole (LVPWs), ejection fraction (EF), fractional shortening (FS). Peak velocities of early (E wave) and late (A wave) trans-mitral flow and deceleration time (DT) were determined, E' wave and A' wave by tissue Doppler

Table 1. Main characteristics of the sample.

PMW	6833
HYPERT	5857
HCMP	3752
MeTs	976
MCMP	550

PMW: postmenopausal women enrolled. HYPERT: postmenopausal women with hypertension. HCMP: postmenopausal women with hypertensive cardiomiophaty. MeTs: postmenopausal women with metabolic syndrome. MCMP: postmenopausal women with hypertensive cardiomiophaty.

imaging were determined at mitral annulus level. E/A ratio, E'/A' ratio and E/E' ratio was calculated. LV mass (LVM) was determined according to the formula by Devereux *et al.* [19] and indexed according to body surface area (BSA) to obtain LV mass index (LVMI), normal values of the above echocardiogram parameters according to the American Society of Echocardiography. LVDD was diagnosed according to current guidelines [20], by PW Doppler of mitral inflow and Doppler Tissue Imaging of the mitral annulus. All LVDD subjects had abnormal diastole, for all different degrees of severity. 3752 patients with arterial hypertension had a diagnosis of hypertensive cardiomyopathy [21], 550 postmenopausal patients were diagnosed with metabolic cardiomyopathy, according to well-established diagnostic criteria [22].

2.3. Exclusion Criteria

Exclusion criteria were systolic heart failure assessed by the diagnosis of left ventricular ejection fraction < 45%, wall motion abnormalities, coronary artery diseases, severe valvular and pericardial diseases, atrial fibrillation on enrolment, pulmonary hypertension estimated by tricuspid regurgitation velocity and the modified Bernoulli equation, renal failure assessed by serum creatinine > 1.2 mg/dl and major non-cardiovascular diseases as cancer or chronic lower respiratory tract disease, because these patients followed a strict disease specific follow up that could interfere with the study.

2.4. Study Design and Data Collection

A combined intervention strategy was tested; a network between patients, general practitioners, and cardiologists was established. Interventions were either delivered directly as healthcare provider supports or using modern technology, such as text messaging, e-mail and an online community. Interventions included education, adequate information to patients, a simplified scheme of treatment, and periodic adherence assessment. At the index date, doctors explained the rationale of the therapy: they described the posology and potential side effects of the therapy. The patient was educated to inform the doctor about a side effect without stopping therapy, using a dedicated h24 email service that promptly generated an alert for the doctor. The doctor answered the patients within 48 hours using clinical assessment or text messaging, or email, depending on the patient's specific problem. Medication adherence was estimated by the proportion of days covered for all classes of drugs after the index date. General practitioners used electronic prescription systems; e-prescription had several advantages: increasing the efficiency and effectiveness of prescribing and dispensing medications, reducing errors, improving prescription, more precise dosage and then preventing adverse drug reactions, and monitoring how prescription drugs are prescribed. The lack of the patient's request for the drug for the next therapeutic cycle generated an alert for the general practitioners, then the prescribers called the patients to clarify the matter of the lack of the request. Then, the pre-

scribers reprogrammed medication regimens if necessary, and re-educated patients on how to incorporate medication use into their daily living.

3. Results

Among 5857 menopausal hypertensive women, 3752 of them were affected by hypertensive cardiomyopathy (64%). Among 976 menopausal women with metabolic syndrome, 550 were affected by metabolic cardiomyopathy (56%). Non-adherent hypertensive women were 297 on 5857 (5%); nonadherent women with metabolic syndrome were 73 on 976 (7.2%). Taking into account only patients with cardiomyopathy, the rate of non-adherence was 5.2% between hypertensive women (194 patients on 3752) and 7.2% among patients with metabolic syndrome (40 on 550); on the other hand, the rate of non-adherence in the arm of postmenopausal patients without cardiomyopathy was 4.9% (103 on 2105) between hypertensive women and 7.7% (33 on 426) between patients with metabolic syndrome (Table 2).

4. Discussion

The main finding of our study is a low rate of non-adherence, ranged from 5 to 7% in all setting of menopausal women. A person is generally considered adherent if he or she takes between 80% and 120% of prescribed medication over a given time period [23]. Non adherence to medications has been reported in up to 50% of patients in different countries and settings [23] [24]; indeed non-adherence is a multifactorial issue and it is likely that no single strategy will be effective in all patient groups. Educational and motivational strategies are likely to be required to address intentional non-adherence, while behavioral and provider-focused strategies, such as a medication review focused on regimen simplification, are more likely to be successful in addressing unintentional non-adherence [25].

We observed an increased rate of non-adherence in women with metabolic syndrome when compared with hypertensive patients; this data was probably related to the complexity of the therapeutic scheme or to a poor consciousness of the disease. Medication regimen-related factors such as number of drugs, dosage

Table 2. Main findings of the study.

	Sample distribution	Non-adherent women	
HYPERT	5857	297	5.0%
HCMP	3752	194	5. 2%
MeTs	976	73	7.5%
MCMP	550	40	7.3%
noCMP	426	33	7.7%

PMW: postmenopausal women enrolled; HYPERT: postmenopausal women with hypertension; HCMP: postmenopausal women with hypertensive cardiomiophaty; MeTs: postmenopausal women with metabolic syndrome; MCMP: postmenopausal women with hypertensive cardiomiophaty; noCMP: postmenopausal women without cardiomiophaty.

frequency, administration instructions, and prescribed dosage forms are known to influence regimen complexity and, in turn, patient adherence. Moreover, it is possible that use of drugs interfering with the lifestyle lead patients to make intentional modifications in the dosing by either reducing the frequency of administration or spacing it with their activities. Educating patients on how to incorporate medication use into their daily living and on strategies to meet challenges to adherence could be beneficial. Another possible cause of lower adherence in this subgroup of patients is strong concern about adverse reactions to treatment. Indeed, a cross-sectional study of patients with various chronic illnesses reported that patients with greater concerns about their medications than perceived necessity had lower adherence rates [26]. On the contrary, the presence of cardiomyopathy did not affect medications' assumption, probably because, as previously reported [26], patients believed that their prescribed drug was necessary for maintaining health. Inadequate compliance is an age-old problem.

Numerous studies have demonstrated that inadequate compliance results in increased morbidity and mortality from a wide variety of illnesses, as well as increased healthcare costs [27] [28]. Patients with higher levels of health literacy have rates of adherence that are higher than patients that have low health literacy skills, in addition, health literacy interventions are effective in improving adherence to treatment. The average correlation between health literacy and patient adherence is higher in studies of patients with cardiovascular disease compared with studies of patients with other disease conditions. Perhaps because the consequences of both medication and lifestyle nonadherence in cardiovascular disease can be severe, patients may be more motivated to adhere when properly educated and given the opportunity to understand their treatment regimens [29].

If several factors have been identified as potential predictors of medication adherence, one cannot expect 'one size intervention, to fit all. In general, many of the interventions for long-term medications tend to be exceedingly complex, labor-intensive, costly, and only loosely patient-centric in design. In addition, questions remain as to how to optimally target interventions to patients in non-research settings, particularly in the current era of cost containment and staff reductions. Self-report questionnaires provide an opportunity to obtain information regarding medication adherence directly from the patient, caregiver, or doctor. However, the most important limitation is the lack of use when the patient is unaware of their nonadherent behavior. Therefore, self-reported questionnaires generally tend to overestimate adherence [16]. Recent evidence in type 1 diabetes treatment, showed that interventions targeting psychological and behavioral influences improve therapeutic adherence [30]. Typically, behavioral interventions aim to impact psychosocial and behavioral processes that will ultimately slow or pause clinical control. It is well known that psycho-social factors associated with medication adherence among older adults, hence, life events may be an important factor in adherence to prescribed medications [12]. Nevertheless, three important gaps remain in the study of behavioral interventions

to promote the management of patients with chronic disease: the development of individualized interventions, integration of evidence-based interventions in health and mental health care delivery settings, and advocacy initiatives to increase access to effective behavioral and mental health support. Mobile health technologies, particularly mobile apps, have the potential to improve medication adherence and clinical outcomes [27] but existing evidence is currently insufficient to unreservedly recommend the use of healthcare apps to improve adherence to CVD medications because of the generally small sample sizes, clinical and methodological heterogeneity between studies, and disparity in-app features, content, and delivery. Traditional patient education programs often increase patients' self-care awareness, disease knowledge, and motivation to change patient behaviors for better adherence [31]. Educating patients about their disease status and their medications can also increase patient confidence and participation to the diagnosis-care pathway [32]. Nevertheless, patient trust in physicians, patient-physician relationships, and quality of communication are more critical factors influencing patient adherence. Both patients and providers benefit from regular, ongoing feedback regarding performance in achieving commonly established treatment goals. Some patients benefit from maintaining a daily medication record of each dose taken or missed with relevant comments. The healthcare provider can then review this medication diary over the telephone or at the next clinic visit with the patient. Additional benefits include identifying potential predisposing factors for a relapse into old behavior and setting appropriate and realistic goals for new behaviors.

Our study showed that team-based care, the collaborative setting between primary care provider and cardiologist, and two types of voice messaging (educational and medication refill reminder calls), medication tailoring, and patient education, were significantly more effective in the promotion of therapeutic adherence to drugs. Patients reported that team-based care improved their comfort in asking clarifying questions, raising concerns about their medication regimen, and collaborating in developing their treatment plan. Assessing patient's adherence to medication in real-world settings can identify areas of unmet need and potential intervention opportunities to improve health outcomes.

5. Conclusion

Personalized approaches are required to address adherence barriers in target populations. This paper shows the effectiveness of a tailored combined intervention strategy in improving medication adherence in a large population of postmenopausal women affected by hypertension or metabolic syndrome. The rate of non-adherence in both settings of postmenopausal women was 7.7%, much lower than that described in the literature, mostly due to awareness and efficient connection among prescriber cardiologists, general practitioners, and patients. However, the rate of non-adherence was increased in patients with metabolic syndrome, maybe due to the complex therapeutic approach or to a poor consciousness of the disease. On the contrary, the presence of cardiomyopathy did

not affect medications' assumption, probably due to high consciousness of the disease. Therefore, in future, characterization of the nature of non-adherence could be essential before using specific interventions to significantly improve patient's adherence to medical therapy in a real-world setting. The most important point of strength of this work is the use of rigorous inclusion criteria, then we enrolled a homogeneous sample of patients. An important limitation of the study is the lack of subgroups stratification based on the pharmacological therapy: as the number of drugs and the side effects could be major components of non-adherence, in future, these results need to be put in the context of the actual therapy the population is treated with. Finally, we propose further research focused on developing innovative ideas for a collaborative setting between primary care providers, cardiologists, and patients with chronic diseases to investigate the efficacy of this method on long-term treatment outcomes and treatment adherence in clinical practice.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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