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Research paper

Antihypertensive medication adherence trends by sex and drug class: A pilot study

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ABSTRACT

Introduction: Antihypertensive medication nonadherence is a prevalent issue but is very difficult to accurately assess. To clarify this problem among hypertensive patients attending a cardiovascular disease outpatient clinic, we utilized high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS) to assess antihypertensive medication adherence and identify trends by sex and drug class.

Methods: Serum was extracted from blood samples obtained from patients with either drug-controlled or drug resistant hypertension (RHTN) and analyzed via HPLC-MS for antihypertensive drugs which were categorized by drug class as beta blockers, aldosterone antagonists, diuretics, ACE inhibitor/ARBs, or calcium channel blockers. Clinic blood pressure (BP), sex, and prescription regimens were extracted from medical records at or near the time of blood collection. "Adherence" or "nonadherence" was determined by comparison of the patient's prescribed drug regimen and the presence/absence of prescribed drug(s) in their serum.

Results: Among 76 patients (47 women; mean age 63; 53% white), nonadherence was confirmed in 29%. RHTN was more frequently identified in women than men (55% vs 38%) and nonadherence was higher in women than men (34% vs 21%). BP in those who were adherent to prescribed antihypertensive drugs was significantly lower than in those who were nonadherent (129/75 vs 145/83 mmHg, $p = 0.0015$). Overall, ACE inhibitors/ARBs were associated with the least nonadherence. Among women, nonadherence was highest for aldosterone antagonists, whereas among men, nonadherence was highest for diuretics.

Conclusion: We observed nonadherence was more frequent among older women in a cohort of HTN and RHTN patients with cardiovascular disease based on HPLC-MS confirmed drug levels.

1. Introduction

Uncontrolled hypertension remains a leading contributor to cardiovascular disease (CVD), kidney disease, and many other health conditions associated with adverse outcomes. The prevalence of uncontrolled hypertension is almost 50% among adults in the United States (US) with hypertension diagnoses, and the global disease burden of this condition has steadily increased over the past 20 years [1,2]. Nonadherence to antihypertensive medications is believed to be a major contributing factor to poor blood pressure (BP) control and is estimated to be a factor in up to 86% of uncontrolled hypertension cases [3,4]. Despite the importance of addressing nonadherence to achieve target BP, nonadherence rates and trends are difficult to accurately assess, especially in the patient care setting. Patient interviews with returned pill counts, reviews of pharmacy databases, and electronic pill boxes have all been utilized to monitor nonadherence, but the lack of reliability and

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practicality of these methods poses challenges [5]. Analysis of blood or urine using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS) has emerged as an inexpensive and accurate approach to assess nonadherence [6]. This approach provides objective evidence of whether prescribed antihypertensive medications are present in the body. HPLC-MS assays with high sensitivity and low limits of detection have been developed for the detection of many cardiovascular drugs and their metabolites, allowing this method to be used in a variety of clinical settings. Previous studies using HPLC-MS have identified polypharmacy, medication side effects, and older age as risk conditions contributing to nonadherence [7]. Among these factors, medication side effects are the most modifiable and can be mitigated by prescribing the best-tolerated medication class. However, nonadherence trends by medication class have not been widely studied with HPLC-MS. Likewise, sex-related disparities and medication adherence are not well understood, although previous work using HPLC-MS has identified an association between female sex and nonadherence [7]. Antihypertensive medication nonadherence using HPLC-MS has been reported in several studies conducted in Europe [7–10], however, biochemically confirmed nonadherence data in the US are limited. Given the variation in study populations, health-care systems, and differences in prescribing patterns between the US and Europe, further studies with HPLC-MS are warranted to determine nonadherence trends in the US. Accordingly, we used HPLC-MS analysis of serum to assess nonadherence trends by sex and antihypertensive drug class among hypertension patients in a cardiovascular specialty clinic.

2. Methods

A total of 76 hypertensive patients with a CVD diagnosis attending an outpatient cardiovascular subspecialty clinic of the University of Florida (UF) Health system agreed to participate in a study that included evaluation of their BP and review of their electronic health record (NCT02133872). A BP $\geq$130/80 mmHg on at least two occasions was required to meet the definition of hypertension. The protocol was approved by the UF Institutional Review Board, and voluntary, written informed consent was obtained from each subject prior to study participation. An automated BP machine (Omron HEM-907XL) was used to record seated BP from the brachial artery using an appropriately sized cuff after a rest of at least 5 min, in accordance with the technique summarized in the 2017 ACC/AHA Hypertension Guideline [1]. All BP measurements were made in duplicate and averaged, unless they widely differed (>10 mmHg SBP), in which case additional readings were obtained. Drug-controlled hypertension was defined as achieving a target BP, <130/<80 mmHg, in response to <3 antihypertension medications. Treatment resistant hypertension (RHTN) was defined as having uncontrolled BP despite use of $\geq$3 antihypertension medications or BP control with 4 medications. All BP lowering regimens included antihypertensive drugs of different pharmacological class, including a diuretic in the case of RHTN patients. All patients were clinically stable and blood samples were obtained during regularly scheduled afternoon clinic visits. While patients were told they were participating in a study about their blood pressure, they were not informed ahead of time that blood obtained during their clinic visit would be used to assess presence of antihypertensive medication.

2.1. Adherence measurement

Serum was extracted from blood and stored at −80 °F. Samples were shipped to the University Medical Center Utrecht, The Netherlands, where they underwent HPLC-MS analysis. Samples were processed using a standardized procedure [11], run in a single batch, and the acquired mass spectra were compared with an in-house library of more than 40 compounds, including metabolites covering the majority of BP lowering drugs [12]. The technique utilized has been proven to be reliable, accurate and precise [11], and with this method, the identification results from spiked samples within therapeutic concentration ranges yielded 95% sensitivity and 91% specificity [12]. Drugs included those from the following five antihypertensive drug classes: beta blockers, aldosterone antagonists, diuretics, angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin receptor blockers [ARBs], or calcium antagonists. The mass spectra of each sample were compared with a library of reference spectra, and the 22 antihypertensive drugs found in our patient sample are shown in Table 1.

Clinic BP measurements, age, body mass index, sex, and prescription regimens were extracted from patient medical records on the day of, or within one month of, blood collection. “Adherence” or “nonadherence” was determined based on a pragmatic comparison of the patient's prescribed drug regimen and the presence or absence of prescribed drug(s) in their serum. A patient was considered nonadherent if one or more prescribed drugs were absent from their serum sample.

The overall nonadherence rate, defined as the ratio of nonadherent patients to all patients, was calculated overall, by sex, and also by medication class. Patient characteristics were summarized as mean $\pm$ standard deviation (SD) or percent. Chi-square tests were used to assess the statistical significance of adherence trends by sex and medication class. A $p < 0.05$ was considered statistically significant.

3. Results

Pertinent demographics of the patients included in the study are summarized in Table 2. There were 29 men and 47 women included in the study, and mean ages and clinic BP measurements were similar. RHTN was present in 38% of men and 55% of women. The majority were taking at least two antihypertensive medications, and 41% of men and 61% of women were taking three or more antihypertensive medications. Angiotensin II active drugs (ACEIs or ARBs) were prescribed most frequently, followed by calcium channel blockers and beta blockers, regardless of sex.

Overall, patients were nonadherent with 29% of antihypertensive medications prescribed. Based on the reconciliation between prescribed antihypertensive medications and medications assayed in the serum, 34% of women were nonadherent, while 21% of men were nonadherent with at least one medication. The impact of sex on overall medication adherence was not statistically significant ($p = 0.3239$). Nonadherence by antihypertensive drug class and sex is summarized in the Fig. 1. Men were least adherent to diuretics (30% nonadherent), whereas women were least adherent to aldosterone antagonists (40%). Importantly, those who were nonadherent had higher mean BP than those who were adherent (145/83 mmHg vs. 129/75 mmHg, $p = 0.0015$). Nonadherence was more common among those with RHTN (38%) than those with controlled HTN (21%), $p = 0.13$.

4. Discussion

Our results confirm that assessment of medication nonadherence, based on HPLC-MS analysis of serum samples, is feasible and that nonadherence is prevalent among clinically stable, CVD subspecialty outpatients with HTN and RHTN. Furthermore, our data demonstrate the

Table 1
Antihypertensive medications identified by the HPLC-MS analysis.

Beta blockers	Atenolol, carvedilol, metoprolol, nebivolol, propranolol
Diuretics	Chlorthalidone, hydrochlorothiazide, furosemide
ACEIs and ARBs	Enalapril, irbesartan, lisinopril, losartan, quinapril, ramipril, trandolapril, valsartan
Calcium channel blockers	Amlodipine, diltiazem, nifedipine, verapamil
Aldosterone antagonists	Canrenone (spironolactone), eplerenone

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2
Characteristics of patients.

		Men (n = 29)	Women (n = 47)
Mean age (years ± SD)		63.4 ± 10.7	63.1 ± 9.1
BMI (kg/m^2 ± SD)		31.5 ± 6.8	31.4 ± 7.2
White (%)		59	49
Non white (%)		41	51
Clinic systolic BP (mmHg ± SD)		133 ± 18	135 ± 19
Clinic diastolic BP (mmHg ± SD)		77 ± 10	78 ± 11
Number of antihypertensive medications prescribed	1 (%)	21	11
	2 (%)	38	28
	3 (%)	31	34
	4 or more (%)	10	27
Hypertension class	Hypertensive (%)	62	45
	Treatment resistant hypertensive (%)	38	55
Drug class[a]	Beta blocker (%)	48	64
	Diuretic (%)	34	45
	Aldosterone antagonist (%)	10	21
	ACEI/ARB (%)	83	89
	Calcium channel blocker	55	62

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI body mass index; BP blood pressure; SD, standard deviation.
[a] More than one medication could be prescribed per patient.

utility of HPLC-MS in detecting nonadherence in a clinical setting where patients admitted to full compliance when questioned by the medical staff, and thus was not suspected by the providers at the clinic. The overall nonadherence rate of 29% we observed is similar to or lower than biochemically confirmed rates reported by others [5]. Differences in observed adherence rates are likely attributed to differences in clinic type (primary vs specialty care) and patient demographics.

While the impact of sex on overall medication adherence in our study was not statistically significant, future studies with larger study populations should be conducted to better determine the impact of sex on nonadherence. Previous reports have provided mixed results with regard to nonadherence between sexes, with either no significant difference or higher nonadherence among women (55% to 65% higher) [13]. The cause(s) for the increased nonadherence risk among women is unknown, although risk factors for nonadherence specific to women have been suggested, including depressive symptoms and lack of social support [13]. However, additional studies are warranted.

The highest overall nonadherence that we observed was to aldosterone antagonists, and to the best of our knowledge this has not been previously reported in the English literature. High nonadherence to aldosterone antagonists among women may be explained by the fact that this class of medication is often added to a prescription regimen after multiple other drugs are tried. Nonadherence increases with the number of antihypertensive medications prescribed [14]. Additionally, many hypertensive patients have comorbidities that require chronic medication therapy. These additional medications may give rise to further side effects and increased pill burden that could influence adherence. Fixed-dose combination drugs are effective at reducing pill burden and improving adherence [15].

Our observation that the lowest nonadherence rate was to ACEIs/ARBs is consistent with other reports [16,17]. ACEIs/ARBs are often tolerated very well compared with other antihypertensive drug classes. Medication side effects, which differ in frequency and intensity, are critical factors in differential nonadherence between medication classes. Diuretics are often reported as having the highest frequency of side effects (~45%), including urinary frequency, orthostatic hypertension, and sexual dysfunction, that have a negative impact on daily life and work routines [17]. Consequently diuretics are typically associated with the most nonadherence and likely explain our results of high diuretic nonadherence in men [18]. Our finding that sex has an impact on nonadherence by medication class may suggest men and women differ in their tolerance to certain side effects, and willingness to tolerate side effects, regardless of sex, may be low for a condition like HTN, which is otherwise asymptomatic.

Detection of nonadherence through HPLC-MS has been shown to improve health outcomes and reduce healthcare costs. Nonadherent patients that were shown their blood-test results and given counseling on adherence experienced an average BP reduction of 40 mmHg [8]. BP reductions associated with adherence have also been shown to decrease the incidence of myocardial infarction and stroke in certain groups, leading to cost reductions of $613 per patient [19].

While biochemically confirmed nonadherence is considered to be the reference standard, the lack of detection of a drug in a patient's serum sample may not necessarily mean that the patient is nonadherent. The gut microbiome has been shown to impact the pharmacokinetics of antihypertensive medications [20]. Certain strains of bacteria commonly found in the gut may metabolize active antihypertension medications into inactive forms within the gastrointestinal tract. Consequently, the bioavailability of active medication could be reduced, and the antihypertensive effects of the medications could be diminished. For example, diltiazem, losartan, and several other antihypertensive drugs are recognized to be extensively metabolized by several bacterial strains in the human gut [21]. Patients with a gut microbiome that metabolizes antihypertensive drugs may exhibit what appears to be nonadherence when tested via HPLC-MS. Further studies to determine the relationship between the gut microbiome, antihypertensive drug metabolism, and HPLC-MS detection are warranted to better interpret

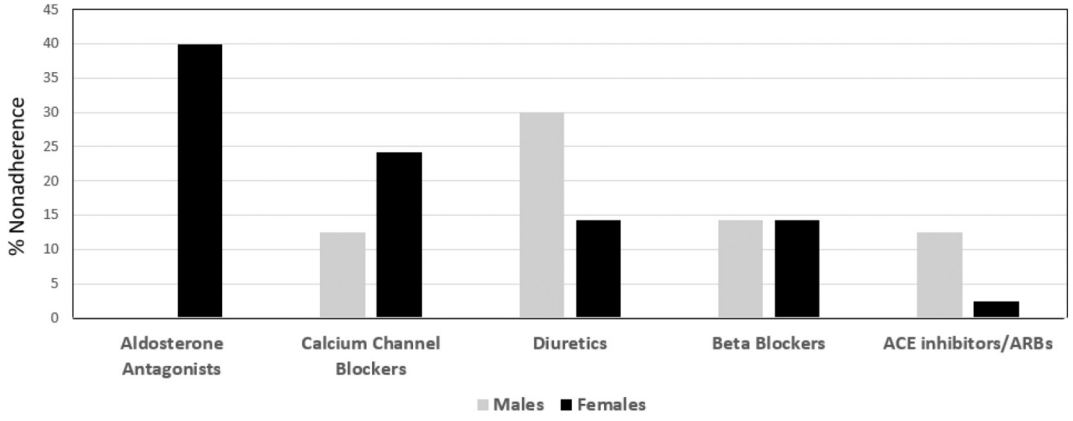

Fig. 1. Percent nonadherence according to sex and antihypertensive drug class. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

drug concentration levels.

This study has some limitations that should be considered in light of its strengths. To our knowledge, this is the first study to apply HPLC-MS methodology to a cardiology subspecialty outpatient clinic where all patients had established, clinically stable CVD. Additionally, all of the BP and blood samples were made in the afternoon after patients presumably had taken their morning doses, and the patients were not approached about participation in this study until they checked into the clinic. This should have minimized so-called "white coat adherence" or "toothbrush effect", where a patient only takes medications prior to clinic visits or brushes their teeth only before a visit to the dentist. Although the BP measurements were obtained from clinic visits using a well-validated automated monitor, those obtained from an ambulatory BP monitoring device would have been useful. Our clinic BP measurements are made several times (usually 2 to 3) and averaged, but they are made over a very brief period, usually ~5 to 10 min. Furthermore, these measurements are susceptible to "white coat effect" and masked hypertension. Also, the sample size of the current pilot study was limited due to logistics and costs, and a larger study is warranted in the future. The size of the study population limited our ability to control for covariates such as comorbidities, insurance coverage, health literacy, RHTN status and socioeconomic status. In future studies, patients should be further stratified by these covariates in order to avoid bias in nonadherence measurements.

5. Conclusion

Nonadherence to antihypertensive medications is a common issue that results in poorer health outcomes and increased healthcare costs. HPLC-MS can be used as a method to detect nonadherence in hypertensive CVD patients attending a subspecialty outpatient clinic. ACEIs/ARBs show the least nonadherence among both men and women, but aldosterone antagonists are associated with increased nonadherence in women. Additional studies should be undertaken to further validate nonadherence trends and identify patients at risk of nonadherence.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that couple have appeared to influence the work reported in this paper.

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