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Research Article

# Characteristics, drug combinations and dosages of primary care patients with uncontrolled ambulatory blood pressure and high medication adherence

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## Abstract

Most studies on the prevalence and determinants of resistant hypertension (RH) do not account for white coat hypertension, medication non-adherence, or use of suboptimal treatment dosages. We studied the characteristics, drug combinations, and dosages of patients on at least three antihypertensives of different classes who had uncontrolled blood pressure on 24-hour ambulatory blood pressure monitoring and high medication adherence measured by electronic monitoring. The data were collected as part of the baseline measures of a hypertension control trial. Of 140 monitored primary care patients, all with uncontrolled office blood pressure, 69 (49%) were on at least three antihypertensives of different classes. Of these 69, 15 (22%) were controlled on ambulatory blood pressure monitoring, 20 (29%) were uncontrolled and non-adherent, leaving only 34 (49%) adherent to their medications and having uncontrolled ambulatory hypertension (uncontrolled RH). Thirty-one (91%) of the 34 uncontrolled RH patients were prescribed a diuretic, of which 24 were on hydrochlorothiazide 25 mg. Less than half of the patients on angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or calcium channel blocker were prescribed maximal doses of these agents. Half of the RH can be attributed to white coat effect and poor medication adherence, and all of the remaining patients were on apparently suboptimal drug combinations and/or dosages. Primary care physicians need to be educated regarding the optimal treatment of RH. J Am Soc Hypertens 2013;7(6):471–476.


*Keywords:* Resistant hypertension; white-coat hypertension; medication adherence; electronic monitoring; drug dosage.

## Introduction

Resistant hypertension (RH), defined as blood pressure (BP) that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes, is an important clinical problem.[1] Patients with RH have high cardiovascular risk and high prevalence of target organ damage.[2] The prevalence of RH has been reported to range from 12% to 15% in the treated hypertensive population.[3,4] However, most studies on the prevalence and determinants of RH do not account for white coat hypertension,[3,5–8] poor medication adherence (MA),[3,4,7,9,10] or use of suboptimal treatment dosages.[3,4,6–9,11] In a recent study including a large cohort of treated hypertensive patients from the Spanish Ambulatory Blood Pressure Monitoring (ABPM) registry, 37.5% of RH patients had normal 24-hour BP.[9] Therefore, a considerable number of RH patients have a ''white coat syndrome'' and do not have true RH. Another group of patients that should be excluded are those with poor MA. Poor MA, an important cause of poor BP control,[12] is common in treated hypertensives.[13,14] Finally, patients with suboptimal drug combinations and/or dosages should not be included in the group of true RHs.

As part of a study on improving hypertension control, we had baseline data including drug regimens and doses, 24-hour ABPM, and adherence as measured by Medication

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Event Monitoring System (MEMS) bottle caps for patients who were uncontrolled based on office BP measurements in 10 Primary Care (PC) settings in a southwestern United States (US) city. We described the characteristics, antihypertensive regimens, and dosages of patients on at least three antihypertensives of different classes who had uncontrolled BP based on 24-hour ABPM and high MA measured by MEMS. We compared them with patients on at least three drugs whose BP was controlled based on 24-hour ABPM.

## Methods

### *Study Population*

Data for this study were collected as part of a cluster-randomized trial on clinical inertia and BP control in 10 PC clinics between 2006 and 2007. The details of the trial have been reported.[15,16] Eligible patients had to be over 21 years and have at least two clinic visits in the previous 12 months, with BP on the most recent two consecutive visits of $\geq$140 mm Hg systolic (SBP) or $\geq$90 mm Hg diastolic (DBP), or if diabetic, $\geq$130 mm Hg SBP or 80 mm Hg DBP. Since the trial was aimed at improving BP control in established hypertensives, some evidence of prior diagnosis and/or treatment of hypertension was required. Research assistants identified potential study participants by screening the medical records of patients who presented for a routine PC appointment. Patients with cognitive impairment, renal insufficiency (recent serum creatinine >2.0), or a serious concomitant illness such as cancer, recent myocardial infarction, or unstable angina, were excluded. Informed consent was obtained from both the patient and provider.

A random subsample of patients at baseline underwent a 24-hour ABPM and an electronic bottle cap monitoring. The Aardex Medication Event Monitoring System (MEMS 6 Track Cap, Sion, Switzerland) was used to record the date and time of each bottle cap opening during the monitoring period. Up to three antihypertensive medications were monitored for 30 days. Standardized quality control procedures included testing each device before it was dispensed to the participant (eg, checking battery status, visually examining the devices for defects and malfunctions, etc), educating participants in the proper use of the devices, debriefing participants when they return devices, and cleaning and analyzing the data. The 24-hour ABPM was performed using the Oscar 2 (Suntech Medical, Morrisville, NC) monitor, programmed to take a reading every 20 minutes during the day, and every 45 minutes at night. Valid registries had to fulfill a series of pre-established criteria, including 80% of both SBP and DBP successful recordings during the daytime and nighttime periods, 24-hour duration, and at least one BP measurement per hour.

Data on age, gender, race/ethnicity, employment status, smoking status, comorbidities, and years of education completed were collected at baseline. Patients were also asked to list all of their current antihypertensive medications, and indicate the number and timing of their prescribed doses. This information was compared with the orders written by the patient's physician in the medical records, and any discrepancies were resolved by further querying the patient or the physician. Combination pills were counted according to the number of different drugs they contained.

Of 248 patients selected to participate in the ABPM and MEMS monitoring substudy,116 completed both ABPM and MEMS monitoring as part of the baseline data collection of a trial. During follow-up in the intervention clinics, an additional 24 patients not included in the baseline sample completed ABPM and MEMS monitoring on referral from their provider, and we included their data in our study. For these 24 patients, data on drug combinations and dosages prescribed at the time of ABPM and MEMS monitoring was collected in the study clinic.

Controlled hypertension was defined as ambulatory BP <135/85 mm Hg (weighted average day and night time) or <125/75 mm Hg if diabetic. Using a widely accepted definition, participants were classified as non-adherent if they took <80% of all prescribed doses, averaged across all monitored antihypertensives.[17,18]

### *Statistical Analysis*

Descriptive statistics and frequencies were calculated. Characteristics of patients with uncontrolled resistant and white-coat hypertension were compared using Fisher exact tests and Mann-Whitney U tests (proportions and medians, respectively). All statistical tests were two-sided at $\alpha = .05$. Data were analyzed using SPSS (version 20) for Windows (SPSS, Inc., Chicago, IL).

## Results

There were 665 patients in the baseline sample of the clinical trial. In this study, we included 140 patients who completed 24-hour ABPM and electronic bottle cap monitoring (including 116 randomly selected at baseline and 24 patients who were referred for monitoring by their physicians in the intervention clinics). In general, characteristics of the monitored sample were similar to those of the 665 patients enrolled in the clinical trial.

Of 140 patients monitored, 23 (16%) were on one antihypertensive drug, 48 (34%) were on two drugs, and 69 (50%) were on at least three drugs of different classes (Figure 1). This group of 69 patients would be classified as RH in some studies where more data were not available. Of these 69 patients, 15 (22%) were controlled based on ABPM (white coat hypertension). An additional 20 (29%) were