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Siddiqui; Short title: Drug adherence in masked uncontrolled hypertension

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Abstract

Masked uncontrolled hypertension (MUCH) in treated hypertensive patients is defined as controlled automated office blood pressure (AOBP <135/85 mmHg) in clinic, but uncontrolled out-of-clinic BP by ambulatory blood pressure monitoring (ABPM; awake (daytime) readings ≥135/85 mmHg or 24-hr ≥130/80 mmHg). To determine if MUCH is attributable to antihypertensive medication non-adherence.

184 enrolled patients were confirmed to have controlled office BP, of these 167 patients were with adequate 24-hr ambulatory BP recordings. Out of 167 patients, 86 were controlled by in-clinic BP assessment, but had uncontrolled ambulatory awake BP, indicative of MUCH. The remaining 81 had controlled in-clinic and ambulatory awake BP, consistent with true controlled hypertension. After exclusion of 9 patients with missing 24-hr urine collections, antihypertensive medication adherence was determined based on detection of urinary drugs or drug metabolites by high-performance liquid chromatography-tandem mass spectrometry.

Of the 81 patients with MUCH, 69 (85.2%) were fully adherent and 12 (14.8%) patients were partially adherent (fewer medications detected than prescribed). Of the 77 patients with true controlled hypertension, 69 (89.6%) were fully adherent with prescribed antihypertensive medications and 8 (10.4%) were partially adherent. None of the patients in either group were fully non-adherent. There was no statistically significant difference in complete or partial adherence between the MUCH and true controlled groups (p =0.403).

Measurement of urinary drug and drug metabolite levels demonstrates a similarly high level of antihypertensive medication adherence in both MUCH and truly controlled hypertensive patients. These findings indicate that MUCH is not attributable to antihypertensive medication non-adherence.

Key words: masked uncontrolled hypertension, medication adherence

Introduction

Masked uncontrolled hypertension (MUCH) in treated hypertensive patients is defined as controlled automated office blood pressure (AOBP < 135/85 mmHg) in clinic, but uncontrolled out-of-clinic BP by 24-hr ambulatory blood pressure monitoring (ABPM awake (daytime) ≥ 135/85 mmHg or 24 hour ≥ 130/80) [1]. The prevalence of MUCH among treated hypertensive patients has been reported as 30-50% [2-5], which is higher than prevalence estimates of masked hypertension (MH) among untreated hypertensive individuals (8-20%) [2, 3, 6]. According to definitions proposed in the 2017 ACC/AHA and ESH/ESC guidelines de la Sierra et al. estimated the prevalence of MUCH from the Spanish ABPM registry to be approximately 66% [1, 7, 8]. The severity of clinic BP predicts the prevalence of MUCH, as higher clinic systolic BP levels are associated with higher rates of MUCH [9]. Prehypertension is also associated with higher prevalence rates of MUCH than in the normotensive population [10]. The prevalence of MUCH is also increased in African Americans [11, 12], the elderly [13], persons with diabetes [3, 4, 14], chronic kidney disease [4, 9, 15-18] and kidney transplant recipients [19-21]. MUCH has been shown to be a precursor of sustained hypertension [22]. In addition, a high prevalence of nocturnal hypertension and non-dipping BP is seen in MH patients [3, 23]. Patients with obstructive sleep apnea (OSA) have also been reported to have an increased prevalence of MH [24, 25].

Patients with MH/MUCH have evidence of higher sympathetic tone compared to those with true controlled hypertension (hypertension controlled in-clinic and out-of-clinic) [15, 26]. In a recent study, we reported that MUCH patients have increased out-of-clinic sympathetic tone compared to true controlled hypertensive patients [27]. MUCH

patients have also been shown to have higher anxiety based on Spielberger's Strait Trait Anxiety Inventory (STAI) & Beck Depression Inventory (BDI) [28].

In the Spanish ABPM registry, MUCH has recently been shown to have greater all-cause and cardiovascular mortality compared to true controlled hypertension and treated but uncontrolled hypertension[29]. A meta-analysis of six studies has also reported that MUCH was associated with increased risk of cardiovascular events and all-cause mortality compared to true controlled hypertension [30].

Antihypertensive medication non-adherence is common in patients with resistant hypertension (RHTN), contributing importantly to poor BP control [31]. Unknown is to what extent MUCH may simply be a consequence of poor medication adherence. The current study tested the hypothesis that MUCH is attributable to low adherence to prescribed antihypertensive agents. To test this hypothesis, we prospectively determined antihypertensive medication adherence in MUCH patients by measurement of 24-hr urinary drug or drug metabolite levels by high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS). Patients with true controlled hypertension served as controls.

Methods

Study data will be available upon request 1 year after completion of the funding grant (April 2021).

Study Population

Patients with automated office BP controlled (AOBP < 135/85 mm Hg) on antihypertensive medications were prospectively recruited from the University of Alabama at Birmingham Hypertension Clinic after having been seen by a hypertension specialist for a minimum of three follow-up visits between April 2014 and March 2019. All study patients had been evaluated for secondary causes of hypertension, including hyperaldosteronism, pheochromocytoma, and renal artery stenosis, as medically indicated. Patients with chronic kidney disease (CKD) stage 4 or 5 (eGFR <30 ml/min/1.73m^2) and pregnancy were excluded. The study was approved by the UAB Institutional Review Board and written informed consent was obtained from all participants.

BP Measurement

Unattended clinic automated office BP measurement (AOBP)

AOBP in clinic was measured after at least 5 minutes of quiet rest in a sitting position with the back supported and the arm supported at heart level [32]. The AOBP was measured using the BpTRU device, which automatically obtains 6 serial BP readings, one minute apart, before displaying the average of the last 5 readings. All BpTRU assessments were unattended, i.e., unobserved in clinic [33-37]. An appropriate sized cuff was used with a cuff bladder encircling at least 80% of the arm [37, 38]. A BP cutoff of < 135/85 mmHg for controlled BP was used validating automated BP devices [6, 39].

Out-of-clinic 24-hr ambulatory BP monitoring (ABPM)

An automated, noninvasive, oscillometric device (Oscar 2; Suntech Medical Inc, Morrisville, NC) was used to perform 24-hr ABPM. Recordings were made every 20 minutes during the awake (daytime) and every 30 minutes during the asleep (nighttime) phases of the 24-hr period. Awake and asleep times were determined by patient self-report. Patients were counselled to take all antihypertensive medications during the ABPM period. ABPM was determined to be valid if >80% of measurements were successful [40] including at least 20 awake (daytime) and 7 asleep (nighttime) valid BP measurements [41]. Uncontrolled ABPM was defined as mean awake (daytime) BP ≥ 135/85 mmHg or as mean 24-hour BP ≥ 130/80 mmHg [1, 42].

Biochemical analysis

Renal function panel

Serum electrolytes, blood urea nitrogen and creatinine were measured in a hospital laboratory using standard methods.

24-hr urine high-performance liquid chromatography-tandem mass spectrometry to detect antihypertensive medication adherence

In all study patients, 24-hour urine samples were collected. Study patients were advised to be adherent with antihypertensive medications but were not informed that medication adherence was being tested in the collected urine samples to avoid a Hawthorne effect (e.g., change in behavior when it is being observed) [43]. The urine samples were stored

and an aliquot was shipped at a temperature of -80° C to the National Centre for Adherence Testing (NCAT) Department of Chemical Pathology and Metabolic Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK; where they were analyzed by high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) to detect antihypertensive medication adherence as previously described[44]. Briefly, the samples were analyzed in batches of 20. Each sample was run in dilution and after extraction. Separation was performed using Agilent technologies Zorbax Elipse column C18 2.1 x 50 mm and then the samples were introduced by electrospray ionization to an Agilent technologies 6140 tandem mass spectrometer. The analyte of interest was confirmed by its unique mass to charge ratios.

The assay provides a binary qualitative result for presence or absence of medications in the urine. Patients whose urine analysis confirmed the presence of all medications prescribed were classified as totally adherent and those with fewer medications detected than prescribed were classified as partially adherent. Patients with no detectable drug or metabolite levels were classified as totally non-adherent.

Statistical analysis

Descriptive analyses were performed to summarize the demographic and biochemical characteristics, as well as the comorbidities of study participants and antihypertensive medication adherence by classes of agents in patients with true controlled hypertension and MUCH. Two sample t-test was used to compare the continuous variables between true controlled hypertensive and MUCH patients. Chi-square test or Fisher's exact test was used to compare the categorical variables

between two study groups. Medication adherence was compared using one way ANOVA for continuous variables and using Chi-square or Fisher's exact test for categorical variables between true controlled hypertensive and MUCH patients. according to total and partial antihypertensive medication adherence, i.e., true controlled hypertension with total medication adherence, true control hypertension with partial medication adherence, MUCH with total medication adherence and MUCH with partial medication adherence. All analyses were performed using SPSS version 25. A two-sided p-value < 0.05 was considered statistically significant.

Results

After three or more consecutive clinic visits, 184 hypertensive patients were prospectively recruited were prescribed antihypertensive medications and had controlled clinic BP in clinic (Figure 1). Of the 184 treated and controlled hypertensive patients, 167 had adequate ABPM recordings. 86 patients (51.5%) were identified as having MUCH, i.e. controlled in clinic (AOBP < 135/85 mmHg), but uncontrolled awake ambulatory (ABPM ≥ 135/85 mmHg). The remaining 81 patients (48.5%) had controlled BP in-clinic (AOBP < 135/85 mmHg) and controlled ambulatory awake BP (ABPM < 135/85 mmHg), indicative of true controlled hypertension. (Figure 1). Of the 86 MUCH patients and 81 true controlled hypertensive, 9 had missing medication adherence data such that 81 MUCH patients and 77 true controlled hypertensive were included in final analysis (Figure 1).

Patient characteristics

The mean age was 58.6±10.6 years for the MUCH patients and 60.6±10.8 years for the true controlled hypertensive (Table 1). Of the MUCH patients, 44.4% were female and 49.4% were African American compared to 45.5% female and 49.4% African American among the true controlled hypertensive patients (Table 1). The mean BMI was not statistically different in both the groups, 34.2±6.2 kg/m^2 for the MUCH patients and 32.3±6.8 kg/m^2 for the true controlled hypertensive (Table 1). MUCH patients had a higher prevalence of diabetes compared to the true controlled hypertensive patients (42.0% vs 23.4%, respectively; p=0.013). All other comorbidities had similar prevalence in both groups (Table 1). There were no significant differences in serum electrolytes, blood urea nitrogen and creatinine in MUCH versus true controlled hypertensive patients (Table1).

BP measurements in- and out-of-clinic

The in-clinic mean AOBP readings were 121.1±8.2 / 73.3±7.7 mmHg in MUCH patients versus 114.1±10.4 / 70.6±7.6 mmHg in patients with true controlled hypertension ($p < 0.001$ and $p = 0.026$ respectively) (Table 1). The out-of-clinic awake (daytime) mean ABPM was 148.1±11.2 / 82.1±8.1 mmHg in the MUCH patients compared to 123.8±7.3 / 70.9±6.9 in true controlled hypertensive patients (both $p < 0.001$) (Table 1).

Antihypertensive medication adherence

Of the 81 MUCH patients, 69 (85.2%) were fully adherent and 12 (14.8%) patients were partially adherent (Table 2). Of the 77 true controlled hypertensive patients, 69

(89.6%) were fully adherent with all of the prescribed antihypertensive medications and 8 (10.4%) were partially adherent (Table 2). The number of antihypertensive medications prescribed was 3.5±1.3 in MUCH patients and 3.2±1.2 in true controlled hypertension; the number of antihypertensive medications detected by 24-hr urine LC-MS/MS was 3.3±1.2 in MUCH patients and 3.1±1.2 in true controlled hypertension. There were no significant differences in medication adherence with the different antihypertensive medication classes for the MUCH versus true controlled hypertensive groups (Table 2).

The number of antihypertensive medications prescribed was 3.4±1.2 in MUCH patients with total adherence and 4.5±1.4 in MUCH patients with partial adherence versus 3.1±1.2 in true controlled hypertension with total adherence and 3.9±1.0 in true controlled hypertension with partial adherence. Patients with partial adherence missed on average one prescribed medication in both the MUCH and true controlled groups; The number of antihypertensive medications detected by 24-hr urine HP LC-MS/MS was 3.4±1.3 in MUCH patients with total adherence and 3.1±1.2 in MUCH patients with partial adherence versus 3.1±1.2 in true controlled hypertension with total adherence and 2.8±1.0 in true controlled hypertension with partial adherence (Table 3). Patients with full medication adherence were significantly more adherent to angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, thiazide diuretics, mineralocorticoid receptor antagonists and β blockers than were patients with partial medication adherence, both in the MUCH and true controlled hypertensive groups.

In addition, analyzing MUCH and true controlled hypertensive patients based on 24hr ABPM cutoff of 130/80 mmHg showed similar antihypertensive medication adherence in MUCH patients, with 86.7% of total adherence and 13.3% patients were partially adherent. In true controlled hypertensive patients, 88.2% were fully adherent with all of the prescribed antihypertensive medications and 11.8% were partially adherent (p=0.483). In addition, based on an ABPM asleep (nighttime) cutoff value of 120/70 mmHg, the medication adherence rates were not different between MUCH and true controlled patients, with 89.4% of the former being fully and 10.6% being partially versus 84.4% of the latter being fully and 15.6% being partially adherent (p=0.246).

Duration between BP measurements and 24-hour urine collection

All the patients completed in-clinic AOBP measurements, out-of-clinic 24-hour ABPM and 24-hour urine collection for antihypertensive medication adherence during a one week period without any change in any antihypertensive medications. The mean duration between the BP measurements and 24-hour urine collection was 1.5±2.9 days (range 2-7).

Post-hoc power analysis

Sample sizes of 81 in the masked uncontrolled hypertension group and 77 in the true controlled hypertension group resulted in a 78% power to detect equivalence. The margin of equivalence, given in terms of the difference, extended from -20% to 10.4% with an actual difference of -4.4% (85.2% vs. 89.6%) using Z test with a significance level of 0.05.

Discussion

This prospective study identified equal antihypertensive medication adherence between patients with MUCH and true controlled hypertension. Precision measurement of drug metabolites in the urine using 24-hr urine LC-MS/MS provided an unbiased assessment of medication adherence. Based on these data, we conclude that MUCH is not attributable to non-adherence.

Multiple assessments of medication adherence in general hypertensive cohorts with use of LC-MS/MS have demonstrated non-adherence (i.e. absence of 1 or more antihypertensive medications) rates of 25-65% among patients with uncontrolled HTN [44, 45]. For example, Gupta et al. found that 30-40% of a cohort of 1348 hypertensive patients were non-adherent with their prescribed antihypertensive medications. Female gender, younger age, higher number of antihypertensive medications and use of certain antihypertensive medication classes i.e. diuretics were associated with greater degrees of non-adherence[46]. In another study of 238 hypertensive patients, serial determinations of medication adherence and subsequent discussion of poor adherence with appropriate patients improved adherence rates from 33% to 100% and lowered systolic and diastolic BP by ~19.5 and 7.5 mmHg [47].

Medication adherence rates have also been determined in patients with RHTN by LC-MS/MS analysis. Jung et al., Strauch et al and Lawson et al. have reported antihypertensive medication non-adherence rates of 47-53% in cohorts of patients with RHTN[48-50]. Schmieder et al. also reported high rates of non-adherence to antihypertensive medications among 79 patients with RHTN undergoing renal

denervation. Medication non-adherence was 44% at baseline and 34% six months after renal denervation [51]. Brinker et al. reported that informing patients with RHTN of documented low medication adherence improved systolic and diastolic BP by 46±10 / 26±14 mm Hg in non-adherent group, 12±17 / 7±7 mm Hg in adherent group and 11±4 / 4±2 mm Hg in the untested group ($p<0.01$) without treatment intensification while no differences in the number of antihypertensive medications were found (5.3±0.7 vs. 4.2±0.4 vs. 3.7±0.2 drugs, respectively, $p>0.05$) [52].

In the current study, antihypertensive medication adherence was measured by detecting urinary drug and drug metabolite levels using LC-MS/MS in MUCH patients versus patients with confirmed controlled hypertension. We found that medication adherence was high in both MUCH and true controlled hypertensive groups (85.2 vs. 89.6%) with no statistically significant difference between the two groups. These findings allow us to exclude reduced medication adherence as a cause of MUCH. Further, there was no significant difference in the total number or classes of antihypertensive agents detected in the MUCH versus true controlled hypertensive groups, suggesting that under treatment was also not contributing to development of MUCH. Patients in both groups i.e. MUCH and true controlled hypertension who were partially adherent were being treated with a higher number of prescribed antihypertensive medications (4.5±1.4 in MUCH, 3.9±1.0 in true controlled) compared to those who were total adherence (3.4±1.2 in MUCH, 3.1±1.2 in true controlled).

As this prospective study was started prior to release of the updated 2017 Hypertension guidelines, we reanalyzed the data with application of the lower BP cutoff value of 130/80mmHg [8]. Based on an out-of-clinic ABPM awake (daytime) cutoff value

of 130/80mmHg [8], we found similar antihypertensive medication adherence levels in MUCH and true controlled patients, with 88.9% of the MUCH patients being totally and 11.1% being partially adherent compared to 88.4% of the true controlled patients being totally and 11.6% partially adherent (p=0.579). In addition, based on newer guidelines out-of-clinic 24hr ABPM cutoff of 125/75 mmHg [8], MUCH patients had similar antihypertensive medication adherence levels compared to true controlled patients (90.1% of MUCH patients were totally and 9.9% partially adherent, while 85.3% of true controlled patients were totally and 14.7% were partially adherent; p=0.326).

Emerging evidence suggests that increase sympathetic tone may play a role in the pathogenesis of MUCH. We have recently observed that MUCH patients have evidence of higher out-of-clinic sympathetic tone assessed by plasma and urinary catecholamine and metanephrine levels and BP and heart rate variability in- and out-of-clinic compared to true controlled hypertensive patients[27]. Other investigators have also reported that MUCH patients have higher anxiety levels as indexed by the Spielberger's Strait Trait Anxiety Inventory (STAI) compared with RHTN after renal denervation [28]. Further, risk of MH has been shown to be increased in patients with OSA who are not receiving antihypertensive medications, suggesting that OSA-related oxygen desaturation, heightened sympathetic tone, nocturnal hypertension, and non-dipping BP may contribute to development of MH [24, 25].

Strengths of the current study include: prospective design; inclusion of a diverse cohort of well characterized patients; rigorous confirmation of MUCH and true controlled hypertension; comparison of MUCH patients to a comparator group of true controlled hypertension; medication adherence tested on uninformed patients to avoid change in

behavior (i.e., Hawthorne effect); and detection of antihypertensive medications by 24-hr urine LC-MS/MS, the current recommended method for determination of medication adherence.

Study weaknesses include binary determination of drug and drug metabolite levels as opposed to a quantitative assessment. In addition, the time duration between ABPM and drug metabolite testing could have introduced some variation in the detection of the urinary drug metabolites by qualitative analysis. These limitations preclude a more nuanced interpretation of drug exposure, such as potential variation in drug levels related to once versus multiple daily dosing in individual patients.

Patients with MUCH have similar levels of antihypertensive medication adherence compared to patients with hypertension controlled both in the office and in the clinic. These findings suggest that poor adherence to antihypertensive medication is not a cause of MUCH.

Perspectives

Patients with MUCH have similar levels of antihypertensive medication adherence compared to patients with true controlled hypertension. These findings suggest that poor adherence to antihypertensive medication is not a cause of MUCH.

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Novelty and Significance

1. What is new: This is the first study to evaluate if masked uncontrolled hypertension (MUCH) attributed to antihypertensive medication non-adherence.

2. What is relevant: This study shows there is similar antihypertensive medication adherence in MUCH patients compared to true controlled hypertension. In a large diverse cohort of hypertensive patients subdivided into MUCH and true controlled hypertension as controls around 85+ % of the patients were adherent to antihypertensive medication in both the groups. This eliminates medication non-adherence as one of the possible causes of MUCH.

Summary

Patients with MUCH have similar antihypertensive medication adherence in MUCH patients compared to true controlled hypertension.

Figure Legends

Figure 1. Schematic of enrolled study participants

Table 1: Demographics, comorbidities, vitals and biochemistry in patients with masked uncontrolled and true controlled hypertension

Variables	Masked uncontrolled hypertension (n=81)	True controlled hypertension (n=77)	p-value
Demographics			
Age (years)	58.6 ± 10.6	60.6 ± 10.8	0.247
Female	36 (44.4%)	35 (45.5%)	0.899
African American	40 (49.4%)	38 (49.4%)	0.997
Comorbidities			
Current smoker	10 (12.3%)	6 (7.8%)	0.343
Dyslipidemia	53 (65.4%)	52 (67.5%)	0.780
Congestive heart failure	5 (6.2%)	4 (5.2%)	1.000
Coronary artery disease	9 (11.1%)	14 (18.2%)	0.208
Peripheral vascular disease	6 (7.4%)	4 (5.2%)	0.568
Diabetes	34 (42.0%)	18 (23.4%)	0.013
Prior stroke/transient ischemic attack	13 (16.0%)	10 (13.0%)	0.585
Body mass index (kg/m^2)	34.2 ± 6.2	32.3 ± 6.8	0.070
Clinic Measurements			
AOBP systolic (mmHg)	121.1 ± 8.2	114.1 ± 10.4	<0.001
AOBP diastolic (mmHg)	73.3 ± 7.7	70.6 ± 7.6	0.026
AOBP heart rate (beats/minute)	73.9 ± 11.6	71.7 ± 12.2	0.252
ABPM Measurements			
24 hour (overall) systolic BP (mmHg)	145.5 ± 11.6	121.5 ± 7.3	<0.001
24 hour (overall) diastolic BP (mmHg)	79.9 ± 8.3	68.8 ± 6.5	<0.001
24 hour (overall) mean arterial pressure (mmHg)	101.9 ± 7.9	86.3 ± 5.6	<0.001
24 hour (overall) pulse pressure (mmHg)	65.7 ± 11.4	52.8 ± 8.2	<0.001
24 hour (overall) heart rate (beats/min)	74.2 ± 11.3	71.1 ± 10.8	0.085
Awake (daytime) systolic BP (mmHg)	148.1 ± 11.2	123.8 ± 7.3	<0.001
Awake (daytime) diastolic BP (mmHg)	82.1 ± 8.1	70.9 ± 6.9	<0.001
Awake (daytime) mean arterial pressure (mmHg)	104.1 ± 7.5	88.0 ± 8.0	<0.001
Awake (daytime) pulse pressure (mmHg)	66.0 ± 11.5	53.5 ± 9.3	<0.001
Awake (daytime) heart rate (beats/min)	75.6 ± 11.4	72.6 ± 11.3	0.091
Asleep (nighttime) systolic BP (mmHg)	138.1 ± 19.2	114.4 ± 12.2	<0.001
Asleep (nighttime) diastolic BP (mmHg)	72.9 ± 11.3	62.2 ± 7.9	<0.001
Asleep (nighttime) mean arterial pressure (mmHg)	94.6 ± 12.7	79.2 ± 9.1	<0.001
Asleep (nighttime) pulse pressure (mmHg)	65.2 ± 14.5	52.8 ± 10.7	<0.001
Asleep (nighttime) heart rate (beats/min)	69.6 ± 11.7	66.7 ± 10.3	0.099
Biochemistry			

Sodium (mMol/L)	137.9 ± 3.3	138.6 ± 2.8	0.213
Potassium (mMol/L)	4.0 ± 0.4	4.0 ± 0.4	0.701
Bicarbonate (mMol/L)	28.3 ± 2.8	27.7 ± 3.1	0.226
Blood urea nitrogen (mg/dL)	17.7 ± 7.1	18.9 ± 7.7	0.370
Creatinine (mg/dL)	1.0 ± 0.3	1.1 ± 0.5	0.227

AOBP, automated office blood pressure; ABPM, ambulatory blood pressure monitoring

Table 2: Antihypertensive medication adherence in patients with masked uncontrolled and true controlled hypertension

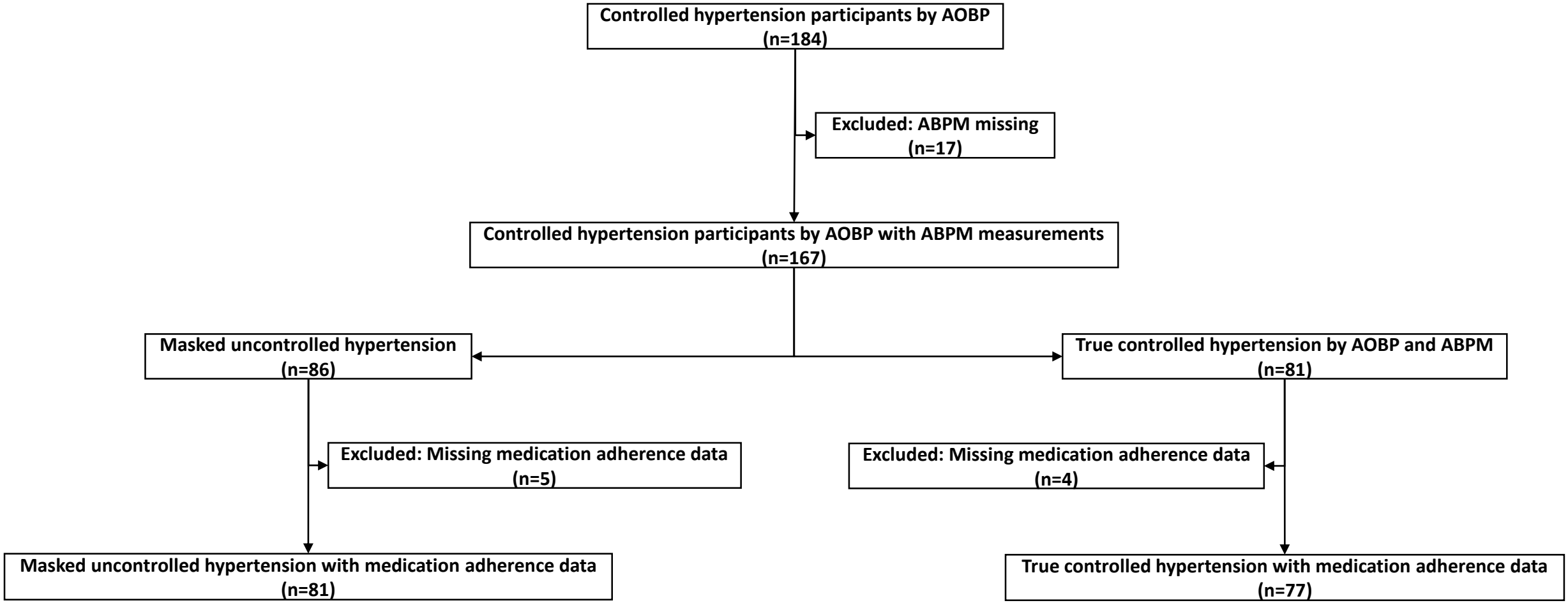
Variables	Masked uncontrolled hypertension (n=81)	True controlled hypertension (n=77)	p-value
Total medication adherence	69 (85.2%)	69 (89.6%)	0.403
Partial medication adherence	12 (14.8%)	8 (10.4%)	0.403
Total antihypertensive medications prescribed	3.5 ± 1.3	3.2 ± 1.2	0.072
Total antihypertensive medications detected	3.3 ± 1.2	3.1 ± 1.2	0.184
Antihypertensive medication classes			
Angiotensin converting enzyme inhibitors (benazepril, fosinopril, lisinopril, quinapril, ramipril)	30 (90.9%)	34 (97.1%)	0.349
Angiotensin II receptor blockers (azilsartan, candesartan, irbesartan, losartan, olmesartan, valsartan)	31 (93.9%)	32 (100.0%)	0.492
Calcium channel blockers (amlodipine, diltiazem, felodipine, nifedipine, verapamil)	59 (95.2%)	48 (98.0%)	0.629
Thiazide diuretics (chlorthalidone, hydrochlorothiazide)	61 (95.3%)	54 (98.2%)	0.623
Loop diuretics (furosemide, torsemide)	4 (100.0%)	1 (50.0%)	0.333
Epithelial sodium channel blockers (triamterene)	2 (100.0%)	2 (100.0%)	--

Mineralocorticoid receptor antagonists (eplerenone, spironolactone)	27 (93.1%)	29 (96.7%)	0.612
α blockers (doxazosin)	5 (100.0%)	2 (100.0%)	--
β Blockers (acebutalol, atenolol, bisoprolol, metoprolol, nebivolol)	16 (94.1%)	17 (85.0%)	0.609
αβ blockers (carvedilol, labetalol)	18 (90.0%)	9 (100%)	1.000
α2 agonists (clonidine, guanfacine)	11 (91.7%)	7 (100.0%)	1.000
Nitric oxide vasodilators (hydralazine)	3 (100.0%)	1 (100.0%)	--
Potassium channel openers (minoxidil)	2 (100.0%)		--

Table 3: Antihypertensive medication adherence in patients with masked uncontrolled and true controlled hypertension subdivided by total and partial antihypertensive medication adherence

Variables	Masked uncontrolled hypertension		True controlled hypertension		p-value
	Total medication adherence (n=69)	Partial medication adherence (n=12)	Total medication adherence (n=69)	Partial medication adherence (n=8)	
Total antihypertensive medications prescribed	3.4 ± 1.2	4.5 ± 1.4	3.1 ± 1.2	3.9 ± 1.0	0.002
Total antihypertensive medications detected	3.4 ± 1.3	3.1 ± 1.2	3.1 ± 1.2	2.8 ± 1.0	0.406
Antihypertensive medication classes					
Angiotensin converting enzyme inhibitors (benazepril, fosinopril, lisinopril, quinapril, ramipril)	29 (100.0%)	1 (25.0%)	30 (100.0%)	4 (80.0%)	<0.001
Angiotensin II receptor blockers (azilsartan, candesartan, irbesartan, losartan, olmesartan, valsartan)	26 (100%)	5 (71.4%)	30 (100%)	2 (100.0%)	0.017
Calcium channel blockers (amlodipine, diltiazem, felodipine, nifedipine, verapamil)	52 (100.0%)	7 (70.0%)	43 (100.0%)	5 (83.3%)	<0.001
Thiazide diuretics (chlorthalidone, hydrochlorothiazide)	52 (100.0%)	9 (75.0%)	49 (100.0%)	5 (83.3%)	<0.001
Loop diuretics (furosemide, torsemide)	4 (100.0%)		1 (100.0%)	0	0.333
Epithelial sodium channel blockers (triamterene)	1 (100.0%)	1 (100.0%)	2 (100%)		--
Mineralocorticoid receptor antagonists (eplerenone, spironolactone)	23 (100.0%)	4 (66.7%)	25 (100.0%)	4 (80.0%)	0.005
α blockers (doxazosin)	5 (100%)		2 (100%)		--
β blockers (acebutalol, atenolol, bisoprolol, metoprolol, nebivolol)	15 (100.0%)	1 (50.0%)	17 (100.0%)	0	<0.001
αβ blockers (carvedilol, labetalol)	13 (100.0%)	5 (71.4%)	8 (100%)	1 (100.0%)	0.121
α2 agonists (clonidine, guanfacine)	8 (100%)	3 (75.0%)	6 (100%)	1 (100.0%)	0.263
Nitric oxide vasodilators (hydralazine)	3 (100.0%)		1 (100%)		--

Potassium channel openers (minoxidil)	1 (100%)	1 (100%)	--


Controlled hypertension participants by AOBP (n=184)
Excluded: ABPM missing (n=17)
Controlled hypertension participants by AOBP with ABPM measurements (n=167)
Masked uncontrolled hypertension (n=86)
True controlled hypertension by AOBP and ABPM (n=81)
Excluded: Missing medication adherence data (n=5)
Excluded: Missing medication adherence data (n=4)
Masked uncontrolled hypertension with medication adherence data (n=81)
True controlled hypertension with medication adherence data (n=77)