Title

Comparison of Morisky Medication Adherence Scale with therapeutic drug monitoring in apparent treatment–resistant hypertension

Journal

International Journal of Cardiology Cardiovascular Risk and Prevention, 9(6)

ISSN

1933-1711

Authors

Pandey, Ambarish
Raza, Fayez
Velasco, Alejandro
et al.

Publication Date

2015-06-01

DOI

10.1016/j.jash.2015.04.004

Peer reviewed

Journal of the American Society of Hypertension 9 (2015) 420–426

Research Article

Comparison of Morisky Medication Adherence Scale with therapeutic drug monitoring in apparent treatment–resistant hypertension

Ambarish Pandey, MD[a], Fayez Raza, MD[b], Alejandro Velasco, MD[c], Stephanie Brinker, MD[b], Colby Ayers, MS[d], Sandeep R. Das, MD, MPH[a], Donald E. Morisky, ScD, MSPH, ScM[e], Ethan A. Halm, MD[b], and Wanpen Vongpatanasin, MD[a,c,*]

[a]*Cardiology Division, University of Texas Southwestern Medical Center, Dallas, TX, USA;*
[b]*Internal Medicine Department, University of Texas Southwestern Medical Center, Dallas, TX, USA;*
[c]*Hypertension Section, University of Texas Southwestern Medical Center, Dallas, TX, USA;*
[d]*Department of Clinical Science, University of Texas Southwestern Medical Center, Dallas, TX, USA; and*
[e]*Department of Community Health Sciences, Univeristy of California, Los Angeles, Fielding School of Public Health, Los Angeles, CA, USA*

Manuscript received December 18, 2014 and accepted April 11, 2015

Abstract

The Morisky Medication Adherence Scale (MMAS–8) is a questionnaire developed for screening of non–adherence in patients with several chronic conditions, including uncomplicated hypertension. However, its accuracy in predicting non–adherence in patients with apparent treatment–resistant hypertension (a–TRH) is not known. Accordingly, we performed a retrospective study in 47 patients with a–TRH who had completed the eight–item MMAS during the initial clinic visit. Non–adherence was defined as presence of undetected serum levels of at least one prescribed antihypertensive drug by therapeutic drug monitoring. We found that 26% of patients were considered to have low adherence score (<6), while the actual prevalence of non–adherence was 51% by therapeutic drug monitoring. Sensitivity of the MMAS–8 was 26% (95% confidence interval, 10.3%–48.4%) with specificity of 75% (95% confidence interval, 53.3%–90.2%). By multivariate analysis, the MMAS–8 score was not an independent predictor of non–adherence, while certain clinical parameters such as heart rate were found to be independent predictors of non–adherence. Our study suggested limited accuracy of the MMAS–8 in detecting medication non–adherence in a–TRH. J Am Soc Hypertens 2015;9(6):420–426.

Keywords: Blood pressure control; self reported adherence; serum drug levels.

Introduction

Adherence to medications is a major challenge that clinicians often face in treatment of chronic medical conditions, including hypertension. This problem is even more pronounced in patients with apparent treatment–resistant hypertension (a–TRH) defined as uncontrolled hypertension with three or more antihypertensive agents or treated hypertension with at least a four–drug regimen regardless of blood pressure (BP).[1] Recent studies from our group and others have reported a high prevalence of non–adherence to antihypertensive medications among patients with a–TRH (50-60%) using the highly sensitive technique of therapeutic drug monitoring.[2–5] Despite the enormous burden of non–adherence to the health care system, practical and reliable methods of adherence detection are not well developed. Adherence can be monitored by several methods such as patient self–report, detailed questionnaire, pill counts, prescription fill rate, or electronic pillboxes.

Among the self-reported measure of adherence, the Morisky Medication Adherence Scale (MMAS) has been used extensively and validated in the primary care setting in the patients with uncomplicated hypertension.[6–8] The

Supported by grants to Dr Vongpatanasin from the University of Texas Southwestern O'Brien Kidney Center P30 DK079328.

Conflict of interest: none.

*Corresponding author: Wanpen Vongpatanasin, MD, Hypertension Section, Cardiology Division, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8586. Tel: (214) 648-2103; Fax: (214) 648-3063.

E-mail: wanpen.vongpatanasin@utsouthwestern.edu

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2015.04.004

questionnaire was originally developed as the four–item scale[9] and subsequently revised to an eight–item scale to address additional factors that may influence medication adherence. The questions in the eight–item scale are designed to avoid patients' tendency to overestimate their adherence to healthcare providers and were shown to have higher reliability than the original four–item scale.[10] However, both four–item and eight–item scales have never been validated in patients with a–TRH.

Accordingly, the goal of present investigation is to determine sensitivity and specificity of the MMAS–8 in a cohort of patients referred to a large tertiary care academic medical center specialty hypertension clinic against therapeutic drug monitoring. Furthermore, we also determine accuracy of other independent questionnaire and clinical predictors of medication non–adherence in detecting non–adherence to medications among patients with a-TRH.

Methods

The Institutional Review Board of the University of Texas Southwestern Medical Center approved this study. Medical records of all new patients referred to the hypertension specialty clinic at the University of Texas Southwestern Medical Center for a–TRH and evaluated between January 2009 and October 2014 were reviewed. Patients were included if they met the American Heart Association/Committee of the Council for High Blood Pressure Research definition of a–TRH: (1) failure to achieve office BP <140/90 mm Hg in patients prescribed three or more antihypertensive medications at optimal doses, including if possible a diuretic, or (2) ability to achieve office BP at goal but patient requiring four or more antihypertensive medications.[1] Patients were excluded if they were intolerant to three or more antihypertensive drug classes. Screening for white coat effect with 24–hour ambulatory BP monitoring was conducted for patients who reported normal home BP (<135/85 mm Hg), and patients with demonstrated BP control at home were also excluded. Either private medical insurance or Medicare covered all patients. All patients had reported that they were adherent to prescribed antihypertensive medications prior to therapeutic drug monitoring.

During each clinic visit, after the patient had been resting quietly for 5 minutes, BP was measured by nursing staff using the same validated oscillometric device (Welch Allyn, Vital Signs, Skaneateles Falls, NY) as recommended by guidelines.[11] BP measurement during a single visit was repeated three times separated by 1 minute, and these BP values were averaged. Since January 2009, serum levels of antihypertensive medications were assessed as part of our routine standard of care for new referrals with presumed a–TRH. Since December 2010, all patients were also asked to fill out an eight–item MMAS survey during the initial clinic visit to assess potential non–adherence to antihypertensive medications. Written permission was obtained from Dr Donald Morisky for use of the eight–item MMAS among the study participants. The study participants were also screened with an additional question ''In the past 7 days, how many times did you skip or miss your BP meds for any reason?'' Screening for non–adherence was conducted at Compliance with Clinical Laboratory Improvement Act (CLIA)–certified laboratories as previously described[2] (Supplemental Table 1 and Supplemental Figure 1). This technique has been validated previously for measuring levels of antihypertensive medications.[12,13] Non–adherence was defined as presence of serum levels below detection limit of at least one antihypertensive medication prescribed to the patient by therapeutic drug monitoring.

Predictive value of medication adherence questionnaire was validated against non–adherence by therapeutic drug monitoring. We also determined clinical factors associated with medication non–adherence and assessed incremental predictive value of these factors when used in conjunction with adherence scale.

Statistical Analysis

Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). All tests were two–sided, and a P–value $< .05$ was considered statistically significant. Data are presented as mean $\pm$ standard deviation (SD) or mean (95%) as appropriate. Baseline characteristics were compared among the adherent and non–adherent groups using the χ^2 test for categorical variables and t–tests for continuous variables. For non–normally distributed variables, the Kruskal–Wallis test was used. Multivariate analysis to determine predictors of non–adherence was conducted with backward selection technique by first entering all candidate predictors in the model. Then, the least significant variable is deleted. The model is then refitted, and the least significant variable is again deleted. The cycle is repeated until the variables left in the model are all significant. Contribution of clinical predictors over and above that of adherence questionnaire in the prediction of medication adherence was analyzed with the use of discrimination (Harrell's C–statistic).

Results

Between 2009 and 2014, 227 consecutive patients were referred to the University of Texas Southwestern Medical Center Hypertension Clinic for a–TRH. Two patients were found to have white coat effect by 24–hour ambulatory BP monitoring. Therapeutic drug monitoring was performed in 78 patients, while 147 did not undergo measurement of serum drug levels because one of the antihypertensive drugs was not prescribed at or near maximal doses. The MMAS–8 was administered in 50 patients and was completed in 47 patients (Figure 1).

Of the 47 patients who underwent both therapeutic drug monitoring and completed the adherence scale, 24 (51%) had at least one antihypertensive drug prescribed below minimal detection limit and thus were non–adherent. Over two–thirds of the non–adherent patients had all the tested antihypertensive drugs below minimum detection limit. Characteristics of adherent and non–adherent patients are shown in Table 1. The non–adherent group was significantly younger, had a higher proportion of females, and a significantly higher resting heart rate (HR). Prevalence of chronic kidney disease (CKD) was higher in the adherent than non–adherent group. In contrast, duration of hypertension, history of side effects to medications, frequency of drug dosing, and number of antihypertensive drugs were not significantly different between the two groups.

By the MMAS–8, 12 (26%) of patients had low adherence (score <6), 16 (34%) had medium adherence (score 6 to <8), and 19 (40%) high adherence (score = 8). Average BP in the group with low, medium, and high adherence score was 155 ± 25/89 ± 11 mm Hg, 155 ± 35/91 ± 13 mm Hg, and 162 ± 32/94 ± 23 mm Hg, respectively ($P = .75$ for systolic and .85 for diastolic BP). Responses to all questions in the 8–item MMAS were not different between the therapeutic drug monitoring-based adherent versus the non–adherent participants (Table 2). Furthermore, the proportion of participants with high (MMAS score = 8), moderate (MMAS score 6 to <8), and low adherence (MMAS score <6) on the MMAS–8 scale was not different among the therapeutic drug monitoring–based adherent versus non–adherent groups (Table 3). Similarly, responses to the independent question #9 (Q9) "In the past 7 days, how many times did you skip or miss your BP meds for any reason?" were not different between the two groups. Using the MMAS–8 cut–off point of six or lower as measure of non–adherence, the sensitivity was found to be 26% (95% confidence interval [CI], 10.3%–48.4%) and specificity of 75% (95% CI, 53.3%–90.2%) with positive predictive value of 50% (95% CI, 21.1%–78.9%) and negative predictive value of 51% (95% CI, 34%–68.6%) when compared against therapeutic drug monitoring. The alpha reliability of the eight–item MMAS is 0.68. Sensitivity and specificity of Q9 was 39% (95% CI, 19.7%–61.5%) and 67% (95% CI, 47.7%–84.4%), respectively, with positive predictive value of 53% (95% CI, 34.3%–71.7%) and negative predictive value of 53% (95% CI, 27.8%–77.0%).

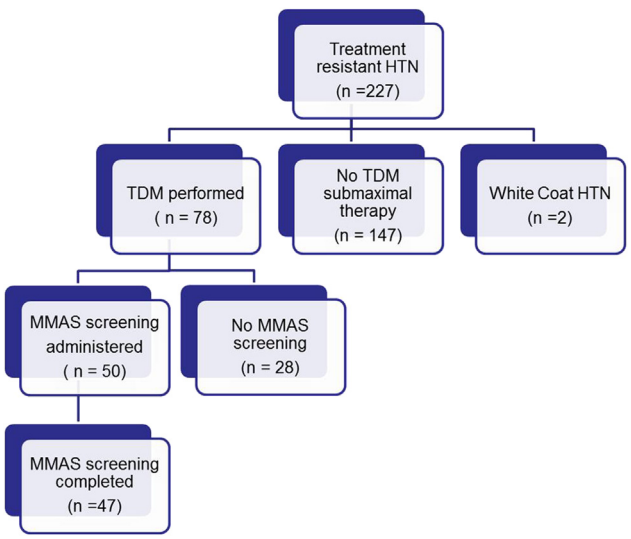


Figure 1. Cohort selection for the study. HTN, hypertension; MMAS, Morisky Medication Adherence Scale; TDM, therapeutic drug monitoring.

To determine clinical predictors of non–adherence using therapeutic drug monitoring, multivariate analysis was conducted using backward selection technique. Elevated HR was identified as an independent predictor of non–adherence (Adjusted Risk Ratio [95% CI], 1.08 (1.02–1.15); $P = .006$) while presence of CKD was a predictor of adherence to medications (Adjusted Risk Ratio [95% CI], 0.808 [0.009–0.78]; $P = .03$). In contrast, the MMAS–8 score and all other variables listed in Table 1, including age, gender, ethnicity, coronary artery disease, congestive heart failure, total daily dosing of antihypertensive medication, duration of hypertension, systolic BP, and diastolic BP, were not independent predictors in the multivariate analysis.

Area under the curve (AUC) resulting from receiver operating characteristic analyses was greater for clinical predictors (HR plus CKD) than the MMAS–8 score alone (Figure 2; $P = .003$). When HR and CKD were added to the MMAS–8 score, the area under the curve increased significantly from 0.52 to 0.84 (Figure 2; $P = .001$).

Discussion

The major findings from our study are 2–fold. First, self–reported medication adherence has limited sensitivity and specificity in detecting medication non–adherence in patients with a–TRH. Second, certain clinical characteristics of patients were stronger predictors of non–adherence than self–reported adherence.

Current guidelines advocate exclusion of pseudo–resistant hypertension from medication non–adherence as the first step in the management of a–TRH. Since physicians' ability to predict patients' adherence to antihypertensive medication is notoriously poor,[14] reliable and practical tools are needed to assess adherence to medications. Self–reported adherence as simply yes or no is well–known to underestimate prevalence of non–adherence.[15] Prescription fill rate may be more accurate than self–reported adherence, but it is time consuming to track, and information may not be accurate if the patients are not in an integrated health care system or fill prescriptions but do not take the dispensed medication. Pill count is also time–consuming and accurate in determining adherence only in 50%–70% of patients when compared with electronic pillbox[16,17]

Table 1
Baseline characteristics of the study participants

Characteristics	TDM Adherent (n = 23)	TDM Non–adherent (n = 24)	*P* Value
Age, y	55 ± 2	50 ± 2	.28
Gender, % female	30% (11.6–49.2)	63%* (43.1–81.9)	**.03**
Ethnicity, % African American	52% (30.6–73.2)	58% (36.7–77.9)	.54
% with employment	46% (25.6–67.2)	57% (34.0–78.2)	.55
BMI, kg/m^2	33.1 ± 1.6	35.8 ± 2.4	.82
Duration of hypertension, y	12.5 ± 4.8	13.8 ± 4.9	.58
Heart rate, bpm	70 ± 3	82 ± 3*	**<.01**
SBP, mm Hg	160 ± 6	156 ± 7	.50
DBP, mm Hg	87 ± 2	96 ± 4	.16
Diabetes, %	43% (23.2–65.5)	30% (13.2–52.9)	.35
Dyslipidemia, %	52% (30.6–73.2)	65% (42.7–83.6)	.37
Current smoker, %	13% (2.8–33.6)	17% (4.9–38.8)	.52
Coronary artery disease, %	17% (4.9–38.8)	13% (2.8–33.6)	.68
Heart failure, %	9% (1.1–28)	17% (4.9–38.8)	.38
CKD (eGFR<60 mL/min 1.73 m^2), %	35% (10.2–48.4)	8%* (1.0–27.0)	**.02**
Numbers of antihypertensive drugs at first encounter	4.0 ± 0.2	4.4 ± 0.3	.75
Frequency of drug dosing, times/day	2.0 ± 0.1	2.0 ± 0.2	.89
OSA, %	39% (19.7–61.5)	35% (16.4–57.3)	.76
Ability to recall drug names, %	74% (51.6–90.0)	92% (73.0–99.0)	.25
History of drug side effects, %	39% (19.7–61.5)	17% (4.9–38.8)	.09
History of ED visit related to high BP, %	48% (26.8–69.4)	42% (22.1–63.4)	.67

BMI, body mass index; BP, blood pressure; bpm, beats per minute; CKD, chronic kidney disease; DBP, diastolic blood pressure; ED, erectile dysfunction; eGFR, estimated glomular filtration rate; OSA, obstructive sleep apnea; SBP, systolic blood pressure; TDM, therapeutic drug monitoring.

Data presented as mean + SD for continuous variables and mean (95% confidence interval) for categorical variables.

*$P < .05$ compared with adherent group & P - value in bold refers to a value <0.05 for comparison between TDM adherent vs. non-adherent groups.

and 68% when compared with therapeutic drug monitoring.[18] More detailed self–reported questionnaires have been developed to detect medication non–adherence and avoid patients' tendency to report yes when they are simply asked if they have taken medications as prescribed. The four–item MMAS was shown to be correlated with level of BP control and found to be reliable when validated against prescription fill rate[7] and pill count.[8] The eight–item scale was also significantly correlated with proportion of patients with adequate BP control[10] and pharmacy refill data in the elderly hypertensive patients.[6] However, predictive accuracy of both four–item and eight–item MMAS in detecting medication non–adherence has not been validated in patients with a-TRH.

In our study, the eight–item MMAS was found to have limited accuracy in detecting non–adherence. Similarly, an independent questionnaire also performed poorly in this population when validated against therapeutic drug monitoring. Mechanisms underlying limited accuracy of questionnaires in detecting non–adherence in patients with a-TRH are unknown. Both four–item and eight–item MMAS address factors contributing to medication non–adherence but these factors may differ among a–TRH patients in the primary care setting versus specialty referral care setting. For example, history of side effects to medications and complexity of regimen were shown to be independent predictors of medication non–adherence in previous studies in the primary care setting.[19–22] In our study, history of drug side effects was paradoxically higher in adherent patients, though the difference was not statistically significant. Furthermore, the number of antihypertensive drugs and frequency of drug dosing were not different between adherent and nonadherent groups. Other determinants, such as ability and availability of medical providers to counsel patients or adjust regimen to minimize drug side effects and maximize drug efficacy, may play a larger role. Alternatively, a–TRH patients may have tendency to provide socially acceptable responses to the questionnaire. This is evident in our study since only 26% of our subjects were found to have a low adherence score of <6, which is considerably less than the actual prevalence of non–adherence of 51% as confirmed by therapeutic drug monitoring. A recent large population–based study in the United States, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, also reported very low prevalence of non–adherence of only 8%, using the four–item MMAS.[23]

We also identified a higher proportion of females in the non–adherent group, which was consistent with findings from the REGARDS study[23] and one previous study in

Table 2
Response to the Morisky Medication Adherence Scale (MMAS–8) questionnaire observed in therapeutic drug monitoring (TDM) based adherent and non–adherent patients

MMAS–8 Adherence Questions	Patient Response (Yes/No)		χ^2	*P* Value
	TDM–adherent (Total = 23)	TDM Non–adherent (Total = 24)		
1. Do you sometimes forget to take your BP pills?	Yes/No = 8/15	Yes/No = 8/16	0.01	.92
2. Over the past 2 weeks, were there any days when you did not take your BP medicines?	Yes/No = 5/18	Yes/No = 17/7	0.36	.56
3. Have you stopped taking medications because you feel worse when you took it?	Yes/No = 3/20	Yes/No = 5/19	0.5	.48
4. When you travel or leave home, do you sometimes forget to bring along your meds? (Yes/No)	Yes/No = 3/20	Yes/No = 3/21	0.003	.96
5. Did you take your BP medicine yesterday? (Yes/No)	Yes/No = 23/0	Yes/No = 21/3	3.07	.08
6. When you feel like your BP is under control, do you sometime stop taking your meds? (Yes/No)	Yes/No = 2/21	Yes/No = 2/22	0.002	.96
7. Do you feel hassled about sticking to your BP treatment plan? (Yes/No)	Yes/No = 4/19	Yes/No = 5/19	0.09	.76
8. How often do you have difficulty remembering to take all your BP meds?			0.07	.96
a) Never/rarely	16	16		
b) Once in a while	5	6		
c) Sometimes	0	0		
d) Usually	0	0		
e) All the time	2	2		

BP, blood pressure.

Data presented as total number of participants and percentage with 95% confidence intervals.

US copyright laws protect use of the MMAS. Permission for use is required. A Licensure agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772; dmorisky@ucla.edu.

the tertiary care center.[4] However, the association between gender and medication non–adherence in our study became weaker after multivariate analysis accounting for HR and presence of other comorbidities. Although small sample size may be responsible for attenuation in the relationship, our study indicated elevated HR was a strong independent predictor of medication non–adherence, which was previously demonstrated in studies using therapeutic drug monitoring in a–TRH.[3,12] Presence of CKD, however, was found to be a predictor of adherence to treatment. It is unlikely that presence of CKD is directly responsible for the adherent behaviour, but older age and higher proportion of male in the adherent group may contribute to differences in the prevalence of CKD.

Table 3
Prevalence of low, medium, and high Morisky Medication Adherence Scale (MMAS–8) scores among therapeutic drug monitoring (TDM)–based adherent and non–adherent patients

Adherence	Low MMAS–8 Score (<6)	Medium MMAS-8 Score (6 to <8)	High MMAS–8 Score (8)
Adherent by TDM, N (%)	6 (26%)	8 (35%)	9 (39%)
Non adherent by TDM, N (%)	6 (25%)	8 (33%)	10 (42%)

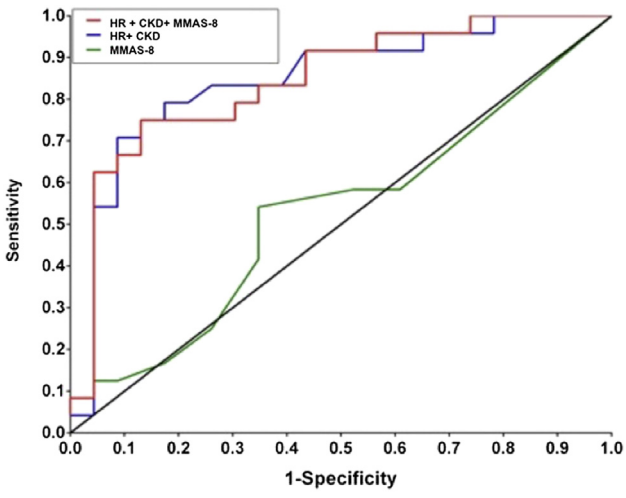


Figure 2. ROC curves for models to predict adherence in patients with apparent treatment resistant hypertension. CKD, chronic kidney disease; HR, heart rate; MMAS-8, Morisky Medication Adherence Scale.

There are several limitations to our study. First, the study was done retrospectively in a referral hypertension specialty clinic population, limiting the generalizability of study findings. Second, only insured patients were included in the study and, thus, the data may not be applicable to the indigent care population who cannot afford health insurance. Third, since there is no gold standard for assessment of non–adherence, the sensitivity and specificity of therapeutic drug monitoring in detecting non–adherence has not been established. Fourth, the sample size of our study is small; 35% of the referred patients were excluded as they did not meet the criteria for therapeutic drug monitoring, and only a subgroup of all referred patients underwent screening with the MMAS–8. Nevertheless, our study has important implications in the evaluation of presumed a–TRH and raises caution against overreliance on the self–report questionnaire at least in the referral specialty care setting. Since therapeutic drug monitoring is already available for clinical use and covered by health insurance plans in the US and many countries worldwide,[22,24] it should be considered for assessment of medication adherence, particularly when other less expensive methods yield inconclusive results. Future studies are needed to develop a cost–effective and time–efficient therapeutic drug monitoring strategy. Furthermore, large prospective studies are still needed to test validity of clinical variables, including HR, in predicting medication non–adherence in a–TRH.

Acknowledgments

We The authors would like to acknowledge Wendy R. Adams, PhD, F-ABFT Assistant Laboratory Director, NMS Labs, for providing details of therapeutic drug monitoring assays analytical data for our manuscript.

References

1. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008;117:e510–26.
2. Brinker S, Pandey A, Ayers C, Price A, Raheja P, Arbique D, et al. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. J Am Coll Cardiol 2014;63:834–5.
3. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens 2013;31:766–74.
4. Strauch B, Petrak O, Zelinka T, Rosa J, Somloova Z, Indra T, et al. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. J Hypertens 2013;31:2455–61.
5. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart 2014;100:855–61.
6. Krousel-Wood M, Islam T, Webber LS, Re RN, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care 2009;15:59–66.
7. Ben AJ, Neumann CR, Mengue SS. The Brief Medication Questionnaire and Morisky-Green test to evaluate medication adherence. Rev Saude Publica 2012;46:279–89.
8. Prado JC Jr, Kupek E, Mion D Jr. Validity of four indirect methods to measure adherence in primary care hypertensives. J Hum Hypertens 2007;21:579–84.
9. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24:67–74.
10. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens 2008;10:348–54.
11. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension 2005;45:142–61.
12. Ceral J, Habrdova V, Vorisek V, Bima M, Pelouch R, Solar M. Difficult-to-control arterial hypertension or uncooperative patients? The assessment of serum antihypertensive drug levels to differentiate non-responsiveness from non-adherence to recommended therapy. Hypertens Res 2011;34:87–90.
13. Chytil L, Strauch B, Cvacka J, Maresova V, Widimsky J Jr, Holaj R, et al. Determination of doxazosin and verapamil in human serum by fast LC-MS/MS: application to document non-compliance of patients. J Chromatogr B Analyt Technol Biomed Life Sci 2010;878:3167–73.
14. Zeller A, Taegtmeyer A, Martina B, Battegay E, Tschudi P. Physicians' ability to predict patients' adherence to antihypertensive medication in primary care. Hypertens Res 2008;31:1765–71.
15. Zeller A, Ramseier E, Teagtmeyer A, Battegay E. Patients' self-reported adherence to cardiovascular medication using electronic monitors as comparators. Hypertens Res 2008;31:2037–43.
16. Lee JY, Kusek JW, Greene PG, Bernhard S, Norris K, Smith D, et al. Assessing medication adherence by pill count and electronic monitoring in the African

American Study of Kidney Disease and Hypertension (AASK) Pilot Study. Am J Hypertens 1996;9:719–25.
17. van Onzenoort HA, Verberk WJ, Kessels AG, Kroon AA, Neef C, van der Kuy PH, et al. Assessing medication adherence simultaneously by electronic monitoring and pill count in patients with mild-to-moderate hypertension. Am J Hypertens 2010;23: 149–54.
18. Pullar T, Kumar S, Tindall H, Feely M. Time to stop counting the tablets? Clin Pharmacol Ther 1989;46:163–8.
19. AlGhurair SA, Hughes CA, Simpson SH, Guirguis LM. A systematic review of patient self-reported barriers of adherence to antihypertensive medications using the world health organization multidimensional adherence model. J Clin Hypertens 2012;14:877–86.
20. Svarstad BL, Chewning BA, Sleath BL, Claesson C. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. Patient Educ Couns 1999;37:113–24.
21. Wetzels G, Nelemans P, van Wijk B, Broers N, Schouten J, Prins M. Determinants of poor adherence in hypertensive patients: development and validation of the ‘‘Maastricht Utrecht Adherence in Hypertension (MUAH)-questionnaire’’. Patient Educ Couns 2006;64: 151–8.
22. Benson J, Britten N. Patients’ views about taking antihypertensive drugs: questionnaire study. BMJ 2003; 326:1314–5.
23. Irvin MR, Shimbo D, Mann DM, Reynolds K, Krousel-Wood M, Limdi NA, et al. Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. J Clin Hypertens 2012;14: 694–700.
24. Chung O, Vongpatanasin W, Bonaventura K, Lotan Y, Sohns C, Haverkamp W, et al. Potential cost-effectiveness of therapeutic drug monitoring in patients with resistant hypertension. J Hypertens 2014;32: 2411–21.

Supplemental Table 1
List of serum/plasma assays of commonly used anti–hypertensive agents available for clinical testing

Drug Name	Reporting Limit	Method of Analysis	Sample Volume	Lab Vendor*	Intra–assay Coefficient of Variability, %	Inter–assay Coefficient of Variability,* %	Accuracy, %	Therapeutic Range
Metoprolol	5.0 ng/mL	LC–MS/MS	2 mL Serum/Plasma	Quest/NMS	2.71	2.8	91.09	20–340 ng/mL for 200–400 mg daily dose
Atenolol	5.0 ng/mL	LC–MS/MS	2 mL Serum/Plasma	Quest/NMS	2.24	3.78	92.04	200–500 ng/mL for 200–400 mg daily dose
Labetalol	5.0 ng/mL	LC–MS/MS	2 mL Serum/Plasma	Quest/NMS	2.02	3.09	90.59	180–200 ng/mL for 200–400 mg daily dose
Hydrochlorothiazide	0.040 mcg/mL	HPLC	2 mL Serum/Plasma	Quest/NMS	4.17	4.03	97	0.08–0.2 mcg/mL for 25–75 mg daily
Chlorthalidone	0.040 mcg/mL	HPLC	2 mL Serum/Plasma	Quest/NMS	4.92	6.76	97.3	0.2–1.4 mcg/mL for 50–100 mg daily dose
Amlodipine	2.0 ng/mL	HPLC	3 mL Serum/Plasma	Quest/NMS	3.09	14	108.8	3–11 ng/mL for 5 mg daily
Diltiazem	2.0 ng/mL	HPLC	3 mL Serum/Plasma	Mayo/NMS	6	11.3	97.6	50–200 ng/mL
Triamterene	5.0 ng/mL	LC-MS/MS	1 mL Serum/Plasma	Quest/NMS	4.1	5.99	101.8	30–50 ng/mL for 37.5–100 mg daily
Spironolactone	0.020 mcg/mL	Spectro–fluorometry	2 mL Serum/Plasma	Quest/NMS	Not available	6.3	91.3	1mcg/mL for 25 mg dose
Furosemide	0.04 mcg/mL	HPLC	1 mL Serum/Plasma	Quest/NMS /Medox	6.56	7.12	94.9	Levels (mcg/mL) 1 hour after a one PO dose: 20 mg: 0.8–1.8 50 mg: 1.5–2.9 80 mg: 2.2–4.8
Clonidine	0.050 ng/mL	LC-MS/MS	1 mL Serum/Plasma	Mayo/NMS	4.14	4.45	95.2	0.5–4.5 ng/mL
Guanfacine	0.5 ng/mL	LC–MS/MS	2 mL Serum/Plasma	NMS	2.85	3.5	90.1	1.6–10 ng/mL for 2–4 mg daily dose
Doxazosin	0.5 ng/mL	HPLC	5 mL Serum/Plasma	Quest/NMS	2	12.2	105.3	8–150 ng/mL for 1–16 mg daily dose
Minoxidil	2.0 ng/mL	LC–MS/MS	3 mL Serum/Plasma	Quest/NMS	1.97	2.37	89.9	20–50 ng/mL after 5 mg daily dose
Hydralazine	0.5 ng/mL	GC	5 mL Serum/Plasma	Quest/NMS	Not available	16	100	15–300 ng/mL for 100–200 mg daily

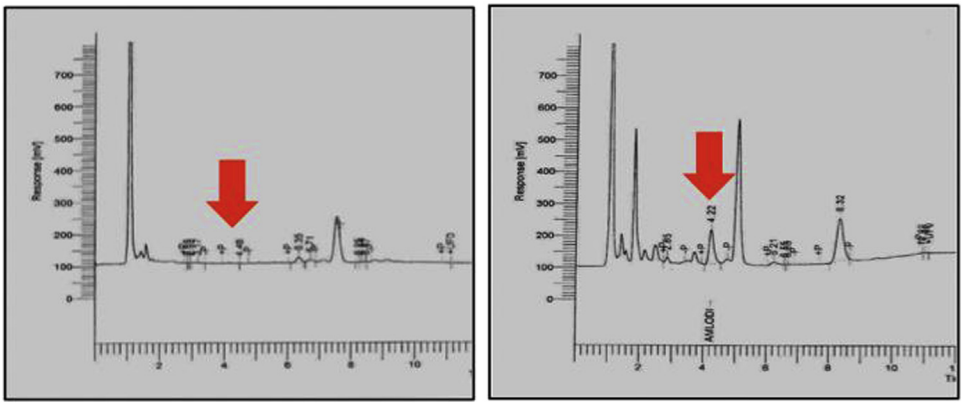
GC, gas chromatography; HPLC, high–performance liquid chromatography; LC–MS, Liquid chromatography–mass spectrometry; MS, mass spectrometry.

* Inter–assay coefficient of variability obtained between run from at least 3 different days. Accuracy is the result divided by the target. A result of 4.5 with a target of 5 would be 90% accurate. For details, please see http://www.nmslabs.com/SearchResults.aspx?search=antihypertensive.

Supplemental Table 2
Comparison of baseline characteristics of patients included versus excluded from the present study

Patient Characteristics	Patients Included in the Study (n = 47)	Patients Excluded from the Study (n = 178)	*P* Value
Age, y	52.6 (11)	55.2 (12.1)	.1
Women, %	47	58	.15
African Americans, %	43	55	.24
Body mass index, kg/m^2	34.5 (10)	34.6 (9)	.52
Systolic BP, mm Hg	158 (31)	149 (32)	.1
Diastolic BP, mm Hg	91 (17)	85 (18)	.008
Heart rate, bpm	76 (17)	73 (15)	.33

BP, blood pressure; bpm, beats per minute.
Data presented as mean (standard deviation) or %.



Supplemental Figure 1. Analytical data from high-performance liquid chromatography analysis of amlodipine in one blank serum (left) and serum from one patient treated with amlodipine (right). The arrow represents amlodipine spectrum.