Association Between Antihypertensive Medication Adherence and Visit-to-Visit Variability of Blood Pressure

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It has been hypothesized that high visit-to-visit variability (VVV) of systolic blood pressure (SBP) may be the result of poor antihypertensive medication adherence. The authors studied this association using data from 1391 individuals taking antihypertensive medication selected from a large managed care organization. The 8-item Morisky Medication Adherence Scale, administered during 3 annual surveys, captured self-report adherence, with scores <6, 6 to <8, and 8 representing low, medium. and high adherence, respectively. The mean (standard deviation [SD]) for SD of SBP across study visits was 12.9 (4.4), 13.5 (4.8), and 14.1 (4.5) mm Hg in participants with high, medium, and low self-reported adherence, respectively. After multivariable adjustment and compared with those with high self-report adherence, SD of SBP was 0.60 (95% confidence interval, 0.13–1.07) and 1.08 (95% confidence interval, 0.29–1.87) mm Hg higher among participants with medium and low self-report adherence, respectively. Results were consistent when pharmacy fill was used to define adherence. These data suggest that low antihypertensive medication adherence explains only a small proportion of VVV of SBP. *J Clin Hypertens (Greenwich).* 2013; 15:112–117. ©2012 Wiley Periodicals, Inc.

Several recent studies have reported a strong association between visit-to-visit variability (VVV) of systolic blood pressure (SBP) and the incidence of coronary heart disease, stroke, and all-cause mortality.[1–3] Substantial VVV of blood pressure (BP) is present in both research studies and routine patient care.[4,5] However, the mechanisms underlying high levels of VVV of BP are unclear.

It has been hypothesized that high VVV of SBP may be the result of poor antihypertensive medication adherence.[6] Low antihypertensive medication adherence is a common and well-known barrier to achieving adequate hypertension control.[7–10] Given the strong BP-lowering effect of antihypertensive medication, it is plausible that individuals who take their medication(s) irregularly may have fluctuations in their BP. However, few data are available on the degree to which high levels of VVV of BP are explained by low medication adherence.

The goal of this analysis was to determine the extent to which poor antihypertensive medication adherence explains VVV of BP. To accomplish this goal, we analyzed data on self-reported and pharmacy fill adherence for antihypertensive medications and VVV of BP from participants in the Cohort Study of Medication Adherence Among Older Adults (CoSMO).

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Manuscript received: July 23, 2012; **revised:** September 9, 2012; **accepted:** September 20, 2012
DOI: 10.1111/jch.12037

METHODS

Study Population and Timeline

The design of CoSMO has been described previously.[8] In brief, a listing of all adults 65 years and older with a primary or secondary diagnosis of essential hypertension (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code 401) insured by a large managed care organization meeting eligibility criteria (ie, enrolled in the Medicare risk product, at least one antihypertensive medication filled in 2005, continuously enrolled in the managed care organization for 2 years prior to baseline, and no in-patient or outpatient discharge diagnoses for cognitive impairment, malignancy or human immunodeficiency virus) was assembled. People on this list were assigned a random number, generated using a computer algorithm, and contacted and further screened for eligibility, in order from lowest to highest number until our recruitment goal was met. The enrollment of 2194 participants occurred between August 21, 2006, and September 30, 2007. Participants were actively followed through February 2010. All participants provided verbal informed consent and the study protocol for CoSMO was approved by the Ochsner Clinic Foundation's institutional review board and the privacy board of the managed care organization.

Study Measures

Of relevance to the current analysis, data collection included the administration of telephone surveys and medical chart abstraction. Survey data were collected during a baseline interview and follow-up interviews

conducted 1 and 2 years following baseline. Demographics were assessed through self-report and the administrative databases of the managed care organization were used to identify a history of diabetes, myocardial infarction, stroke, and heart failure. The classes of antihypertensive medications being taken by each participant were extracted from the managed care organization's pharmacy database.

Medication Adherence

During each interview, self-reported antihypertensive medication adherence was assessed using the 8-Item Morisky Medication Adherence Scale (MMAS-8). The full scale has been published previously.[11] Level of adherence on the MMAS-8 has been reported to be significantly associated with BP control and pharmacy fill rates for antihypertensive medication.[11,12] Scores on the MMAS-8 can range from 0 to 8. Based on published cut points, MMAS-8 scores of <6, 6 to <8, and 8 were used to reflect low, medium, and high adherence, respectively.[11] Participants were categorized as having low, medium, and high self-reported adherence based on their average MMAS-8 score across the 3 survey administrations. In secondary analyses, self-reported adherence was based on the lowest MMAS-8 score across survey administrations.

Since patients may provide socially desirable responses regarding their medication adherence, we also assessed adherence using antihypertensive medication fill data. Antihypertensive medication persistency was defined using the medication possession ratio (MPR).[13,14] Pharmacy fill data were extracted from administrative databases for the year prior to completion of the baseline survey through the end of the second annual follow-up interview (ie, approximately 2 years following baseline). Abstracted data included a listing of all antihypertensive prescriptions, date filled, drug class, and number of pills dispensed. Using pharmacy fill data, the MPR was calculated as the sum of the days' supply obtained between the first pharmacy fill and the last fill, with the supply obtained in the last fill excluded, divided by the total number of days in this time period. MPR for each antihypertensive medication class was averaged across all classes to assign a single MPR to each participant. MPR was categorized as <0.5, 0.5 to <0.8, and ≥ 0.8 reflecting low, medium, and high adherence, respectively.[15]

BP Data

BP data were abstracted from electronic medical records for out-patient clinic visits occurring in the year preceding the baseline interview through the date of the second CoSMO follow-up interview. BP measurements were obtained as part of participants' routine clinical care. Data abstraction included SBP and diastolic BP (DBP) levels, patient position, and date of BP measurement. Only seated BP measurements were used in the current analyses. Only one BP measurement was recorded at the majority (79%) of visits; 2 and ≥ 3 BP measurements were recorded at 19% and <3% of visits, respectively. When more than one BP level was recorded in a visit, the values were averaged.

VVV of BP

VVV metrics were calculated using all abstracted BP measurements. In order to obtain a reliable estimate of VVV, we limited all analyses to participants with at least 7 outpatient visits wherein BP was measured (median, 14 visits; range, 7–48 visits). BP measurements occurred over a median period of 2.8 years (range, 1.4–3.9 years). Since adherence was assessed during a period of 3 years, we also restricted our analysis to participants who had at least one outpatient visit each year with valid BP measurements. For the primary analyses, we used standard deviation (SD) as the VVV metric. This statistic represents the variability of an individual's SBP at multiple visits around their mean SBP from these visits. SD was chosen as the primary measure because it has been used in prior studies and is easy to interpret.[2,16] In secondary analyses we calculated SD independent of the mean (SDIM), coefficient of variation, peak size, trough size, successive variation (SV), and average real variability (ARV).[5]

Statistical Analysis

Participant characteristics were calculated by level of self-report medication adherence. We calculated the SD of SBP for patients with low, medium, and high self-reported adherence. Using linear regression, we calculated the adjusted mean difference in the SD of SBP associated with low and medium vs high self-reported adherence. Three levels of adjustment were performed: (model 1) age, race, and sex adjusted; and (model 2) variables in model 1 plus number of visits with BP recorded (as a linear and quadratic term), mean SBP, DBP, hypertension duration, current or former smoking status, number of classes of antihypertensive medication, diabetes, and history of myocardial infarction, stroke, and heart failure; (model 3) variables in model 2 and use of antihypertensive medication classes including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics. To determine the statistical significance of trends in the SD of SBP across adherence category, we modeled adherence category as an ordinal variable. Next, we calculated the Spearman correlation coefficient between adherence and SD of SBP. Using the fully adjusted regression model, we calculated the partial R^2 as a measure of the percentage of the variation in SD of SBP explained by adherence. The mean level and fully-adjusted (ie, model 3) difference in SDIM, coefficient of variation, peak size, trough size, SV, and ARV were calculated across level of self-reported adherence. Analyses of self-reported adherence and SD of SBP were repeated (1) using only the first 7 outpatient visits to calculate the SD of SBP (ie, the same number of measurements for all participants), and (2) defining self-reported adherence using each participant's lowest MMAS-8 score across

the three survey administrations. Results were markedly similar so the data are not presented. The above analyses were repeated using pharmacy fill to evaluate the association between antihypertensive medication persistency (MPR of <0.5, 0.5 to <0.80, and ≥0.80) and VVV of SBP. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Of the 2194 participants enrolled in CoSMO, we excluded 488 participants for not having at least 7 visits wherein BP was measured and available to calculate VVV of BP. Also, we excluded participants who did not have pharmacy fill data available for analysis (n=23), did not complete the MMAS-8 at all three time points (n=186), did not have at least one BP measurement annually (n=70), or were no longer prescribed antihypertensive medication after their baseline survey (n=36). After these exclusions, all analyses included 1391 CoSMO participants. Excluded participants were more likely to be male (44.6% of those excluded were men compared with 39.8% of those included; *P*=.027). However, there were no significant differences between excluded and included participants with respect to age, race, MMAS-8 score, or MPR (data not shown).

Self-Reported Adherence and VVV

Black patients and participants with diabetes had lower self-reported adherence (Table I). No other statistically significant differences in participant characteristics across self-reported adherence were present. The average (SD) for the SD of SBP was 12.9 (4.4), 13.5 (4.8), and 14.1 (4.5) mm Hg among participants with high, medium, and low self-reported adherence, respectively (*P*=.007). An association between low self-reported adherence and higher SD of SBP remained present after age, race, sex, and full multivariable adjustment (Table II). The partial R^2 for self-reported adherence on SD of SBP was 0.6%. Associations were present between self-reported adherence and SDIM, coefficient of variation, peak size, SV, and ARV in unadjusted and multivariable-adjusted analyses (Table S1).

Pharmacy Fill Persistency and VVV

Participant characteristics are presented by level of MPR in Table III. The average (SD) for the SD of SBP was 12.9 (4.5), 14.2 (4.9), and 14.8 (5.0) mm Hg for participants with MPRs of ≥0.80, 0.50 to <0.80, and <0.50, respectively (*P*<.001). A graded association between lower MPR and higher SD of SBP remained after age, race, sex, and full multivariable adjustment (Table IV). The partial R^2 for MPR on SD of SBP in the fully adjusted model was 1.9%. Lower levels of MPR were associated with higher SDIM, coefficient of variation, peak size, trough size, SV, and ARV (Table S2).

DISCUSSION

In the current study, worse antihypertensive medication adherence was associated with higher VVV of SBP. This association was present when medication adherence was defined using self-report or pharmacy

TABLE I. Characteristics of Participants by Level of Self-Reported Adherence

	Self-Reported Adherence (MMAS-8 Score)			
	High (8) (n=423)	Medium (6 to <8) (n=835)	Low (<6) (n=133)	*P* Value[a]
Age, y	75.2 (5.7)	75.1 (5.4)	74.4 (5.1)	.286
Women, %	60.5	59.0	66.9	.224
Black, %	24.8	31.1	51.9	<.001
Mean number of visits with blood pressure recorded	14.5 (6.1)	14.8 (6.5)	14.4 (5.7)	.630
Mean SBP, mm Hg	133.3 (9.3)	133.6 (9.8)	135.6 (10.6)	.055
Mean pulse pressure, mm Hg	59.4 (9.4)	58.8 (9.1)	59.5 (9.5)	.459
Hypertension duration ≥10 y, %	64.8	64.4	57.1	.239
Current or past smoker, %	57.7	52.7	60.2	.108
Diabetes mellitus, %	48.9	56.1	63.2	.006
History of myocardial infarction, %	27.4	27.8	22.6	.449
History of stroke, %	26.0	26.6	23.3	.725
History of heart failure, %	35.0	35.8	29.3	.346
Mean number of antihypertensive medication classes	2.7 (1.0)	2.7 (1.1)	2.7 (1.1)	.895
Antihypertensive medication class, %				
ACE inhibitors	58.4	57.8	63.9	.417
β-Blockers	56.3	56.1	46.6	.111
Calcium channel blockers	53.7	54.9	51.9	.787
Angiotensin receptor blockers	29.3	30.7	33.1	.702
Diuretics	70.9	72.0	71.4	.925

Abbreviations: ACE, angiotensin-converting enzyme; MMAS-8, 8-Item Morisky Medication Adherence Scale; SBP, systolic blood pressure. Self-reported adherence was based on the average of the three MMAS-8 administrations. [a]*P* value of chi-square test for categorical variables and analysis of variance test for continuous variables.

TABLE II. Association Between Self-Reported Medication Adherence and SD of Systolic Blood Pressure

	Self-Reported Adherence (MMAS-8 Score)			
	High (8)	Medium (6 to <8)	Low (<6)	*P* Value
Mean (SD), mm Hg	12.9 (4.4)	13.5 (4.8)	14.1 (4.5)	.007
Adjusted differences in mm Hg (95% confidence interval)				
Age, race, sex	0 (reference)	0.62 (0.08–1.15)	1.22 (0.32–2.12)	.008
Multivariable model 1	0 (reference)	0.60 (0.12–1.07)	1.10 (0.31–1.89)	.006
Multivariable model 2	0 (reference)	0.60 (0.13–1.07)	1.08 (0.29–1.87)	.007

Abbreviations: MMAS-8, 8-Item Morisky Medication Adherence Scale; SD, standard deviation. Self-reported adherence was based on the average of the three MMAS-8 administrations. Model 1 includes adjustment for age, race, sex, number of visits with blood pressure recorded, mean systolic blood pressure, mean diastolic blood pressure, hypertension duration, smoker status, number of classes of antihypertensive medication, diabetes, history of myocardial infarction, stroke, and heart failure. Model 2 includes variables in model 1 and use of antihypertensive medication classes including angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, angiotensin receptor blockers, and diuretics.

TABLE III. Characteristics of Participants by Level of Medication Possession Ratio

	Medication Possession Ratio			
	High (0.80) (n=925)	Medium (0.50 to <0.80) (n=394)	Low (<0.50) (n=72)	*P* Value
Age, y	75.1 (5.6)	75.0 (5.3)	75.1 (4.9)	.989
Women, %	60.2	59.1	66.7	.486
Black, %	25.4	43.2	40.3	<.001
Mean number of visits with blood pressure recorded	14.4 (6.1)	15.4 (6.8)	14.7 (5.5)	.034
Mean SBP, mm Hg	133.1 (9.4)	134.8 (10.2)	136.2 (10.5)	.001
Mean pulse pressure, mm Hg	58.7 (9.1)	59.8 (9.7)	59.2 (8.7)	.137
Hypertension duration ≥10 y, %	66.4	59.9	52.1	.009
Current or past smoker, %	54.4	57.9	45.8	.143
Diabetes mellitus, %	53.4	57.1	55.6	.459
History of myocardial infarction, %	26.0	30.7	23.6	.161
History of stroke, %	24.8	28.2	31.9	.221
History of heart failure, %	34.2	37.3	31.9	.472
Mean number of antihypertensive medication classes	2.7 (1.1)	2.8 (1.0)	2.5 (1.1)	.018
Antihypertensive medication class, %				
ACE inhibitors	59.7	56.9	54.2	.468
β-Blockers	55.7	56.9	40.3	.031
Calcium channel blockers	54.5	53.6	54.2	.953
Angiotensin receptor blockers	28.5	36.3	23.6	.009
Diuretics	68.7	77.7	76.4	.003

Abbreviations: ACE, angiotensin converting enzyme; SBP, systolic blood pressure. [a]*P* value of chi-square test for categorical variables and analysis of variance for continuous variables.

TABLE IV. Association Between Medication Possession Ratio and Standard Deviation of Systolic Blood Pressure

	Medication Possession Ratio			
	High (≥0.80)	Medium (0.50 to <0.80)	Low (<0.50)	*P* Value
Mean (SD), mm Hg	12.9 (4.5)	14.2 (4.9)	14.8 (5.0)	<.001
Adjusted differences in mm Hg (95% confidence interval)				
Age, race, sex	0 (reference)	1.18 (0.64–1.73)	1.74 (0.65–2.83)	<.001
Multivariable model 1	0 (reference)	0.76 (0.28–1.24)	1.48 (0.51–2.45)	<.001
Multivariable model 2	0 (reference)	0.78 (0.30–1.26)	1.52 (0.54–2.49)	<.001

Abbreviations: SD, standard deviation. Model 1 includes adjustment for age, race, sex, number of visits with blood pressure recorded, mean systolic blood pressure, mean diastolic blood pressure, hypertension duration, smoker status, number of classes of antihypertensive medication, diabetes, history of myocardial infarction, stroke, and heart failure. Model 2 includes variables in model 1 and use of antihypertensive medication classes including angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, angiotensin receptor blockers, and diuretics.

fill rates. However, only a small proportion of participants' VVV of SBP was explained by poor medication adherence. Additionally, substantial VVV of SBP was present among participants with high antihypertensive medication adherence. These data suggest that poor medication adherence is not a major determinate of high VVV of SBP.

Although it does not explain VVV of SBP, low antihypertensive medication adherence is considered a key barrier to achieving adequate BP control. Suboptimal antihypertensive adherence has been reported to be common in many studies.[7,9,17,18] Maintaining high antihypertensive medication adherence is particularly important given its strong association with achieving BP control.[9]

VVV of SBP has been associated with stroke, coronary heart disease, and all-cause mortality in prior studies.[2] Most of the prior studies of VVV of SBP and outcomes have been secondary analyses of randomized trials.[2] In some of these studies, individuals who were taking antihypertensive medication had higher VVV of SBP compared with their peers not taking antihypertensive medications.[19] The association between adherence to antihypertensive medication and VVV of SBP was not reported in these studies. Low adherence to antihypertensive medication has been hypothesized as a cause of high VVV of BP. For example, it was stated in a recent editorial "Erratic Adherence in High-Risk Populations for Which Sustained Control of Hypertension Is Most Needed May Well Lead to Greater Differences for Intervisit Pressures (Increased Variability) and Worse Outcomes."[6] While this seems plausible, antihypertensive medication adherence accounted for only a small proportion of the VVV of SBP in the current study. Our data suggest that other pathophysiologic or behavioral mechanisms explain the presence of high VVV of SBP.

STUDY LIMITATIONS

The current analysis should be interpreted within the context of several known and potential limitations. The BP measurements used in this analysis were not collected following a standard protocol. Also, a single BP measurement was recorded for 79% of visits. In this respect, however, the data used in the current analysis could be viewed as a strength in that it provides real-world data. The CoSMO study was restricted to participants 65 years and older and these results may not be generalizable to younger individuals. Although 2194 participants were enrolled in CoSMO, only two thirds met all of the inclusion criteria for the current analysis. Most of the exclusions were the result of not having at least 7 SBP measurements during the study period. While cardiovascular and renal outcomes are being collected as part of CoSMO, these are not currently available and therefore we were unable to ascertain whether VVV of SBP is a possible intermediate factor in the association between low antihypertensive medication adherence and outcomes. However, given the weak association between medication adherence and VVV of SBP, such a pathway seems unlikely. We were unable to control for daily vs twice-daily dosing of antihypertensive medication. Higher VVV of SBP may be a result of subclinical inflammation, arterial stiffness and baroreflex dysregulation.[1,20–22] In addition, medication-related factors (eg, drug half-life, dosing interval) and lifestyle factors (eg, sodium intake) may underlie VVV of SBP. These factors were not measured in CoSMO but their relationship with VVV of SBP should be investigated in future studies.

STUDY STRENGTHS

Despite these limitations, the current analysis has several strengths. These include the use of both self-report and pharmacy fill to define antihypertensive medication adherence, the inclusion of 3 years of BP measurements, a large sample size, and the inclusion of a relatively large number of blacks and whites.

CONCLUSIONS

In the current analysis, antihypertensive medication adherence accounted for only a small percentage of VVV of SBP and individuals with high adherence had substantial VVV of SBP. The results were consistent using self-reported and pharmacy fill adherence and across multiple definitions of VVV of SBP. These data suggest that low medication adherence does not explain high VVV of SBP. Studies are needed to determine the mechanisms underlying high VVV of SBP and its association with cardiovascular disease.

Acknowledgments and disclosures: The project described is supported by grant number R01 AG022536 from the National Institute on Aging (Dr Krousel-Wood, principal investigator). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Aging or the National Institutes of Health. The authors have no conflicts of interest related to this work. The 8-item Morisky Medication Adherence Scale is copyrighted. Permission to use the scale in the CoSMO study was obtained from Dr. Donald Morisky (dmorisky@ucla.edu).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Association between self-reported medication adherence and visit-to-visit variability of systolic blood pressure.

Table S2. Association between medication possession ratio and visit-to-visit variability of systolic blood pressure.