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MEDICATION ADHERENCE AND VISIT-TO-VISIT VARIABILITY OF SYSTOLIC BLOOD PRESSURE IN AFRICAN AMERICANS WITH CHRONIC KIDNEY DISEASE IN THE AASK TRIAL

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Abstract

Lower adherence to antihypertensive medications may increase visit-to-visit variability of blood pressure (VVV of BP), a risk factor for cardiovascular events and death. We used data from the African American Study of Kidney Disease and Hypertension (AASK) Trial to examine whether lower medication adherence is associated with higher systolic VVV of BP in African Americans with hypertensive CKD. Determinants of VVV of BP were also explored. AASK participants (n=988) were categorized by self-report or pill count as having perfect (100%), moderately high (75–99%), moderately low (50–74%), or low (<50%) proportion of study visits with high medication adherence over a one year follow-up period. We used multinomial logistic regression to examine determinants of medication adherence, and multivariable-adjusted linear regression to examine the association between medication adherence and systolic VVV of BP, defined as the coefficient of variation or the average real variability. Participants with lower self-reported adherence were generally younger and had a higher prevalence of comorbid conditions. Compared with perfect adherence, moderately high, moderately low, and low adherence was associated with 0.65% (±0.31%), 0.99% (±0.31%) and 1.29% (±0.32%) higher systolic VVV of BP (defined as the coefficient of variation) in fully adjusted models. Results were qualitatively similar when using

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average real variability or when using pill counts as the measure of adherence. Lower medication adherence is associated with higher systolic VVV of BP in African Americans with hypertensive CKD; efforts to improve medication adherence in this population may reduce systolic VVV of BP.

Keywords

compliance; adherence; blood pressure variability; renal insufficiency; hypertension

INTRODUCTION

Blood pressure fluctuates from day to day—a phenomenon known as visit-to-visit variability of blood pressure (VVV of BP)(ref. [1]). VVV of BP is emerging as an important independent risk factor for cardiovascular events and death (ref. [2,3,4,5,6,7]), although there is still no consensus on what constitutes "high" *versus* "normal" VVV of BP. Lower medication adherence has been postulated as a determinant of higher VVV of BP, but few studies have systematically tested this hypothesis. One recent study found that lower medication adherence was associated with higher VVV of BP, but only explained a small proportion of overall VVV of BP(ref. [8]). However, that study was limited by the fact that blood pressure was not measured according to a standardized protocol, and had only one blood pressure measurement per visit in most cases.

African Americans have a higher prevalence of hypertension than other racial groups, lower medication adherence rates, and are more likely to develop cardiovascular disease compared to whites (ref. [9,10,11,12]). Additionally, chronic kidney disease (CKD) is associated with more severe hypertension and higher VVV of BP (ref. [13,14,15,16]). Understanding the association between medication adherence (a potentially modifiable risk factor) and VVV of BP in African Americans with CKD may provide additional impetus for improving medication adherence in this high-risk population. Therefore, we conducted a secondary analysis of the African American Study of Kidney Disease and Hypertension (AASK) Trial to examine correlates of lower antihypertensive medication adherence and whether it is associated with higher VVV of BP in African Americans with hypertensive CKD.

PARTICIPANTS AND METHODS

Cohort Assembly

Details of the AASK Trial have been previously reported(ref. [17]). AASK was a multicenter clinical trial that enrolled 1094 African American participants aged 18 to 70 years with hypertensive kidney disease (measured glomerular filtration rate [GFR] 20–65 mL/min per 1.73m^2) from February 1995 to September 1998. Participants were randomized in a 3×2 factorial design to receive one of three antihypertensive medications (ramipril, metoprolol or amlodipine) and to one of two BP targets (mean arterial pressure 92 mm Hg or 102–107 mm Hg). Exclusion criteria included a history of diabetes mellitus, diastolic BP <95 mm Hg, and urinary protein to creatinine ratio >2.5 g/g.

Systolic Visit-to-Visit Variability of Blood Pressure

For the current study, we calculated systolic VVV of BP based on systolic BP recorded during the first year of follow-up after randomization. Participants who reached end-stage renal disease or who died within the first 12 months were excluded from the analysis. Participants had study visits monthly for the first 6 months following randomization and every other month for the remainder of the study. However, participants could be seen more frequently to guide antihypertensive treatment. At each study visit, BP was measured in triplicate with participants in the seated position after at least 5 minutes of rest using a random zero sphygmomanometer; the mean of the last two measurements was used to define BP at the study visit. For this analysis, we excluded BP measured during the first two months as there were frequent medication titrations during this period. Participants were only included if they had BP measurements from at least 6 follow-up visits. For each participant, we calculated systolic VVV of BP using the coefficient of variation (standard deviation divided by mean systolic BP). We also examined systolic VVV of BP using the average real variability (ARV), which is calculated as the average of the absolute difference in blood pressure between consecutive visits. As such, ARV accounts for the order in which the blood pressure measurements were made(ref. [18],[19]). For example, if a participant had six study visits with the following systolic BP measurements (in mm Hg): 120, 140, 185, 155, 150, 160, the ARV would be calculated as: $(|120-140| + |140-185| + |185-155| + |155-150| + |150-160|)/5 = 22$ mm Hg.

Antihypertensive Medication Adherence

For our primary analysis, we used self-reported medication adherence, which was assessed at each study visit by asking participants the following yes/no questions: (1) "Have you ever had difficulty taking your BP medicine on schedule?" (2) "Have you ever forgotten to take your BP medicine?" (3) "Have you ever stopped taking your BP medicine because you felt better?" (4) "Have you ever taken less of your BP medicine than the doctor prescribed because you felt better?" (5) "Have you ever stopped taking your BP medicine because you felt worse?" (6) "Have you ever taken more of your BP medicine than the doctor prescribed because you felt your BP was too high?" Participants who responded "no" to all six questions were considered to have perfect adherence at the study visit. We calculated the proportion of study visits with perfect adherence over the first 12 months of follow-up, grouping participants into the following four adherence categories: Perfect (100%); Moderately High (75–99%); Moderately Low (50–74%); and Low (<50%).

In a companion analysis, we examined medication adherence by pill count. At each study visit, participants were instructed to bring all of their antihypertensive medications to be counted by the study coordinators. If a participant took at least 80%, but not more than 110% of the prescribed medications (or if the BP was controlled without any antihypertensive medications), then they were considered adherent at that study visit. We calculated the proportion of study visits at which each participant was adherent using the same cut-points as described above for self-reported adherence.

Covariates

Demographic factors including age, sex, annual income (<$15,000), education (<high school degree), whether the participant lived alone, insurance status (Private, Medicare/Medicaid, or none), and employment status were determined by self-report. The following 13 comorbid conditions were assessed at baseline (current or past): cancer, ischemic heart disease, congestive heart failure, left ventricular hypertrophy, arrhythmias or conduction problems, cerebrovascular disease, peripheral vascular disease, hepatitis (B or C), cirrhosis, legally blind, deaf, shoulder, chest, or left arm pain on exertion lasting over 3 minutes, psychiatric problems. Comorbidities were summed and participants were categorized into three groups (0, 1 or 2+ comorbidities). The lifestyle measures included any amount of exercise, any alcohol use, and current or former smoking history. We also included baseline measured GFR category (60, 30–59 and 15–29 mL/min per $1.73m^2$) and baseline proteinuria (> 0.22 grams/day).

Statistical Analysis

We compared participant baseline characteristics by categories of medication adherence and assessed the statistical significance of differences using general linear models or the Cochrane-Armitage test for trend, as appropriate. We used multinomial logistic regression to examine determinants of medication adherence (moderately high, moderately low, and low, each versus perfect adherence). We calculated the mean VVV of BP by adherence category and used linear regression to evaluate the association of medication adherence with systolic VVV of BP. After conducting unadjusted and age, sex, mean SBP adjusted models, a multivariable adjusted model was conducted which included all variables listed in Table 1. As all covariates were available for >90% of participants, we conducted complete case analyses. This analysis was deemed exempt by the Institutional Review Board at Stanford University as all data were de-identified. All analyses were conducted using SAS Enterprise Guide 4.3 (Cary, NC).

RESULTS

Of the 1094 participants in the AASK trial cohort, we included 988 in the present analysis after applying the inclusion and exclusion criteria. Excluded participants did not significantly differ from included participants by age, sex, or comorbid conditions (data not shown). However, they did have lower average GFR (44 vs 47 ml/min per $1.73m^2$, p=0.04) and a higher prevalence of proteinuria (49% versus 31%, p<0.001).

Factors Associated with Lower Adherence

Of the 981 participants with information on self-reported adherence, participants with lower adherence were generally younger, were more often uninsured, and generally had a higher prevalence of comorbid conditions (Table 1). After multivariable adjustment, older age and lower eGFR were associated with lower odds of less-than-perfect adherence (Figure 1). Females, participants who attended more visits and those randomized to the lower blood pressure target group had higher odds of moderately high, moderately low and low adherence versus perfect adherence. Results were similar when we examined adherence

using pill count (Supplemental Table 1), with the exception that more visits was associated with higher odds of perfect adherence (Supplemental Figure 1).

Adherence and Systolic Visit-to Visit Blood Pressure Variability

The average systolic VVV of BP using the coefficient of variation for the overall cohort was 10.3% (±4.0%), and it increased with progressively lower levels of self-reported adherence (Figure 2A). In unadjusted models, participants with low self-reported medication adherence had, on average, 2.21% (± 0.33%) higher coefficient of variation compared with participants with perfect self-reported adherence (Table 2). Results were attenuated after multivariable adjustment for baseline characteristics, but remained statistically significant.

When defined using ARV, the average systolic VVV of BP was 15.2 mm Hg (±6.8 mm Hg), and it increased with progressively lower levels of self-reported adherence (Figure 2B). In unadjusted models, participants with low self-reported medication adherence had 3.96 mm Hg (±0.6 mm Hg) higher ARV on average compared with participants with perfect self-reported adherence (Table 3). Results were attenuated but remained significant after multivariable adjustment. We saw similar patterns of results when adherence was assessed using pill counts (Supplemental Figure 2 & Table 2).

DISCUSSION

Using data from the AASK trial, we show that in African Americans with hypertensive CKD, lower medication adherence is associated with higher systolic VVV of BP. Our results are robust, as they remained statistically significant even after adjusting for differences in baseline characteristics and for mean systolic BP. Moreover, our results did not materially change when adherence was assessed using self-report or objective pill counts, or when VVV of BP was defined as the coefficient of variation or the ARV.

Our findings are consistent with a previous study evaluating the association of antihypertensive medication adherence and VVV of BP conducted in a sample of enrollees in a Medicare managed care program on at least one antihypertensive medication(ref. [8]). In that study, low medication adherence was associated with 1.08 mm Hg higher systolic VVV of BP (defined as the standard deviation) in fully adjusted models. Our study extends the findings of that study to a younger cohort of African American participants with CKD. Moreover, that study used only a single non-standard blood pressure measurement at each visit while our analysis used the average of the last two of three BP measurements and all BP measurements were standardized.

Less than one-third of participants included in our analysis had perfect adherence by self-report or pill count at all study visits; conversely 20–24% of participants had consistently low medication adherence, despite the fact that they were all carefully followed participants in a randomized controlled trial. We found that younger participants were more likely to have medication non-adherence, confirming findings from a variety of populations, including an urban health center in New Orleans(ref. [20]), Italian adults with hypertension(ref. [21]), and older adults in a managed care organization(ref. [22]). Alcohol use was not associated with medication non-adherence in our analysis, similar to a recent

systematic review, which found that only 1 out of 3 studies showed a significant association of hypertensive medication adherence with alcohol use(ref. [23]). A history of smoking was also not associated with adherence in our analysis, consistent with some(ref. [24,25]), though not all(ref. [26,27]), previous studies. Differences in study results likely stem from differences in specific definitions used (current, former, ever or never smokers) and differences in participant demographics. Notably, we did not find a consistent association of socioeconomic factors such as low income, education and lack of insurance with lower medication adherence. Taken together, our results highlight the complexities of finding consistent identifiers of high-risk populations for medication non-adherence.

Our analysis has several strengths. First, the AASK Trial included a socioeconomically diverse participant population with detailed demographic and clinical information. Second, we had repeated objective and subjective assessments of medication adherence. Third, we were able to use multiple, standardized BP measurements to calculate VVV of BP. However, there are also several limitations. First, all participants were enrolled in a clinical trial that included randomization to one of two BP targets. Therefore, participants' BP was closely monitored during follow-up, which may have dampened the degree of VVV of BP. However, the average VVV of BP in our study is similar to reports in other studies using data from other randomized clinical trials(ref. [28,29]) and some observational cohorts(ref. [30,31,32]). Second, participants with diabetes and significant proteinuria were excluded from the study, which, coupled with the fact that clinical trial participants are often healthier and more adherent than unselected populations, may limit the generalizability of our findings. Finally, the instruments we used to assess medication adherence, self-report and pill count, cannot be used to confirm whether participants took medications on a day-to-day basis. Misclassification of medication adherence could have biased our results towards the null, underestimating the true association with VVV of BP.

In summary, our results suggest that in African Americans with hypertensive CKD, lower medication adherence is associated with higher systolic VVV of BP. In turn, recent studies demonstrate that VVV of BP confers an increased risk for cardiovascular events and mortality(ref. [2,3,4,5,6,7]). Lower medication adherence has known associations with poor outcomes such as cardiovascular hospitalizations and all-cause mortality(ref. [33,34,35]), and our analysis provides yet another reason to work to improve medication adherence. Whether improving medication adherence will reduce VVV of BP and ultimately improve outcomes remains to be tested in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

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Summary Table

What is known about this topic

- African Americans with hypertensive CKD are at high risk for adverse cardiovascular events, yet are often underrepresented in research studies.

- Higher visit-to-visit variability of blood pressure (VVV of BP) is associated with poorer outcomes

- Identification of potentially modifiable risk factors for higher VVV of BP is needed.

What this study adds

- In African Americans with hypertensive kidney disease, participants with lower medication adherence were generally younger and had a higher prevalence of comorbid conditions.

- Analyses using self-reported adherence or pill count showed that lower medication adherence is associated with higher systolic VVV of BP, defined as the coefficient of variation or as the average real variability.

- Results were robust and significant, even after adjusting for differences in baseline characteristics and for mean systolic BP.

Figure 1.
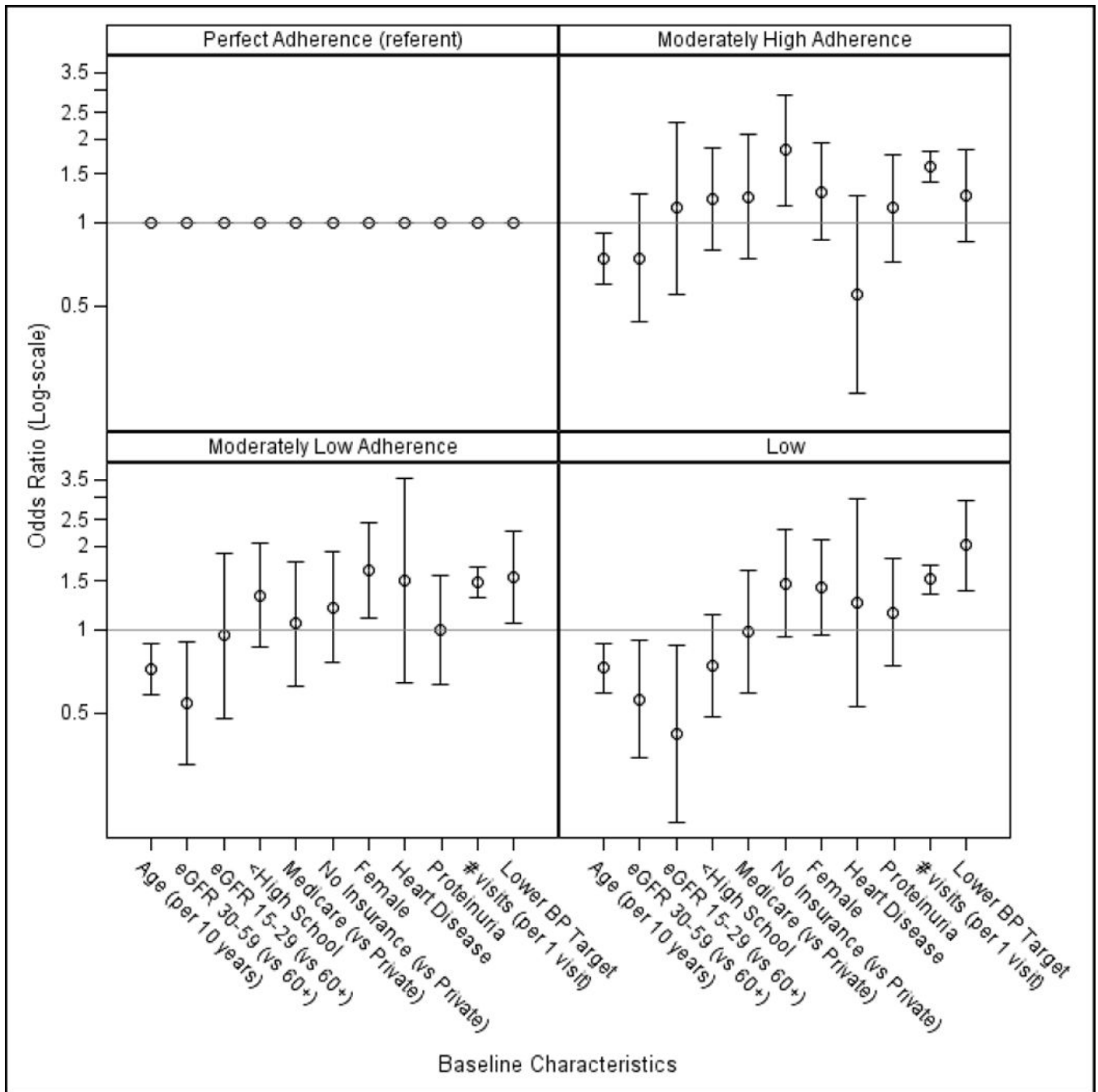Odds ratio of membership in one of the lower adherence groups versus perfect adherence group (as measured by self-report) for the specified baseline characteristics. Bars indicate 95% confidence limits. Models included all baseline characteristics shown, plus income group, lives alone, employed, number of comorbidities, body mass index, exercise, alcohol use, smoking, and randomized drug type.
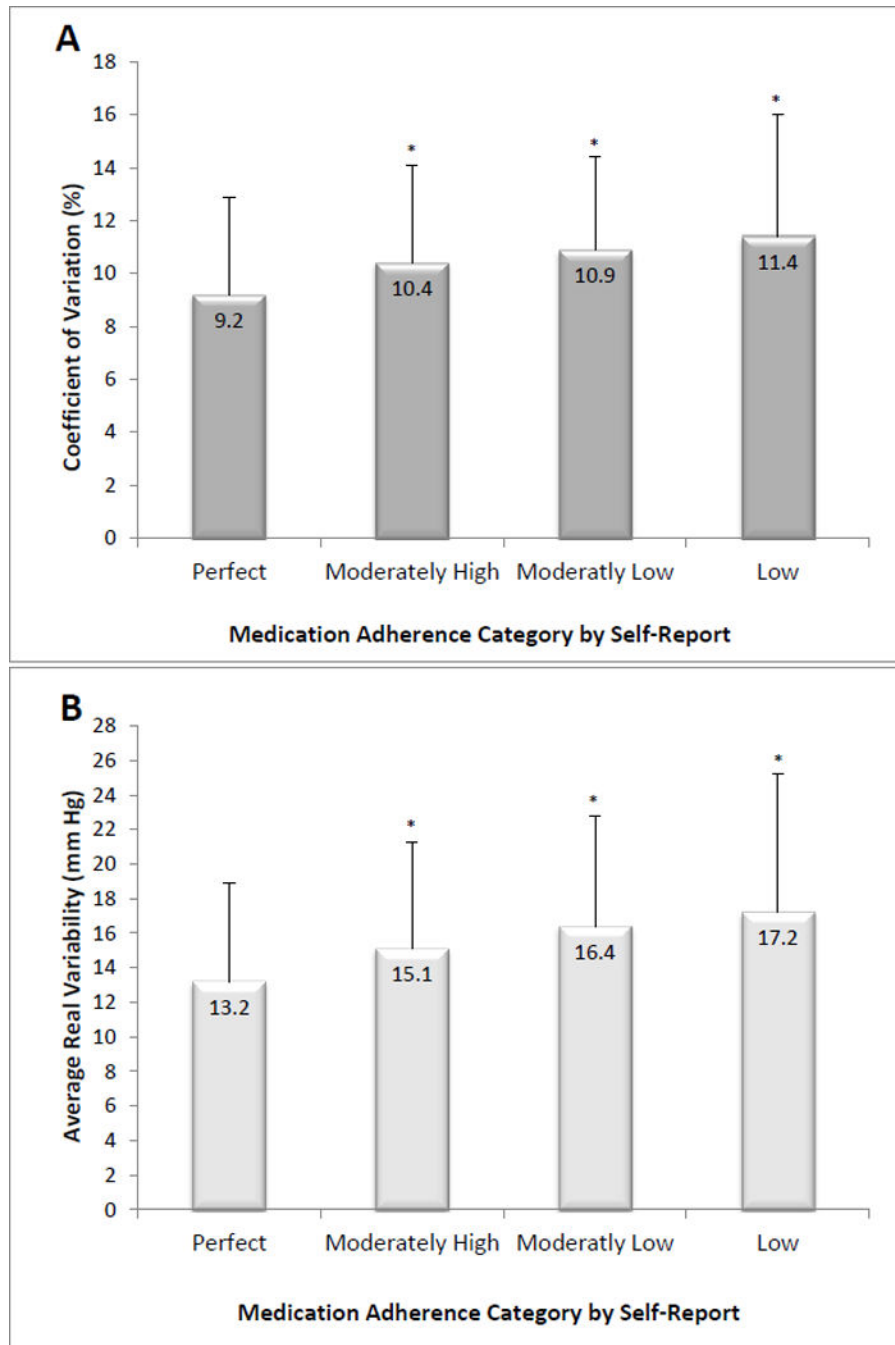
Figure 2.
Mean systolic visit-to-visit variability of blood pressure by medication adherence category assessed by self-report. Systolic visit-to-visit variability of blood pressure defined as A) coefficient of variation and B) average real variability. Values indicate mean and error bars indicate one standard deviation.

*p-value <0.001 (*versus* perfect adherence).

Table 1

Baseline characteristics of the cohort, stratified by medication adherence group during 12M of follow-up, measured by self-report. All values listed are % unless otherwise indicated.

	Group 1 Perfect	Group 2 Moderately High	Group 3 Moderately Low	Group 4 Low	p-trend
N	326	207	216	232	
Number of visits with adherence assessment (median, interquartile range)	6 (4–7)	7 (6–8)	7 (6–8)	7 (6–8)	<.0001
Number of visits with blood pressure measurements (median, interquartile range)	12 (9–14)	13 (10–16)	12 (10–15)	12 (9–16)	0.1
Age (years, mean, SD)	57.1 (10.1)	53.6 (10.7)	53.4 (10.7)	53.0 (11.1)	<.0001
Female sex	35.0	39.6	43.1	39.7	0.15
Annual income < $15,000	46.3	45.4	50.0	51.7	0.15
No High School Degree	42.3	43.0	43.1	33.6	0.07
Lives alone	23.0	21.3	24.1	21.6	0.84
Insurance status					
Private/HMO/Other	46.3	35.7	41.7	39.7	0.19
Medicare/Medicaid	27.0	25.1	24.5	22.0	0.18
None	26.7	39.1	33.8	38.4	0.01
Employed	36.8	38.2	43.5	32.3	0.62
History of heart disease	44.2	45.4	58.8	57.8	0.0001
Number of other comorbidities					
0	54.6	50.7	41.7	42.2	0.0007
1	33.1	33.8	43.5	41.8	0.01
2+	12.3	15.5	14.8	15.9	0.24
BMI (kg/m^2)					
<25	19.9	21.3	23.1	17.2	0.64
25–29.9	30.4	32.4	32.9	35.3	0.22
30	49.7	46.4	44.0	47.4	0.44
Exercises	45.4	41.5	42.6	42.2	0.47
Drinks alcohol	25.2	27.5	31.0	28.4	0.23
Current smoker	24.8	25.1	35.2	32.8	0.008

	Group 1 Perfect	Group 2 Moderately High	Group 3 Moderately Low	Group 4 Low	p-trend
Past smoker	35.6	31.4	23.1	21.6	<.0001
Randomized Groups					
Lower BP Goal	45.1	44.4	52.3	59.5	0.0004
Ramipril	39.0	41.1	43.1	36.6	0.79
Metoprolol	40.5	37.7	40.7	43.5	0.44
Amlodipine	20.6	21.3	16.2	19.8	0.52
Systolic blood pressure (mm Hg, mean, SD)	145 (21)	148 (24)	153 (23)	156 (26)	<.0001
Diastolic blood pressure (mm Hg, mean, SD)	92 (13)	95 (14)	97 (14)	99 (15)	<.0001
Glomerular filtration rate (mL/min)					
60	16.3	15.9	19.9	21.1	0.09
30–59	69.6	65.2	59.7	69.0	0.46
15–29	14.1	18.8	20.4	9.9	0.41
Proteinuria >0.22 grams / 24 hours	26.1	34.8	33.3	32.3	0.11

Table 2

Mean differences in systolic visit-to-visit variability of blood pressure, defined as the coefficient of variation (%), associated with self-reported medication adherence.

Level of adherence	Unadjusted Estimate (SE)	p	Model 1* Estimate (SE)	p	Model 2* Estimate (SE)	p
Perfect	Ref		ref	-	ref	
Moderately High	1.16 (0.34)	<.0001	1.06 (0.34)	0.0022	0.65 (0.31)	0.04
Moderately Low	1.66 (0.34)	0.0008	1.48 (0.34)	<.0001	0.99 (0.31)	0.002
Low	2.21 (0.33)	<.0001	1.88 (0.34)	<.0001	1.29 (0.32)	<.0001

*
Model 1 adjusted for age, sex, and mean systolic blood pressure; Model 2 adjusted for all variables listed in Table 1.

Abbreviation: ref= referent; SE = standard error

Table 3

Mean differences in systolic visit-to-visit variability of blood pressure defined as the average real variability(mm Hg) associated with self-reported medication adherence.

Level of adherence	Unadjusted Estimate (SE)	p	Model 1* Estimate (SE)	p	Model 2* Estimate (SE)	p
Perfect	ref	-	ref	-	ref	
Moderately High	1.86 (0.6)	0.002	1.62 (0.6)	0.004	0.98 (0.5)	0.06
Moderately Low	3.19 (0.6)	<.0001	2.69 (0.6)	<.0001	1.90 (0.5)	0.0003
Low	3.96 (0.6)	<.0001	2.83 (0.5)	<.0001	1.91 (0.5)	0.0003

*
Model 1 adjusted for age, sex, and mean systolic blood pressure; Model 2 adjusted for all variables listed in Table 1.

Abbreviation: ref= referent; SE = standard error