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Prevalence and correlates of low medication adherence in apparent treatment resistant hypertension

Marguerite R. Irvin, Ph.D.[1], **Daichi Shimbo, M.D.**[2], **Devin M. Mann, M.D.**[3], **Kristi Reynolds, Ph.D.**[4], **Marie Krousel-Wood, M.D.**[5],[6], **Nita A. Limdi, Pharm.D, Ph.D.**[7], **Daniel T. Lackland, Ph.D.**[8], **David A. Calhoun, M.D.**[9], **Suzanne Oparil, M.D.**[9], and **Paul Muntner, Ph.D.**[1]

[1]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL

[2]Department of Medicine, Columbia University Medical Center, Columbia University, New York, NY

[3]Division of General Internal Medicine, Mount Sinai School of Medicine, New York, NY

[4]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA

[5]Department of Clinical Outcomes Research, Ochsner Clinic Foundation, New Orleans, LA

[6]Department of Epidemiology, Tulane School of Public Health and Tropical Medicine, New Orleans, LA

[7]Department of Neurology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL

[8]Department of Neurosciences, Medical University of South Carolina, Charleston, SC

[9]Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

Abstract

Low medication adherence may explain part of the high prevalence of apparent treatment resistant hypertension (aTRH). We assessed medication adherence and aTRH among 4,026 participants taking ≥ 3 classes of antihypertensive medication in the population-based REGARDS Study using the 4-item Morisky Medication Adherence Scale (MMAS). Low adherence was defined as a MMAS score ≥ 2. Overall, 66% of participants taking ≥ 3 classes of antihypertensive medication had aTRH. Perfect adherence on the MMAS was reported by 67.8% and 70.9% of participants with and without aTRH, respectively. Low adherence was present among 8.1% of participants with aTRH and 5.0% of those without aTRH ($p<0.001$). Among those with aTRH, female gender, residence outside the US stroke belt or stroke buckle, physical inactivity, elevated depressive symptoms, and a history of coronary heart disease were associated with low adherence. In the current study, a small percentage of participants with aTRH had low adherence.

*Corresponding Author: Marguerite R Irvin, Department of Epidemiology, University of Alabama at Birmingham, 1665 University Blvd, RPHB Room 220P, Birmingham, Alabama 35294-0022, Phone: (205) 934 6459; Fax: (205) 934 8665, irvinr@uab.edu.

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Keywords

Hypertension; Treatment Resistant Hypertension; Medication adherence; Risk Factors

Introduction

Apparent treatment resistant hypertension (aTRH) is defined by the use of three classes of antihypertensive medication with uncontrolled hypertension or the use of four or more classes regardless of blood pressure (BP) control. [1] Using data from the National Health and Nutrition Examination Survey (NHANES) 2005–2008, Egan and colleagues estimated 11.8% of all hypertensive US adults have aTRH. [2] This represents an almost 100% increase since 1988–1994 when the prevalence of aTRH among US adults with hypertension was 5.5%. The diagnosis of TRH is complex and requires the exclusion of secondary causes of uncontrolled hypertension. [1]

Many individuals with aTRH may not undergo a comprehensive assessment of the potential causes of their condition. Of particular relevance is low adherence to antihypertensive medication. Low medication adherence is common among persons with hypertension and many studies have reported low adherence to antihypertensive treatment to be associated with worse BP control. [3–8] However, few data are available on antihypertensive medication adherence among individuals with aTRH. Documenting the prevalence of low adherence in aTRH may help better explain the high prevalence of this condition. Additionally, identifying factors associated with low medication adherence can help target future interventions to improve adherence in persons with aTRH. Therefore, we examined levels of medication adherence compared to individuals taking three antihypertensive medication classes who had controlled BP levels. Additionally, factors associated with low medication adherence among individuals with aTRH were identified. For this investigation, we analyzed data from a large, sample of US adults enrolled in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. [9]

Methods

Study Population

The REGARDS study has been described previously. [9] Briefly, the REGARDS study included adults ≥ 45 years of age from all 48 continental US states and the District of Columbia. Between January 2003 and October 2007, 30,239 individuals were enrolled into the REGARDS study. By design, blacks and residents of the stroke belt and stroke buckle region of the US were oversampled. The “stroke buckle” was defined by coastal North Carolina, South Carolina, and Georgia and the “stroke belt” as the remainder of North Carolina, South Carolina, and Georgia as well as Alabama, Mississippi, Tennessee, Arkansas and Louisiana. The current study population was restricted to individuals treated with three or more classes of antihypertensive medication (n=4,128) in order to make comparisons for those with aTRH to a group treated with a comparable number of antihypertensive medications. Participants missing BP data (n=17) or information on medication adherence (n=85) were excluded leaving 4,026 participants for the analysis. The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers and all participants provided informed consent.

Data Collection

The current analysis used data from the baseline visit of the REGARDS study. Baseline REGARDS study data were collected via a telephone interview, a self-administered

questionnaire, and in-home examination. Of relevance to the current analysis, computer-assisted telephone interviews administered by trained staff were used to collect information on participants' age, smoking status, education, physical activity, alcohol consumption, symptoms of depression and self-reports of prior physician diagnosed co-morbid conditions (e.g., diabetes, hypertension, stroke, and myocardial infarction). Elevated symptoms of depression were defined as being present for participants with scores ≥ 4 on the 4-item Centers for Epidemiologic Studies of Depression scale.[10] Trained health professionals conducted in-home examinations which included weight, height, BP measurements, an electrocardiogram (ECG), the collection of blood and a spot urine sample, plus a review of prescription and over the counter medications used over the prior 2 week period. Medication names were recorded and subsequently coded into drug classes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Coronary heart disease (CHD) was defined by a self-reported history or ECG evidence of myocardial infarction or a self-reported history of a revascularization procedure. Diabetes was defined as a serum glucose ≥126 mg/dL for participants who had fasted ≥ 8 hours prior to their blood draw, serum glucose ≥200 mg/dL for those who had not fasted, or self-report of a prior diagnosis of diabetes while not pregnant with current use of insulin or oral hypoglycemic medications. Using isotope-dilution mass spectrometry (IDMS)–traceable serum creatinine, estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. [11] Low eGFR was defined as levels < 60 ml/min/1.73 m^2. Albuminuria was defined as being present for individuals with a urinary albumin to urinary creatinine ratio ≥ 30 mg/g. Chronic kidney disease was defined by the presence of low eGFR or albuminuria.

Blood pressure measurement, medication use and aTRH

During the in-home examination, BP was measured two times using aneroid sphygmomanometers following a standardized protocol by trained examiners. Participants were asked to sit for three minutes with both feet on the floor prior to the BP measurement. Based on the average of the two measurements, uncontrolled hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg except for individuals with diabetes or chronic kidney disease wherein uncontrolled hypertension was defined as SBP ≥ 130 mmHg or DBP ≥ 80 mmHg, respectively. Antihypertensive medication classes were defined using those listed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). [12] They included ACE-inhibitors, aldosterone receptor blockers, alpha blockers, angiotensin receptor blockers, beta blockers, calcium channel blockers, central acting agents, diuretics, and direct vasodilators. One pill-combinations were classified into individual medication classes. Information on medication dose was not recorded. aTRH was defined as being present for participants taking three antihypertensive medication classes with uncontrolled hypertension or taking four or more classes regardless of hypertension control status.

Adherence

During the telephone interview, medication adherence was assessed using the 4-item Morisky Medication Adherence Scale (MMAS). [13] The 4 items on the MMAS are (1) Do you ever forget to take medications? (2) Are you ever careless in taking your medications? (3) Do you ever miss taking your medications when you are feeling better? (4) Do you ever miss taking any of your medications because you are feeling sick? Each item has a yes/no response option. One point is assigned to each "yes" response, and points were summed (totaling 0–4) with a higher score indicating worse adherence. [14] MMAS scores of 3 and 4 were pooled together for the current analysis due to a low number of participants in these groups. Additionally, consistent with a previous analysis of REGARDS study data, [15]

individuals with MMAS scores of ≥ 2 were categorized as having low medication adherence. In a prior study, the MMAS was reported to have acceptable internal consistency (Cronbach's a=0.61) and the items maintained a high item-to-total correlation (>0.4 for each item). [13] Additionally, scores on the MMAS have been correlated with BP control previously. [13]

Statistical Analysis

The prevalence of aTRH was calculated for all REGARDS participants with hypertension and for those with hypertension taking three or more antihypertensive medication classes. Characteristics of REGARDS study participants taking three or more antihypertensive medication classes were calculated by aTRH status with the statistical significance of differences for those with controlled BP on three classes of antihypertensive medication versus aTRH determined using chi square and t-tests, as appropriate. The percent of participants with controlled BP (SBP/DBP < 140/90 mmHg except for individuals with diabetes or chronic kidney disease wherein < 130/80 mmHg was required) was calculated by MMAS scores. Responses to each MMAS item and the distribution of MMAS scores were calculated by aTRH status and compared using chi-square tests. Next, for individuals with aTRH, the odds ratios for low medication adherence associated with participant characteristics were calculated using logistic regression. These characteristics included age, race, gender, geographic region of residence, education, income, marital status, smoking status, alcohol consumption, physical activity level, BMI, diabetes, reduced eGFR, albuminuria, history of CHD or stroke, and elevated depressive symptoms. These variables were chosen based on their observed association with low medication adherence in the general population of persons with hypertension. [16] An initial model included adjustment for age, race, gender, and geographic region of residence. A subsequent model included all variables simultaneously. Data analysis was conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Prevalence of apparent treatment resistant hypertension (aTRH)

In the REGARDS study, 16,927 participants had hypertension. For the current analysis, we focused on the 4,026 (24% of those with hypertension) who were treated with three or more antihypertensive medication classes. Overall, 2,654 REGARDS participants had aTRH. This represents 16% of all REGARDS participants with hypertension and 66% of REGARDS participants taking three or more antihypertensive classes. Of those with aTRH, 58% were taking three classes of antihypertensive medication and had uncontrolled hypertension (n=1,547) and 42% were taking four or more classes of antihypertensive medication (n=1,107).

Participant characteristics

In comparison to those with controlled BP on three classes of antihypertensive medications, those with aTRH were more likely to be black, men, have less than a high school education, an annual household income less than $20,000, participate in less physical activity, and have elevated depressive symptoms (Table 1). Each comorbidity (low eGFR, albuminuria, diabetes and a history of CHD and stroke) was more common among individuals with aTRH. Also, mean BMI was higher for individuals with versus without aTRH.

Level of medication adherence

The distribution of MMAS scores of 0 (best adherence) and 1, 2, and 3 or 4 (worst adherence), was 68.8%, 24.1%, 5.0%, and 2.0%, respectively among the entire study

population (N=4026). Individuals with worse adherence were less likely to have controlled hypertension (Figure 1). The prevalence of controlled hypertension was 46.8%, 46.6%, 37.9%, and 27.2% for MMAS scores of 0, 1, 2, and 3 or 4, respectively.

While 28.9% of individuals with aTRH reported sometimes forgetting to take their medication, this was reported by 26.4% of individuals taking three BP medications with controlled hypertension (Table 2, p=0.088). Compared to participants with controlled BP on three medications, those with aTRH were more likely to report being careless about taking their medication and to stop taking their medication when they were feeling better or when they were feeling worse. However, none of these three poor medication taking behaviors was reported by more than 6% of individuals with aTRH. Overall MMAS scores were significantly higher, indicating worse adherence, for individuals with aTRH (Figure 2). Overall, 8.1% of individuals with aTRH and 5.0% of individuals with controlled BP while taking three antihypertensive medications had low adherence defined by MMAS score ≥ 2 ($p<0.001$).

Factors associated with low medication adherence in aTRH

After adjustment for age, gender, and geographic region of residence, blacks were more likely to have low medication adherence (Table 3, Model 1). After age, race, and geographic region of residence adjustment, women were more likely than men to have low medication adherence. After age, race, gender and geographic region of residence adjustment, individuals with an annual household income < $20,000, elevated depressive symptoms and a history of CHD were more likely to have low medication adherence. Additionally, participants residing in the stroke belt or stroke buckle versus non-belt regions and those participating in physical activity 1 to 3 or > 3 times per week were less likely to have low medication adherence. The results were similar after full multivariable adjustment (Table 3, Model 2) with the exception that the associations of black race and an annual household income < $20,000 with low medication adherence were attenuated and no longer statistically significant.

Discussion

Studies have consistently demonstrated low antihypertensive medication adherence is a barrier for achieving adequate BP control. [8, 16] Therefore, low medication adherence may be a major cause of aTRH among individuals taking multiple antihypertensive medications. Low adherence to antihypertensive medications should be evaluated and excluded as a cause of uncontrolled BP before a diagnosis of true TRH is made. [1] In the current study we examined the association between low medication adherence and aTRH in individuals taking antihypertensive medications from three or more classes using a validated scale in a large population-based sample of US adults. While medication adherence was statistically significantly better among individuals without versus with aTRH, the differences were small. Almost 70% of individuals with and without aTRH reported good medication taking behaviors according to all 4 adherence items in the 4 item MMAS. Furthermore, less than 10% of REGARDS participants with aTRH had low medication adherence, defined by scores ≥ 2 on the 4-item MMAS. Our findings suggest that overall self-reported low medication adherence in aTRH is quite low.

The prevalence of aTRH in the US has only recently been reported and is estimated to be 11–15% among persons with hypertension [2, 17, 18]. The estimate we report in the REGARDS cohort is slightly higher (16%) which may be due to over sampling of black participants in the REGARDS study compared with other studies. For example, approximately 15% of the NHANES 2005–2008 sample was black and that group was 2 times more likely to have aTRH [2]. More recently using patient data collected over a 4-year

period in the Kaiser Permanente Colorado and Northern California healthcare systems, Daugherty and colleagues identified 205,750 patients who were started on antihypertensive therapy for newly diagnosed hypertension [19]. During follow-up, close to 21% were eventually prescribed three or more medications and 24,499 participants were found eligible for determination of aTRH status. Among that group the prevalence of aTRH was 16%. In the current study the prevalence of aTRH among persons treated with three or more antihypertensive medications was 66%. Differences between the current study and that of Daugherty may be explained by the sampling of incident hypertension cases, low percentage of blacks, and the relatively younger age of the cohort (on average 7 years younger) reported on by Daugherty and colleagues. Among the 24,499 participants found eligible for determination of aTRH status in the Daugherty study, only 587 (2.3%) were excluded from further analysis for low medication adherence based on proportion of days covered <80% determined by pharmacy fill rates. Like in the current study, the Daugherty study found a small percentage of persons treated with 3 or more antihypertensive medications had low adherence.

Small studies have previously examined the prevalence of non-adherence to antihypertensive medication in the context of aTRH. One prospective study from Brazil in 44 persons with hypertension resistant to a three-drug regimen assessed adherence using the 4 item MMAS and pill count method. Overall, 36% of participants reported perfect adherence at study initiation and this figure rose to 68% at one year. By pill count, 64% of the population was adherent at the start of the study and 94% at the end, yet 60% of participants did not achieve BP control. [20] In contrast, another study evaluated serum drug levels in persons with difficult to treat hypertension (N=84) and found only 35% of study participants to be perfectly adherent. [21] Whether low medication adherence is more prevalent in aTRH than in a comparison group with a similar treatment regimen is less studied. While significant differences in low medication adherence were present between the REGARDS study participants with and without aTRH in the current analyses, these differences were small. These results suggest factors other than low medication adherence may contribute to hard-to-control BP in most persons with aTRH.

Despite the low rate of poor adherence in the current study, it is still important to evaluate adherence among all persons with hypertension given the established association of medication adherence with BP control. The strengths and weaknesses of various approaches to assess medication adherence have been published previously. [22] The consequences of uncontrolled BP are serious due to increased risk for poor clinical outcomes and increased health care costs. [23–25] Few large population-based studies have examined the relationship between adherence and BP control in individuals taking multiple antihypertensive medications. In the current large population-based sample of US adults taking three or more antihypertensive medication classes, we show a graded relationship between better adherence and higher rates of BP control. The evaluation of low medication adherence in the context of aTRH is especially important as some persons may not need to undergo comprehensive clinical tests required for the diagnosis of true TRH. [1]

While low medication adherence remains an important consideration when determining the causes of aTRH, other factors including genes, environment, and their interactions may be worthy of exploration in future studies. Recent reviews targeting strategies to uncover the genetic background of complex traits (such as hypertension) have suggested extreme phenotype samples (such as TRH) may be enriched for variants underlying the disease. [26, 27] Several small candidate gene studies have reported associations with TRH that warrant follow-up investigations. [28–30] For instance, one study reported the angiotensinogen (AGT) M235T polymorphism was associated with increased risk for TRH, especially after age 50, highlighting a potential gene variant by age interaction. [29] Replication of preliminary results

from smaller studies should be carried out in larger cohorts. Such studies will continue to shed light on the mechanisms underlying TRH and could translate to better understanding of the genetic background of less extreme forms of hypertension.

Many studies have considered factors affecting medication adherence in the general population of hypertensives. [16, 31–35] However, factors affecting medication adherence in aTRH have not been widely studied. In the current study of individuals with aTRH, women were more likely to have low medication adherence. Previous studies in the general population of individuals with hypertension have reported either no association of gender with adherence or that women newly diagnosed with hypertension were more adherent than men. [33, 36, 37] Consistent with reports in other chronic conditions and in hypertension, [34, 38–42] elevated depressive symptoms were associated with low medication adherence. We also found any physical activity to be protective against low medication adherence. This may reflect a healthier lifestyle among people who are adherent. Interestingly, our results suggest a history of CHD was associated with low medication adherence. Low adherence to antihypertensive and lipid lowering medication has been reported after myocardial infarction in prior studies. [43] Whether very complex treatment regimens and/or persistence of behaviors associated with low medication adherence underlie this association in aTRH requires further study.

There are several strengths and limitations regarding the current analysis which should be mentioned. The adherence scale used in the REGARDS study was not specific to antihypertensive medications and adherence was assessed only at a single time point. Additionally, adherence was assessed using self-report only. Electronic data on medication adherence (e.g., pharmacy fill data) is not available in the REGARDS study. While the 4-item MMAS has been validated, participants may have provided socially desirable responses. Additionally, we were unable to confirm optimal dosing of antihypertensive medications as a criterion to define aTRH as dose was not recorded in the REGARDS study. Despite these limitations, this study is the largest to characterize medication adherence in aTRH and is strengthened by the population-based sample in REGARDS and use of an adherence tool validated for studies of blood pressure control. Additionally, the large sample size of the REGARDS study allowed for comparison of aTRH with people who had controlled hypertension while on three antihypertensive medication classes. Finally, the REGARDS study recruited individuals irrespective of socioeconomic or health insurance status and used standardized protocols with stringent quality control procedures to collect data.

In this population-based sample of black and white adults with hypertension treated with at least three antihypertensive medication classes, better adherence was associated with higher BP control rates. Among individuals with aTRH, 67.8% reported perfect adherence and only 8.1% had low medication adherence and this was comparable to participants on three antihypertensive medication classes with controlled BP. Further, many factors previously reported to be associated with low medication adherence in persons with hypertension were also associated with low medication adherence when investigated among individuals with aTRH. Taken together these results help to distinguish TRH as an extreme phenotype within uncontrolled hypertension and emphasize the need for further studies to help better define its etiology. In the meantime, health care providers should continue to assess adherence and assist patients with aTRH in overcoming barriers to taking their medication, similarly to other patients with hypertension.

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References

1. Calhoun DA, Jones D, Textor S, 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. Jun; 2008 117(25):e510–526. [PubMed: 18574054]
2. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation. Aug; 2011 124(9):1046–1058. [PubMed: 21824920]
3. Elliott WJ. Improving outcomes in hypertensive patients: focus on adherence and persistence with antihypertensive therapy. J Clin Hypertens (Greenwich). Jul; 2009 11(7):376–382. [PubMed: 19583634]
4. Mazzaglia G, Mantovani LG, Sturkenboom MC, et al. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. J Hypertens. Nov; 2005 23(11):2093–2100. [PubMed: 16208153]
5. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. J Hypertens. Nov; 2005 23(11):2101–2107. [PubMed: 16208154]
6. Yiannakopoulou, ECh; Papadopulos, JS.; Cokkinos, DV.; Mountokalakis, TD. Adherence to antihypertensive treatment: a critical factor for blood pressure control. Eur J Cardiovasc Prev Rehabil. Jun; 2005 12(3):243–249. [PubMed: 15942423]
7. Romanelli RJ, Schiro TA, Jukes T, Wong KS, Ishisaka DY. Disparities in blood pressure control within a community-based provider network: an exploratory analysis. Ann Pharmacother. Dec; 2011 45(12):1473–1482. [PubMed: 22147145]
8. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. Mar; 2004 42(3):200–209. [PubMed: 15076819]
9. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005; 25(3):135–143. [PubMed: 15990444]
10. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Applied Psychological Measurement. 1977:385–401.
11. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. May; 2009 150(9):604–612. [PubMed: 19414839]
12. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. Dec; 2003 42(6):1206–1252. [PubMed: 14656957]
13. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. Jan; 1986 24(1):67–74. [PubMed: 3945130]
14. Shalansky SJ, Levy AR, Ignaszewski AP. Self-reported Morisky score for identifying nonadherence with cardiovascular medications. Ann Pharmacother. Sep; 2004 38(9):1363–1368. [PubMed: 15238622]
15. Muntner P, Halanych JH, Reynolds K, et al. Low medication adherence and the incidence of stroke symptoms among individuals with hypertension: the REGARDS study. J Clin Hypertens (Greenwich). Jul; 2011 13(7):479–486. [PubMed: 21762360]

16. Krousel-Wood M, Thomas S, Muntner P, Morisky D. Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. Curr Opin Cardiol. Jul; 2004 19(4):357–362. [PubMed: 15218396]
17. Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. Hypertension. Jun; 2011 57(6):1076–1080. [PubMed: 21502568]
18. Pimenta E, Calhoun DA. Resistant hypertension: incidence, prevalence, and prognosis. Circulation. Apr; 2012 125(13):1594–1596. [PubMed: 22379111]
19. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. Apr; 2012 125(13):1635–1642. [PubMed: 22379110]
20. de Souza WA, Sabha M, de Faveri Favero F, Bergsten-Mendes G, Yugar-Toledo JC, Moreno H. Intensive monitoring of adherence to treatment helps to identify “true” resistant hypertension. J Clin Hypertens (Greenwich). Apr; 2009 11(4):183–191. [PubMed: 19614802]
21. 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. Jan; 2011 34(1):87–90. [PubMed: 20882030]
22. Krousel-Wood M, Hyre A, Muntner P, Morisky D. Methods to improve medication adherence in patients with hypertension: current status and future directions. Curr Opin Cardiol. Jul; 2005 20(4):296–300. [PubMed: 15956826]
23. Esposti LD, Saragoni S, Benemei S, et al. Adherence to antihypertensive medications and health outcomes among newly treated hypertensive patients. Clinicoecon Outcomes Res. 2011; 3:47–54. [PubMed: 21935332]
24. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care. Jun; 2005 43(6):521–530. [PubMed: 15908846]
25. Stroupe KT, Teal EY, Tu W, Weiner M, Murray MD. Association of refill adherence and health care use among adults with hypertension in an urban health care system. Pharmacotherapy. Jun; 2006 26(6):779–789. [PubMed: 16716131]
26. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature. Oct; 2009 461(7265):747–753. [PubMed: 19812666]
27. Shi G, Rao DC. Optimum designs for next-generation sequencing to discover rare variants for common complex disease. Genet Epidemiol. Sep; 2011 35(6):572–579. [PubMed: 21618604]
28. Hannila-Handelberg T, Kontula K, Tikkanen I, et al. Common variants of the beta and gamma subunits of the epithelial sodium channel and their relation to plasma renin and aldosterone levels in essential hypertension. BMC Med Genet. Jan.2005 6:4. [PubMed: 15661075]
29. Yugar-Toledo JC, Martin JF, Krieger JE, et al. Gene variation in resistant hypertension: multilocus analysis of the angiotensin 1-converting enzyme, angiotensinogen, and endothelial nitric oxide synthase genes. DNA Cell Biol. Aug; 2011 30(8):555–564. [PubMed: 21438754]
30. Cruz-Gonzalez I, Corral E, Sanchez-Ledesma M, Sanchez-Rodriguez A, Martin-Luengo C, Gonzalez-Sarmiento R. An association between resistant hypertension and the null GSTM1 genotype. J Hum Hypertens. Aug; 2009 23(8):556–558. [PubMed: 19279659]
31. World Health Organization. Hypertension in Adherence to Long-Term Therapies: Evidence for Action. 2003.
32. Furberg CD, Black DM. The systolic hypertension in the elderly pilot program: methodological issues. Eur Heart J. Feb; 1988 9(2):223–227. [PubMed: 3350031]
33. Marentette MA, Gerth WC, Billings DK, Zarnke KB. Antihypertensive persistence and drug class. Can J Cardiol. Jun; 2002 18(6):649–656. [PubMed: 12107422]
34. Wang PS, Bohn RL, Knight E, Glynn RJ, Mogun H, Avorn J. Noncompliance with antihypertensive medications: the impact of depressive symptoms and psychosocial factors. J Gen Intern Med. Jul; 2002 17(7):504–511. [PubMed: 12133140]
35. Kim MT, Han HR, Hill MN, Rose L, Roary M. Depression, substance use, adherence behaviors, and blood pressure in urban hypertensive black men. Ann Behav Med. Aug; 2003 26(1):24–31. [PubMed: 12867351]

36. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. CMAJ. Jan; 1999 160(1):31–37. [PubMed: 9934341]

37. Krousel-Wood MA, Muntner P, Islam T, Morisky DE, Webber LS. Barriers to and determinants of medication adherence in hypertension management: perspective of the cohort study of medication adherence among older adults. Med Clin North Am. May; 2009 93(3):753–769. [PubMed: 19427503]

38. Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. J Acquir Immune Defic Syndr. Oct; 2011 58(2):181–187. [PubMed: 21857529]

39. Morris AB, Li J, Kroenke K, Bruner-England TE, Young JM, Murray MD. Factors associated with drug adherence and blood pressure control in patients with hypertension. Pharmacotherapy. Apr; 2006 26(4):483–492. [PubMed: 16553506]

40. Maguire LK, Hughes CM, McElnay JC. Exploring the impact of depressive symptoms and medication beliefs on medication adherence in hypertension--a primary care study. Patient Educ Couns. Nov; 2008 73(2):371–376. [PubMed: 18692978]

41. Wang PS, Avorn J, Brookhart MA, et al. Effects of noncardiovascular comorbidities on antihypertensive use in elderly hypertensives. Hypertension. Aug; 2005 46(2):273–279. [PubMed: 15983239]

42. Krousel-Wood M, Islam T, Muntner P, et al. Association of depression with antihypertensive medication adherence in older adults: cross-sectional and longitudinal findings from CoSMO. Ann Behav Med. Dec; 2010 40(3):248–257. [PubMed: 20703839]

43. Akincigil A, Bowblis JR, Levin C, Jan S, Patel M, Crystal S. Long-term adherence to evidence based secondary prevention therapies after acute myocardial infarction. J Gen Intern Med. Feb; 2008 23(2):115–121. [PubMed: 17922172]

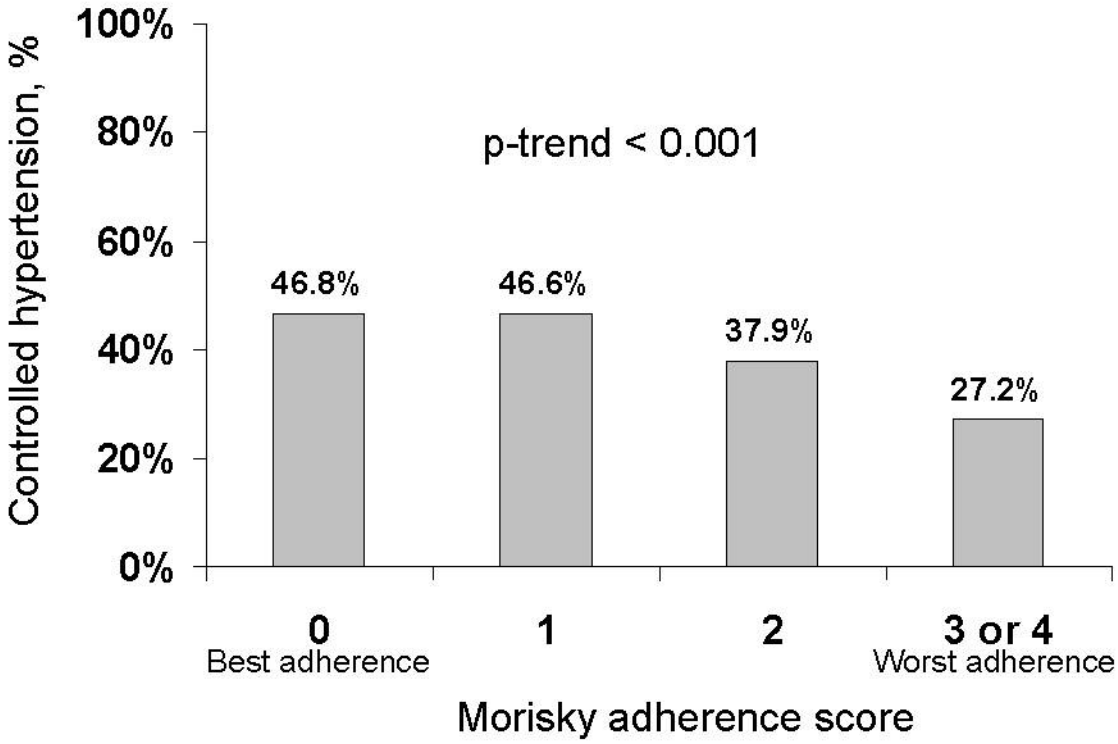

Figure 1.
Hypertension control rates associated with level of medication adherence among REGARDS participants taking at least three antihypertensive medication classes.

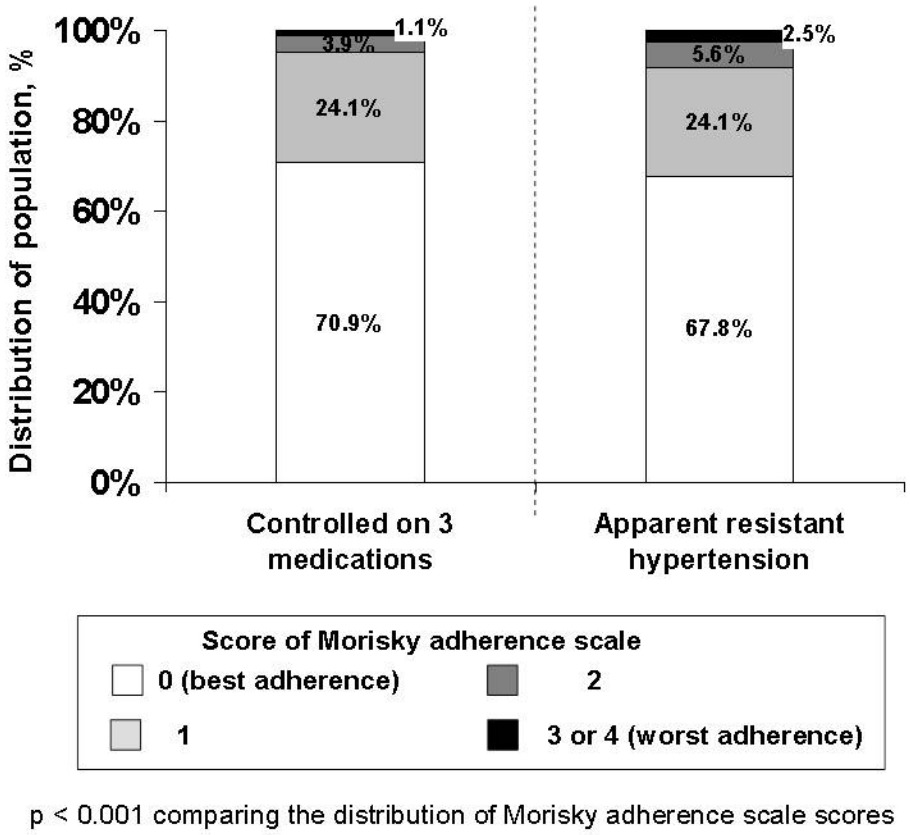

Figure 2.
Level of adherence among REGARDS study participants by apparent treatment resistant hypertension status.

Table 1

Characteristics of REGARDS study participants taking three or more antihypertensive medication classes by apparent treatment resistant hypertension status.

	Controlled on 3 medications[a] (n=1,372)	Apparent treatment resistant hypertension[b] (n=2,654)	p-value
Age, years	67.3 (8.8)	67.4 (8.7)	0.69
Black, %	46.9%	60.0%	<0.001
Male, %	40.7%	48.2%	<0.001
Region of residence			
Non-belt	42.1%	45.3%	0.08
Stroke belt	35.1%	34.6%	
Stroke buckle	22.8%	20.2%	
< HS education	14.1%	19.9%	<0.001
Household Income < $20K per year	23.6%	28.5%	0.002
Currently married	55.0%	53.7%	0.41
Current smoking	11.4%	12.5%	0.33
Physical activity			
None	40.4%	44.4%	0.007
1 to 3 times per week	32.7%	32.9%	
> 3 times per week	26.9%	22.7%	
Alcohol consumption			
None	68.1%	70.0%	0.30
Moderate	28.3%	27.1%	
Heavy	3.6%	2.9%	
BMI, kg/m^2	30.8 (6.2)	32.4 (6.8)	<0.001
Depressive symptoms, %[c]	11.5%	14.4%	0.01
Low eGFR < 60 ml/min/1.73 m^2	22.9%	33.6%	<0.001
Albuminuria, %	12.8%	35.7%	<0.001
Diabetes, %	27.3%	49.6%	<0.001
History of CHD, %	29.2%	34.6%	<0.001
History of stroke, %	11.2%	13.4%	0.05

Abbreviations: BP – blood pressure, HS – high school, BMI – body mass index, eGFR – estimated glomerular filtration rate, CHD – coronary heart disease

[a] Controlled blood pressure was defined as systolic/diastolic blood pressure < 140/90 mmHg except for individuals with diabetes or chronic kidney disease wherein controlled blood pressure was systolic/diastolic blood pressure <130/80 mmHg.

[b] Treatment resistant hypertension was defined as having uncontrolled blood pressure while on 3 antihypertensive medication classes or taking 4 antihypertensive medication classes regardless of blood pressure control.

[c] Score ≥ 4 on the 4-item Centers for Epidemiologic Studies of Depression scale.

Table 2

Responses to individual 4-item Morisky Medication Adherence Scale (MMAS) questions by apparent treatment resistant hypertension status.

Morisky question:	Controlled on 3 medications[a] (n=1,372)	Apparent treatment resistant hypertension[b] (n=2,654)	p-value
1. Sometimes forget to take medication (Yes)	26.4%	28.9%	0.09
2. Careless about taking medication (Yes)	2.6%	4.6%	0.003
3. Stop taking medication when feeling better (Yes)	3.5%	5.9%	<0.001
4. Stop taking medication when feeling worse (Yes)	3.0%	4.3%	0.04

[a]Controlled blood pressure was defined as systolic/diastolic blood pressure < 140/90 mmHg except for individuals with diabetes or chronic kidney disease wherein controlled blood pressure was systolic/diastolic blood pressure <130/80 mmHg.

[b]Treatment resistant hypertension was defined as having uncontrolled blood pressure while on 3 antihypertensive medication classes or taking 4 antihypertensive medication classes regardless of blood pressure control.

Table 3

Odds ratios for low medication adherence defined as 4-item Morisky Medication Adherence Scale (MMAS) score ≥2 among REGARDS study participants with apparent treatment resistant hypertension.

	Odds ratio (95% CI) for low adherence	
	Model 1[a]	**Model 2[b]**
Age, per 10 years	0.88 (0.75 – 1.04)	0.83 (0.68 – 1.01)
Black	1.47 (1.07 – 2.02)	1.33 (0.93 – 1.91)
Male	0.70 (0.53 – 0.94)	0.64 (0.44 – 0.93)
Residence in stroke belt	0.69 (0.50 – 0.95)	0.66 (0.46 – 0.95)
Residence in stroke buckle	0.50 (0.33 – 0.76)	0.49 (0.31 – 0.78)
< HS education	1.30 (0.93 – 1.84)	1.09 (0.73 – 1.63)
Household Income < $20K per year	1.56 (1.12 – 2.16)	1.32 (0.88 – 1.97)
Currently married	0.99 (0.72 – 1.36)	1.22 (0.84 – 1.97)
Current smoking	1.36 (0.92 – 2.00)	1.18 (0.75 – 1.85)
Body mass index, kg/m^2		
< 25	1 (ref)	1 (ref)
25 to 29	0.70 (0.44 – 1.10)	0.71 (0.42 – 1.19)
≥ 30	0.73 (0.48 – 1.10)	0.75 (0.47 – 1.21)
Physical activity		
None	1 (ref)	1 (ref)
1 to 3 times per week	0.58 (0.42 – 0.81)	0.60 (0.42 – 0.87)
> 3 times per week	0.61 (0.41 – 0.89)	0.66 (0.43 – 1.00)
Alcohol consumption		
None	1 (ref)	1 (ref)
Moderate	0.94 (0.67 – 1.33)	0.98 (0.67 – 1.43)
Heavy	0.92 (0.36 – 2.34)	0.86 (0.29 – 2.50)
Depressive symptoms	1.74 (1.23 – 2.46)	1.62 (1.09 – 2.40)
Low eGFR < 60 ml/min/1.73 m^2	0.93 (0.68 – 1.26)	0.83 (0.58 – 1.18)
Albuminuria	1.08 (0.79 – 1.47)	1.06 (0.76 – 1.48)
Diabetes	0.88 (0.66 – 1.18)	0.87 (0.63 – 1.20)
History of CHD	1.61 (1.20 – 2.16)	1.54 (1.11 – 2.15)
History of stroke	1.07 (0.72 – 1.61)	0.75 (0.47 – 1.20)

[a] Model 1 included age, race, gender, and geographic region of residence.

[b] Model 2 included all variables simultaneously.

[c] Score ≥ 4 on the 4-item Centers for Epidemiologic Studies of Depression scale.