January 2018

Disparities In Socioeconomic Context And Response To Antihypertensive Medication In The Antihypertensive And Lipid-Lowering Treatment To Prevent Heart Attack Trial (allhat)

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Disparities in Socioeconomic Context and Response to Antihypertensive Medication in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

by

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2018

Abstract

Where one lives affects one's blood pressure. Observational studies demonstrate that living in communities of low socioeconomic status is associated with higher blood pressure and worse cardiovascular outcomes. In understanding the reasons for these disparities, a key question is whether evidence-based antihypertensive medication therapy is less effective in lowering blood pressure and improving cardiovascular outcomes in lower socioeconomic communities. If so, then anti-hypertensive therapies derived from randomized clinical trials (RCTs) may be suboptimal in achieving expected outcomes. Despite standardized protocols and balancing of demographic and clinical characteristics between study arms of RCTs, the socioeconomic environment in which people live is rarely examined, potentially exerting an unmeasured effect on study outcomes.

To determine the impact of socioeconomic context on response to antihypertensive medication in clinical trials, we analyzed data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the largest existing RCT of hypertension treatment. This trial, conducted from 1994 to 2002, randomized 42,418 people, 55 years or older, with hypertension and at least one other cardiovascular risk factor, to chlorthalidone, lisinopril, amlodipine or doxazosin (mean follow-up of 4.9 years). After excluding non-continental U.S. sites and the doxazosin arm (terminated early in ALLHAT) our study included 27,862 participants. We defined socioeconomic context by mapping study site ZIP codes to counties and stratifying these counties into income quintiles based on the national distribution of county median household income, adjusted for cost-of-living, from the 2000 U.S. census.

We compared baseline and clinical characteristics, visit and medication adherence, blood pressure control, and cardiovascular outcomes between ALLHAT participants in the lowest and highest income sites using multivariable regression models. Participants receiving care in Quintile 1 (Q1, lowest income sites) (n = 2169, 7.8%) were more likely to be female, black, Hispanic, have fewer total years of education, live in the South, and have fewer cardiovascular risk factors than participants in Quintile 5 (Q5, highest income sites) (n = 10458, 37.6%). Compared with Q5, participants in Q1 were less likely to achieve blood pressure control (<140/90 mmHg) (OR, 0.48; 95% CI, 0.37-0.63), and experienced higher all-cause mortality (HR, 1.25; 95% CI, 1.10-1.41), heart failure hospitalizations or mortality (HR, 1.26; 95% CI, 1.03-1.55) and end-stage renal disease (ESRD) (HR, 1.86; 95% CI, 1.26-2.73), though lower angina hospitalizations (HR, 0.70; 95% CI, 0.59-0.83) and coronary revascularization (HR, 0.71; 95% CI, 0.57-0.89). There were no differences in stroke, myocardial infarction, or peripheral arterial disease.

Despite having access to standardized treatment protocols, participants in the lowest income sites experienced poorer blood pressure control, higher mortality, ESRD and heart failure morbidity, and decreased coronary revascularization compared to those in the highest income sites. These findings suggest a need to better measure and bolster the socioeconomic context beyond the medical environment to eliminate disparities in outcomes for RCTs of antihypertensive medications. Understanding these relationships may guide the generalizability of RCT findings, promote the assessment of participants' socioeconomic context in clinical trials and hypertension treatment guidelines, and

inform broader strategies for combating hypertension in populations living in low socioeconomic environments.

Acknowledgements

My interest in medicine was sparked early in life by the difficulties my young immigrant family encountered in attempting to access high-quality health care. As I grew older and realized that the health care delivered in the real world was often not equitable, I resolved to become a culturally competent physician who worked to address disparities in health care, and discovered that one way in which I could accomplish this goal was through research. However, when I first entered medical school, I had virtually no clinical research experience. Fortunately, I was lucky enough to connect with a great mentor, and in the ensuing years, as I acquired the clinical knowledge and skills I would need to become a physician, I concurrently learned how to think through clinical research problems. This thesis, which draws from research that I conducted during my fifth year, marks the culmination of my transformation into a clinical researcher. In the process, I have also discovered my passion for research that has the potential to shape health care policy and confront the health disparities that plague this country.

Research, like medicine, is a team sport. The work presented here would not be possible without the support, help, and guidance of numerous team players.

I would first and foremost like to thank Dr. Erica Spatz, my amazing mentor of four years, and one of my first and most inspiring physician role models. Thank you for taking a chance on me four years ago, for offering calm guidance and wisdom when I did not know what to do, for teaching me how to develop and investigate clinical research questions in a thorough and critical way, for teaching me about work-life balance, for helping me become a better scientific writer, for responding to my late-night emails with

even later emails, and for showing me through your own clinical practice that practicing medicine in a patient-centered way is not only possible, but absolutely necessary.

I would like to thank our statistical wizard, Dr. Jeph Herrin for his patience and skill in helping us navigate difficult statistical analyses. I would like to thank Dr. Sanket Dhruva, Dr. Nihar Desai, and Dr. Harlan Krumholz, for supporting this project since its inception and offering their valuable feedback throughout. I would also like to thank Dr. Barry Davis and Sara Pressel for collaborating with us and sharing data from ALLHAT with us (as well as providing feedback), and Tara Liptak for helping us acquire the data.

I would like to especially thank my MD/MHS thesis committee – Dr. Nihar Desai, Dr. Julie Goodwin, Dr. Shuta Ishibe and Dr. Erica Spatz – for providing the crucial advice that led to the development of the final methodology presented here and for contributing their feedback for this thesis. I would like to thank the Office of Student Research at the Yale School of Medicine for supporting all of my research activities during my time at Yale. This work was funded by the National Institutes of Health-National Heart, Lung & Blood Institute Award and the Richard K. Gershon M.D. Student Research Fellowship.

I would also like to thank my parents, Milena and Agron Shahu, for being courageous enough to transplant our family from Albania to the United States, for instilling in me the importance of work ethic, and for teaching me to lead a life of integrity. Last, I would like to thank my little sister, Anja Shahu, for designing Figure 1 and for helping me realize when I was only 10 years old that I liked taking care of others.

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Foreword

This research was conducted during my time as a medical student at the Yale School of Medicine, with investigators in the Center for Outcomes Research & Evaluation, and in collaboration with original investigators from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). As the lead author, I presented our findings at the American Heart Association (AHA) Council on Hypertension/AHA Council on Kidney in Cardiovascular Disease/American Society of Hypertension/Joint Scientific Sessions 2017, where it was accepted as an oral presentation and received the AFHRE Travel Award for Patient-Oriented or Clinical Research in Hypertension. A manuscript is in preparation for submission for publication in the biomedical literature.

Shahu A, Herrin J, Dhruva SS, Desai NR, Krumholz HM, Spatz ES. Abstract 148: Association of Socioeconomic Context with Blood Pressure Response and Cardiovascular Outcomes in ALLHAT. *Hypertension*. 2017;70(Suppl 1):A148-A. (Abstr.)

> Also presented as a poster, under the title: Variation in Blood Pressure Response and Cardiovascular Outcomes by Socioeconomic Context in ALLHAT. Medical Student Research Day, Yale School of Medicine, New Haven, CT, 2017.

Shahu A, Herrin J, Dhruva SS, Desai NR, Pressel SL, Davis BR, Krumholz HM, Spatz ES. Association of Socioeconomic Context with Response to Antihypertensive Medication in ALLHAT. (*in preparation for submission*)

Introduction

Beyond the guidelines: new paradigms in treatment of hypertension

Hypertension, a medical condition wherein arterial blood pressure is persistently elevated, is one of the most prevalent medical conditions in the world. It is the most common condition seen in primary care offices and poses a significant public health challenge, with an estimated global prevalence of 24.6% in 2000 in people aged 20 years and older, and projections of up to 29.2% in 2025 (1, 2). In the U.S., the prevalence of hypertension among adults remained stable from 1999 to 2014 (at about 29%), and the prevalence of controlled hypertension in adults increased from 31.5% to 53.3% from 1999 to 2009; however, in the years since, the proportion of people with controlled hypertension has plateaued (3). These statistics indicate that while some progress has been made over the years in treating hypertension, there remains considerable room for improvement, with millions of Americans still in need of improved blood pressure control.

Moreover, hypertension also plays a causative role in cardiovascular disease (myocardial infarction, stroke, heart failure, peripheral vascular disease) as well as renal disease, and inadequate treatment has been associated with increased mortality (4). Furthermore, countless studies have shown that treatment of hypertension is vitally important. For every 10-mmHg reduction in systolic blood pressure (SBP), there is a 22% reduction in the rates of major cardiovascular disease events, coronary heart disease, stroke, heart failure, and all-cause mortality (5, 6).

However, despite the large, well-documented body of evidence emphasizing the importance and benefits of antihypertensive treatment, the medical community has long debated thresholds for defining hypertension, modalities for diagnosis and treatment of hypertension, as well as blood pressure targets. In an effort to standardize treatment for a common but treatable condition, the first clinical practice guidelines for the treatment of hypertension were developed in 1977 by the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure, appointed by the National, Heart, Lung and Blood Institute (NHLBI) (7). This committee of experts offered six key recommendations in a consensus document, based on a combination of existing evidence and expert opinion: 1) anyone evaluating blood pressure should have resources available for referral, confirmation, and follow-up; 2) antihypertensive therapy should be started in all adults with a diastolic blood pressure (DBP) of 105 mmHg or greater; 3) adults with DBP between 90 and 104 mmHg should be treated on a case-by-case basis depending on their cardiovascular risk factors; 4) evaluation of hypertension could usually be limited to a few baseline tests; 5) providers should take a cost-effective stepped-care approach to treatment (i.e. begin treatment with one drug, titrate to maximal dose, and add additional drugs in a step-wise fashion if therapeutic goal is not achieved); and 6) providers should make plans with patients for long-term control of blood pressure (8). Although existing data suggested an increased risk from elevated SBP, no recommendations were made regarding SBP in order to minimize complexity in the guidelines.

Clinical practice guidelines for hypertension management were updated over the ensuing decades, becoming increasingly comprehensive thanks to evidence from major observational studies and large clinical trials of antihypertensive medications. Thresholds

for diagnosis of hypertension grew more stringent, leading to the JNC 7 guidelines, published in 2003, which defined hypertension in adults as having an average SBP of 140 mmHg or greater *or* DBP of 90 mmHg or greater (9). Prehypertension was defined as having an average SBP between 130 and 139 mmHg or DBP between 80 and 89 mmHg. Greater emphasis was placed on standardization of methods; for example, it was recommended that office blood pressure be measured with the patient in a seated position after resting for 5 minutes (9). Lifestyle modifications were recommended for early treatment of prehypertension or hypertension. Step-wise treatment with antihypertensive medications was recommended at a threshold of 140 mm Hg SBP or 90 mm Hg DBP (with a treatment goal of <130/80 mmHg for patients with diabetes and chronic kidney disease [CKD]), recognizing that many people would likely need more than one medication. Thiazide diuretics (e.g., chlorthalidone or hydrochlorothiazide) were recommended as first-line medications, although other medications were also deemed effective in patients with additional cardiovascular risk: calcium channel blockers (CCBs, e.g., amlodipine), and angiotensin-converting-enzyme inhibitors (e.g., lisinopril), angiotensin receptor blockers (ARBs, e.g., losartan), and beta blockers (e.g., metoprolol). These recommendations were strongly influenced by findings from the then-recent randomized clinical trial (RCT) titled Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT, described in detail later) (10).

However, about a decade later, some experts questioned the strength of the evidence supporting the blood pressure treatment recommendations in JNC 7. Moreover, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, found that a more intensive treatment target of 120/80 mmHg, versus the standard 140/90 mmHg in

low-risk people with diabetes, did not reduce cardiovascular outcomes (11). This led to the convening of a new guideline committee (JNC 8), which focused their review on 3 questions: does initiating hypertension treatment at specific blood pressure thresholds improve outcomes; does treating blood pressure to specific blood pressure targets improve outcomes; and do antihypertensive medications differ in their comparative benefits and harms on health outcomes (12). In alignment with the evidence, the published guidelines recommended a treatment threshold of 150/90 mmHg in patients 60 years or older, and 140/90 mmHg for adults younger than 60 years. They determined that based on the negative trial results of ACCORD and the absence of other data sources, there was insufficient evidence to support lower treatment targets in people over 60 years of age, and younger people with CKD or diabetes; this represented a break from past guidelines and concurrent clinical practice (12). Additionally, after reevaluation of clinical trial data, thiazide diuretics, ACE inhibitors/ARBs, and calcium channel blockers were equally recommended as first-line agents, though CCBs and thiazides were recommended as first-line agents in black adults. The JNC 8 guidelines resulted in considerable controversy. Critics argued that the absence of data to support more stringent SBP targets did not necessarily point to an absence of effect, and that until new data were generated, guideline committees should offer their expert opinion and providers should use their own clinical judgment when helping patients make decisions about hypertension treatment (4, 13). It is unknown whether the JNC 8 guidelines had an impact on clinical practice or outcomes; they were again updated only three years later.

Just after the JNC 8 guidelines were published, the results of two trials of antihypertensive medications were reported: the Systolic Blood Pressure Intervention

Trial (SPRINT) and the Heart Outcomes Prevention Evaluation (HOPE)–3 trial (14). SPRINT enrolled people aged 50 or older at high risk for cardiovascular disease but without diabetes or prior stroke, and found that patients randomized to a treatment SBP goal of 120 mmHg experienced fewer cardiovascular events as well as a survival benefit compared to patients treated to a SBP goal of 140 mmHg (15). HOPE-3 enrolled men aged 55 or older and women aged 65 or older with an intermediate 10-year risk for cardiovascular events but no cardiovascular disease, and found that antihypertensive therapy was not associated with a lower risk of adverse cardiovascular events, as compared to treatment with a placebo, though benefit was observed in the subgroup in the highest tertile of baseline systolic blood pressure (16). As, a result, there was a push to revisit the guidelines.

In response, a joint task force, led by the American College of Cardiology (17) and American Heart Association (AHA) and including 11 different medical organizations, assumed the role of developing new guidelines from the NHLBI. In the most comprehensive hypertension guidelines ever, which were more focused around class of recommendation and the level of existing evidence, this task force made 106 recommendations on the basis of an extensive systematic literature review (18, 19). Among them, a blood pressure below systolic of 120 mmHg and diastolic <80 mmHg was categorized as normal, systolic blood pressure of 120-129 and a diastolic blood pressure <80 mmHg was categorized as "elevated," 130-139 mmHg or 80-89 mmHg was categorized as stage 1 hypertension, and ≥140/90 mmHg was categorized as stage 2 hypertension (20). These classifications were reminiscent of the JNC 7 taxonomy, acknowledging observational data that the risks associated with hypertension start with

an SBP as low as 110-115 mmHg (2). Moreover, in somewhat of a reversal from the JNC 8 guidelines, antihypertensive medication was recommended for patients with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an SBP ≥130 mmHg or DBP ≥80 mmHg. Additional emphasis was also placed on out-of-office blood pressure monitoring (home-based monitoring and 24-hour ambulatory blood pressure monitoring) and nonpharmacological interventions (21).

These new guidelines promise to radically alter the landscape of hypertension diagnosis and treatment. If they are incorporated into clinical practice, the impact would be massive: the prevalence of U.S. adults diagnosed with hypertension would increase from 31.9% to 45.6%, and among U.S. adults taking blood pressure-lowering medication, the proportion of people with blood pressure above goal would increase from 39.0% to 54.3% (22). Among U.S. adults aged 45-75, the prevalence of hypertension would rise to 63.0% (70.1 million people). In other countries such as China, the impact would be even greater, with prevalence rates increasing from 38.0% to 55.0% (23). These statistics indicate that more people than ever, especially younger adults, would be considered to have hypertension, to be eligible for antihypertensive medication, and to potentially require more intensive blood pressure lowering.

With millions of additional Americans newly labeled as having hypertension, the 2017 guidelines raise new concerns about the shortcomings of hypertension management in the modern medical era. First, even among guidelines produced by different medical organizations, there is inconsistency. In 2017, the American College of Physicians (ACP) and American Academy of Family Physicians (ACP/AAFP) recommended that patients be treated to a goal SBP of 140 or 150 mmHg, depending on age and level of

cardiovascular risk (24). This disagreement among professional organizations may lead to additional confusion among clinicians as well as patients. More aggressive antihypertensive treatment, some experts say, may result in more adverse events– such as syncope and renal dysfunction – as observed in SPRINT and ACCORD (11, 15, 25). Moreover, the risk of adverse events observed in SPRINT may be much greater in clinical practice, since in this trial, blood pressure measurements were attained under ideal conditions (and thus a target of 120/80 mmHg may represent the lowest possible blood pressure achieved); targeting 120/80 mmHg using more traditional methods to measure BP may result in even lower blood pressures and thus, more adverse events (21, 26). Additionally, the burden associated with increasing prescriptions and pill numbers may not be considered 'worth it' to patients, many of whom are already overwhelmed by polypharmacy (27). For these reasons and others, it is unclear whether the new guidelines will result in changes in clinical practice. Historically, there are considerable gaps between guideline recommendations and clinical practice – perhaps because physicians are unfamiliar with the guidelines, find them impractical to implement in real life, or do not agree with the recommendations based on their own clinical experience (28). Other patient- and system-level factors may also impact guideline adoption.

Perhaps most importantly, however, guidelines should be considered to provide just that – guidance. No matter how comprehensive they are, they are not intended to be adopted by everyone. By nature, guidelines will always be reductive in that they can never truly capture the unique combination of medical, personal, and contextual factors that should be considered in clinical decision making. Guidelines have transformed medicine to where it is today. They may be helpful in establishing proper methods of

blood pressure measurement or diagnosis of hypertension, or offering guidance on approaches to treatment of hypertension. Yet, guidelines alone will not be enough to reduce the prevalence of hypertension, improve rates of hypertension control, or further reduce cardiovascular outcomes resulting from hypertension. Debate around what specific blood pressure goals should be, as well as how these goals should differ and what medications are optimal for different patient populations will persist, which is why we must move beyond the guidelines in order to break new ground in the fight against hypertension, especially given the global impact of hypertension on cardiovascular outcomes.

In order to make further progress in the treatment of hypertension, future approaches will need to incorporate precision-based medicine, personalized decision-making, and contextual factors contributing to health disparities. In recent years, as methods to analyze "big data" have improved, new studies have attempted to develop more personalized approaches to antihypertensive treatment, namely by developing methods to better characterize heterogeneity in outcomes from large RCTs of hypertension. One study used advanced modeling techniques to examine heterogeneity in response to blood pressure treatment in the first 6 months of ALLHAT and discovered two distinct blood pressure trajectory patterns: immediate responders whose blood pressure decreased immediately following the start of the trial, and non-immediate responders whose blood pressure initially rose before declining following the start of treatment (29). These data may be important for expectation setting and planning appropriate follow-up. Other studies used patient-level data from SPRINT to develop prediction models that could allow providers to tailor the intensity of blood pressure

treatment to the calculated risk and benefit for an individual patient or for a subgroup of patients (30, 31). By developing a better understanding of how different populations respond to different medications and developing personalized estimates of risks and benefits, we may be better able to tailor blood pressure goals and treatment for each individual rather than implementing a one-size-fits-all approach.

The decision-making process offers yet another opportunity to further personalize treatment of hypertension. Principles of shared decision-making – which has become more important in recent years as medicine has shifted away from paternalism and physician-led decision-making – encourage patients who so desire to take an active role in their clinical care (32). In sharing with patients the range of reasonable treatment options, the associated risks and benefits of treatment, and the prognosis with and without intervention, patients can develop more informed preferences and treatment goals (33). Here again guidelines fall short in that practically speaking not all patients may be able to tolerate equally intensive blood pressure lowering or may even seek the same outcome out of treatment. For some patients, pill-taking is difficult and burdensome – the act of swallowing pills may even be difficult – making some patients more reluctant than others to take medications (34). One study found that patients may differ in the disutility (or burden) they associate with taking an idealized version of statin medications, and that for some patients this disutility may outweigh the benefits they would receive in lifetime gain (35). We are currently conducting a similar study using an idealized antihypertensive medication to better understand the disutility patients associate with blood pressure-lowering interventions. By using guidelines as a starting point for making clinical decisions that are more in line with patients' values, clinicians can empower

patients to meet their own goals instead of setting them up for failure and difficulties with medication adherence.

Last, differences in hypertension and hypertension outcomes between different people are not dependent solely on individual characteristics. While the approaches described above are important, as with the guidelines, they focus only on targeting factors at the individual level, and do little to address the community-level factors that contribute to prevalent disparities in hypertension, blood pressure control, and cardiovascular outcomes. In order for true progress to be made, we must develop new methods to investigate and address the contextual factors in which people live and obtain care. Such contextual factors – socioeconomic status or context, access to school or level of education, poverty, neighborhood violence, unemployment, access to healthy foods and exercise, social cohesion, and more – are known to worsen disparities in health outcomes (36-41). However, in the key studies (i.e. RCTs) used to develop guidelines, calculate risks and benefits, and base clinical decisions, little attention has been given to how contextual factors affect outcomes. Until we better characterize these factors, we may never be able to fully generalize outcomes from clinical studies or mitigate the burden of hypertension. We have selected one of the most studied contextual factors – socioeconomic context – in order to better understand how it may impact outcomes from important studies of hypertension. This will be the main subject of the remainder of this thesis.

Socioeconomic context and hypertension outcomes

Where one lives affects one's health. People living in communities of lower socioeconomic status historically have had lower income, worse housing, poorer access to nutrition, more environmental risks, and lower educational or job opportunities, than their counterparts living in wealthier areas (42). Additionally, studies dating back to the 1980s have shown that people living in these communities experience poorer health and greater mortality (43, 44). In recent decades, socioeconomic disparities in various health outcomes have only widened – as measured by differences in median household income, education level, median housing value, housing occupancy, education level, occupation, and to some extent, race – suggesting that interventions to improve social risk factors may result in more equitable outcomes (45-48).

Notably, the effect of the socioeconomic context of a neighborhood, community, or county on health outcomes is distinct from that of an individual's socioeconomic status. Studies have demonstrated that neighborhood– or area–level socioeconomic deprivation, measured by a combination of factors such as housing indicators, wealth and income, education, and occupation, leads to worse health outcomes (e.g. incidence of heart failure, hospital readmissions for heart failure, cancer incidence and mortality, all-cause mortality, depression, type 2 diabetes), even after accounting for individual-level factors such as individual socioeconomic status (39, 49-53). These findings suggest that person-level factors alone cannot explain disparities in health outcomes, perhaps because indicators such as area-level income may give a sense of both an individual's general socioeconomic status as well as the amount of resources available to the overall community living in an area. Furthermore, these results underline the need to more

closely examine the impact that community-level factors such as socioeconomic context may have on the overall health and well-being of diverse populations.

Where one lives also affects one's blood pressure. Studies consistently show an inverse relationship between socioeconomic status and mean blood pressure (54-56). Moreover, numerous observational studies demonstrate that living in a neighborhood of lower socioeconomic status is associated with a higher prevalence of hypertension, worse blood pressure control, and higher rates of sequelae of hypertension, including secondary heart disease, renal failure and stroke (57-59). In understanding the reasons for these disparities, a key question is whether antihypertensive medication therapy is less effective in lowering blood pressure and improving cardiovascular outcomes in lower socioeconomic communities. If so, then the implementation of evidence-based therapies for hypertension derived from RCTs may be suboptimal in achieving expected outcomes in differing socioeconomic populations.

Antihypertensive medication may be less effective when used in low socioeconomic communities for a number of reasons. Living in an under-resourced community may be associated with other factors that affect blood pressure, including unhealthy lifestyle behaviors related to access to food or facilities, poorer perceived health status, differing cultural norms, or practical barriers to eating healthily, exercising, and quitting smoking (60-64). Additionally, people living in disadvantaged communities may experience changes in blood pressure due to an allostatic load resulting from stress associated with unemployment, housing conditions, mental health, financial burdens, poor social cohesion, neighborhood safety and violence, and other social ills, further contributing to disease progression (65-69). In low income communities, access to high-

quality primary care is often inadequate, and there may be greater acceptance that hypertension is inevitable (70-72). This culture can affect people's sense of control or capacity to lower their risk of cardiovascular events through regular follow-up, medication adherence or adoption of lifestyle modifications to halt the progression of chronic diseases such as hypertension (73-75).

Although relationships between these contextual factors and health outcomes have been observed and reported in countless observational studies, they are rarely measured in RCTs; potentially, some contextual factors may be exerting an unmeasured effect on study outcomes. Specifically, in RCTs, while efforts are made to balance differences in patient demographic and clinical characteristics, even measurable indicators of the socioeconomic environments in which people live, such as area-level income are rarely taken into account. To our knowledge, there are no existing studies of RCTs of antihypertensive medication therapy which have examined the possible effect of socioeconomic context on study participants' response to antihypertensive medication. Thus, despite the provision of standardized hypertensive care and interventions within and between study arms in RCTs of antihypertensive medications, unmeasured factors related to participants' socioeconomic environments may contribute to heterogeneity in outcomes and limit the generalizability of research findings to some populations (76, 77). This is especially problematic because the findings from these RCTs often form the cornerstone of treatment guidelines and inform the clinical decisions that practicing physicians make every day. Therefore, investigation of the socioeconomic context in an RCT may partly explain why the results of RCTs are often not uniformly observed in real-world settings (78, 79).

The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial

To examine the effect of socioeconomic context on response to antihypertensive medication in RCTs, we analyzed data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT is the largest randomized, double-blinded clinical trial of antihypertensive medical therapy ever, conducted from 1994 to 2002 with 42,418 original study participants from 623 clinical sites across the U.S., Puerto Rico & Virgin Islands, and Canada (10). The study enrolled men and women ≥55 years old with untreated or treated systolic and/or diastolic hypertension and at least one additional cardiovascular risk factor (80).

As the largest ever prospective RCT of antihypertensive treatment, ALLHAT is the richest and most reliable data source for secondary analysis. The trial population, considered to be demographically diverse, was comprised of nearly 50% women; black and Hispanic participants accounted for 36% and 19% of the overall study population, respectively (81). The study was considered highly generalizable and sampled across a broad socio-geographic distribution, as it enrolled patients from clinical sites throughout North America, where blood pressure ascertainment by trained staff was deemed consistent and reliable (82, 83). High-quality data was obtained through careful adjudication of enrollment criteria, documentation, and confirmation of 99% of cardiovascular disease events resulting in death or hospitalization (10). Information was collected on potential clinical confounders such as visit-to-visit variability (82). Less than 1% of drug identities were revealed to either participants or investigators, supporting the rigor of blinding (84).

Additionally, the findings from ALLHAT have been validated, and extended follow-up data are available for most participants using national administrative databases (84, 85). The most recent extended follow-up data included fatal outcomes for 98% and nonfatal outcomes for 65% of participants (86, 87). Key strengths of the study included its design as a randomized double-blind trial, statistical power enabling detection of clinically meaningful differences in certain cardiovascular outcomes, a diverse participant population, and varied primary care-based clinical settings (private practice, community health center, Veterans Affairs Medical Center, academic centers, and HMOs) (10). Given that recent guidelines recommend any of the three main classes of antihypertensive drugs tested in ALLHAT as first-line medications and the majority of patients in the trial needed multiple medications, no future trial will likely provide such undiluted data of the effect of first-line antihypertensive agents (85).

ALLHAT participants were assigned to one of four representative anti-hypertensive medications: a thiazide diuretic (chlorthalidone), an ACE inhibitor (lisinopril), a calcium channel blocker (amlodipine), or an alpha-adrenergic blocker (doxazosin) (80). The purpose was to determine whether newer medication classes, such as ACE inhibitors and calcium channel blockers – which at the time were costlier than the historically-used thiazide diuretics – were as good or better than thiazides in preventing adverse cardiovascular outcomes (i.e. fatal coronary heart disease or nonfatal myocardial infarction) resulting from hypertension (80). The doxazosin arm was stopped early due to inferior treatment effect, but most participants in the other arms were followed from 1994 to 2002, with an average of 4.9 years of follow-up (88, 89). The main findings, published in 2002, showed that neither amlodipine nor lisinopril were

superior to chlorthalidone in improving all-cause mortality or reducing the risk of major coronary events (10). Chlorthalidone was superior to amlodipine in preventing heart failure but not other kinds of cardiovascular disease, and superior to lisinopril in preventing some cardiovascular events, such as stroke, heart failure and coronary revascularization.

A follow-up study indicated that blood pressure control was achieved in a majority of patients regardless of randomization, with mildly improved rates of blood pressure control in the chlorthalidone group (90). A subsequent comparison of lisinopril and amlodipine showed that risk for coronary events was similar, but the risks of stroke, gastrointestinal bleeding, and angioedema were higher for lisinopril, possibly due to less effective blood pressure control (91). On the basis of cost and overall clinical equivalence of thiazides – and even superiority in outcomes such as heart failure and blood pressure control – to ACE inhibitors and calcium channel blockers, investigators recommended that thiazide diuretics be considered as first-line therapy for treatment of hypertension (10, 92). These findings were revisited in the context of subsequent subgroup analyses, meta-analyses, and new clinical trials, but the conclusions remained the same (86). Meanwhile, a subtrial of ALLHAT was conducted in which participants were randomized to pravastatin 40 mg or usual care. In that study, pravastatin did not significantly reduce all-cause mortality or coronary heart disease compared with usual care (93).

The findings from ALLHAT were among the most consequential of any trial of hypertension ever conducted, going on to heavily influence recommendations made in the JNC 7 and JNC 8 hypertension guidelines described earlier, and even resulting in an increase in diuretic prescriptions (9, 12, 94). Numerous follow-up studies and secondary

post-hoc analyses of ALLHAT data have been published over the past 15 years, examining the effect of various factors acting at the person level, such as race, sex, medication adherence, visit adherence, blood pressure control, comorbidities including diabetes or chronic kidney disease, medication randomization, medication cost-effectiveness, statin treatment, and others on study outcomes (29, 82, 83, 85, 87, 95-107). However, to date no studies of ALLHAT have considered the effect of socioeconomic context or other community-level contextual factors on study outcomes.

We define socioeconomic context here as the median household income of the county in which ALLHAT participants obtained their care (e.g. the ALLHAT clinical sites). Postulating that socioeconomic context, a proxy for unmeasured contextual factors such as social stressors and lifestyle behaviors, may impact overall treatment response in the trial, we compared baseline and clinical characteristics, visit and medication adherence, blood pressure control, and cardiovascular outcomes among ALLHAT participants of varying socioeconomic context. Understanding the relationship between socioeconomic context and outcomes can guide the generalizability of RCT findings, promote the assessment of participants' socioeconomic context in clinical trials, and ultimately, inform broader strategies for combating hypertension in populations living in low socioeconomic environments.

Statement of purpose

Specific Aim: In this study, I aim to assess the relationship between the socioeconomic context in which participants obtained clinical care with response to antihypertensive medication, as measured by blood pressure control and key adverse cardiovascular outcomes in ALLHAT, the largest-ever RCT of hypertension.

Hypothesis: ALLHAT participants obtaining care in lower income areas will have a lower likelihood of achieving blood pressure control (defined as a blood pressure less than 140/90 mmHg) and a higher risk of experiencing the main primary and secondary adverse cardiovascular outcomes defined in the original trial.

Methods

Contributions

I, the student, was the intellectual driver of this research. I was responsible for conducting the literature review, creating the research proposal, formulating a plan for data acquisition, designing an analytic plan, and working closely with our statistician to analyze and interpret our data. As the lead author on this project, I was also responsible for creating all posters and presentations, and writing the resulting manuscript.

Overview

We conducted a secondary analysis of ALLHAT to examine the effect of socioeconomic context on study outcomes. To measure socioeconomic context, we used the income level of the county in which the clinical site was located, assuming participants lived in nearby communities and therefore were exposed to a similar socioeconomic context as the clinical site. We then assessed the distribution of participants' income status compared with the national mean in 2000 (when the trial was underway), and compared baseline characteristics and outcomes of participants in quintile 1 (Q1, lowest socioeconomic status) with participants in quintile 5 (Q5, highest socioeconomic status). To better understand whether demographic factors such as race and region of care, previously associated with hypertension outcomes but also associated with socioeconomic status, confounded any differences observed, we also assessed differences by income quintile among two subgroups, black participants and clinical sites in the South.

ALLHAT study design and organization

Details of the rationale, study design, and main findings for ALLHAT have been explained above and are extensively described in the literature (10, 80, 88). ALLHAT originally enrolled 42,418 men and women ≥55 years old with untreated systolic (defined as 140 ≤ 180 mmHg) and/or diastolic (90 ≤ 110 mmHg) hypertension present on ≥2 visits, or treated hypertension (≤160/110 mmHg on 1-2 antihypertensive medications at visit 1 [where participants were assessed for study eligibility] and ≤180/110 mmHg at visit 2 [where participants were randomized after stepdown from any pre-study antihypertensive drugs]) (80). Eligible study participants also had at least one additional cardiovascular risk factor (80). These risk factors included: history of atherosclerotic cardiovascular disease (CVD); history of myocardial infarction or stroke; history of coronary revascularization; other atherosclerotic CVD; history of ST depression or T-wave inversion on electrocardiogram (ECG); type 2 diabetes; a high-density lipoprotein C (HDL-C) of <35 mg/dL at least twice in the five years prior to the trial; left ventricular hypertrophy (LVH) by ECG in the 2 years prior to the trial; LVH by echocardiogram in the 2 years prior to the trial; history of coronary heart disease (CHD) at baseline; body mass index (BMI); aspirin use at the start of the trial; cigarette smoking; and estrogen supplementation at the time of the trial.

The study was conducted from 1994 to 2002, with a mean of 4.9 years of follow-up (108). Visit frequency included follow-up at 1 month; 3, 6, 9, and 12 months; and every 4 months thereafter (more often as needed), which was considered usual for

hypertension care (10, 85). Patients were assigned to one of four representative anti-hypertensive medications – a thiazide diuretic (chlorthalidone), an ACE inhibitor (lisinopril), a calcium channel blocker (amlodipine), or an alpha-adrenergic blocker (doxazosin, stopped early due to inferior treatment effect) – with discouragement of mixing therapies (89). Because blood response was one of the main outcomes and most participants continued to have uncontrolled blood pressure (defined as >140/90 mmHg) despite titration of the assigned study drug, second-line medications (atenolol, clonidine, or reserpine) were added as needed in a step-wise fashion (10). Study outcomes were collected through a variety of means: at follow-up visits, from clinical investigator reports, or other documentation such as a death certificate or a hospital discharge summary; 99% of cardiovascular events were documented across all 3 treatment groups (10). Protocols outlining follow-up visits, treatment procedures, and endpoint ascertainment have been described elsewhere in the biomedical literature (80, 88). Participating sites acquired institutional review board (IRB) approval and obtained written informed consent from all participants (10).

The primary study outcome was coronary heart disease [CHD] (fatal CHD and nonfatal myocardial infarction [MI] combined). Four major pre-specified secondary outcomes were also defined: (1) all-cause mortality, (2) stroke, combined CHD (CHD, coronary revascularization, or hospitalized angina), and (4) combined cardiovascular disease [CVD] (combined CHD, stroke, other treated angina, heart failure [HF], or peripheral arterial disease). The original trial investigators also assessed subcomponents of these major outcomes as well as other pre-specified secondary outcomes, including

cancer, left ventricular hypertrophy by ECG, hospitalization for GI bleed, end-stage renal disease (ESRD), quality of life, and health care costs (10).

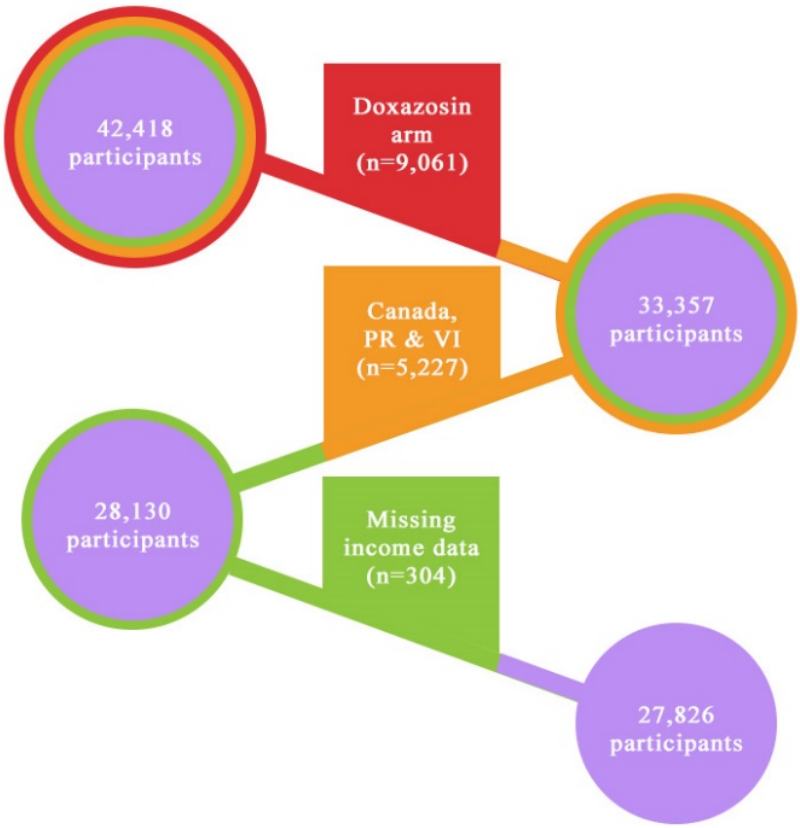
Income data

ALLHAT data was obtained from the NHLBI's Biologic Specimen and Data Repositories Information Coordinating Center (BioLINCC). We did not have access to the ZIP codes or counties in which participants resided, so we instead used enrollment site ZIP codes, obtained from the original ALLHAT investigators, and mapped these to one or more site-specific counties. We selected county-level median household income as a proxy for the socioeconomic context in which patients received their care, derived from the 2000 U.S. Census, the closest year to the period in which the study was conducted. County-level incomes were adjusted for cost of living in each state in the year 2000. If the ZIP code mapped to more than one county, we calculated the population-weighted average median income across those counties. County-level incomes were assigned to study participants at that site. Based on the national distribution of county-level household median income, individuals were stratified into income quintiles.

Exclusion criteria

We excluded participants enrolled in sites outside of the continental U.S. (n=5,277), due to potential confounders when comparing socioeconomic context of those sites with sites in the continental U.S., participants in sites lacking income data (n=304) and participants randomized to doxazosin (n=9,061 participants). After these exclusions, a total of 27,826 participants were included in this study (see **Figure 1**).

Figure 1. Flow chart of study exclusion criteria



Outcomes

We assessed blood pressure control and major adverse cardiovascular events as pre-specified in ALLHAT. Blood pressure control was defined as the proportion achieving the ALLHAT treatment goal of 140/90 in years 1-6, regardless of age (80). The primary and four key secondary cardiovascular outcomes, defined in ALLHAT, were: (1) CHD, (2) all-cause mortality, stroke, (4) combined CHD, and (5) combined CVD (each defined above). We also evaluated the following individual components of these

outcomes: heart failure, hospitalized/fatal heart failure, angina, coronary revascularization, peripheral arterial disease, and ESRD.

Statistical Analysis

We compared baseline characteristics, treatment, visit and medication adherence, unadjusted blood pressure response and unadjusted cardiovascular outcomes of the study population by income quintile. As captured in the original trial, we defined visit adherence as the number of attended visits divided by the protocol-determined number of expected visits in the six-year duration of the trial. Adequate visit adherence was defined as attending at least 80% of expected visits. We defined adequate medication adherence as taking at least 80% of study medications at all visits, per participants' self-report. We then tested the association between socioeconomic context with blood pressure control and cardiovascular outcomes in the lowest and highest income quintiles, with the highest income quintile (Q5) serving as the reference group, using logistic regression and Cox proportional hazards regression analysis, respectively. In this model, we adjusted for treatment group, age, sex, qualifying ALLHAT risk factors (see *ALLHAT study design and organization*, above), and baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP), using imputation if study participants had missing values for certain risk factors.

Next, we performed subgroup analyses of blood pressure response and cardiovascular outcomes across socioeconomic strata (1) among black participants, and (2) among participants in the South. Last, to assess whether fidelity to the protocol explained any of the differences between groups, we performed an exploratory analysis

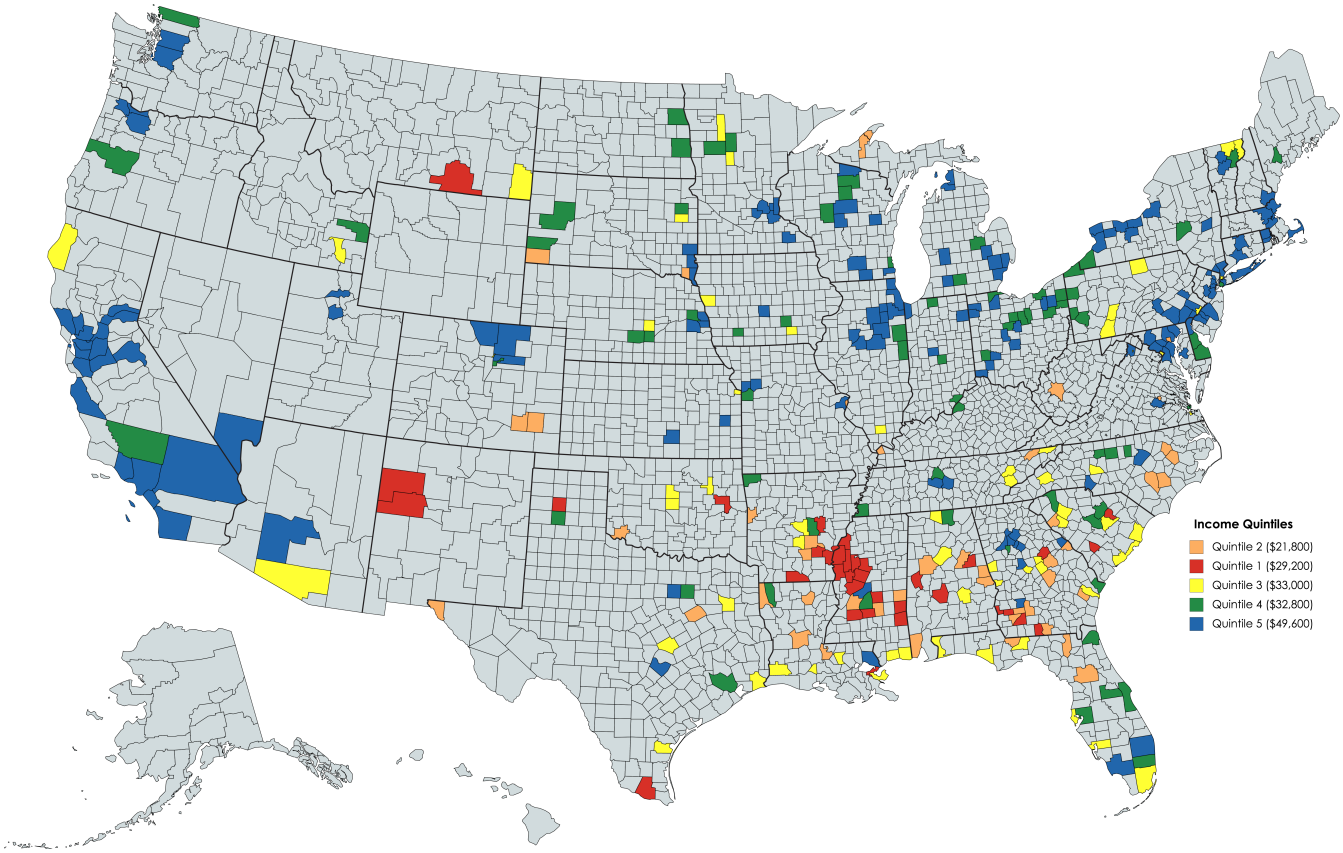
adjusting for visit adherence in addition to baseline and clinical characteristics. Though visit adherence is potentially endogenous with the outcome – that is, patients with a clinical outcome prior to the six-year endpoint may be more likely to adhere to subsequent visits – we included it in the final model to assess whether it attenuated the main differences. There was insufficient data of participants' medication adherence to include it in the model. This study was approved by the Yale Human Investigations Committee.

Results

Geographic distribution of clinical sites

The 27,826 participants included in this study obtained care in clinical sites representing 372 U.S. counties, depicted in **Figure 2**. Nearly all (32/35, 91%) of the lowest-income counties (Q1) were in the South, whereas the highest-income counties (Q5) were more evenly distributed across geographic regions.

Figure 2. Geographic distribution and socioeconomic (income) stratification of U.S. counties with clinical sites participating in ALLHAT[A]



[a] Image created using mapchart.net.

Baseline characteristics

Baseline demographic and clinical characteristics, qualifying risk factors, and treatment group randomization across income strata in ALLHAT are shown in **Table 1**. Participants enrolled in the lowest income sites (Q1, bottom income quintile) comprised 7.8% of the study population, while those enrolled in the highest income sites (Q5, top income quintile) comprised 37.6% of the study population. Participants in Q1 tended to be younger, female, black or Hispanic, and had attained lower levels of education than participants in Q5. The county-level cost-of-living-adjusted median household income was 2.8 times higher in Q5, as compared to Q1. Participants from the South made up more than 98% of people in Q1 but only 18.6% of people in Q5. Participants across economic strata entered the trial with similar clinical characteristics, including similar baseline blood pressures, GFR, potassium, fasting glucose, and numbers of antihypertensive medications prior to the trial. Compared to Q5, fewer participants in Q1 had a history of atherosclerotic cardiovascular disease, had ever smoked, or were on aspirin. A greater proportion of Q1 participants enrolled in the lipid trial portion of ALLHAT, as well. Participants across strata were equally likely to have type II diabetes. Additionally, there were similar numbers of participants in each treatment arm across socioeconomic strata, consistent with randomization.

Table 1. Baseline characteristics of study population across socioeconomic strata

Characteristic	County income level Q1[A] N (%) or Mean (SD)	Q2 N (%) or Mean (SD)	Q3 N (%) or Mean (SD)	Q4 N (%) or Mean (SD)	Q5 N (%) or Mean (SD)
Demographics					
Total participants	2169	3562	4916	6721	10458
Age	66.1 (8.4)	66.4 (7.4)	67.1 (7.7)	67.1 (7.4)	67.0 (7.5)
Female	1285 (59.2)	1645 (46.2)	2242 (45.6)	2899 (43.1)	4570 (43.7)
Race					
White	242 (11.2)	1353 (38.0)	3208 (65.3)	4121 (61.3)	6830 (65.3)
Black	1524 (70.3)	2189 (61.5)	1477 (30.0)	2432 (36.2)	2910 (27.8)
American Indian	1 (0.1)	6 (0.2)	20 (0.4)	9 (0.1)	31 (0.3)
Asian/Pacific Islander	1 (0.1)	2 (0.1)	15 (0.3)	26 (0.4)	322 (3.1)
Other	401 (18.5)	12 (0.3)	196 (4.0)	133 (2.0)	365 (3.5)
Hispanic	433 (20.0)	54 (1.5)	332 (6.8)	276 (4.1)	592 (5.7)
Education					
High School or Less	1855 (85.5)	2807 (78.8)	3383 (68.8)	4221 (62.8)	6090 (58.2)
College	163 (7.5)	499 (14.0)	978 (19.9)	1630 (24.3)	2924 (28.0)
Post-graduate	46 (2.1)	111 (3.1)	209 (4.3)	373 (5.6)	774 (7.4)
County characteristics					
COLA median income ($ k)	21.8 (2.4)	29.2 (1.1)	33.0 (1.3)	38.2 (1.6)	49.6 (8.7)
Number of counties	35	45	62	75	155
Number of participants by geographic region					
East	2 (0.1)	12 (0.3)	748 (15.2)	1687 (25.1)	2545 (24.3)
South	2134 (98.4)	3216 (90.3)	3399 (69.1)	2919 (43.4)	1941 (18.6)
Midwest	2 (0.1)	322 (9.0)	510 (10.4)	1892 (28.2)	3299 (31.6)
West	31 (1.4)	12 (0.3)	259 (5.3)	223 (3.3)	2673 (25.6)
Baseline clinical characteristics					
Systolic blood pressure (SBP)	145.0 (16.8)	145.3 (15.8)	145.7 (15.9)	147.5 (15.6)	145.7 (15.5)
Diastolic blood pressure (DBP)	83.7 (10.7)	82.9 (10.0)	82.3 (10.2)	84.1 (9.9)	83.7 (10.0)
GFR[B]	80.4 (21.8)	79.7 (21.3)	76.5 (19.2)	77.0 (19.6)	76.8 (18.9)
Creatinine[B]	1.0 (0.3)	1.1 (0.3)	1.0 (0.3)	1.0 (0.3)	1.0 (0.3)
Potassium[B]	4.3 (0.7)	4.3 (0.7)	4.3 (0.7)	4.3 (0.7)	4.4 (0.6)
Fasting glucose[B]	127.2 (61.7)	128.4 (63.0)	121.5 (55.3)	123.0 (58.7)	120.9 (53.1)
Receiving anti-hypertensive treatment					
On 1-2 meds >= 2 months	1831 (84.4)	3086 (86.6)	4270 (86.9)	5809 (86.4)	9080 (86.8)
On meds < 2 months	58 (2.7)	126 (3.5)	137 (2.8)	273 (4.1)	365 (3.5)
Untreated at baseline	280 (12.9)	350 (9.8)	509 (10.4)	639 (9.5)	1012 (9.7)
Qualifying risk factors for ALLHAT					
History of atherosclerotic CVD[C]	904 (41.7)	1706 (47.9)	2556 (52.0)	3786 (56.3)	5721 (54.7)
History of MI or stroke	309 (14.3)	876 (24.6)	1202 (24.5)	1731 (25.8)	2585 (24.7)
History of coronary revascularization	102 (4.7)	391 (11.0)	780 (15.9)	986 (14.7)	1693 (16.2)
Other atherosclerotic CVD	398 (18.4)	563 (15.8)	1117 (22.7)	1792 (26.7)	2720 (26.0)
History of ST dep/T-wave inv	286 (13.2)	448 (12.6)	472 (9.6)	768 (11.4)	1003 (9.6)
Type II diabetes	770 (35.5)	1450 (40.7)	1773 (36.1)	2333 (34.7)	3624 (34.7)
HDL-C <35 mg/dL twice in past 5 years	72 (3.3)	270 (7.6)	606 (12.3)	913 (13.6)	1491 (14.3)
LVH by ECG in past 2 years	640 (29.5)	674 (18.9)	692 (14.1)	977 (14.5)	1547 (14.8)
LVH by echocardiogram in past 2 years	86 (4.0)	117 (3.3)	231 (4.7)	231 (3.4)	568 (5.4)
History of CHD at baseline	14 (0.7)	41 (1.2)	71 (1.4)	81 (1.2)	132 (1.3)
BMI	30.4 (6.4)	29.9 (6.2)	29.5 (5.8)	30.0 (6.0)	29.7 (6.1)
Current aspirin use	568 (26.2)	1186 (33.3)	1916 (39.0)	2705 (40.3)	4089 (39.1)
Current estrogen supplementation[D]	146 (6.7)	240 (6.7)	471 (9.6)	518 (7.7)	1059 (10.1)
Lipid trial participants	720 (33.2)	922 (25.9)	1264 (25.7)	1362 (20.3)	2303 (22.0)
Cigarette Smoker					

Current	485 (22.4)	907 (25.5)	1114 (22.7)	1531 (22.8)	2173 (20.8)
Past	678 (31.3)	1338 (37.6)	2046 (41.6)	2963 (44.1)	4616 (44.1)
Never	1006 (46.4)	1317 (37.0)	1755 (35.7)	2227 (33.1)	3668 (35.1)
Treatment Group (antihypertensive randomization group)					
Chlorthalidone	994 (45.8)	1625 (45.6)	2254 (45.9)	3077 (45.8)	4774 (45.7)
Amlodipine	587 (27.1)	967 (27.2)	1333 (27.1)	1807 (26.9)	2851 (27.3)
Lisinopril	588 (27.1)	970 (27.2)	1329 (27.0)	1837 (27.3)	2833 (27.1)

Abbreviations: N, number of participants; SD, standard deviation; COLA, cost-of-living-adjusted median income; GFR, glomerular filtration rate; CVD, cardiovascular disease; MI, myocardial infarction; dep, depression; inv, inversion; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; ECG, electrocardiogram; CHD, coronary heart disease; BMI, body mass index.

[A] Q1 represents study participants who obtained care at clinical sites located in counties that fall into the lowest income quintile nationally. Q5 represents the highest income quintile.
[B] Numbers may not add to total because of missing data.
[C] History of atherosclerotic CVD contains the following categories: history of MI or stroke, history of coronary revascularization, history of major ST segment depression or T-wave inversion on any ECG in the past 2 years, and other atherosclerotic CVD.
[D] Applies to female participants only.

Visit and medication adherence

Table 2 shows differences in visit and medication adherence for participants across income strata. Participants in Q1 had lower visit adherence (29.7%) than those in Q5 (40.8%; $P<0.001$). Adequate medication adherence was also lower among participants in Q1 (36.3%) compared with participants in Q5 (55.6%; P<0.001). Overall, both visit and medication adherence were similar for participants in Q2-Q5, though participants in Q2 had the highest adequate visit adherence (44.6%) and medication adherence (61.1%). Importantly, data on medication adherence was missing in 21.8-38.0% of participants in each income quintile, while visit adherence was only missing in 0.8-1.5% of participants in each income quintile.

Table 2. Visit and medication adherence of study population across socioeconomic strata

Characteristic	County income level				
	Q1[A]	Q2	Q3	Q4	Q5
	N (%)	N (%)	N (%)	N (%)	N (%)
Total participants	2169	3562	4916	6721	10458
Visit adherence[B]					
< 80%	1498 (69.1)	1946 (54.6)	2812 (57.2)	4099 (61.0)	6085 (58.2)
≥ 80%	644 (29.7)	1588 (44.6)	2044 (41.6)	2524 (37.6)	4264 (40.8)
Missing	27 (1.2)	28 (0.8)	60 (1.2)	98 (1.5)	109 (1.0)
Medication adherence[C]					
Ever < 80%	557 (25.7)	610 (17.1)	930 (18.9)	1300 (19.3)	2289 (21.9)
Always ≥ 80%	788 (36.3)	2176 (61.1)	2766 (56.3)	3668 (54.6)	5810 (55.6)
Missing	824 (38.0)	776 (21.8)	1220 (24.8)	1753 (26.1)	2359 (22.6)

Abbreviations: Q1, lowest income quintile, Q5, highest income quintile; N, number of participants.

[A] Q1 represents study participants who obtained care at clinical sites located in counties that fall into the lowest income quintile nationally. Q5 represents the highest income quintile.

[B] Visit adherence was defined as the number of visits at six years divided by the number of expected visits. Adequate visit adherence was defined as attending ≥80% of expected visits.

[C] Adequate medication adherence was defined as always taking ≥80% of medications (self-reported by participants).

Blood pressure control

To assess blood pressure response across socioeconomic strata, we first compared absolute and relative changes in blood pressure between participants in the two income groups. Participants in Q1 on average experienced a smaller decrease in SBP (-2.6 mmHg) and DBP (-5.8 mmHg) than those in Q5 (SBP, -12.1 mmHg; DBP, -9.9 mmHg) during the trial (P<0.001). By the end of the trial, Q1 participants had an average blood pressure of 140/78; meanwhile, participants in Q5 had an average blood pressure of 133/74 (**Tables 3A-B**). We then calculated the unadjusted rates of participants achieving blood pressure control (<140/90 mmHg) across socioeconomic groups and treatment arms (**Tables 4A-D**). Blood pressure control was substantially lower in Q1 than in the

remaining income quintiles (Q2-5). Overall, by year 6 of the trial, 50.0% of participants in Q1 had attained blood pressure control, as compared with 70.2% of participants in Q5. Notably, the share of Q1 participants who attained blood pressure control plateaued at 50% after year 3 or 4; on the other hand, for Q5 participants, this percentage increased year after year. These results were similar for each of the treatment arms. Finally, we compared the likelihood of achieving blood pressure control in Q1 and Q5 participants, adjusting for baseline demographics, clinical characteristics, risk factors, and treatment arm, with Q5 serving as the reference group (**Table 5**). Participants in Q1 were significantly less likely to achieve blood pressure control than those in Q5 after 1 year in the trial (44.8% vs 57.3%; OR, 0.63; 95% CI, 0.56-0.70), a difference which persisted each year of the trial and even increased after 6 years (50.0% vs 69.3%; OR, 0.48; 95% CI, 0.37-0.63).

Table 3A. Mean blood pressure at years 1-6, stratified by income level

	County Income Level				
Outcome	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Systolic blood pressure					
Year 1	140.5 (18.6)	139.5 (16.9)	138.4 (17.3)	138.9 (16.2)	137.7 (16.0)
Year 2	140.8 (19.1)	138.2 (16.3)	137.0 (17.2)	137.6 (16.2)	136.7 (15.9)
Year 3	139.8 (18.4)	136.5 (16.6)	135.7 (16.6)	136.2 (16.2)	135.4 (15.5)
Year 4	138.5 (18.4)	136.3 (17.0)	134.9 (16.5)	135.1 (16.3)	134.1 (15.3)
Year 5	138.3 (19.0)	135.9 (16.7)	134.7 (16.7)	134.4 (15.6)	134.0 (14.9)
Year 6	139.9 (21.3)	135.2 (17.6)	134.6 (16.1)	133.4 (15.9)	133.2 (15.9)
Diastolic blood pressure					
Year 1	80.8 (11.1)	79.3 (9.9)	78.1 (10.1)	79.6 (9.8)	79.2 (9.8)
Year 2	80.0 (10.8)	78.4 (9.9)	77.3 (10.5)	78.2 (9.9)	78.1 (9.7)
Year 3	78.8 (10.5)	77.1 (10.0)	76.3 (10.3)	76.7 (10.3)	76.8 (9.6)
Year 4	78.7 (10.9)	76.6 (9.9)	75.5 (10.2)	75.9 (10.0)	76.0 (9.8)
Year 5	78.5 (11.1)	75.6 (10.0)	74.4 (10.6)	74.3 (10.0)	75.1 (9.8)
Year 6	78.2 (11.5)	73.8 (10.6)	73.6 (10.2)	73.4 (9.8)	74.0 (10.0)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; SD, standard deviation.

Table 3B. Mean change in blood pressure from baseline at years 1-6, stratified by income level

Outcome	County Income Level Q1 Mean (SD)	Q2 Mean (SD)	Q3 Mean (SD)	Q4 Mean (SD)	Q5 Mean (SD)
Change in systolic blood pressure compared with baseline					
Year 1	-4.0 (21.5)	-5.7 (19.2)	-7.1 (20.1)	-8.4 (19.3)	-7.8 (19.0)
Year 2	-3.2 (22.5)	-6.9 (19.6)	-8.5 (21.1)	-9.6 (19.2)	-8.7 (19.1)
Year 3	-4.3 (21.8)	-8.5 (20.5)	-9.8 (20.4)	-11.0 (20.0)	-9.9 (19.1)
Year 4	-5.3 (21.7)	-8.5 (20.9)	-10.5 (20.6)	-11.9 (20.0)	-11.1 (19.3)
Year 5	-4.6 (21.8)	-9.2 (20.7)	-11.1 (21.2)	-12.4 (19.9)	-11.3 (19.5)
Year 6	-2.6 (24.5)	-9.8 (21.6)	-10.9 (20.5)	-13.1 (20.1)	-12.1 (20.3)
Change in diastolic blood pressure compared with baseline					
Year 1	-2.7 (12.1)	-3.5 (10.6)	-4.2 (11.3)	-4.4 (10.9)	-4.4 (10.7)
Year 2	-3.4 (12.2)	-4.3 (11.2)	-5.0 (11.8)	-5.9 (11.1)	-5.5 (11.0)
Year 3	-4.7 (12.1)	-5.5 (11.8)	-6.0 (12.1)	-7.4 (11.6)	-6.8 (11.0)
Year 4	-4.9 (12.3)	-6.0 (11.7)	-6.7 (12.2)	-8.1 (11.4)	-7.5 (11.3)
Year 5	-5.2 (12.3)	-7.1 (11.6)	-7.8 (12.8)	-9.2 (11.3)	-8.6 (11.4)
Year 6	-5.8 (12.8)	-8.7 (12.0)	-8.4 (12.5)	-10.4 (11.4)	-9.9 (11.6)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; SD, standard deviation.

Table 4A. Blood pressure control[A] for all treatment groups combined, stratified by income level

Outcome	County Income Level Q1 N (%)	Q2 N (%)	Q3 N (%)	Q4 N (%)	Q5 N (%)
Year 1	786 (44.8)	1625 (51.2)	2299 (54.9)	3037 (53.2)	5284 (57.3)
Year 2	695 (45.2)	1578 (54.7)	2170 (57.6)	2916 (57.1)	5073 (59.6)
Year 3	657 (48.1)	1580 (59.8)	2099 (61.0)	2867 (61.3)	4950 (63.6)
Year 4	561 (50.2)	1489 (62.0)	1950 (63.4)	2734 (64.8)	4715 (67.1)
Year 5	344 (51.2)	1055 (63.9)	1224 (65.0)	1635 (67.5)	2874 (68.0)
Year 6	140 (50.0)	575 (64.3)	677 (64.7)	956 (71.6)	1499 (69.3)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; N, number of participants.

[A] Blood pressure control is represented as the unadjusted number or percentage of participants achieving blood pressure control (<140/90 mmHg) in years 1-6 of ALLHAT, for each income level.

Table 4B. Blood pressure control[A] for chlorthalidone treatment arm

Outcome	County Income Level				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	N (%)	N (%)	N (%)	N (%)	N (%)
Year 1	394 (48.9)	787 (53.5)	1103 (57.1)	1490 (56.7)	2522 (59.7)
Year 2	356 (50.7)	783 (57.9)	1049 (60.0)	1432 (60.2)	2437 (62.1)
Year 3	325 (51.8)	780 (63.2)	997 (62.7)	1360 (62.8)	2317 (64.6)
Year 4	274 (53.4)	736 (65.8)	911 (63.5)	1299 (67.0)	2196 (67.9)
Year 5	153 (50.2)	510 (67.3)	577 (65.9)	779 (69.8)	1392 (71.1)
Year 6	63 (50.0)	278(69.7)	310 (64.0)	454 (72.2)	694 (70.2)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; N, number of participants.

[A] Blood pressure control is represented as the unadjusted number or percentage of participants achieving blood pressure control (<140/90 mmHg) in years 1-6 of ALLHAT, for each income level.

Table 4C. Blood pressure control[A] for amlodipine treatment arm

Outcome	County Income Level				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	N (%)	N (%)	N (%)	N (%)	N (%)
Year 1	197 (41.8)	455 (52.7)	610 (53.6)	799 (52.5)	1472 (58.3)
Year 2	171 (41.0)	427 (54.9)	580 (56.3)	788 (57.6)	1368 (58.7)
Year 3	179 (47.7)	437 (60.0)	574 (60.5)	782 (61.8)	1411 (65.7)
Year 4	148 (47.4)	395 (59.8)	553 (64.8)	740 (64.2)	1336 (68.4)
Year 5	100 (54.1)	308 (65.1)	349 (65.1)	444 (67.1)	800 (68.3)
Year 6	37 (46.3)	162 (60.9)	203 (67.4)	254 (71.3)	405 (68.3)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; BP, N, number of participants.

[A] Blood pressure control is represented as the unadjusted number or percentage of participants achieving blood pressure control (<140/90 mmHg) in years 1-6 of ALLHAT, for each income level.

Table 4D. Blood pressure control[A] for lisinopril treatment arm

Outcome	County Income Level Q1 N (%)	Q2 N (%)	Q3 N (%)	Q4 N (%)	Q5 N (%)
Year 1	195 (40.8)	383 (45.7)	586 (52.5)	748 (48.1)	1290 (52.3)
Year 2	168 (40.2)	368 (48.6)	541 (54.8)	696 (51.2)	1268 (56.1)
Year 3	153 (42.1)	363 (53.5)	528 (58.5)	725 (58.4)	1222 (59.7)
Year 4	139 (47.4)	358 (57.5)	486 (61.5)	695 (61.6)	1183 (64.3)
Year 5	91 (50.0)	237 (56.4)	298 (63.1)	412 (63.8)	682 (62.2)
Year 6	40 (54.1)	135 (59.0)	164 (62.8)	248 (70.7)	400 (68.8)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; N, number of participants.

[A] Blood pressure control is represented as the unadjusted number or percentage of participants achieving blood pressure control (<140/90 mmHg) in years 1-6 of ALLHAT, for each income level.

Table 5. Association between income and blood pressure control across income strata

Outcome	County Income Level Q1 % with BP <140/90 mmHg	Q5 % with BP <140/90 mmHg	Low Income Effect Risk-Adjusted OR[A] OR (95% CI)
Year 1	44.8	57.3	0.63 (0.56-0.70)
Year 2	45.2	59.6	0.58 (0.52-0.66)
Year 3	48.1	63.6	0.55 (0.49-0.62)
Year 4	50.2	67.1	0.53 (0.46-0.60)
Year 5	51.2	68.0	0.51 (0.43-0.61)
Year 6	50.0	69.3	0.48 (0.37-0.63)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; OR, odds ratio; BP, blood pressure; CI, confidence interval.

[A] Risk-adjusted OR represents odds of achieving blood pressure control (< 140/90 mmHg), with the highest income quintile, Q5, serving as the reference group. Model adjusts for treatment group, age, sex, baseline SBP and DBP, and qualifying risk factors for ALLHAT (BMI[B], history of MI or stroke, history of coronary revascularization, history of CHD at baseline, other ASCVD, participation in lipid-lowering trial, type II diabetes, history of major ST depression or T-wave inversion[B], aspirin use, HDL-C < 35 mg/dL, LVH by ECG, LVH by echocardiogram[B], cigarette smoking[B], and estrogen supplementation[B]).
[B] A minority of study participants have missing values for these risk factors. The missing values for these participants were imputed.

Among black participants, we observed similar trends in attainment of target blood pressure between economic strata (**Table 6A**); black participants receiving care in

Q1 were less likely than black participants receiving care in Q5 to achieve blood pressure control after 1 year (OR, 0.70; 95% CI, 0.61-0.81) and each year through year 6 (OR, 0.53; 95% CI, 0.38-0.74). Similarly, among clinical sites located in the South, participants in Q1 were less likely to achieve blood pressure control each year including year 1 (OR, 0.66; 95% CI, 0.56-0.77) and year 6 (OR, 0.51; 95% CI, 0.34-0.76) compared with participants in Q5 (**Table 6B**). In the exploratory analyses, which included visit adherence in the model, results were unchanged (**Table 7**). Participants in Q1 were less likely to achieve blood pressure control, even when visit adherence was taken into account, at year 1 (OR, 0.63; 95% CI, 0.57-0.70) and year 6 (OR, 0.48; 95% CI, 0.36-0.62).

Table 6A. Association between income and blood pressure control among black ALLHAT participants across socioeconomic strata

Outcome	County Income Level Q1 % with BP <140/90 mmHg	County Income Level Q5 % with BP <140/90 mmHg	Low Income Effect Risk-Adjusted OR[A] OR (95% CI)
Year 1	43.5	51.7	0.70 (0.61-0.81)
Year 2	44.8	52.8	0.73 (0.62-0.85)
Year 3	46.4	57.6	0.65 (0.55-0.76)
Year 4	50.8	61.3	0.69 (0.58-0.82)
Year 5	49.1	63.7	0.55 (0.44-0.69)
Year 6	46.5	63.2	0.53 (0.38-0.74)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; OR, odds ratio; BP, blood pressure; CI, confidence interval.

[A] Risk-adjusted OR represents odds of achieving blood pressure control (< 140/90 mmHg), with the highest income quintile, Q5, serving as the reference group. Model adjusts for treatment group, age, sex, baseline SBP and DBP, and qualifying risk factors for ALLHAT (BMI[B], history of MI or stroke, history of coronary revascularization, history of CHD at baseline, other ASCVD, participation in lipid-lowering trial, type II diabetes, history of major ST depression or T-wave inversion[B], aspirin use, HDL-C < 35 mg/dL, LVH by ECG, LVH by echocardiogram[B], cigarette smoking[B], and estrogen supplementation[B]).

[B] A minority of study participants have missing values for these risk factors. The missing values for these participants were imputed.

Table 6B. Association between income and blood pressure control among ALLHAT participants living in the South across socioeconomic strata

Outcome	County Income Level Q1 % with BP <140/90 mmHg	County Income Level Q5 % with BP <140/90 mmHg	Low Income Effect Risk-Adjusted OR[A] OR (95% CI)
Year 1	44.5	57.6	0.66 (0.56-0.77)
Year 2	44.9	57.0	0.72 (0.61-0.85)
Year 3	47.5	60.4	0.63 (0.53-0.75)
Year 4	49.9	63.7	0.61 (0.51-0.74)
Year 5	50.9	62.3	0.67 (0.52-0.86)
Year 6	50.0	69.7	0.51 (0.34-0.76)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; OR, odds ratio; BP, blood pressure; CI, confidence interval.

[A] Risk-adjusted OR represents odds of achieving blood pressure control (< 140/90 mmHg), with the highest income quintile, Q5, serving as the reference group. Model adjusts for treatment group, age, sex, baseline SBP and DBP, and qualifying risk factors for ALLHAT (BMI[B], history of MI or stroke, history of coronary revascularization, history of CHD at baseline, other ASCVD, participation in lipid-lowering trial, type II diabetes, history of major ST depression or T-wave inversion[B], aspirin use, HDL-C < 35 mg/dL, LVH by ECG, LVH by echocardiogram[B], cigarette smoking[B], and estrogen supplementation[B]).

[B] A minority of study participants have missing values for these risk factors. The missing values for these participants were imputed.

Table 7. Association between income and blood pressure control across socioeconomic strata, adjusted for visit adherence

Outcome	County Income Level Q1 % with BP <140/90 mmHg	Q5 % with BP <140/90 mmHg	Low Income Effect Risk-Adjusted OR[A] OR (95% CI)
Year 1	44.8	57.3	0.63 (0.57, 0.70)
Year 2	45.2	59.6	0.58 (0.52, 0.66)
Year 3	48.1	63.6	0.55 (0.49, 0.63)
Year 4	50.2	67.1	0.53 (0.46, 0.60)
Year 5	51.2	68.0	0.52 (0.44, 0.63)
Year 6	50.0	69.3	0.48 (0.36, 0.62)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; OR, odds ratio; BP, blood pressure; CI, confidence interval.

[A] Risk-adjusted OR represents odds of achieving blood pressure control (< 140/90 mmHg), with the highest income quintile, Q5, serving as the reference group. Model adjusts for treatment group, age, sex, baseline SBP and DBP, qualifying risk factors for ALLHAT (BMI[B], history of MI or stroke, history of coronary revascularization, history of CHD at baseline, other ASCVD, participation in lipid-lowering trial, type II diabetes, history of major ST depression or T-wave inversion[B], aspirin use, HDL-C < 35 mg/dL, LVH by ECG, LVH by echocardiogram[B], cigarette smoking[B], and estrogen supplementation[B]), and six year visit adherence[B].
[B] A minority of study participants have missing values for these risk factors. The missing values for these participants were imputed.

Cardiovascular outcomes

We then compared rates of pre-specified time-to-event cardiovascular outcomes that occurred throughout the trial, across socioeconomic strata and treatment arms (**Tables 8A-D**). The rate of the primary outcome, CHD, was lower in Q1 than in Q5 overall (6.9% vs 9.6%); this was consistent across the treatment groups. Fewer participants in Q1 (compared with Q5) received coronary revascularization (4.2% vs 8.7%) or were hospitalized or treated for angina (6.7% vs 12.4%). However, after calculating the likelihood of attaining these cardiovascular outcomes and adjusting for baseline characteristics and treatment arm, there was no significant difference in CHD, between participants in Q1 and Q5 (HR, 0.93; 95% CI, 0.78-1.11) (**Table 9**). Moreover,

after risk adjustments were made, participants in Q1 experienced significantly higher all-cause mortality (HR, 1.25; 95% CI, 1.10-1.41), heart failure hospitalization/mortality (HR, 1.26; 95% CI, 1.03-1.55) and ESRD (HR, 1.86; 95% CI, 1.26-2.73). Participants in Q1 also had lower likelihood of angina treatment/hospitalization (HR, 0.70; 95% CI, 0.59-0.83), combined CVD (HR, 0.89; 95% CI, 0.81-0.99) and coronary revascularization (HR, 0.71; 95% CI, 0.57-0.89). There were no significant differences in combined CHD, stroke, diagnosis of new onset heart failure, or peripheral arterial disease.

Table 8A. Adverse time-to-event unadjusted cardiovascular outcomes, for all treatment groups combined, separated by income level

Outcome	County Income Level				
	Q1 N (%)	**Q2** N (%)	**Q3** N (%)	**Q4** N (%)	**Q5** N (%)
Primary outcome					
CHD[A]	150 (6.9)	374 (10.5)	494 (10.0)	699 (10.4)	1000 (9.6)
Secondary Outcomes					
All-cause mortality	342 (15.8)	596 (16.7)	833 (16.9)	1066 (15.9)	1571 (15.0)
Combined CHD[B]	264 (12.2)	631 (17.7)	932 (19.0)	1269 (18.9)	1868 (17.9)
Stroke	107 (4.9)	220 (6.2)	247 (5.0)	332 (4.9)	492 (4.7)
Combined CVD[C]	475 (21.9)	1065 (29.9)	1521 (30.9)	1987 (29.6)	3077 (29.4)
Components of secondary outcomes					
Heart Failure	140 (6.5)	290 (8.1)	358 (7.3)	522 (7.8)	739 (7.1)
Hospitalized/fatal heart failure	125 (5.8)	218 (6.1)	290 (5.9)	447 (6.7)	572 (5.5)
Angina[D]	146 (6.7)	379 (10.6)	632 (12.9)	825 (12.3)	1299 (12.4)
Coronary revascularization	91 (4.2)	275 (7.7)	469 (9.5)	625 (9.3)	909 (8.7)
Peripheral arterial disease[E,F,G]	48 (2.2)	153 (4.3)	209 (4.3)	204 (3.0)	397 (3.8)
ESRD	38 (1.8)	62 (1.7)	62 (1.3)	130 (1.9)	120 (1.1)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; N, number of participants; CHD, coronary heart disease; CVD, cardiovascular disease; ESRD, end-stage renal disease.

[A] CHD: fatal CHD or nonfatal MI combined.
[B] Combined CHD: Fatal CHD, coronary revascularization, hospitalized angina.
[C] Combined CVD: Combined CHD, stroke, other treated angina, HF, and peripheral artery disease.
[D] Angina includes both hospitalized and treated angina.
[E] Peripheral arterial disease (PAD) includes both hospitalized and treated PAD.
[F] The following secondary outcomes are not included in this table: cancer, hospitalized for GI bleeding.
[G] The following component of secondary outcomes was not included in this table: angina (hospitalized).

Table 8B. Adverse cardiovascular outcomes for chlorthalidone treatment arm

Outcome	County Income Level Q1 N (%)	Q2 N (%)	Q3 N (%)	Q4 N (%)	Q5 N (%)
Primary outcome					
CHD[A]	74 (7.4)	162 (10.0)	225 (10.0)	327 (10.6)	468 (9.8)
Secondary Outcomes					
All-cause mortality	171 (17.2)	270 (16.6)	378 (16.8)	498 (16.2)	734 (15.4)
Combined CHD[B]	125 (12.6)	275 (16.9)	428 (19.0)	567 (18.4)	860 (18.0)
Stroke	49 (4.9)	89 (5.5)	94 (4.2)	160 (5.2)	231 (4.8)
Combined CVD[C]	214 (21.5)	451 (27.8)	694 (30.8)	883 (28.7)	1374 (28.8)
Components of secondary outcomes					
Heart Failure	54 (5.4)	112 (6.9)	162 (7.2)	216 (7.0)	276 (5.8)
Hospitalized/fatal heart failure	48 (4.8)	83 (5.1)	135 (6.0)	188 (6.1)	224 (4.7)
Angina[D]	64 (6.4)	172 (10.6)	287 (12.7)	358 (11.6)	578 (12.1)
Coronary revascularization	46 (4.6)	115 (7.1)	206 (9.1)	271 (8.8)	399 (8.4)
Peripheral arterial disease[E]	19 (1.9)	73 (4.5)	105 (4.7)	96 (3.1)	183 (3.8)
ESRD[F,G]	16 (1.6)	20 (1.2)	30 (1.3)	65 (2.1)	53 (0.9)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; N, number of participants; CHD, coronary heart disease; CVD, cardiovascular disease; ESRD, end-stage renal disease.

[A] CHD: fatal CHD or nonfatal MI combined.
[B] Combined CHD: Fatal CHD, coronary revascularization, hospitalized angina.
[C] Combined CVD: Combined CHD, stroke, other treated angina, HF, and peripheral artery disease.
[D] Angina includes both hospitalized and treated angina.
[E] Peripheral arterial disease (PAD) includes both hospitalized and treated PAD.
[F] The following secondary outcomes are not included in this table: cancer, hospitalized for GI bleeding.
[G] The following component of secondary outcomes was not included in this table: angina (hospitalized).

Table 8C. Adverse cardiovascular outcomes for amlodipine treatment arm

Outcome	County Income Level Q1 N (%)	Q2 N (%)	Q3 N (%)	Q4 N (%)	Q5 N (%)
Primary outcome					
CHD[A]	41 (7.0)	107 (11.1)	136 (10.2)	203 (11.2)	248 (8.7)
Secondary Outcomes					
All-cause mortality	85 (14.5)	159 (16.4)	221 (16.6)	284 (15.7)	417 (14.6)
Combined CHD[B]	68 (11.6)	173 (17.9)	256 (19.2)	363 (20.1)	483 (16.9)
Stroke	31 (5.3)	50 (5.2)	64 (4.8)	88 (4.9)	123 (4.3)
Combined CVD[C]	128 (21.8)	292 (30.2)	412 (30.9)	558 (30.9)	833 (29.2)
Components of secondary outcomes					
Heart Failure	45 (7.7)	99 (10.2)	106 (8.0)	106 (9.0)	239 (8.4)
Hospitalized/fatal heart failure	41 (7.0)	78 (8.1)	85 (6.5)	142 (7.9)	184 (6.5)
Angina[D]	38 (6.5)	100 (10.3)	168 (12.6)	230 (12.7)	349 (12.2)
Coronary revascularization	27 (4.6)	77 (8.0)	136 (10.2)	179 (9.9)	251 (8.8)
Peripheral arterial disease[E]	14 (2.4)	35 (3.6)	48 (3.6)	52 (2.9)	99 (3.5)
ESRD[F,G]	12 (2.0)	26 (2.7)	15 (1.1)	31 (1.7)	36 (1.3)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; N, number of participants; CHD, coronary heart disease; CVD, cardiovascular disease; ESRD, end-stage renal disease.

[A] CHD: fatal CHD or nonfatal MI combined.
[B] Combined CHD: Fatal CHD, coronary revascularization, hospitalized angina.
[C] Combined CVD: Combined CHD, stroke, other treated angina, HF, and peripheral artery disease.
[D] Angina includes both hospitalized and treated angina.
[E] Peripheral arterial disease (PAD) includes both hospitalized and treated PAD.
[F] The following secondary outcomes are not included in this table: cancer, hospitalized for GI bleeding.
[G] The following component of secondary outcomes was not included in this table: angina (hospitalized).

Table 8D. Adverse cardiovascular outcomes for lisinopril treatment arm

Outcome	County Income Level Q1 N (%)	Q2 N (%)	Q3 N (%)	Q4 N (%)	Q5 N (%)
Primary outcome					
CHD[A]	35 (6.0)	105 (10.8)	133 (10.0)	169 (9.2)	284 (10.0)
Secondary Outcomes					
All-cause mortality	86 (14.6)	167 (17.2)	234 (17.6)	284 (15.5)	420 (14.8)
Combined CHD[B]	71 (12.1)	183 (18.9)	248 (18.7)	339 (18.5)	525 (18.5)
Stroke	27 (4.6)	81 (8.4)	89 (6.7)	84 (4.6)	138 (4.9)
Combined CVD[C]	133 (22.6)	322 (33.2)	415 (31.2)	546 (29.7)	870 (30.7)
Components of secondary outcomes					
Heart Failure	41 (7.0)	79 (8.1)	90 (6.8)	143 (7.8)	224 (7.9)
Hospitalized/fatal heart failure	36 (6.1)	57 (5.9)	69 (5.2)	117 (6.4)	164 (5.8)
Angina[D]	44 (7.5)	107 (11)	177 (13.3)	237 (12.9)	372 (13.1)
Coronary revascularization	18 (3.1)	83 (8.6)	127 (9.6)	175 (9.5)	259 (9.1)
Peripheral arterial disease[E]	15 (2.6)	45 (4.6)	56 (4.2)	56 (3.0)	115 (4.1)
ESRD[F,G]	10 (1.7)	16 (1.6)	17 (1.3)	34 (1.9)	41 (1.4)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; N, number of participants; CHD, coronary heart disease; CVD, cardiovascular disease; ESRD, end-stage renal disease.

[A] CHD: fatal CHD or nonfatal MI combined.
[B] Combined CHD: Fatal CHD, coronary revascularization, hospitalized angina.
[C] Combined CVD: Combined CHD, stroke, other treated angina, HF, and peripheral artery disease.
[D] Angina includes both hospitalized and treated angina.
[E] Peripheral arterial disease (PAD) includes both hospitalized and treated PAD.
[F] The following secondary outcomes are not included in this table: cancer, hospitalized for GI bleeding.
[G] The following component of secondary outcomes was not included in this table: angina (hospitalized).

Table 9. Association between income and cardiovascular outcomes across income strata

Outcome	County Income Level Q1 Incidence, %	Q5 Incidence, %	Low Income Effect Risk-Adjusted HR[A] HR (95% CI)
Primary outcome			
CHD[B]	6.9	9.6	0.93 (0.78-1.11)
Secondary outcomes			
All-cause mortality	15.8	15.0	1.25 (1.10-1.41)
Combined CHD[C]	12.2	17.9	0.89 (0.78-1.01)
Stroke	4.9	4.7	1.16 (0.93-1.45)
Combined CVD[D]	21.9	29.4	0.89 (0.81-0.99)
Components of secondary outcomes			
Heart Failure	6.5	7.1	1.07 (0.88-1.29)
Hospitalized/fatal heart failure	5.8	5.5	1.26 (1.03-1.55)
Angina[E]	6.7	12.4	0.70 (0.59-0.83)
Coronary revascularization	4.2	8.7	0.71 (0.57-0.89)
Peripheral arterial disease[F]	2.2	3.8	0.87 (0.64-1.18)
ESRD[G,H]	1.8	1.1	1.86 (1.26-2.73)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; ESRD, end-stage renal disease.

[A] Risk-adjusted hazard ratios represent likelihood of having an adverse cardiovascular event, with the highest income quintile, Q5, serving as the reference group. Model adjusts for treatment group, age, sex, baseline SBP and DBP, and qualifying risk factors for ALLHAT (BMI[I], history of MI or stroke, history of coronary revascularization, history of CHD at baseline, other ASCVD, participation in lipid-lowering trial, type II diabetes, history of major ST depression or T-wave inversion[I], aspirin use, HDL-C < 35 mg/dL, LVH by ECG, LVH by echocardiogram[I], cigarette smoking[I], and estrogen supplementation[I]).
[B] CHD: fatal CHD or nonfatal MI combined.
[C] Combined CHD: Fatal CHD and nonfatal MI combined, coronary revascularization, hospitalized angina.
[D] Combined CVD: Combined CHD, stroke, other treated angina, HF, and peripheral artery disease.
[E] Angina includes both hospitalized and treated angina.
[F] Peripheral arterial disease (PAD) includes both hospitalized and treated PAD.
[G] The following secondary outcomes from ALLHAT are not included: cancer, hospitalized for GI bleeding.
[H] The following components of secondary outcomes was not included in this table: angina (hospitalized).
[I] A minority of study participants have missing values for these risk factors. The missing values for these participants were imputed.

Among black participants, those in Q1 still had higher all-cause mortality after risk adjustment (HR, 1.24; 95% CI, 1.06-1.44), and greater (although not significant)

hospitalized/fatal heart failure (HR, 1.29; 95% CI, 0.99-1.68) and ESRD (HR, 1.47; 95% CI, 0.91-2.36). They also had lower angina treatment/hospitalization (HR, 0.69; 95% CI, 0.55-0.87) and coronary revascularization (HR, 0.69; 95% CI, 0.48-0.99) (**Table 10A**). There were no significant differences between income groups among black participants for other outcomes, including CHD, combined CHD, stroke, combined CVD, new-onset heart failure, or peripheral arterial disease. Among participants in the South, the risk of adverse cardiovascular outcomes followed similar trends as the overall study population (**Table 10B**). Southern participants in Q1 were more likely to experience all-cause mortality (HR, 1.14; 95% CI, 0.96-1.36) and ESRD (HR, 1.57; 95% CI, 0.87-2.82), and less likely to have angina (HR, 0.81; 95% CI, 0.64-1.03) and receive coronary revascularization (HR, 0.76; 95% CI, 0.57-1.01). However, none of these findings were statistically significant.

Table 10A. Association between income and time to cardiovascular outcomes among black ALLHAT participants across socioeconomic strata

Outcome	County Income Level Q1 Incidence, %	Q5 Incidence, %	Low Income Effect Risk-Adjusted HR[A] HR (95% CI)
Primary outcome			
CHD[B]	7.0	8.5	0.90 (0.71-1.14)
Secondary outcomes			
All-cause mortality	17.8	15.9	1.24 (1.06-1.44)
Combined CHD[C]	11.2	14.4	0.89 (0.74-1.07)
Stroke	5.2	5.5	1.07 (0.81-1.41)
Combined CVD[D]	22.1	26.8	0.90 (0.79-1.03)
Components of secondary outcomes			
Heart Failure	6.9	6.7	1.18 (0.92-1.50)
Hospitalized/fatal heart failure	6.0	5.3	1.29 (0.99-1.68)
Angina[E]	6.3	10.3	0.69 (0.55-0.87)
Coronary revascularization	2.8	4.8	0.69 (0.48-0.99)
Peripheral arterial disease[F]	2.1	3.3	0.75 (0.49-1.13)
ESRD[G,H]	2.0	1.6	1.47 (0.91-2.36)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; ESRD, end-stage renal disease.

[A] Risk-adjusted hazard ratios represent likelihood of having an adverse cardiovascular event, with the highest income quintile, Q5, serving as the reference group. Model adjusts for treatment group, age, sex, baseline SBP and DBP, and qualifying risk factors for ALLHAT (BMI[I], history of MI or stroke, history of coronary revascularization, history of CHD at baseline, other ASCVD, participation in lipid-lowering trial, type II diabetes, history of major ST depression or T-wave inversion[I], aspirin use, HDL-C < 35 mg/dL, LVH by ECG, LVH by echocardiogram[I], cigarette smoking[I], and estrogen supplementation[I]).

[B] CHD: fatal CHD or nonfatal MI combined.

[C] Combined CHD: Fatal CHD and nonfatal MI combined, coronary revascularization, hospitalized angina.

[D] Combined CVD: Combined CHD, stroke, other treated angina, HF, and peripheral artery disease.

[E] Angina includes both hospitalized and treated angina.

[F] Peripheral arterial disease (PAD) includes both hospitalized and treated PAD.

[G] The following secondary outcomes from ALLHAT are not included: cancer, hospitalized for GI bleeding.

[H] The following component of secondary outcomes was not included in this table: angina (hospitalized).

[I] A minority of study participants have missing values for these risk factors. The missing values for these participants were imputed.

Table 10B. Association between income and time to cardiovascular event outcomes among participants in ALLHAT living in the South across socioeconomic strata

Outcome	County Income Level Q1 Incidence, %	Q5 Incidence, %	Low Income Effect Risk-Adjusted HR[A] HR (95% CI)
Primary outcome			
CHD[B]	6.8	9.0	0.94 (0.73-1.19)
Secondary outcomes			
All-cause mortality	15.8	14.7	1.14 (0.96-1.36)
Combined CHD[C]	12.1	16.4	0.94 (0.78-1.13)
Stroke	5.0	4.2	1.22 (0.89-1.68)
Combined CVD[D]	21.8	26.7	0.92 (0.80-1.06)
Components of secondary outcomes			
Heart Failure	6.4	7.3	0.93 (0.71-1.20)
Hospitalized/fatal heart failure	5.8	5.7	1.09 (0.82-1.45)
Angina[E]	6.7	10.5	0.81 (0.64-1.03)
Coronary revascularization	4.3	8.1	0.76 (0.57-1.01)
Peripheral arterial disease[F]	2.2	3.3	1.02 (0.68-1.55)
ESRD[G,H]	1.7	1.1	1.57 (0.87-2.82)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; ESRD, end-stage renal disease.

[A] Risk-adjusted hazard ratios represent likelihood of having an adverse cardiovascular event, with the highest income quintile, Q5, serving as the reference group. Model adjusts for treatment group, age, sex, baseline SBP and DBP, and qualifying risk factors for ALLHAT (BMI[I], history of MI or stroke, history of coronary revascularization, history of CHD at baseline, other ASCVD, participation in lipid-lowering trial, type II diabetes, history of major ST depression or T-wave inversion[I], aspirin use, HDL-C < 35 mg/dL, LVH by ECG, LVH by echocardiogram[I], cigarette smoking[I], and estrogen supplementation[I]).

[B] CHD: fatal CHD or nonfatal MI combined.

[C] Combined CHD: Fatal CHD and nonfatal MI combined, coronary revascularization, hospitalized angina.

[D] Combined CVD: Combined CHD, stroke, other treated angina, HF, and peripheral artery disease.

[E] Angina includes both hospitalized and treated angina.

[F] Peripheral arterial disease (PAD) includes both hospitalized and treated PAD.

[G] The following secondary outcomes from ALLHAT are not included: cancer, hospitalized for GI bleeding.

[H] The following component of secondary outcomes was not included in this table: angina (hospitalized).

[I] A minority of study participants have missing values for these risk factors. The missing values for these participants were imputed.

In exploratory analyses adjusting for visit adherence, results also followed similar trends, but all-cause mortality (HR, 1.03; 95% CI, 0.91-1.16) and heart failure treatment/hospitalizations (HR, 1.19; 95% CI, 0.97-1.46) were no longer significantly greater among Q1 participants (**Table 11**). Other outcomes were unchanged from the main findings. ESRD was still significantly higher among Q1 participants (HR, 1.70; 95% CI, 1.16-2.51). As before, participants in Q1 were less likely to have angina (HR, 0.69; 95% CI, 0.58-0.83) and receive coronary revascularization (HR, 0.70; 95% CI, 0.56-0.88).

Table 11. Association between income and time to cardiovascular event outcomes across economic strata, adjusted for visit adherence

Outcome	County Income Level Q1 Incidence, %	Q5 Incidence, %	Low Income Effect Risk-Adjusted HR[A] HR (95% CI)
Primary outcome			
CHD[B]	6.9	9.6	0.87 (0.72,1.04)
Secondary outcomes			
All-cause mortality	15.8	15.0	1.03 (0.91,1.16)
Combined CHD[C]	12.2	17.9	0.85 (0.74,0.97)
Stroke	4.9	4.7	1.06 (0.85,1.32)
Combined CVD[D]	21.9	29.4	0.86 (0.78,0.95)
Components of secondary outcomes			
Heart Failure	6.5	7.1	1.01 (0.84,1.23)
Hospitalized/fatal heart failure	5.8	5.5	1.19 (0.97,1.46)
Angina[E]	6.7	12.4	0.69 (0.58,0.83)
Coronary revascularization	4.2	8.7	0.70 (0.56,0.88)
Peripheral arterial disease[F]	2.2	3.8	0.86 (0.63,1.17)
ESRD[G,H]	1.8	1.1	1.70 (1.16,2.51)

Abbreviations: Q1, lowest income quintile; Q5, highest income quintile; HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; ESRD, end-stage renal disease.

[A] Risk-adjusted hazard ratios represent likelihood of having an adverse cardiovascular event, with the highest income quintile, Q5, serving as the reference group. Model adjusts for treatment group, age, sex, baseline SBP and DBP, qualifying risk factors for ALLHAT (BMI[i], history of MI or stroke, history of coronary revascularization, history of CHD at baseline, other ASCVD, participation in lipid-lowering trial, type II diabetes, history of major ST depression or T-wave inversion[i], aspirin use, HDL-C < 35 mg/dL, LVH by ECG, LVH by echocardiogram[i], cigarette smoking[i], and estrogen supplementation[i]), and six year visit adherence[i].
[B] CHD: fatal CHD or nonfatal MI combined.
[C] Combined CHD: Fatal CHD and nonfatal MI combined, coronary revascularization, hospitalized angina.
[D] Combined CVD: Combined CHD, stroke, other treated angina, HF, and peripheral artery disease.
[E] Angina includes both hospitalized and treated angina.
[F] Peripheral arterial disease (PAD) includes both hospitalized and treated PAD.
[G] The following secondary outcomes from ALLHAT are not included: cancer, hospitalized for GI bleeding.
[H] The following components of secondary outcomes was not included in this table: angina (hospitalized).
[I] A minority of study participants have missing values for these risk factors. The missing values for these participants were imputed.

Discussion

In a large, nationally dispersed RCT of antihypertensive therapy, we observed significant variation in blood pressure control and cardiovascular outcomes according to the socioeconomic context in which clinical care was provided. Participants receiving care in the lowest income sites as compared with the highest income sites had significantly worse blood pressure control with antihypertensive medications, irrespective of medication study arm, and higher rates of heart failure hospitalizations, ESRD and mortality, even after adjusting for demographic and clinical characteristics. These disparities persisted in subgroup analyses of black participants and those living in the South, populations that have previously been shown to have worse hypertension-associated cardiovascular outcomes, demonstrating that socioeconomic context is independently important.

Although the impact of socioeconomic context on health outcomes is known, the differences in clinical outcomes in this study are notable because they occurred in the context of a large RCT, which typically affords participants equal access to health care resources by 1) assigning them to standardized protocols in which study medications are provided free-of-charge, and 2) providing specific guidelines for the intensification of medication and provision of follow-up visits. Moreover, although ALLHAT enrolled a geographically and ethnically diverse population, only 8% of participants came from the lowest income sites, whereas 38% came from the highest income sites, potentially reducing the generalizability of trial findings to low socioeconomic populations and opportunities to more fully understand the disparities observed in this analysis.

The association between sociodemographic characteristics and hypertension is already well-documented. Studies have shown that improvement in cardiovascular risk factors over recent decades in the U.S. have disproportionately occurred among adults of higher socioeconomic strata (14, 109). Moreover, RCTs of pharmacologic interventions for hypertension have demonstrated an effect of person-level demographic factors, such as race, gender and income, on cardiovascular outcomes, though not of community-level factors (83, 85, 99, 104, 110). However, to date no studies have examined the influence of socioeconomic context on outcomes resulting from antihypertensive treatment. While the relationships between person-level factors and hypertension outcomes are important to understand and address, inattention to the effect of community-level factors related to socioeconomic context may obscure data that are important for achieving improved cardiovascular outcomes.

Specifically, the differences in outcomes we report here may be a result of differences in any number of factors: a community's health behaviors (e.g., diet, exercise, smoking, and alcohol trends), clinical factors (e.g., access to care, quality of care, visit adherence, or medication adherence), or other aspects of the physical and social environment (e.g., housing, access to healthy foods and exercise, neighborhood violence, social cohesion), all of which may impact pharmacoeffectiveness. The disparities we observed may also indicate that despite the efforts of RCTs to standardize treatment protocols, clinical sites in low-resource areas may have fewer overall resources and capabilities than those in wealthier areas. Unfortunately, existing methods are limited in their ability to isolate the impact of these other factors on clinical outcomes in RCTs. To

rectify this problem, future clinical trials could attempt to explicitly measure these factors.

Notably, participants in the lowest income sites had lower visit adherence than those in the highest income sites, though the reasons for this are uncertain. Visit adherence may have a direct effect on outcomes, wherein attending visits more frequently provides more opportunities to improve outcomes. Additionally, factors associated with adherence to visits (e.g. access to transportation, health behaviors, physician-patient relationship) may indirectly impact outcomes. Our exploratory analysis adjusting for six year visit adherence supports the possibility that fidelity to the protocol may explain some of the difference in outcomes between the two groups. However, differences in blood pressure control were unchanged even after adjusting for visit adherence. In addition, visit and medication adherence were actually highest in the second-lowest income quintile, making it difficult to determine to what extent adherence varies by socioeconomic context. Regrettably, in this study, medication adherence was inadequately assessed and was missing in up to 1/3 of participants, limiting interpretation of findings. Ultimately, to fully understand the importance of adherence on outcomes in clinical trials, more rigorous and complete assessment of adherence is needed, especially to the study medication.

Potentially related, participants in the lowest income sites were significantly less likely to receive coronary revascularization, or be hospitalized or treated for angina. An aggregate outcome, combined CVD (which contains coronary revascularization and angina as subcomponents) was also less likely among participants in the lowest income sites. These findings were contrary to our hypothesis that socioeconomic context could

lead to greater cardiovascular morbidity and related procedural interventions. However, given the racial and socioeconomic make-up of participants in low income sites, it is plausible that these findings reflect differences in presentation by race (111) or in utilization patterns related to cultural norms for seeking care, access to care, or other unmeasured factors. Numerous studies have previously shown that patients who are black or of lower socioeconomic status are less likely to receive procedures such as coronary revascularization (112-114). Unfortunately, in this study design we are not able to discern whether these outcomes are measuring the effect of true differences in cardiovascular events or differences in access to or quality of care beyond the standardized protocol of the trial.

Furthermore, we noted a substantial difference in blood pressure control, visit and medication adherence, coronary revascularization, and hospitalized or treated angina between the lowest income quintile and the other four income quintiles, which tended to have greater similarities in outcomes. The median household income in the lowest income quintile was $21,800; by comparison, the federal poverty level – the threshold or minimum level of income one would need to secure the necessities of life – for a family of 4 was $17,050 in the year 2000 (115). This suggests that participants in the lowest income sites obtained care (and potentially lived) in some of the poorest counties in the United States, where many people may not have access to sufficient resources to secure these basic necessities. Similar to the federal poverty level, there may exist a threshold of resources that a community must surpass in order for its inhabitants to be able to live and maintain their health or well-being, and thus achieve hypertension outcomes similar to those of less deprived communities. Although the existing literature has been unable to

shed further light on this question, the relationship between area-level socioeconomic deprivation and hypertension outcomes is likely more nuanced, in that different communities may require different resources in order to thrive.

In addition, we attempted to separate the effects of race from socioeconomic context by assessing socioeconomic groups within racial strata and found that the results did not differ from the overall findings; however, participants in the lowest income sites were more likely to be black, making it difficult to fully distinguish any association of race with cardiovascular outcomes. Genetic factors may contribute to racial disparities in these outcomes. For example, participants in the lowest income sites, many of whom were minorities, had significantly higher risk for ESRD. Genetic studies have demonstrated that there is a higher prevalence of a high-risk variant of the apoliprotein L-1 (APOL1) gene in African-American populations, as compared to European-American populations (116). The presence of this allele is associated with a higher risk of end-stage kidney disease attributed to hypertension. Differences in clinical characteristics may also play a role. Previous studies have shown that black participants are less likely to achieve blood pressure control, even in the context of RCTs (including ALLHAT), possibly due to difference in medication and visit adherence (85, 110, 117-119). Such racial disparities in outcomes are well documented for other cardiovascular conditions, as well, with some studies identifying economic and social barriers affecting blood pressure control in black patients (60, 120-122). One such factor, residential neighborhood segregation has been associated with changes in systolic blood pressure, indicating that there may be overlap between individual factors such as race and contextual factors such as disparate household incomes within a community (123).

Additionally, structural racism leading to increased stress exposure and reactivity, along with differences in quality of care may impact outcomes, though are seldom assessed in RCTs (124). The United States has a long history of socioeconomic and racial disparities, and there may be shared or unique structural disparities leading to these differences that we may not be able to capture, given the limitations of existing clinical trial data. Thus, other methodological approaches may be necessary to better and more rigorously encapsulate the effect of these complex and interrelated disparities on health outcomes.

Geographic location may also be important. Nearly all participants in the lowest income sites lived in the South, consistent with studies dating back as far as the 1980s which have shown that poverty rates have historically been higher in the South than in the rest of the country (125). Prior studies from ALLHAT demonstrate that living in the South predicted a lower likelihood of achieving blood pressure control as compared with other U.S. and non-U.S. regions (85). This finding is consistent with a recent CDC report that indicated worse hypertension control in Southern states thought to be part of the "stroke belt" (119). Another secondary analysis of ALLHAT found that there were no statistically significant differences in medication adherence among patients based on the geographic region in which their clinical site was located (117). However, both of these studies considered broad geographic regions encompassing many counties, rather than singular counties. Other studies of hypertension and cardiovascular RCTs have evaluated the effect of geographic region on study outcomes, but these studies were conducted at the country level or at similarly broad regional geographic levels, potentially obscuring heterogeneity within large geographic areas (126-135). Moreover, many RCTs do not

enroll enough patients to be able to study geographic effect at a more granular level. Still, these studies are consistent with our findings and demand that more work be done to understand the nature of regional disparities in hypertension outcomes, which persist even within large, robust RCTs.

Limitations

There are several limitations to this study. First, it is possible that the county in which a clinical site is located may differ from a participant's county of residence. While distance from residence to medical care varies by rurality, in an RCT, we assumed that people who decided to participate in the study would live reasonably close. More importantly, counties differ in size and may comprise several socioeconomic contexts; though we did not have data to study the effect of socioeconomic context at a more granular level (such as census tract), our use of county level measures would tend to bias our findings towards the null, as it dilutes the true income status of a community. Third, area income may not be a perfect indicator of social risk factors, such as neighborhood violence or access to healthy foods, which can impact health outcomes. However, county-level analyses can serve as a reasonable proxy for the amount of resources available in a community and can be important for directing policy interventions and resources.

Fourth, though it is the largest completed randomized hypertension trial, the data from ALLHAT is now nearly 20 years old and progress may have been made in the interim in addressing disparities in hypertension outcomes. Fifth, although the population enrolled in ALLHAT was indeed socio-demographically and geographically diverse, only

12% of U.S. counties were represented by the clinical sites in this study, potentially limiting the generalizability of our findings. Sixth, although we performed subgroup analyses for black participants and those living in the South, we were unable to perform similar stratified analyses for participants of other races or those living in other regions. This was due to an insufficient number of participants with these identifiers in either the top or bottom income quintiles. Given that clinical sites in the South were more likely to be low income and enroll black participants, we may not have been able to fully discern the effects of race and geography from socioeconomic context. Seventh, because we did not have access to unique location or clinic identifiers for each patient, we were unable to account for correlation of outcomes within an area. Though this may have resulted in overnarrow confidence intervals, none of our key findings were marginal and thus it is reasonable to expect that they would have been unchanged even if we had accounted for such correlation. Last, data on medication adherence was insufficient to include in our secondary analyses, making it more difficult to delineate the extent to which medication adherence may have attenuated outcomes. However, medication adherence was likely influenced by contextual factors which were not measured in this trial.

Conclusions

Observational studies have previously shown that socioeconomic context is associated with hypertension and worse hypertension outcomes. This study extends these findings to the largest randomized clinical trial of antihypertensive treatment, in which participants had equal access to resources afforded by such a trial. Although participants across income strata were appropriately randomized to the main treatment arms, we

observed disparities in participant characteristics and visit and medication adherence across socioeconomic strata, and found that study enrollment favored participants from higher socioeconomic strata. We also observed disparities in blood pressure control, heart failure morbidity, ESRD, all-cause mortality and coronary revascularization across socioeconomic strata, even after controlling for medication treatment arm, demographics, and clinical characteristics; furthermore, there may be some suggestion that visit adherence may have impacted outcomes.

These results bring into question whether the anticipated benefits of antihypertensive therapy, derived from landmark trials such as ALLHAT, are truly generalizable to all communities within the U.S. The heterogeneity in treatment effect by socioeconomic context observed in this study is important knowledge because it may have implications for guideline recommendations and clinical decision making. Our findings thus underscore the importance of measuring socioeconomic context in RCTs and suggest the need to develop better methods to capture contextual data and understand their association with outcomes, so that findings from clinical trials can inform treatment guidelines and also be generalized to populations encountered in everyday clinical practice.

Moreover, to attain equity in hypertension outcomes, we must not only work to implement guideline recommendations for antihypertensive therapy, but we must also work within communities to address the underpinnings of disparities by socioeconomic context. In the context of RCTs, investigators of future trials of antihypertensive medications should make more concerted efforts to recruit socioeconomically diverse participants or offer additional resources to participants in disadvantaged areas to

eliminate disparities in trial outcomes and ensure that study results are meaningful for these populations. In clinical practice, physicians could offer additional support or resources to patients from under-resourced communities seeking treatment for hypertension; physicians and researchers might encourage elected leaders and professional societies at the local, state, and federal levels to focus on contextual factors impacting cardiovascular outcomes. For example, public policy efforts and grants could focus on addressing the underlying factors that disproportionally affect low socioeconomic communities today and which may relate to hypertension and cardiovascular outcomes, including improving local infrastructure to support exercise and access to healthy foods, reduce stress, improve neighborhood safety, and increase access to medicines, primary care, mental health resources, and more. Finally, recognition of and sensitivity to the contextual socioeconomic factors influencing response to antihypertensive medication can support more effective, patient- and community-centered approaches that go beyond the guidelines to manage hypertension.

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