Blood Pressure and Medication Adherence Among Patients in the Emergency Department

By

Candace D. McNaughton, MD MPH

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Approved:

Christianne L. Roumie, MD MPH

Edmond K. Kabagambe, DVM, MS, PhD

Phillip Levy, MD MPH

Dandan Liu, PhD

To the patients who seek care in the ED and the clinicians who care for them.

To my Grandmother, who was the impetus for this work.

To my husband, family and mentors, for their unfailing support.

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LIST OF ABBREVIATIONS

ACEP, American College of Emergency Physicians
ARMS, adherent to refills and medications survey
AUC, area under the curve
BMI, body mass index
BP, blood pressure
CI, confidence interval
CMR, cardiac magnetic resonance imaging
DAG, directed acyclic graph
DBP, diastolic blood pressure
ED, Emergency Department
eGFR, estimated glomerular filtration rate
HCTZ, hydrochlorothiazide
LC-MS, liquid chromatography mass spectrometry
LOWESS, locally weighted scatterplot smoothing
MAP, mean arterial pressure
MEMS, medication event monitoring system
MPR, medication possession ratio
No., number
PDC, proportion of days covered
PIV, peripheral intravenous catheter
OR, odds ratio
ROC, receiver operator characteristics
SBP, systolic blood pressure
SD, standard deviation
VUMC, Vanderbilt University Medical Center
WSU, Wayne State University

CHAPTER 1: BACKGROUND

Despite the clear health importance of hypertension, little is known regarding whether elevated blood pressure (BP) in the emergency department (ED) setting can or should be addressed. Furthermore, non-adherence to BP lowering medications remains an uncertain but possible contributor to those elevated BP measurements in the ED setting. In Aims 1 through 3, we address these knowledge and evidence gaps, to guide future work.

Hypertension

Despite great strides, hypertension remains an important chronic disease and public health problem.[1] Worldwide, hypertension affects more than 1 billion adults and is the number one risk factor for cardiovascular and all-cause disease burden and mortality.[2-5] In the United States in 2014, more than 37 million Americans have high blood pressure,[6-10] with associated costs of $46 billion per year.[11] Hypertension control and adherence to blood pressure medication remains an important national goal. HealthyPeople2020 set forth the following goals[12]:

1. Increase the proportion of adults with hypertension who are taking their prescribed medications to lower their blood pressure, and
2. Increase the proportion of adults with hypertension whose blood pressure is under control (typically defined as <140/90mmHg).

According to the Centers for Disease Control and Prevention, "improved hypertension control…require[s] an expanded effort and an increased focus on blood pressure from health-care systems, clinicians, and individuals."[13] Delays of even six weeks in achieving BP control are associated with increased risk of acute cardiovascular events and death.[5]

Aim 1 (Chapter 2) addresses this critical need to better understand the ability of BP measured during an acute care visit in the ED to predict the trajectory of BP after that visit. The focus is on patients who are moderately healthy and who therefore may benefit most from early interventions to address high BP. This piece is a critical first step in the ability to identify patients who are both most likely to benefit from an antihypertensive adherence intervention (see below) and also at relatively high risk for poor cardiovascular outcomes.[14-18] This aim focuses on patients with low to intermediate health risk factors, i.e., patients without severe comorbidities such as end stage renal disease or cancer or multiple ED visits. Patients with low to intermediate risk may be more likely to have modifiable risk factors but also may be less likely to access the healthcare system before developing disease. Thus, the potential opportunities for improving health are great.

Blood Pressure and Hypertension in the Emergency Department

Emergency Department: Potential Role in Screening for Elevated Blood Pressure

ED visits can be viewed as missed opportunities to impact chronic disease control and complement care of a chronic illness.[19-21] The ED is a common access point into the healthcare system, with more than 120 million visits annually among 20% of Americans.[22] As more patients gain access to the healthcare system, ED visits for chronic conditions, including hypertension, are rising rapidly.[22-25] More than 80% of frequent ED users have health insurance and access to primary care; furthermore, patients who frequently seek ED care are also more likely to use their primary care frequently.[26,27] ED visits specifically for hypertension are also common, nearly 5 million visits per year and rising rapidly as more newly insured and chronically ill patients seek care in the ED.[22-24] ED visits for and related to

hypertension have risen more than 25% since 2006.[28] Moderately or significantly elevated blood pressure (BP) is noted in 15-25% of all ED visits.[29,30] ED visits with elevated BP are opportunities to address chronic disease management, which could be used to improve long-term cardiovascular outcomes and reduce healthcare utilization.

ED visits are teachable moments that can be leveraged to maximize adherence to medications among patients who are who are likely to gain benefit and who are at risk for poor cardiovascular outcomes.[31-34] Given that even 6 weeks of uncontrolled blood pressure is associated with increased risk of cardiovascular events and death,[5] a small improvement in antihypertensive adherence or blood pressure achieved through lifestyle or medication changes addressed during an ED visit may impact cardiovascular outcomes on a population level.

The potential role of the ED in evaluation, management, and coordination with primary care for chronic hypertension is not well understood.[17] More than 80% of ED patients have health insurance and reported access to a primary care provider, and between 10-30% of primary care patients seek ED care annually.[35] The ED is uniquely suited to provide teachable moments,[31-34] particularly if action is initiated in the ED rather than deferring interventions. Among the unique, high-risk primary care patients who seek ED care, even incremental improvements in adherence, self-care, or blood pressure are important on a population level and will advance our understanding of barriers to achieving disease control.

Blood Pressure: Clinic versus Other Healthcare Locations

Given that 10-20% of American's seek care in the ED annually,[22,36] many of whom only access the healthcare system through the ED, the ED has long been looked at as a potential location for hypertension screening,[20,37-40] as well as for other diseases or conditions.[41,42] To date, however, few studies have evaluated the relationship between ED and clinic BPs in large, longitudinal populations. Measurement error, regression to the mean, anxiety, pain, and acute events are cited as potential threats to validity of BP measured in the ED.

Similar concerns have been expressed regarding the validity of BPs measured on the day of surgery, where elevated BP is often attributed to anxiety, lack of oral intake, and not taking medication (as instructed) on the day of surgery. A recent study by Schonberg et al. found that while SBP and DBP on the day of surgery are slightly higher (5.5 mmHg for SBP, 1.5 mmHg for DBP) when compared to clinic BP measured within 6 months following the day of surgery, these differences were small, and a single perioperative SBP greater than or equal to 146 mmHg had 95.9% specificity (95% confidence interval [CI] 94.4 to 97.0) for identifying uncontrolled hypertension, defined as primary SBP greater than or equal to 140 mm Hg, with sensitivity of 26.8% (95% CI 22.0 to 32.0) in a VA population.[43] Pearson's correlation coefficients for SBP on the day of surgery vs. primary care was 0.41 (95% CI 0.37 to 0.44) and 0.48 (95% CI 0.45 to 0.51) for DBP. Interestingly, addition of patient characteristics did not improve model fit beyond use of two elevated perioperative BPs.

Emergency Department versus Clinic Blood Pressure

In the ED setting, four studies have focused on whether elevated blood pressure readings obtained in the ED are also elevated at follow-up.[37,44-46] Three of these studies formed the primary basis for the American College of Emergency Physicians (ACEP) 2006 Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients With Asymptomatic Hypertension in the Emergency Department,[47] which included a Level B recommendation for referral for possible hypertension and blood pressure management "[i]f blood pressure measurements are persistently elevated" in the ED and a Level C recommendation that "[p]atients with a single elevated blood pressure reading may

require further screening for hypertension in the outpatient setting."

The following studies have small sample sizes and may lack sufficient power to detect potentially clinically important relationships between ED and clinic BP. In addition, these studies were conducted among heterogeneous patient populations, making generalizations difficult. It is also not known, for example, what proportion of patients in these studies had access to primary care and what proportion followed up with their primary care provider. The available prior studies described below are also summarized in the Chapter 1 Appendix.

Backer et al[44] enrolled 407 patients without hypertension who sought care at an ED or minor injury clinic with elevated blood pressure during that clinical encounter (2.8% of all visits). "[E]levated blood pressure" was not specifically defined but is assumed to have been anything over a BP of 140/90 mmHg). Patients enrolled were asked to return for repeated BP measurements. Only 65% of subjects returned for repeat BP measurements. Among the 201 subjects with follow up BP, higher initial BP was associated with higher follow up BP: among those with initial BP 140-159/90-99 mmHg, 64.4% had elevated follow up BP; among those with initial BP 160-179/100-109 mmHg, 77.1% had elevated follow up BP; and of those with initial BP ≥180/110 mmHg, 97.1% had elevated follow up BP. Compared with blood pressures taken during the ED visit, matched blood pressures taken before or after were not statistically different. There was no evidence for a difference in BP by location (ED vs. minor injury clinic), pain, or degree of elevation at the initial visit.

In 1984, Chernow et al[37] enrolled 239 patients with an ED SBP greater than 159 mmHg or DBP greater than 94 mmHg in an observational study to determine the relationship with BP after the ED visit. Patients with and without diagnosed hypertension were enrolled. Follow-up, via letter, was successful for only 107 (45%) of those enrolled. Of these, 35% had BP>159/95 mmHg based on the single follow-up BP, 33% had a SBP between 140-159 mmHg or DBP between 90 and 94 mmHg, and 32% had a BP <140/90 mmHg. Overall 68 (64%) have no prior diagnosis of hypertension, and 42 of these 68 (62% of those without a history of hypertension, 34% of those with follow-up) "had follow-up blood pressure measurements requiring further attention." Of the 27 subjects with diagnosed and treated hypertension, 23 had a BP ≥140/90 mmHg at the time of follow up. There was no obvious difference in pain among patients who had normal vs. elevated BP at the time of follow up. The authors note that their findings were similar to those in the clinic setting.[48]

In their very brief publication in 1987, Slater et al[45] enrolled 60 subjects with no known diagnosis of hypertension and a single elevated BP in the Accident and Emergency Department; they excluded patients who were admitted to the hospital from the ED. They were able to obtain follow up BP in 53; of these, 15 were found to have DBP ≥95 mmHg, fourteen of whom were being treated for hypertension at the time the paper was published.

More recently, Shiber-Ofer et al. enrolled patients with at least two ED BP measurements of at least 140/90 mmHg and no prior diagnosis of hypertension in an observational study.[46] Of the 195 patients enrolled and followed, 142 (73%) were diagnosed with hypertension following the index ED visit, with a mean follow up time of 30.14 months (sd 15.96 months). There was no evidence for a difference in BP by chief complaint for the index ED visit, although the pain score was higher among those who were not diagnosed with hypertension (3.55 +/- 3.02 compared to 2.34 +/- 3.04, respectively; P=.04). Elevated DBP and low pain scores were found to predict higher follow up BP.

Blood Pressure Measurement and Variability in the Emergency Department

Lack of evidence guiding the potential role of the ED in chronic management of hypertension is further complicated by prior work that suggests that elevated BP in the ED may decrease during an ED visit. Cienke et al. (2011) measured BP in the ED for 76 patients and found a statistically

significant decline in SBP over two hours only for patients who presented with a SBP ≥160/100 mmHg; the authors note there was more variability in BP than anticipated using manual BP measurement method without standard patient positioning.[49] During a randomized trial of furosemide plus chlorpromazine, dihydralazine, or diazoxide, patients with the highest BPs also experienced the greatest decrease after a period of rest.[50] Others have found evidence for regression to the mean after the initial, triage ED BP measurement; an 11.6 mm Hg decline in DBP, or 4.4 mmHg greater decline than predicted. This additional reduction in DBP was attributed to regression to the mean and overcoming the "alerting reaction" associated with "white coat hypertension".[51]

In 1987, Mamon et al[20] published their work to develop a protocol for detection and follow up of patients with and without diagnosed hypertension who sought care in an urban ED. Of the 203 patients enrolled, 71 had elevated blood pressure based on the initial ED measurement. The authors noted that the most conservative estimate of blood pressure was the mean of three BP measurements. Post hoc analysis suggested that while the protocol required obtaining three measure of BP, 68 of 71 of the patients with high blood pressure during their ED visit would have been identified using the mean of two BP measurements. The authors concluded that a minimum of two ED BPs was sufficient for screening for elevated BP in the ED.

The work by Edmonds et al[52] focused on the reproducibility of BP measured manually in the ED. They enrolled 140 ED patients and compared vital signs values measured by two independent observers. Blood pressure was measured manually, using the auscultation of Korotkoff sounds. They found a mean difference of 1.3 mmHg between observers, an expected range of agreement of 24.2 mmHg in systolic blood pressure. For patients with a SBP≥160 mmHg, the kappa was 0.75 (95% CI 0.56 to 0.93); for those with DBP≥90 mmHg, kappa was 0.74 (95% CI 0.60 to 0.89).

Multiple studies in the ED and other acute care settings have not demonstrated clear relationships between pain or anxiety with blood pressure (summarized in the Chapter 1 Appendix).[53-57] In their work, Marco et al[54] reviewed ED records of 1,063 patients with painful conditions (25% nephrolithiasis, 23% fractures) and found no clinically significant associations between triage pain scores and heart rate, blood pressure or respiratory rate. In 2008, Tanabe et al.[56] found that among 156 ED patients without hypertension but who had a minimum of two BPs ≥140/90 mmHg during their ED visit, 51% had a mean home BP ≥140/90 mmHg. The relationship between pain and difference between ED and home BP was small and in the opposite direction of that expected (r=0.18, p=0.03). In the prehospital setting, Bendall et al in 2011[55] evaluated the relationship between pain and vital signs using prehospital records of over 53,000 patients complaining of acute pain. They found no clinically important associations between pain and BP using correlations or ordinal regression. Among all their analyses, the only relationship between pain and BP was detected among patients aged ≥65 years, for whom having SBP≥140 mmHg was associated with 14% increased odds of having severe pain, or a pain score of 8-10. Prior diagnosis of hypertension was not available.

Summary and Significance BP in the ED

Taken together, prior work suggests that two elevated measure of BP in the ED setting may indicate higher risk of elevated BP after an ED visit. High BP in the ED setting should not be attributed solely to pain or anxiety. There remain, however, important knowledge gaps regarding the relationship between ED measured BP and chronic BP, which Chapter 2, Aim 1 begins to address.

Medication Adherence

Antihypertensive medication adherence is crucial for BP control.[58] Accurate measurement of antihypertensive adherence is vital to identify change in related clinical outcomes.[59] Until recently, measuring antihypertensive adherence in the ED has been limited to self-report, which is influenced by recall bias, social desirability bias, and lack of an established patient-provider relationship.[58,60-62] As a result little is known about medication adherence – in particular antihypertensive adherence—among patients who seek ED care. There are no formal recommendations for identification, evaluation, or treatment of inadequate medication adherence in the ED. To overcome limitations of existing measures of antihypertensive adherence in the ED this proposal evaluates a validated mass spectrometry assay as a direct measure of medication adherence in the ED settings.

Medication adherence is "the degree to which patients take medication as prescribed," and therefore includes multiple behaviors: filling medication prescriptions, taking the medication as instructed (correct dose, correct number of times per day, correct time of day), and persistence in medication taking.[58,60] As a result, a single measurement technique that completely describes every aspect of medication adherence has been difficult to develop, despite considerable interest and effort.[63-70] Commonly used adherence measures, including surveys, often address only one of these components of adherence. Therefore relatively low or modest correlations among different measures of adherence may be explained in part by the fact that they are measuring different aspects of adherence, e.g., refill adherence vs. administration adherence. In addition, optimal measures of adherence are likely to be different for drugs of different half-lives and prescription durations. As a result, comprehensive and accurate measurement of antihypertensive adherence, particularly in the ED setting, has proven difficult.

Directly Observed Therapy

Directly observed therapy, in which the patient is observed ingesting medication by a healthcare or trained professional is typically considered the gold standard measure for medication adherence.[71-73] Also known as "continuous dose observations," directly observed therapy is reserved for conditions such as tuberculosis, where medication non-adherence has significant public health consequences. It is worth noting, however, that even directly observed therapy can be manipulated by patients, for example, by "cheeking" medication.[74]

Indirect Measures of Medication Adherence

Because directly observed therapy is not feasible under most research or outpatient clinical conditions, alternative measures have been developed. The most commonly used measures are indirect, that is, they do not directly measure levels of drug in the body. Indirect measures of adherence include surveys, which rely on self-reported behaviors, medication refill data, pill bottles with electronic records to indicate the number of times the bottle has been opened, and pill counts.

Each of these methods has limitations. Pill bottle caps have been shown to overestimate adherence. For example, adherence measured by pill bottle caps for seizure medications have no association with drug serum concentration.[65] Surveys require time for administration, have been validated for use only in research settings, and rely on accurate recall and reporting. Complete prescription refill data is difficult to obtain and assumes that pharmacy filled medications are ingested. As a general rule, the indirect adherence measures overestimate medication adherence compared to directly observed therapy, and correlation among the multiple measures of adherence is poor to moderate.[75]

Two study populations are used for Aims 2 and 3, which compare direct measures of adherence to indirect; and also seeks to understands the predictive validity of direct adherence measures. Population A and Population B, include multiple measures of indirect adherence. In Population A, medication adherence was measured by a survey, patient report, and an assay during an ED visit. In Population B, medication adherence was measured by a survey, pill counts, and an assay at Week 16 and Week 52 as part of a randomized controlled study.

Medication Adherence Surveys

The Adherence to Refills and Medications Survey (ARMS) was developed, piloted tested, and administered to 435 patients with coronary heart disease who were recruited from an urban primary care clinic.[76] The ARMS consists of 12 questions on a 4-point Likert-like scale ("None – Some – Most – All"). After reverse scoring the last item, items are summed to generate a single score, where a lower score indicates greater adherence. Prior work has utilized a threshold of ARMS score >12 to indicate low medication adherence.[77] Among primary care patients, there may be ceiling effect for measurement of adherence by the ARMS; in prior work, as much as 80% of primary care patients reported complete adherence, or a perfect score of 12.[77] The ARMS was validated by comparison against the Morisky scale (Spearman's rho -0.65, $p<0.01$), medication refill adherence (i.e., pharmacy records, where available; the ARMS correlated more strongly than the Morisky), and blood pressure measurements (patients with low ARMS were more likely to have controlled DBP). Validation also included test-retest, reliability (Cronbach's alpha of 0.81), and primary factor analysis. According to Lexile analysis, the reading level of the test is less than the eighth grade. The ARMS addresses the domains patient-reported **medication-taking** and **medication-refill** behaviors.

The Morisky 4-item Medication Adherence Questionnaire[78] consists of 4 items with yes/no answers. As with the ARMS, a lower Morisky score is indicates higher medication adherence. Internal reliability in the initial validation study revealed a Cronbach's alpha of 0.61; lower adherence measured by the Morisky score predicts BP control at 2 and 5 years. The following threshold has been developed to categorize Morisky scores: >2 = low adherence, 1-2 = medium adherence, 0 = high adherence. The single question, "How many days in the past week have you missed any blood pressure pills?" which was drawn from the Morisky survey, has also been used as a sensitive indicator of any degree of non-adherence when the response is >0 days.[79] As with the ARMS, the Morisky questionnaire addresses the domains of patient-reported **medication-taking** and **medication refill** behaviors.

Patients in Population A completed the ARMS, while patients in Population B have completed the Morisky 4-item Medication Adherence Questionnaire.

Pill Counts, Medication Event Monitoring Systems, and Prescription Refills

Pill counts are often used in clinical trials to measure adherence and have been validated against Medication Event Monitoring Systems (MEMS).[80] They require patient participation, can be manipulated to overestimate adherence, and do not directly measure the accuracy of medication taking (e.g., time of day). Patients in Population B completed pill counts at the Week 16 follow up visit. Pill counts are reported as the proportion of pills ingested compared to pills that should have been ingested. Using pill counts, high medication adherence is defined as a pill count ratio greater than or equal to 0.80.

The following measures of medication are described for completeness, but they are not available in the data collected from subjects in either Population A or B.

MEMS are child-resistant pill bottle caps that record the date and times when pill bottles are opened. The caps can wirelessly transfer data and can display the number of doses taken in the past 24 hours.[81,82] The systems are relatively expensive, can be manipulated by patients to overestimate adherence, and do not measure adherence to ingestion of medication.

Prescription refill data is also used as an estimate of medication adherence.[75] This method assumes that refilled medications are taken as prescribed and uses a lapse in refills to indicate non-adherence. Use of this measure requires full access to prescription data, which is difficult to obtain in many health systems. In addition, variable refill intervals can make it difficult to compare refill data across patients and health care providers. Despite these limitations, refill adherence has been associated with all cause and cardiovascular mortality.[83] Prescription refill data can be used to compute two closely related measures of adherence – the medication possession ratio (MPR)[84-87] and the proportion of days covered (PDC). The maximum PDC is 1.0, which is used to indicate complete adherence; the MPR can exceed 1.0.[88-90] For population based analyses, the PDC measure has been put forwards as the preferred measurement of refill adherence because it is based on fill dates and days supply for each prescription medication, therefore allowing non-persistence to be measured[91-94]. Both the PDC and MPR were designed for use on population levels, rather than individual patient level measures of adherence, primarily for quality of care metric reporting.

Direct Measures of Medication Adherence: Drug Presence and Drug Levels

Direct measurement of medication adherence using plasma, serum, or urine assays have been used for more than 30 years. Their use in clinical practice, however, is primarily as a way to detect deviation from recommended behaviors, for example, urine drug screens to detect illicit drug use. Such measures have been used rarely in other clinical settings, although interest in such measures is gaining popularity.[95]

The liquid chromatography mass spectrometry assay used to measure adherence for Aims 2 and 3 was developed to detect and, where possible, quantify levels of 19 antihypertensive drugs using plasma or serum. The assay has been validated among 294 patients who were administered cardiovascular medication by a healthcare professional (Table 1).[96] The assay is sensitive and specific for accurate and reliable detection of drug presence within 24-48 hours of most recent drug administration, depending on the drug half-life, which varies by formulation, and whether the drug was in steady state at the time of blood draw.

Table 1: Sensitivity and Specificity of the Mass Spectrometry Assay, Among 294 Hospitalized Patients

	Drug Name	$T_{1/2}$	Sensitivity	Specificity
1	**Amlodipine**	33h	0.98	0.99
2	**Atenolol**	6.5h	1.00	1.00
3	**Captopril**	1.9h	0.25	1.00
4	**Carvedilol**	7-10h	1.00	1.00
5	**Clonidine**	12-16h	1.00	0.99
6	**Diltiazem**	3-4.5h	1.00	0.99
7	Enalapril	36h	1.00	1.00
8	**HCTZ**	6-15h	1.00	1.00
9	**Hydralazine**	7-16h	0.97	1.00
10	**Lisinopril**	12.6h	1.00	0.99
11	Losartan	1.5-2h	1.00	1.00
12	**Metoprolol**	2.5-7.5h*	0.99	1.00
13	**Nifedipine**	2-7h	1.00	1.00
14	**Propranolol**	5.2-7.5h	1.00	1.00
15	**Ramipril**	>50h	1.00	1.00
16	Telmisartan	24h	1.00	1.00
17	**Valsartan**	6h	1.00	0.98
18	**Verapamil**	2.8-7.4h	1.00	0.99

$T_{1/2}$, plasma elimination half-life in hours; HCTZ, hydrochlorothiazide; * varies by metabolizer phenotype; **bold** indicates use as inclusion criteria for Population A in Aims 2 and 3

While the assay is sensitive and specific for detection of multiple cardiovascular medications among clinical samples, several aspects of the assay are important to note.

First, assay results should be interpreted in light of specific medication half-lives and variations in drug absorption, metabolism, and elimination. For example, the half-life of captopril is only 1.9 hours; thus the assay has low sensitivity although the specificity is 1.00. Losartan also has a short half-life of several hours and is better detected in plasma samples compared to serum samples. Thus, low levels of captopril or losartan must be interpreted in light of their half-lives, in contrast to other drugs such as warfarin or chlorthalidone, which are detectible in the blood for weeks after the last ingestion. Drug degradation and storage conditions are important for drugs including simvastatin and niacin (not of interest for these analysis), as well as nifedipine (which must be kept out of UV light in order to prevent degradation). The level of quantitation is determined for each batch and is determined by stock and diluted solutions.

Drug absorption, metabolism, and elimination vary between individuals and within individuals over time. Factors that are known to influence pharmacodynamics include co-ingestants (other medications, tobacco, alcohol, diet changes), vital signs (e.g., fever), and body composition. These factors together and individually influence the level of drug detected in plasma and serum for specific medications.

The mass spectrometry assay used in Aims 2 and 3 was developed and validated using both plasma and serum samples. Sensitivity and specificity for plasma and serum are shown in the Chapter Appendix. Overall, assay performance was better using plasma samples.

Second, used as a direct measure of medication adherence, the assay represents an estimate at a *single point in time*, unless measured serially. Interpretation of the assay presumes that detection of medication is representative of long-term adherence and that drug levels correspond to medication adherence, with minimal impact from drug absorption or metabolism or other drug-drug interactions.

Third, the assay has not previously been utilized as a measure of adherence, nor has it been used in the ED setting. There are, however, several potential advantages to use of the assay over other currently available methods. Use of this assay is not limited by recall or social desirability biases. There is little to no subject burden, particularly among patients already undergoing blood draws. Because only 100 microliters of plasma or serum are needed to perform the assay, left over clinical blood can be used. In the ED, more than 90% of patients receive a peripheral IV (PIV), and 5 tubes of blood are drawn in anticipation of possible laboratory studies; left-over blood from these tubes is ideal for the assay. Performing the assay does not require additional subject time, in contrast to use of surveys, which require between 5 and 10 minutes per survey. Although the assay provides a relatively short-term measure of adherence, 24-48 hours for most medications, this is also true for self-reported measures of adherence, which have been shown to change over time.[97]

Medication Adherence and Blood Pressure: ED setting, clinic setting

The relationship between measured antihypertensive adherence and BP during an ED visit is not known. Prior work has shown that among clinic patients, lower medication adherence is associated with poor clinical outcomes, including elevated BP, adverse cardiovascular events, and ED visits.[6,60,98-103] General medication non-adherence is associated with increased risk of ED visits.[103-110] Whether these findings can be generalized to the relationship between antihypertensive adherence and BP during an ED visit is not known. Until development of the cardiovascular mass spectrometry assay described in Aim 2, the cross sectional evaluation of the relationship between antihypertensive adherence and BP in the ED was not feasible due to concerns about the accuracy of patient-reported medication adherence in the ED.

A relationship between adherence and BP during an ED visit would provide evidence for emergency medicine providers that high BP and medication non-adherence in the ED should be identified and addressed by either treatment or close outpatient follow up, as appropriate, rather than dismissed as an isolated series of high BP measurements attributable to the ED setting. Currently, there is very little evidence to guide clinical practice addressing blood pressure and medication adherence in the ED setting. Prior work has shown that ED patients are interested in addressing chronic health issues during their ED visits,[111] and that issues such as adherence can be addressed.[31,33,34] Evidence that there is a strong relationship between medication adherence and BP in the ED may influence how hypertension and medication management are addressed in the emergency setting.

Summary and Significance

Despite the ubiquitous measurement and use of BP in the ED setting and its use to guide acute management of care, there is relatively little evidence available to guide ED physicians in identification and short- or long-term medical management of patients who present to the ED with elevated BP. Many clinicians attribute elevated BP in the ED to pain or anxiety. Often patients in the ED have very high BP (e.g., SBP≥160 mmHg) or persistently high BP (e.g., >2 BPs that measure >140 mmHg) and little evidence exists to help clinicians understand whether these values are associated with chronically elevated BP after the ED visit. Given that even six weeks of uncontrolled hypertension are associated with increased risk of death, it is important to understand the long term risks that may be associated with high BP in the ED setting. In Chapter 2, a large retrospective cohort of adult ED patients who had follow up BP available within the year after an ED visit is used to begin addressing these knowledge gaps. Furthermore, to understand elevated BP in the ED setting, it is imperative to understand if patients are taking their prescribed antihypertensive medications.

Prior measures of medication adherence in the ED setting have been limited primarily to patient self-report or use of surveys. In Chapter 3 of this work, we compare a direct measure of adherence (mass spectrometry blood assay that detects 35 cardiovascular medications, including 19 antihypertensives), to other indirect measures of medication adherence and examine the relationship between these measures of adherence with SBP, using two different patient populations.

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CHAPTER 2: COMPARISON OF BLOOD PRESSURE MEASURED DURING AN EMERGENCY DEPARTMENT VISIT TO SUBSEQUENT BLOOD PRESSURES

Aim 1: Among adult patients who had a single ED visit at Vanderbilt University Medical Center (VUMC) between January 1, 2010 and December 31, 2013, determine the relationship between emergency department (ED) blood pressure (BP) and BP within the year following that ED visit among patients with a single ED visit during the study period. Subgroup analyses will examine whether this relationship is modified by a diagnosis of hypertension.

Hypothesis 1: ED SBP is associated with SBP over the year after an ED visit.

Aim 1 Background

This aim focuses on understanding the relationship between BP measured during ED visits and subsequent BP among patients with low to intermediate health risk factors. Patients with low to intermediate risk may be less likely to have chronic illnesses and more likely to have modifiable risk factors for elevated BP but also less likely to access the healthcare system.[1-5] Thus, the potential opportunities for improving health are great.

As outlined in Chapter 1, the lack of clarity regarding the potential long-term clinical importance of BP measured during ED visits is a significant barrier to integration of ED care in chronic hypertension management. Simply, the relationship between an elevated BP measured during ED visits and chronically elevated BP (hypertension) is not well understood. Therefore, the aim of this study is to examine the relationship between BP measured in the ED and BP within the year following the ED visit.

Aim 1 Study Population

This study utilizes data abstracted from the electronic health record of patients who had a single adult ED visit at VUMC from January 1, 2010 to December 31, 2013. All BP values, antihypertensive medication classes, patient demographic and clinical characteristics were extracted from the electronic data warehouse (EDW) or the synthetic derivative (SD), which is a de-identified shadow the electronic health record. The earliest date for data extraction for covariates, e.g., for identifying comorbid conditions by ICD-9 CM, was January 1, 2007. Patients were censored at death or December 31, 2014, whichever occurred first. Informed consent waiver was approved by the IRB.

In order to address the question of the relationship between ED and chronic BP, the analysis was limited to patients with a single ED visit during the study period. Patients with multiple ED visits are likely to have more comorbid conditions and a different BP trajectory following multiple ED visit compared to patients with only a single ED visit during the study period. In addition, events or medication changes that occur during hospitalizations or even multiple ED visits may change the trajectory of BP over time, regardless of the initial ED BP. Therefore, the following analyses are limited to patients with a single ED visit during the study time. Future work will evaluate the trajectory of BP after an ED visit among patients with multiple ED visits.

Inclusion criteria included the following:

- Adult (≥ 18 years of age at the time of the ED visit)
- One adult VUMC ED visit between January 1, 2010 and December 31, 2013
- At least one BP within 365 days after the index ED visit; this included BPs measured in the hospital among patients who were admitted via the index ED visit

- At least one VUMC clinical encounter between January 1, 2003 and the index ED visit
- No evidence of pregnancy during the study timeframe or 9 months before the start of the study

Exclusion criteria included the following:

- More than 1 ED visit during the study time period
- Patients with significant co- morbid illness likely to affect BP measures:
  end stage renal disease (ESRD) on hemodialysis (HD); end stage liver disease (ESLD); cancer undergoing active therapy; hospice care at the time of their ED visit
- Evidence of multiple hospitalizations after the ED visit, defined as >128 follow up BPs, or the 90th percentile for the number of follow up BPs among patients with only one ED visit during the study period

Chapter 2 Appendix outlines the ICD-9 CM codes used to define the conditions in the inclusion and exclusion criteria.

Exposure: Blood Pressure During the Emergency Department Evaluation

Systolic BP (SBP) was used as the primary measure of BP because it is most closely related to cardiovascular, stroke, and mortality risk.[6-8] Diastolic BP (DBP) and mean arterial pressure (MAP) will be evaluated as secondary measures of BP in future work.

SBPs measured for eligible patients during the ED visit was used to define the exposure groups in analyses. ED BP's were those recorded in the EHR between the time of check-in to the ED and ED discharge. For patients discharged to home, ED discharge was defined as the time stamp when the patient was removed from the ED whiteboard. For patients who were hospitalized, time of ED discharge was defined as the time stamp for the bed request, which was when care of the patient transitions from the ED team to the hospital team. Where there was incomplete data about the time of ED discharge (7% of total rows), ED discharge was capped at 16 hours from the time of ED arrival.

For the subset of patients with more than one ED BP (i.e., an ED BP other than the BP measured during triage), the following additional distributions of BP in the ED were examined: mean, median, maximum, minimum, and 90th percentile, excluding triage BP. The number of BPs measured during the ED visit after triage was also computed.

For clinical interpretation and implementation, lowest ED SBP was categorized (<140 mmHg, ≥140/<160 mmHg, and ≥160 mmHg). For patients with either only triage SBP (N = 17,198) or only post-triage mean ED SBP (N = 145), the single lowest SBP available was categorized. Where both triage and post-triage lowest SBP were available (N = 9,426), the lower value (triage or post-triage) was used to categorize lowest ED SBP. Additionally, the overall lowest ED SBP was examined, using the lowest available SBP from either triage or post-triage values.

During the process of extracting SBP from the EDW and SD, the following BP values were filtered and removed from the data because they are consistent with data entry errors (i.e., they are physiologically impossible or implausible): SBP ≥ 400 mm Hg, difference between SBP and DBP ≤ 10mm Hg, or DBP ≥ SBP. Less than 1% of BPs were filtered and excluded for these reasons.

Outcome: Mean Systolic Blood Pressure Over the Year Following the Index Emergency Department Visit

The primary outcome measure was mean follow-up SBP over the year following the index ED visit. Measures of follow up BP were computed using BPs extracted from the EHR each week for 52 weeks after the index ED visit. All available BPs, including clinic and hospital BPs, were utilized. Mean SBP for the 365 days after the index ED visit was used as the primary measure of follow up BP after examination of other summary measures of follow up SBP (median, minimum, maximum, and 90^{th} percentile SBP over the year following the index ED visit; results included in the Chapter 2 Appendix). The number of SBP measured per week for 52 weeks after the ED visit were also extracted from the EHR.

Mean follow up SBP over the year following an ED visit was chosen as the primary outcome because it is conservative measure of follow up SBP. While it may underestimate the proportion of patients with elevated SBP and the variation in post-ED SBP, it also minimizes the risk of potential overtreatment or unnecessary follow up recommendations for patients in the ED setting.

Variable Definitions

Covariates were chosen *a priori.* Details of variable definitions are found in the Chapter 2 Appendix. Briefly, all data were abstracted from the electronic health record, where the earliest available date was January 1, 2007. Age was defined as the age in years at the time of the ED visit. Health insurance was identified at the time of the ED visit and was classified as private, Medicare/Medicaid/Federal, or self-pay/unknown. Race was extracted from the health record, where it was recorded based on patient-report. The comorbid conditions of diabetes, heart failure, HIV, and organ transplantation were identified by ICD-9 CM codes and CPT codes (Chapter 2 Appendix) between January 1, 2007 and the date of the index ED visit.

Patients discharged from the ED were identified by both their location of discharge ("ED") and by <3 BPs recorded in Week 1 after the index ED visit. Number of post-ED SBPs was used as additional criteria to identify ED discharge status because hospitalized patients who boarded in the ED through their entire hospitalization were coded in the electronic health record as having been discharged from the ED.

Evidence of diagnosed hypertension, which was examined as a potential effect modifier, was defined as an ICD-9 CM diagnosis code of 401.X-405.X between January 1, 2007 and the ED visit.

Antihypertensive medications were identified by natural language processing of clinical notes and extraction of outpatient and inpatient prescriptions. We looked for evidence of a prescription within the 15 months prior to the ED visit. Antihypertensive medications were classified into seven categories: beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitor/angiotensin receptor blockers, loop diuretics, thiazide diuretics, alpha antagonists, and other (e.g., clonidine, hydralazine, methyldopa, minoxidil).

ED chief complaints, which are based on patient report at the time of ED arrival, were categorized into 10 mutually exclusive categories: hypertension, chest pain, other cardiovascular symptoms, other pain, symptoms associated with low BP (nausea, vomiting, diarrhea, bleeding, syncope, failure to thrive), injury, infection, neurological/psychiatric symptoms, arrest, and other.

Subgroups: Discharge Status From the ED, ED Chief Complaint

Hospitalization from the ED may influence or obscure the relationship between ED and follow up SBP. On the one hand, patients hospitalized from the ED may undergo an intervention such as life style modification counseling or initiation/titration of BP medication, which may more rapidly lower follow up SBP after an ED visit. On the other hand, hospitalized patient may experience illness or other intervention that results in higher follow up SBP. In the available data, we are unable to account for these potential factors, e.g., medication changes, development of acute stroke or renal failure, frequency of follow up clinic visits after hospitalization, etc. Therefore, multivariable logistic and linear regressions were stratified *a priori* by ED discharge status.

We also examined whether the ED chief complaint influenced analyses results. Patients with cardiovascular complaints, that is a patient reported chief complaint of hypertension, chest pain, or other cardiovascular symptoms, were examined as a subgroup.

Effect Modification: Evidence of Diagnosed Hypertension

We anticipated that relationship between ED and subsequent SBPs might differ by evidence of diagnosed hypertension. Patients with hypertension have greater variability in blood pressure[9] and may experience greater fluctuations due to acute illness. In addition, patients with diagnosed hypertension who are found to have severely elevated BP may be more likely to receive closer outpatient follow up and medication titration. In contrast, patients without diagnosed hypertension but who had elevated BP in the ED may not receive such close attention because it is assumed that their SBP will return to normal after the ED visit; the portion of these patients who have undiagnosed hypertension may then continue to remain untreated for a longer period of time compared to their counterparts with diagnosed hypertension.

We used a P-value threshold of <0.10 to identify evidence of effect modification by diagnosed hypertension. The P-value was <0.001 for the interaction term between lowest ED SBP and diagnosed hypertension in the full imputed model (described below). Therefore, the interaction term was included in the full model for both subgroups.

Aim 1 Statistical Analyses

Patients were the unit of analysis. Patient demographics and clinical characteristics were examined for differences across ED SBP category and ED discharge status. Chapter 3 Appendix includes tables stratifying cohort demographics by hypertension diagnosis as well as by race and sex.

ED and follow up SBP distributions were examined using boxplots and non-parametric correlations. Details of these are included in the Chapter 2 Appendix and were used to support the decision to use lowest ED SBP as the primary independent variable and mean follow up SBP as the primary dependent variable. Receiver operating characteristic (ROC) curves with 95% confidence intervals (CI) examined the test characteristics of measures of ED SBP as predictors of follow up SBP, where mean follow up SBP ≥ 140 mm Hg and ≥ 160 mm Hg were used to define elevated follow up BP. The optimal cutpoint according to the Liu method,[10] which maximizes the product of the sensitivity and specificity, was examined for lowest ED SBP for mean follow up SBP ≥140 mmHg.

Multiple Regression Models

Multiple logistic and linear regression models stratified by ED discharge status were used to examine the relationship between lowest ED BP and follow up SBP. An interaction term was included in each model to address effect modification by hypertension diagnosis.

Lowest ED SBP, the primary independent variable, was categorized as <140 mmHg, ≥140/<160 mmHg, and ≥160 mmHg. For patients with either only triage SBP or only post-triage mean ED SBP, the single available value was used to categorize lowest ED SBP. Where both triage and post-triage mean SBP were available, the lowest value was used to categorize ED SBP.

Logistic regression was performed to compute the odds of having elevated mean follow up BP (mean follow up SBP ≥ 140 mmHg) for each category of ED SBP. Linear regression was performed to examine the relationship between each category of ED SBP and mean follow up SBP.

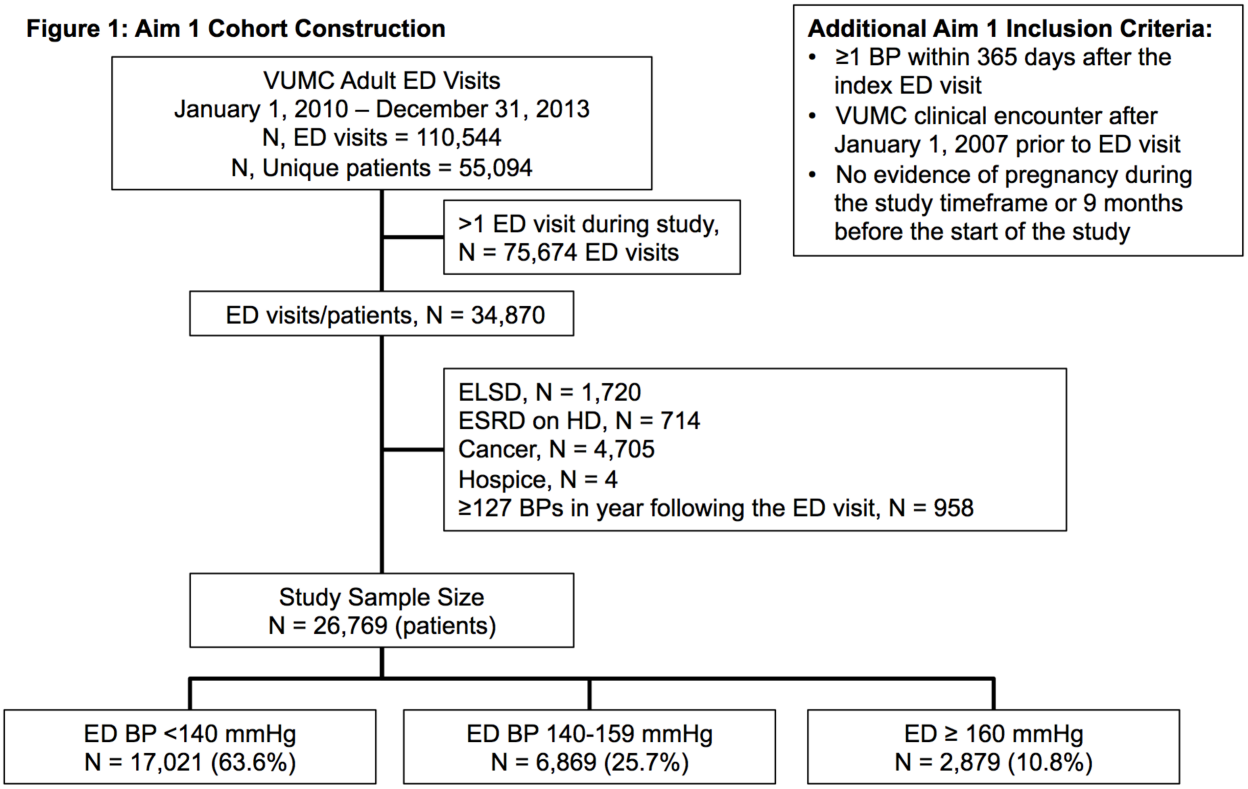
Multivariable models were adjusted for: the number of BPs used to compute mean follow up SBP, age, sex, race (white, non-white), insurance status (private, Medicare/Medicaid/federal, uninsured), BMI, comorbid conditions (evidence of heart failure, liver disease, diabetes, HIV, and organ transplantation), and total number of medication classes at the time of the ED visit. As described below, evidence of diagnosed hypertension was examined as a potential effect modifier of the relationship between ED and follow up SBP.

Model fit for all models was evaluated with model diagnostics. Multiple imputation with 12 imputed data sets was performed for BMI (8,744, 32.7% missing) and white/non-white race (313, 1.2% missing).[11,12] Future analyses will examine the relationship between ED and follow up SBP using repeated measures and longitudinal data.

Aim 1 Results

Figure 1 illustrates cohort construction. Over the 3-year study period, 26,769 patients met inclusion and exclusion criteria; of these, 17,198 (64.2%) had only a triage ED SBP, 145 (0.5%) had only a post-triage SBP, and 9,426 (35.2%) had both a triage and post-triage SBP. For the 9,571 patients with any post-triage SBP, they had a mean of 2.6 BPs measured in the ED after triage.

Figure 1: Aim 1 Cohort Construction



Demographics by Lowest ED SBP Category

Age, race, and insurance status were similar in distribution to the general adult VUMC ED patient population (Table 1). The vast majority of patients were insured by federal or state health insurance, and this proportion increased with higher ED BP category. As anticipated, the proportion of patients in the cohort with comorbid conditions was lower than in the general population, with a median of 0 comorbid conditions and 36.9% of patients with evidence of a diagnosis of hypertension. Overall, 71.7% of patients did not have evidence for prescription for an antihypertensive medication prior to the ED visit, although 21.3% of these had evidence of a diagnosis of hypertension. Of the 9,873 patients with evidence of diagnosed hypertension, 41.4% did not have evidence of a prescription of antihypertensive medications, 23.8% had evidence of 1 class of antihypertensive medications, and 34.8% had evidence of a prescription for ≥2 classes of antihypertensive medications.

Across categories of rising ED SBP, the mean age rose, the proportion of white patients decreased, the proportion of patients with private insurance decreased. Number of comorbid conditions, number of antihypertensive medication classes, and BMI rose with ED SBP category. The number of follow up BPs was similar across ED BP category. The BP category with the lowest proportion of patients hospitalized was the middle BP category; similarly, patients with the lowest ED SBP between 140 mmHg and 159 mmHg had on average the fewest post-triage SBP measurements. Patients with extremely high or extremely low ED SBP may have their BP measured more often and may be more likely to be hospitalized.

Patients who were excluded slightly older, on average, than patients included in the cohort (Chapter 2 Appendix). Excluded patients were more likely to have multiple comorbid conditions, a slightly higher BMI, and were prescribed more antihypertensive medications, and they had a mean of 81.5 (sd 175.0) follow up SBPs measured over the course of the year after their first ED visit.

Table 1: Demographics by Lowest ED SBP Category (N = 26,769)				
Variable	ED SBP <140 mmHg	ED SBP ≥140, <160 mmHg	ED SBP ≥160 mmHg	Missing N (%)
Demographics	N = 17,021	N = 6,869	N = 2,879	
Age in years, mean (sd) median (Q_1, Q_3)	44.7 (18.8) 44 (28, 58)	48.9 (18.6) 49 (33, 62)	57.1 (17.3) 58 (44, 69)	0
Female, no. (%)	9,932 (58.4)	3,483 (50.7)	1,637 (56.9)	0
Race, no. (%)				313 (1.2)
White	13,819 (82.3)	5,445 (80.1)	2,220 (77.7)	
Insurance, no. (%)				0
Private	3,967 (23.3)	1,444 (21.0)	474 (16.5)	
Medicare/Federal/Medicaid	11,650 (68.4)	4,917 (71.6)	2,213 (78.8)	
Self-Pay/unknown	1,404 (8.3)	508 (7.4)	192 (6.7)	
Discharged from the ED, no. (%)	9,023 (53.0)	4,204 (61.2)	1,586 (55.1)	0
Admitted to an ICU, no. (%)	792 (3.0)	474 (2.8)	113 (3.9)	0
Comorbid Conditions, %				--
Hypertension	5,185 (30.5)	2,834 (41.3)	1,854 (64.4)	
Diabetes	2,171 (12.8)	992 (14.4)	638 (22.2)	
Heart Failure	493 (2.9)	221 (3.22)	183 (6.4)	
HIV	289 (1.7)	91 (1.3)	31 (1.1)	
Organ Transplant	151 (0.9)	49 (0.7)	11 (0.4)	
Total Number of Comorbidities, mean (sd) median (Q_1, Q_3)	 0.6 (0.7) 0 (0, 1)	 0.6 (0.8) 0 (0, 1)	 1.0 (0.8) 1 (1, 2)	--
BMI, kg/m^2, mean (sd) median (Q_1, Q_3)	27.4 (7.0) 26.1 (22.4, 30.8)	29.3 (7.3) 27.9 (24.2, 33.2)	30.7 (8.0) 29.2 (25.2, 34.9)	8,744 (32.7)
Prescribed BP Medications (at the time of the ED visit), no. (%)				--
ACE/ARB	2,313 (13.6)	1,204 (17.5)	700 (24.3)	
Beta blocker	1,899 (11.2)	808 (11.8)	492 (17.1)	
Calcium channel blocker	871 (5.1)	492 (7.2)	310 (10.8)	
Loop diuretic	1,070 (6.3)	392 (5.7)	221 (7.7)	
Thiazide diuretic	1,523 (9.0)	764 (11.1)	437 (15.2)	
Alpha adrenergic blocker	132 (0.8)	52 (0.8)	35 (1.2)	
Other	588 (3.5)	276 (4.0)	189 (6.6)	
Number of ED BP's measured during ED visit, excluding triage mean (sd) median (Q_1, Q_3)	 2.7 (3.5) 2 (1, 3)	 1.9 (1.6) 1 (1, 2)	 2.0 (2.4) 2 (1, 2)	--

Subgroup: Demographics by ED Discharge Status

Compared to patients who were discharged from the ED, patients who were hospitalized were older, more likely to be male and white, and were less likely to have private health insurance (Table 2). Hospitalized patients were also more likely to have comorbid conditions and were more often prescribed antihypertensive medications. While the number of BPs measured during the ED visit were similar, as expected given that follow up SBP included both clinic and hospital measures, the number of follow up SBPs was significantly higher among hospitalized patients.

Table 2: Demographics by ED Discharge Status (N = 26,769)

Variable	Discharged from the ED	Hospitalized or Transferred
Demographics	N = 14,813	N = 11,956
Age in years, mean (sd) median (Q_1, Q_3)	43.0 (17.2) 42 (27, 55)	52.3 (19.7) 53 (37, 67)
Female, no. (%)	5,868 (39.6)	6,107 (51.1)
Race, no. (%)		
White	11,479 (77.5)	10,005 (83.7)
Insurance, no. (%)		
Private	3,734 (25.2)	2,151 (18.0)
Medicare/Federal/Medicaid	10,025 (67.7)	8,755 (73.2)
Self-Pay/unknown	1,054 (7.1)	1,050 (8.8)
Admitted to an ICU, no. (%)	--	791 (6.6)
Comorbid Conditions, %		
Hypertension	4,075 (27.5)	5,798 (48.5)
Diabetes	1,465 (9.9)	2,336 (19.5)
Heart Failure	251 (1.7)	646 (5.4)
HIV	222 (1.5)	189 (1.6)
Organ Transplant	80 (0.5)	131 (1.1)
Total Number of Comorbidities, mean (sd) median (Q_1, Q_3)	 0.4 (0.7) 0 (0, 1)	 0.8 (0.9) 0 (0, 1)
BMI, kg/m^2, mean (sd) median (Q_1, Q_3)	28.1 (7.2) 26.7 (23.0, 31.7)	28.5 (7.4) 27.3 (23.4, 33.1)
Prescribed BP Medications (at the time of the ED visit), no. (%)		
ACE/ARB	2,079 (14.0)	2,138 (17.9)
Beta blocker	1,358 (9.2)	1,841 (15.4)
Calcium channel blocker	792 (5.4)	881 (7.4)
Loop diuretic	608 (4.1)	1,075 (9.0)
Thiazide diuretic	1,432 (9.7)	1,292 (10.8)
Alpha adrenergic blocker	97 (0.7)	122 (1.0)
Other	449 (3.0)	604 (5.1)
Number of ED BP's measured during ED visit, excluding triage mean (sd) median (Q_1, Q_3)	 2.4 (3.1) 2 (1, 3)	 2.7 (3.4) 2 (1, 3)
Number of BP's measured after the ED visit		

mean (sd) median (Q_1, Q_3)	4.3 (7.9) 2 (1, 4)	24.5 (23.9) 16 (9, 31

Subgroups: Hypertension, Race and Sex

Cohort demographics stratified by diagnosed hypertension, sex, and race are reported in the Chapter 2 Appendix. Patients with hypertension were on average older, more likely to be male, and less likely to be white (19.6%, compared to 80.6% white for patients without hypertension). Patients with hypertension were also less likely to have private health insurance; they had more comorbid conditions, were more likely to be hospitalized, had higher BMI, and were more likely to have evidence of prescriptions for antihypertensive medication at the time of the ED visit. Number of post-triage ED SBPs measured were similar; patients with hypertension had more follow up SBPs measured.

Non-white patients tended to be younger, were less likely to have private health insurance, and were less likely to hospitalized or admitted to an ICU; they were also more likely to have diabetes and their BMI was higher than white patients, and they had fewer follow up BPs, though it is difficult to determine whether this is related to fewer clinic visits versus the lower proportion hospitalized.

Non-white men had much higher proportion with HIV (6.4%) compared to non-white women or white patients; white men had the highest prevalence of evidence of a diagnosis of heart failure. White women had the lower proportion of patients with a documented comorbid condition, and they had the lowest BMI. As expected in light of current antihypertensive guidelines,[13,14] the proportion of non-white patients with evidence of a prescription of calcium channel blockers was higher than their white counterparts, while white patients had a higher proportion of prescriptions for beta blockers. Total number of prescribed antihypertensive medication classes within 1 year prior to the ED visit was similar across groups, as was the number of BPs measured during the ED visit.

ED SBP

Overall, 3.4% of ED patients in the cohort had at least one ED SBP <140 mmHg, while 25.7% had a lowest ED SBP between 140-159 mmHg. For 10.8% of patients, all ED SBP were ≥160 mmHg. SBP measured in triage was on average higher than BP measured after triage, and variance was greatest for triage BP compared to other summary measures of ED BPs with the exception of maximum ED SBP. There was very little difference between the median and mean ED SBP after triage. For more than 48% of patients, ED triage SBP was ≥ 140 mmHg; this decreased to just over 24% for mean post-triage ED SBP. The proportion of triage SBPs ≥160 mmHg was 16.9%, which decreased to 6.5% for mean post-triage ED SBP.

Table 3: Emergency Department Systolic Blood Pressures	
	Summary Statistic
Lowest ED SBP, N = 26,769 (lowest of triage or post-triage ED SBP)	
Lowest ED SBP, mean (sd)	133.0 (22.7)
Lowest ED BP Categorized, no. (%)	
<140 mmHg	17,021 (63.6)
140 mmHg to 159 mmHg	6,869 (25.7)
≥160 mmHg	2,879 (10.8)
ED Triage SBP, N = 26,624	
Triage SBP mmHg, mean (sd)	139.8 (22.2)
Post-triage ED SBP, N = 9,571	
Min SBP mmHg, mean (sd)	122.8 (20.5)
Mean SBP mmHg, mean (sd)	128.4 (19.9)
Median SBP mmHg, mean (sd)	128.4 (20.1)
90^{th} percentile SBP mmHg, mean (sd)	132.9 (21.3)
Max SBP mmHg (sd)	134.3 (22.2)
ED SBP ≥ 140mmHg, no. (%)	
Triage SBP, no. (%)	12,833 (47.9)
Mean SBP, no. (%)	2,375 (24.8)
ED SBP ≥ 160mmHg, no. (%)	
Triage SBP, no. (%)	4,260 (15.9)
Mean SBP, no. (%)	625 (6.5)

Follow Up SBP

Each measure of follow up SBP, summarized over the year following the index ED visit, was examined. As expected mean and median follow up SBP were similar, and there was a range of 29.2 mmHg between the average minimum and maximum follow up SBP. Mean SBP was chosen as the primary measure of follow up SBP, and this was categorized at a threshold of >140 mmHg, which is the threshold used to diagnose hypertension and titrate antihypertensive medications among patients with diagnosed hypertension. The proportion of follow up mean SBPs 140 mmHg or higher was 15.1%, and 1.7% of patients had mean follow up SBP ≥160 mmHg. The number of follow up SBPs measured was similar across categories of lowest ED SBP:

Number of BP's measured after the ED visit:	ED SBP<140	ED SBP 140-159	ED SBP≥ 160
mean (sd)	13.5 (19.8)	12.0 (18.7)	14.8 (21.2)
median (Q_1, Q_3)	5 (2, 16)	5 (2, 13)	6 (2, 18)

Table 4: Follow Up Systolic Blood Pressure (N = 26,769)	
Measures of Follow UP SBP	Summary Statistic
Mean SBP mmHg, mean (sd)	124.5 (15.1)
Median SBP mmHg, mean (sd)	124.3 (15.4)
90^{th} percentile SBP mmHg, mean (sd)	134.2 (18.4)
Min SBP mmHg, mean (sd)	110.5 (17.5)

Max SBP mmHg (sd)	139.7 (22.0)
Mean Follow Up SBP, Categorized	
SBP ≥ 140mmHg, no. (%)	4,042 (15.1)
SBP ≥ 160mmHg, no. (%)	470 (1.8)

Univariate and Unadjusted Analysis

The following examination of univariate relationships between measures of ED SBP and follow up SBP guided our decision to choose the lowest ED SBP as the primary measure of ED SBP and mean follow up SBP as the primary dependent variable.

Boxplots: Lowest ED Triage and Mean Post-triage ED SBP versus Mean Follow up SBP

Boxplot visualization of the relationship between mean lowest ED SBP and mean follow up SBP, as well as the relationship between mean post-triage ED SBP with mean follow up SBP is included in the Chapter 2 Appendix. Although post-triage mean ED SBP was most closely related to mean follow up SBP, lowest ED SBP was chosen because it is easier to implement clinically.

Comparison of lowest ED SBP versus mean follow up SBP revealed a mean difference of 8.5 mmHg (133.0 mmHg versus 124.5 mmHg, respectively). The difference between mean post-triage ED SBP and mean follow up SBP was 3.2 mmHg (128.4 mmHg versus 125.2 mmHg; P<0.001, N = 9,571). On average, the difference between triage SBP and mean follow up SBP (N = 26,624) was 15.3 mmHg.

Nonparametric Correlations between ED and Mean Follow up SBP

Overall, ED SBP was moderately correlated with follow up BP, with the strongest correlation between mean ED SBP and mean follow up BP (rho 0.61). Similar correlations were found between ED median and ED 90th percentile SBP with mean follow up SBP. The correlation between lowest ED SBP and mean follow up SBP was 0.45, moderate strength.

Table 5: Non-Parametric Correlations of ED SBPs and Follow Up SBPs*

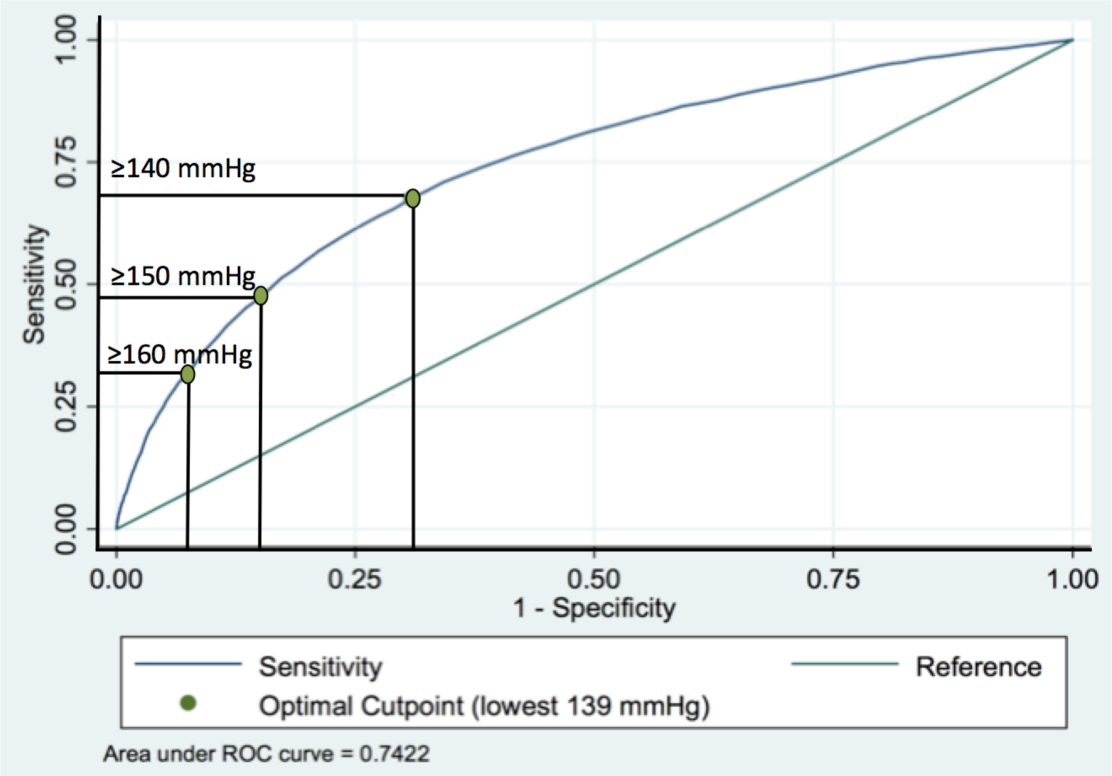
	Mean Follow Up SBP	Median Follow Up SBP	90th Percentile Follow Up SBP	Minimum Follow Up SBP	Maximum Follow Up SBP
Lowest ED SBP (N = 26,769)	0.45	0.44	0.40	0.35	0.33
Triage SBP (N = 26,624)	0.50	0.49	0.47	0.35	0.41
Post-triage ED SBP (N = 9,571)					
Mean ED SBP	0.61	0.60	0.58	0.39	0.51
Median ED SBP	0.61	0.60	0.58	0.39	0.51
90th Percentile ED SBP	0.60	0.59	0.58	0.37	0.52
Minimum ED SBP	0.54	0.53	0.51	0.37	0.44
Maximum ED SBP	0.59	0.58	0.57	0.36	0.51
* All p<0.001					

Receiver Operating Characteristics Curves

The c-statistic of the lowest ED SBP compared to mean follow up SBP (≥140 mmHg) was 0.74 (95% CI 0.74-0.75). The cutoff point that maximized the product of the sensitivity and specificity was 139 mmHg, which resulted in 68% sensitivity and 69% specificity for elevated mean follow up SBP.

Results for mean or median ED SBP were consistently similar, as expected given that SBP is generally normally distributed, and these measures of ED SBP had the strongest relationship with follow up SBP. Unfortunately, mean and median ED SBP are not easily available in clinical settings. Lowest ED SBP was chosen for ease in clinical implementation and understanding. Overall, the strength of the relationship between the various measures of ED SBP and mean follow up SBP ≥ 140 mmHg was fair to good, with c-statistics ranging from 0.82 for mean, median, and 90th percentile ED SBP to 0.76 for triage ED SBP and minimum post-triage ED SBP. For mean follow up SBP ≥ 160 mmHg, c-statistics ranged from 0.87 (mean and median ED SBP) to 0.81 (triage ED SBP).
The c-statistics for each of these measures of ED SBP are found in the Chapter 2 Appendix.

Figure 2: Receiver Operating Characteristics Curve of Lowest ED SBP for Mean Follow Up SBP ≥ 140 mmHg



Thresholds: Mean ED SBP versus Elevated Mean Follow Up SBP

Several thresholds were evaluated to examine the relationships between mean ED and mean follow up SBP (Table 6). Defining elevated ED BP by the lowest recorded ED SBP using a threshold of ≥140 mmHg, ≥150 mmHg, of ≥160 mmHg increased the positive predictive value for correctly identifying elevated mean follow up (mean follow up SBP ≥ 140 mmHg) from 28.0% to 35.3% to 43.7%, respectively. The unadjusted odds of having elevated mean follow up SBP increased with use of a higher threshold of lowest ED SBP.

Table 6: Elevated ED SBP (by *lowest* ED SBP ≥140 mmHg, ≥150 mmHg, or ≥ 160 mmHg) Versus Elevated Mean Follow Up SBP (≥ 140 mmHg)

Lowest ED SBP ≥ 140 mmHg versus mean follow up SBP ≥ 140 mmHg

	Follow Up SBP ≥ 140 mmHg	Follow Up SBP < 140 mmHg	
ED SBP ≥ 140 mmHg	2,732	7,016	9,748
ED SBP < 140 mmHg	1,310	15,711	17,021
	4,042	22,727	26,769

OR 4.7 (95% CI 4.3 to 5.0)

Sensitivity	Pr(+| D)	67.59%	66.12% 69.03%
Specificity	Pr(-|~D)	69.13%	68.52% 69.73%
Positive predictive value	Pr(D| +)	28.03%	27.14% 28.93%
Negative predictive value	Pr(~D| -)	92.30%	91.89% 92.70%

Lowest ED SBP ≥ 150 mmHg versus mean follow up SBP ≥ 140 mmHg

	Follow Up SBP ≥ 140 mmHg	Follow Up SBP < 140 mmHg	
ED SBP ≥ 150 mmHg	1,976	3,622	5,598
ED SBP < 150 mmHg	2,066	19,105	21,171
	4,042	22,727	26,769

OR 5.0 (95% CI 4.7 to 5.4)

Sensitivity	Pr(+| D)	48.89%	47.33% 50.44%
Specificity	Pr(-|~D)	84.06%	83.58% 84.54%
Positive predictive value	Pr(D| +)	35.30%	34.05% 36.57%
Negative predictive value	Pr(~D| -)	90.24%	89.83% 90.64%

Lowest ED SBP ≥ 160 mmHg versus mean follow up SBP ≥ 140 mmHg

	Follow Up SBP ≥ 140 mmHg	Follow Up SBP < 140 mmHg	
ED SBP ≥ 160 mmHg	1,258	1,621	2,879
ED SBP < 160 mmHg	2,784	21,106	23,890
	4,042	22,727	26,769

OR 5.9 (95% CI 5.4 to 6.4)

Sensitivity	Pr(+| D)	31.12%	29.70% 32.58%
Specificity	Pr(-|~D)	92.87%	92.53% 93.20%
Positive predictive value	Pr(D| +)	43.70%	41.87% 45.53%
Negative predictive value	Pr(~D| -)	88.35%	87.93% 88.75%

Regressions: ED SBP versus Mean Follow Up SBP

Figure 3 in the Chapter 2 Appendix compares the unadjusted fitted linear slopes for patients discharged from the ED to patients who were hospitalized or transferred from the ED. Discharged patients had a steeper slope (beta 0.32 for discharged patients, compared to beta of 0.30 for hospitalized/transferred patients), indicating a larger difference between lowest ED SBP and mean follow up SBP among discharged patients. Multiple logistic and linear regression models stratified by ED discharge status are presented below (Tables 7 and 8).

Multiple logistic and linear regression using imputed data included adjustment for the following covariates: number of post-ED discharge BPs measured, age, sex, race, insurance status, comorbid conditions, number of prescribed antihypertensive classes. Each model included an interaction term for evidence of diagnosed hypertension.

Logistic Regression

Among patients who were discharged from the ED, the odds of having a mean follow up SBP ≥140 mmHg over the year following the ED visit rose with each level of lowest ED SBP. These odds were lower among patients who were discharged from the hospital, compared to patients who were hospitalized or transferred. Evidence for effect modification by diagnosed hypertension was strong, with all P-values for the interaction term levels <0.05 in both logistic regression models. The negative beta coefficients for the interaction term indicates that patients with diagnosed hypertension had lower odds of having elevated follow up SBP compared to patients who had not been diagnosed with hypertension.

Table 7: Multiple Logistic Regression of Categorized ED SBP for Elevated Mean Follow up SBP*

	Discharged: Adjusted OR (95% CI)	Interaction Coefficient and P-value	Not Discharged Adjusted OR (95% CI)	Interaction Coefficient and P-value
Lowest ED SBP 140-159 mmHg	2.7 (2.3 to 3.1)	-0.2 (0.13)	3.9 (3.2 to 4.8)	-0.3 (0.01)
Lowest ED SBP ≥ 160 mmHg	6.6 (5.4 to 8.0)	-0.3 (0.02)	9.4 (7.1 to 12.4)	-0.4 (0.02)

*Adjusted for number of post-ED discharge BPs measured, age, sex, race, insurance status, comorbid conditions, number of prescribed antihypertensive classes, and included an interaction term for evidence of diagnosed hypertension

Linear Regression

Among patients who were discharged from the ED, mean follow up SBP rose with each level of lowest ED SBP, approximately 6-7 mmHg among discharged patients and approximately 7-8 mmHg among hospitalized patients. P-values for the interaction terms with diagnosed hypertension were all <0.10; their negative beta coefficients indicate that patients with diagnosed hypertension had lower follow up SBP than their counterparts who did not have evidence of diagnosed hypertension.

Table 8: Multiple Linear Regression of Categorized ED SBP for Mean Follow Up SBP*				
	Discharged: Beta (mmHg) (95% CI)	Interaction Coefficient (P-value)	Not Discharged Beta (mmHg) (95% CI)	Interaction Coefficient and P-value
Lowest ED SBP 140-159 mmHg	6.7 (6.2 to 7.3)	-1.2 (0.02)	8.1 (7.3 to 8.9)	0.1 (0.94)
Lowest ED SBP ≥ 160 mmHg	13.2 (12.2 to 14.2)	-1.4 (0.06)	14.9 (13.4 to 16.3)	-0.1 (0.93)
*Adjusted for number of post-ED discharge BPs measured, age, sex, race, insurance status, comorbid conditions, number of prescribed antihypertensive classes, and included an interaction term for evidence of diagnosed hypertension				

Cardiovascular Chief Complaints

Restricting analyses to the 6.3% of patients who presented to the ED with a cardiovascular chief complaint (e.g., hypertension, chest pain, or other cardiovascular chief complaint) produced similar results. With a sample size of 2,212 subjects, the OR for having mean follow up SBP ≥140 mmHg was 2.2 (95% CI 1.6 to 3.0) for patients with a lowest ED SBP between 140 and 159 mmHg, and 5.3 (95% CI 3.8 to 7.3) for patients whose lowest ED SBP was ≥160 mmHg.

Aim 1 Discussion

In a cohort of 26,769 adult patients who had a single ED visit between January 1, 2010 and December 31, 2013, we found that a conservative measure of ED SBP - the lowest recorded SBP during the ED visit – was related to the mean SBP within the year after the ED visit.

The PPV for elevated mean follow up SBP was 28.0% for patients whose lowest ED SBP was ≥140 mmHg; the PPV rose to 35.3% for patients whose lowest ED SBP was ≥150 mmHg, and to 43.7% for patients whose lowest ED SBP was ≥160 mmHg. For each 10 point increase in lowest ED SBP from 140 mmHg to 160 mmHg, the unadjusted odds of having elevated mean follow up SBP rose, from 4.7 (95% CI 4.3 to 5.0) to 5.0 (95% CI 4.7 to 5.4) and then to 5.9 (95% CI 5.4 to 6.4).

The adjusted odds of having elevated mean follow up SBP, stratified by ED discharge status, rose for each level of lowest ED SBP. Interestingly, patients with hypertension were less likely to have elevated mean follow up SBP compared to their counterparts without diagnosed hypertension. This may be related to clinical inertia in diagnosing and treating hypertension; patients with diagnosed hypertension may be more frequently monitored by their healthcare providers, giving more opportunities to control BP. The same patterns were found in the stratified linear regression models.

Limitations

These results should be interpreted in the context of the following limitations. First, all data was extracted from the electronic health records of eligible patients and is subject to the inherent limitations of all analyses that utilize administrative data (e.g., manual clinical data entry errors, missing data, and potential risk of variable misclassification). For example, patients who were discharged from the ED were identified by their discharge location as well as the number of BPs measured within the week after the ED visit because patients who spent their entire hospitalization in the ED were coded in the electronic health record as having been discharged from the ED. Similarly, we excluded patients with >128 follow up BPs over the year following the ED visit because on manual chart review many of these patients had been hospitalized for the entire duration of follow up. To address the potential risks of potential errors in data extraction, samples of 20-50 patient records were examined to evaluate data accuracy for each variable. However, is it possible that misclassification of the exposure, outcome, and adjusting variables may have occurred.

Similarly, interventions that may have affected SBP measurement or SBP trajectory, such as administration of antihypertensive medication or other vasoactive medications during the ED visit or hospitalization, changes in BP medication regimen, and changes in health (such as initiation of hemodialysis, development of heart failure after a heart attack) were not accounted for in the primary outcome measure of mean follow up SBP. It is possible that these factors may have influenced mean follow up SBP in either direction, although there were not obvious differences in the number of follow up SBPs to suggest systematic differences across ED BP groups.

We chose to examine the lowest recorded ED SBP as the primary measure of ED BP because it can be implemented easily in the clinical setting. This measure of ED SBP, however, is not the composite measure of ED SBP that was most closely related to follow up SBP – mean and median ED SBP after triage both had stronger associations with follow up SBP. Computation of these values in clinical practice is not feasible and is unlikely to be used with any regularity.

Finally, these analyses were restricted the study population to patients with a single VUMC Adult ED visit and to patients who had at least one clinical encounter at VUMC prior to the ED visit. These patients may be more likely to have private or other health insurance, they may have received more education, and they may have demographics of more urban populations, with differences in body mass index, smoking, etc. Future work is planned to address this question in larger, more diverse patient populations.

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CHAPTER 3: MEDICATION ADHERENCE AND BLOOD PRESSURE IN THE EMERGENCY DEPARTMENT

Antihypertensive medication adherence, or the degree to which patients take their antihypertensive medications as prescribed, is crucial for BP control.[1-3] Until now, measuring antihypertensive adherence in the emergency department (ED) setting has been limited to patient-report or use of surveys, which may be influenced by recall and social desirability biases and lack of an established patient-provider relationship.[4-6] As a result, little is known regarding factors related to antihypertensive adherence in the ED setting or about the relationship between antihypertensive adherence and blood pressure in the ED setting.

In Aims 2 and 3, we examined the construct and predictive validity of a recently developed mass spectrometry blood assay as a direct measure of antihypertensive adherence in two different patient populations. Associations are made with multiple indirect measures of antihypertensive adherence. Primary analyses compared the mass spectrometry assay, a direct measure of adherence, to other, indirect measures of medication adherence and an evaluation of the relationship between adherence and systolic BP (SBP) were performed in Population A. Selected analyses were repeated in Population B for external validation of the assay as a measure of antihypertensive adherence in a different patient population and clinical setting.

Population A: 300 Vanderbilt University Medical Center (VUMC) primary care patients with hypertension who were prescribed at least one of 15 blood pressure (BP) medications at the time of their emergency department (ED) visit and who also completed the Adherence to Refills and Medications Scale (ARMS) as a measure of general medication adherence.

Population B: 99 African American patients with hypertension enrolled in a clinical trial, who were prescribed at least one of six BP medications, and who completed the Morisky measure of global medication adherence at their Week 16 study visit; for the subset of patients who brought their pill bottles to the Week 16 visit, pill count ratios were also available.

The mass spectrometry blood assay used in Aims 2 and 3 as a measure of antihypertensive adherence is also described in Chapter 1. Briefly, this assay underwent analytic chemistry validation for detection of 35 cardiovascular medications, including 19 antihypertensive medications. These are the first studies to examine use of this assay as a measure of antihypertensive adherence.

Aim 2: Evaluate the mass spectrometry assay's test characteristics as a measure of antihypertensive adherence by comparing it against previously validated indirect measures of adherence.

> ***Hypothesis 2:*** *The mass spectrometry assay has weak to moderate strength correlation with other measures of medication adherence.*

Because the mass spectrometry assay measures different aspects of medication adherence compared to more global measures of adherence, we anticipated that correlations among the measures would be weak to moderate in strength.

Aim 3: Determine the relationship between adherence, measured by both direct and indirect means, and SBP.

> ***Hypothesis 3A:*** *Lower antihypertensive adherence is associated with higher SBP.*

Hypothesis 3B: *The assay provides meaningful information about antihypertensive adherence beyond that obtained from patient characteristics or an adherence survey.*

Population A, Aims 2 and 3: VUMC Adult ED Patients

From July 2012 to April 2013, 300 VUMC primary care patients with hypertension treated with at least one of 15 BP medications on the assay were enrolled in a prospective, observational cohort at the time of an ED visit. IRB approval was obtained; patients provided written informed consent to participate.

Participants were enrolled by research assistants, who collected demographic and clinical information, administered measures of numeracy, health literacy, self-reported adherence (referent standard for medication adherence - Aim 2), and drew ~10 ml of blood from an existing peripheral IV. BP was measured in a standardized fashion with the BP cuff at heart height; patients were either seated or sitting up on a gurney. BP (dependent variable Aim 3) was measured once by the trained research assistant using the automated oscillometric method; all recorded measures of BP that occurred during the course of ED care were included in manual data extraction. Details of the collected variables are included in the Chapter 3 Appendix.

One week after discharge, participants returned a log of home or clinic BP and a measurement of trust (Primary Care Assessment Survey) via phone, email, or letter.[7] Subjects agreed to measure their BP approximately one week after discharge from the hospital or emergency department. Prior work has shown that trust in providers is associated with medication adherence.[8] For patients who expressed a preference, an email with the same information was sent. Patients who did not return either a paper log or an email received up to three phone calls in an attempt to complete follow-up. The electronic health records of all subjects were reviewed for up to one year following enrollment to obtain the first clinic-based BP measurement. We also obtained clinical outcomes, including repeat ED visits, hospitalization, and death. Future work will examine the relationship between medication adherence at the time of an ED visit with follow up BP, resource utilization, and mortality after the ED visit and whether these relationships may be mediated by trust in healthcare providers.

Aim 3 Exposure: Measures of Medication Adherence

Patients in Population A underwent a blood draw to measure antihypertensive adherence by the mass spectrometry assay, and subjects completed the Adherence to Refills and Medications Survey (ARMS). One patient was later found to have been prescribed propranolol for tremor and did not have hypertension. This subject was excluded from all analyses; thus, for 299 subjects in Population A, both measures of medication adherence were available for Aim 2 analyses of the association between direct and indirect measures of adherence.

Aim 2 evaluates the validity of the assay ratio as a measure of antihypertensive adherence by comparing it against existing, previously validated measures of medication adherence. In Population A, the ARMS was used as the reference standard against which the assay ratio was compared.

Mass Spectrometry Assay – Assay Ratio

The direct measure of antihypertensive adherence in Population A, the assay ratio, was computed from mass spectrometry assay results as follows:

Assay Adherence Ratio = (number of detected antihypertensives) / (number of prescribed antihypertensives).

The assay ratio was dichotomized to classify patients who were adherent (assay ratio = 1.0) versus non-adherent (assay ratio<1.0; Table 1). The assay ratio was also evaluated as a continuous measure.

Table 1: Measures of Medication Adherence (N = 299)

Measure of Adherence	Variable Modeling
Assay ratio	Continuous Dichotomized (assay ratio = 1.0, assay ratio <1.0) Subgroups: Continuous (raw chromatograph output) for lisinopril, metoprolol, HCTZ, amlodipine, losartan
ARMS	Continuous, reverse-scored Dichotomous (Adherent = 12 ; Nonadherent >12)

Abbreviations: HCTZ, hydrochlorothiazide; ARMS, Adherence to Refills and Medications Scale

Of the 19 antihypertensives detected by the assay, the following 15 were used to compute the assay ratio: amlodipine, atenolol, carvedilol, diltiazem, clonidine, hydrochlorothiazide (HCTZ), hydralazine, lisinopril, losartan, metoprolol, nifedipine, ramipril, valsartan, and verapamil. The remaining antihypertensive medications (captopril, chlorthalidone, enalapril, propranolol, and telmisartan) were prescribed rarely in Population A (N < 10) and were therefore not included in computation of the assay ratio.

For each patient, the Assay Adherence ratio was calculated by review of the results of the mass spectrometry assay (numerator for the ratio). Each assay was reviewed manually twice by two trained researchers. All chromatographs for each drug on the assay were reviewed and were combined with acceptance criteria, including retention time, area under the curve, chromatogram shape, and qualifying ions, to determine drug presence (Chapter 3 Appendix). Where appropriate, metabolites of parent drug (e.g., metoprololic acid, enalapril, ramipril) were also utilized to determine drug presence. Agreement between the two researchers for drug detection was achieved for all subjects and drugs by second review.

The denominator for the Assay Adherence ratio was the number of prescribed medications, i.e., drugs for which assay results were expected. This was determined by standardized review of the medication list derived from the following sources: ED triage documentation, most recent clinic note, review of pharmacy records, discharge summary records, and patient report.

To further examine the mass spectrometry assay as a measure of antihypertensive adherence, raw output for the chromatograph response for five individual medications was also examined: lisinopril, metoprolol, HCTZ, amlodipine, losartan. Raw chromatograph output was standardized for all analyses by subtracting the mean and then dividing by the standard deviation for the raw chromatograph output (i.e., response) for each BP medication. Mass spectrometry response, or raw chromatograph output, is used to compute drug concentration levels in the blood at the time of the blood draw.

Adherence to Refills and Medications Survey

The ARMS measures medication adherence by patient-report. Two major themes are medication-taking and medication-refill behaviors. The ARMS has 12 items, and each item has a 4-point Likert-like response; higher ARMS score indicates lower medication adherence behaviors. As was done for the assay ratio, the ARMS was dichotomized to identify adherent versus non-adherent patients (adherent: ARMS = 12; non-adherent: ARMS>12. For consistency across adherence measures, when used as a continuous measure, the ARMS was reverse-scored so that higher scores indicated higher medication adherence. The reverse-scored ARMS ranges from 1 to 37, where 37 indicated complete medication adherence according to patient-report.

Aim 3 Outcome - Systolic Blood Pressure in the ED

SBP was the outcome for Aim 3, which examined the relationship between medication adherence and SBP. Systolic blood pressure is closely associated with cardiovascular outcomes across age ranges and race.[9-12] Diastolic and mean arterial blood pressure will be evaluated as outcomes in future work. All BPs were measured using the oscillometric method. Mean ED SBP and research SBP were examined as primary and secondary measures of ED SBP; ED triage SBP is reported for completeness but was not used as a measure of ED SBP given concerns about measurement error.

Primary Measure of ED SBP: Mean ED SBP

The primary measure of BP in Population A was mean ED SBP. Mean ED SBP was computed using up to 10 BP's measured and recorded in the electronic health record by ED staff during routine clinical care; triage SBP and SBP's measured after administration of BP medication or vasoactive medication, typically nitroglycerin, were excluded. SBP measured during triage was excluded because of concern for measurement error. During triage, BP is often measured over clothing using a universal BP cuff; there is no opportunity to allow patients to rest for the recommended 5 minutes; positioning is often suboptimal (e.g., patients may have legs crossed, sitting forward); and measurement typically occurs while the patient is describing the reasons for seeking ED care. These factors all introduce error into BP measurement. These analyses examine ED SBP as an indicator of chronic SBP; therefore, SBP measured after administration of medication that lowers BP was excluded.

Secondary Measure of ED SBP: Research ED SBP

A single measure of BP performed by trained research staff was evaluated as secondary measure of SBP in the ED. For completeness, triage SBP was also examined. Triage SBP is the first BP measured after patients arrive in the ED; this measurement may occur while a nurse obtains a brief medication history and patients are seated in a reclining chair, or it may occur in an ED examination room with patients supine on a gurney. A minority of ED patients have BP measured only during triage.

Aim 2 Statistical Analyses: Comparison of Assay Ratio to the ARMS

In Aim 2, we examined the mass spectrometry assay as a measure of antihypertensive adherence by comparing the assay ratio's distribution and non-parametric correlation with the ARMS. Despite the limitations of patient report, recall bias, and social desirability bias, the ARMS was used as the reference standard because it is the currently available, validated measure of medication adherence available in the ED setting. Comparison of the assay ratio to the ARMS was done using scatter plots with locally weighted scatterplot smoothing (LOWESS) lines and Spearman's correlation coefficients with 95% confidence intervals (CI).

Test characteristics of the assay ratio were evaluated using receiver operating characteristic (ROC) curves, with computation of sensitivity, specificity, positive predictive value, and negative predictive value of the assay ratio against the referent standard of adherent/non-adherent measured by the currently available approach of indirect adherence measure (ARMS). The odds of being non-adherent according to the ARMS, with 95% CI, were computed. Sensitivity and specificity of the assay ratio for classifying adherent/non-adherent according to the ARMS are reported in the Chapter 3 Appendix.

In planned exploratory analyses, alternative thresholds defining adherence by the assay and ARMS were examined: assay ratio of at least 0.80 and ARMS <15. These results are included in the Chapter 3 Appendix as there were no clinically important differences based on these changes in thresholds to defining adherent/non-adherent. The assay ratio and ARMS were also compared where the assay ratio was used as the referent standard; these results are included in the Chapter 3 Appendix, as well.

Subgroups By Individual Antihypertensive Medications

Given the wide range and variable number of drugs prescribed to patients in Population A and different biological properties for individual drugs, we conducted analyses for the five most common antihypertensives (lisinopril, metoprolol, hydrochlorothiazide, amlodipine, and losartan). For each of these drugs, ROC curves were generated for the ARMS, using the assay as the reference standard (adherent/non-adherent), and visa versa.

Aim 3 Statistical Analyses: Adherence and ED SBP

Demographics and clinical characteristics for patients classified as adherent versus non-adherent by the assay ratio were compared. Unadjusted relationships between adherent/non-adherent (by assay and ARMS) with SBP (mean ED SBP and research SBP) were examined using boxplots. Boxplots stratified by total number of prescribed antihypertensive medications are reported in the Chapter 3 Appendix.

Effect Modification by Number of BP Medications

Medication adherence decreases as the number of medications increases, and the number of prescribed medications often increases with disease severity.[1] In addition, patients with resistant hypertension, defined as the use of three or more blood pressure medications including a thiazide diuretic, often have greater difficulty achieving BP control.[13-20] Patients with resistant hypertension may be eligible for invasive procedures such as renal denervation and may be at higher risk for cardiovascular disease, either due to more severe disease or worse disease control. Therefore, we looked for evidence of effect modification by number of prescribed BP medications (<3 prescribed antihypertensives, ≥3 prescribed antihypertensives). An interaction term P-value <0.10 was used as

the threshold to identify evidence of effect modification, and the relationships were visualized using locally weighted scatterplot smoothing (LOWESS) lines.

In Population A, there was evidence for effect modification by the number of prescribed antihypertensives with mean ED SBP and with research SBP (Mean ED SBP: $P < 0.001$ for the assay ratio, $P = 0.001$ for the ARMS; research SBP: $P < 0.001$ for the assay ratio, $P = 0.03$ for the ARMS). Therefore, analyses were stratified by the number of prescribed antihypertensive medications: <3 prescribed antihypertensives, and ≥3 prescribed antihypertensives. Given this evidence for effect modification, analyses for Population B were similarly stratified.

Multivariable Models: Adherence and Blood Pressure

The approach to building multivariable models was based on prior causal knowledge regarding the relationships between medication adherence and SBP, drawn from work conducted in other settings. Multiple factors are thought to confound the relationship between medication adherence and BP (Figure 1)[21-23]: demographics (age, sex), socioeconomic status (measured by income, race, health insurance, access to a primary care provider), health status (measured by BMI, smoking, comorbid conditions, duration of hypertension diagnosis, and number of prescribed medications), and health knowledge (measured by health literacy, numeracy, and education). The following section describes the theoretical framework and prior work used to develop the theoretical relationship between adherence and SBP that was evaluated in Aim 3.

Model Covariates: Frameworks and Associated Factors

Theoretical frameworks for medication adherence have been developed from clinic-based research, including frameworks by Murray, Krousel-Wood, Bosworth, and Gellad.[2,6,24-26] While similar in many ways, these frameworks also have important differences, particularly in the specific patient level factors thought to be associated with adherence. Some of these differences may be related to the various methods used to measure adherence.

The adherence framework developed by Murray et al. in 2004[6] was developed with a focus on geriatric patients and integrates the external environment, healthcare system, and medication use system with the following patient characteristics: age, which is related to knowledge, attitudes, beliefs, and expectations; perceptual-cognitive resources; health specific cognitive resources, and medical/disability related factors; these in turn are related to income, distance to health serves, transportation, insurance, relationships with providers, support, and supervision; and these are further in turn related to patient perceptions of illness, severities of outcomes, and responses to prescriptions.

In contrast, the Krousel-Wood medication adherence framework[2] does not specifically address age, but it ties quality of life, medication (complexity and side effects), health care system issues, and demographic/behavioral/treatment/clinical variables to increased use of non-conventional therapies and low medication adherence. Bosworth et al.'s adherence framework[27] focuses on causes of nonadherence that are preventable (patient understanding; identifying lack of initial prescription fill; lack of medication effectiveness, irregular refills, and cost) and non-preventable (serious mental illness, side effects, or adverse effects). The Gellad framework[24] includes illness representation, cognitive function, demographics, coexisting illness, medication characteristics, external cues, and health-system and provider factors.

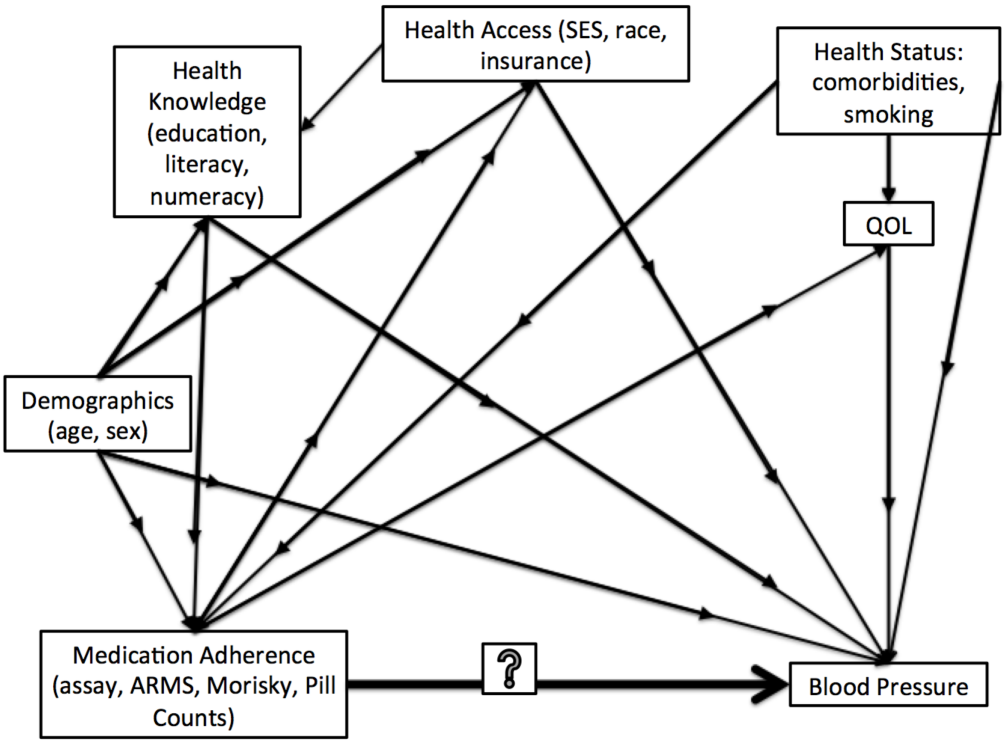
There is conflicting evidence for these frameworks. Sex, age, income, and healthcare access are variably associated with medication adherence.[28-30] Chaos and stress have been associated with

lower adherence in several studies.[28,30] Health literacy may be associated with adherence,[21] although other work has found that hopelessness and psychological distress outweigh the influence of health literacy.[31]

In the ED setting, work by Davis et al.[32] examined multiple risk factors for medication non-adherence and found that the strongest predictors of medication non-adherence were primarily psychological: health attitude, beliefs, depression, anxiety, social support, and locus of control. Of the extensive sociodemographic factors examined, they found that only age >54 years, smoking status, and current/historical drug use predicted self-reported medication non-adherence; they found no associations with race, marital status, education, employment, income, diseases, access to a primary care provider, prescription coverage. Others have tried unsuccessfully to develop easily reproducible and generalizable "risk factor profiles" in primary care populations.[33,34] While individual patient factors have been associated with adherence in some studies, sociodemographics, primary care provider characteristics, and patterns of medication prescriptions do not clearly predict medication nonadherence. Although psychosocial factors such as depression, quality of life, and trust have been associated with adherence and BP, these were not included in our models because they are thought to be on the causal pathway from between medication adherence and BP.

Based on this prior work, we constructed the following directed acyclic graph (DAG) to represent the theoretical relationship between medication adherence and SBP in the ED setting (Figure 1).

Figure 1: Directed Acyclic Graph of Medication Adherence and Blood Pressure



The DAG was used to identify the following variables, which were used in the multiple regression models for Population A in Aim 3 (Table 2).

Table 2: Multiple regression covariates for Population A, Aim 3

Covariate	Coding
Age	Continuous
Sex	Female/Male
Race	White/Non-White
Insurance Status	Private/Not private
Numeracy	SNS, continuous
Health literacy	BHLS, continuous
Comorbidities	Elixhauser summary score, continuous
BMI	Continuous
Duration of hypertension diagnosis, by patient report	Categorized: <1 year 1-4 years 5-10 years >10 years
Chronic renal insufficiency	Not present/present
Effect Modifier: Number of prescribed antihypertensive medications	Continuous, based on patient report combined with systematic chart review

Abbreviations: SNS, subjective numeracy scale; BHLS, brief health literacy survey

Multiple imputation was performed for 18 subjects with missing numeracy in Population A.[35,36] Model assumptions and fit was examined using residuals, R-squared, AIC, and BIC. Variance inflation factors for each model were computed to evaluate for possible model overfitting.

Comparison of Assay Ratio, ARMS versus SBP

The Wald test P-value of the full, imputed model that included both the ARMS and assay ratio was examined was evidence for whether the assay ratio explained variance in mean ED SBP beyond that explained by the ARMS.

In secondary analyses included in the Chapter 3 Appendix, models were also repeated using a 4-level variable created from both the assay ratio and ARMS as the exposure (1- non-adherent by both assay ratio and ARMS; 2 - non-adherent by the assay ratio but adherent by the ARMS; 3 - adherent by the assay ratio but non-adherent by the ARMS; and 4 – adherent by assay ratio and ARMS) to examine the relationship between adherence and SBP.

Secondary Analyses: Raw Chromatograph Output versus SBP

To evaluate whether the relationship between adherence and SBP differed among specific medications, linear regression was performed, with mean ED SBP as the dependent variable and antihypertensive adherence measured by raw chromatograph output (standardized) as the independent variable. In Population A, this was conducted for subjects for whom the following medications were detected: lisinopril, metoprolol, hydrochlorothiazide, amlodipine, or losartan.

Aim 2 Results: Comparison of Assay Ratio and ARMS

Aim 2: Evaluate the mass spectrometry assay's test characteristics as a measure of antihypertensive adherence by comparing it against previously validated measures of adherence.

Hypothesis 2: *The mass spectrometry assay has weak to moderate strength correlation with other measures of medication adherence.*

Demographics and Clinical Characteristics

Detailed demographics and clinical characteristics for the 299 patients in Population A are included in the Chapter 3 Appendix. Overall, mean age was 59.1 years, 54.0% of patients were female, and 62.3% were White. Comorbidities were common, with 38.0% also having diabetes and 24.7% having chronic renal insufficiency as of the date of their ED visit. Overall, 19.7% had not completed high school, mean health literacy was 13.3 (out of a maximum of 15), and mean numeracy score was 31.6 (out of a maximum of 48).

Antihypertensive Adherence: ARMS and Mass Spectrometry Assay

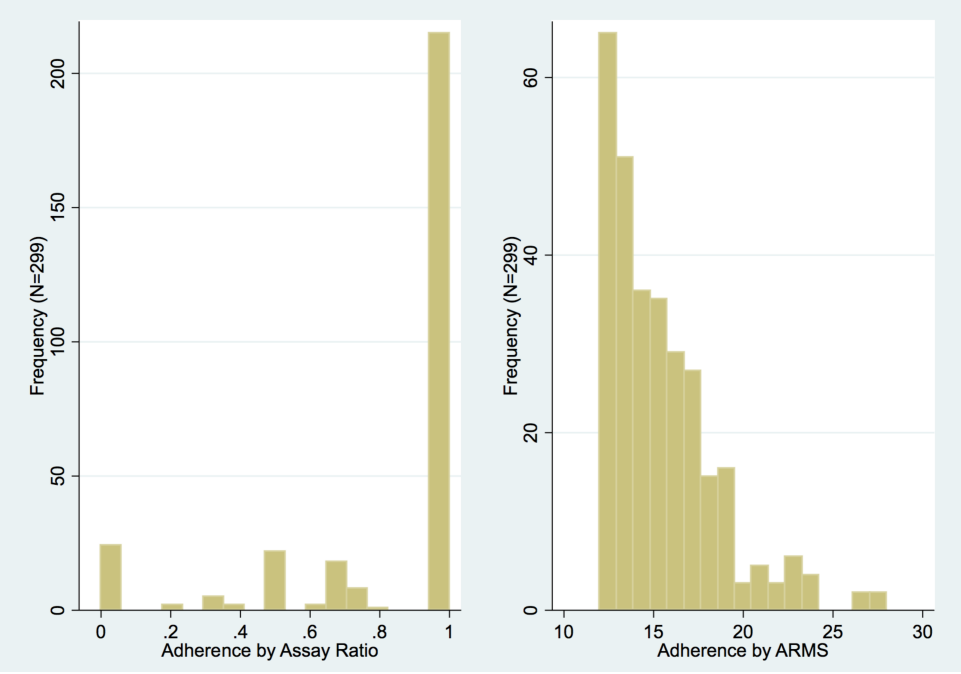
Patients were prescribed on average 2.2 antihypertensive medications (sd 1.0; median 2.0, interquartile range 1.0 to 3.0; range 1 to 5). The number of prescribed antihypertensive medications was, on average, higher than the number of antihypertensives detected by the assay (Chapter 3 Appendix). The most commonly prescribed antihypertensive was lisinopril (44.2%), followed by metoprolol (35.5%), HCTZ (30.1%), amlodipine (25.4%), and losartan (12.0%). The 14 antihypertensive medications used to compute the assay ratio are found in Table 3.

The frequency and percentage for all of the medications detected by the mass spectrometry assay are reported in detail in the Chapter 3 Appendix (antihypertensive medications examined in the planned subgroup analyses are in bold). The proportion of subjects with detected antihypertensive medication varied by the prescribed antihypertensive (Table 3) and was lowest for clonidine, ramipril, HCTZ, and nifedipine. For all other antihypertensive medications, the proportion detected was >80%, but it did not reach 100% for any other medications. These 14 antihypertensives were used to compute the adherence assay ratio. Details of the number of prescribed and detected antihypertensive medications, stratified according to the total number of prescribed antihypertensives are reported in the Chapter 3 Appendix.

Table 3: Prescribed and Detected Antihypertensives for Population A (N = 299)			
	Prescribed	Detected	Percent Detected
Amlodipine	76	67	88.2%
Atenolol	21	18	85.7%
Carvedilol	48	48	95.8%
Diltiazem	24	23	95.8%
Clonidine	**25**	**13**	**52.0%**
Hydrochlorothiazide	**90**	**61**	**67.8%**
Hydralazine	20	18	90.0%
Lisinopril	132	111	84.1%
Losartan	36	29	80.6%
Metoprolol	106	88	83.0%
Nifedipine	**37**	**26**	**70.3%**
Ramipril	**8**	**4**	**50.0%**
Valsartan	13	11	84.6%
Verapamil	10	9	90.0%
Bold indicates <80% of expected medications were detected by the assay			

The assay ratio was skewed, with more than 200 subjects having an assay ratio of 1.0, or complete adherence (Figure 2). The ARMS was also skewed towards perfect adherence, though not to the same degree as the assay ratio.

Figure 2: Population A, Distribution of Medication Adherence, Measured by Assay Ratio and the ARMS



In Population A, 235 patients (78.3%) reported some degree of non-adherence, or an ARMS score greater than 12 (Table 4). Changing the threshold for defining adherent by the ARMS from 12 to 15 (the median ARMS score) reclassified 87 subjects.

Table 4: Distribution of Medication Adherence Measures (N = 299)	
Assay Ratio	
Assay Ratio, mean (sd) median (Q_1, Q_3)	0.83 (0.31) 1.00 (0.67, 1.00)
Adherent (Assay ratio = 1.0), no. (%)	215 (71.9)
Adherent (Assay ratio ≥ 0.80), no. (%)	216 (72.2)
Adherence, Categorized Assay ratio = 1.0 Assay ratio between 0 and 1.0 Assay ratio = 0	 215 (71.9) 60 (20.1) 24 (8.3)
Adherence to Refills and Medications Scale (ARMS)	
ARMS (range 12-48), mean (sd) median (Q_1, Q_3)	15.2 (3.2) 14 (13, 17)
ARMS, reverse-coded (range 1-37), mean (sd) median (Q_1, Q_3)	33.8 (3.2) 35 (32, 36)
Adherent (ARMS = 12), no. (%)	65 (21.7)
Adherent (ARMS <15, median), no. (%)	152 (50.8)

Continuous Assay Ratio vs. ARMS

By locally weighted scatterplot smoothing (LOWESS), the relationship between the assay and ARMS (reverse-scored) was approximately linear (Figure 3), although there were patients with an assay ratio of 1.0 who had evidence of non-adherence by the ARMS, and visa versa, across the range of both the assay ratio and ARMS.

Figure 3: Population A, Scatterplot and LOWESS of Adherence Measured by the Assay Ratio and ARMS (reverse-scored; N = 299)

Correlation between the assay ratio and reverse-scored ARMS was weak-to-moderate globally (Spearman's rho 0.23) and when examining individual antihypertensive drugs, with a range of Spearman rhos of 0.11 to 0.40 (Table 5). By individual medication, the strongest correlations between the assay ratio and ARMS were for amlodipine and losartan, with weaker correlations for lisinopril and HCTZ. There was not evidence of correlation between the assay ratio and ARMS when restricted to patients prescribed metoprolol.

Table 5: Population A – Spearman Rank Correlations for Adherence Measures

	Spearman's rho	(95% CI)	P-value
Assay ratio vs. ARMS (N = 299)	0.23	0.11 to 0.33	<0.001
By medication:			
Lisinopril (N = 132)	0.18	0.01 to 0.34	0.04
Metoprolol (N = 106)	0.11	0.08 to 0.29	0.26
HCTZ (N = 90)	0.22	0.02 to 0.41	0.04
Amlodipine (N = 76)	0.40	0.19 to 0.57	<0.001
Losartan (N = 36)	0.34	0.01 to 0.60	0.04

Evidence for non-parametric correlation between the reverse-scored ARMS and raw chromatograph output was found only for losartan (Table 6), with weak-to-moderate strength of the correlation. For lisinopril, metoprolol, HCTZ, and amlodipine, there was not evidence of association between raw chromatograph output and the reverse-scored ARMS, although samples sizes were small.

Table 6: Population A – Spearman's Correlations of Raw Chromatograph Output with Reverse-Scored ARMS, by Medication*

	Correlation Coefficient	95% CI	P-value
Lisinopril detected (N = 132)	0.12	-0.05 to 0.29	0.16
Metoprolol detected (N = 106)	0.09	-0.10 to 0.28	0.36
Hydrochlorothiazide detected (N = 90)	0.10	-0.10 to 0.31	0.33
Amlodipine detected (N = 76)	0.10	-0.13 to 0.32	0.40
Losartan detected (N = 36)	0.34	-0.02 to -0.60	0.04

* Standardized raw chromatograph output
Abbreviations: ARMS, adherent to refills and medications scale; CI, confidence interval

Dichotomous: Assay Ratio vs. ARMS

The relationships between the assay ratio and ARMS were examined after dichotomizing both measures to indicate non-adherence vs. adherence, as described above (Table 1); these results guided modeling approaches used in Aim 3 analyses. Because it is the currently available measure of medication adherence, the ARMS was used as the reference standard. Analyses were also conducted using the assay ratio as the reference standard; these are reported in the Chapter 3 Appendix.

Non-adherence classified by the assay ratio had a 90.5% PPV for non-adherence by the ARMS, in a population with a prevalence of non-adherence (by the ARMS) of 78.2% (Table 7).

Table 7: Population A - Non-Adherent by Assay vs. ARMS (Referent)

	Non-Adherent by ARMS (ARMS > 12)	Adherent by ARMS (ARMS = 12)	
Non-Adherent (assay ratio < 1.0)	76	8	84
Adherent (assay ratio = 1.0)	158	57	215
	234	65	299

OR 3.4 (95% CI 1.5 to 8.7)

Sensitivity	Pr(+| D)	32.48%	30.82% 34.18%
Specificity	Pr(-|~D)	87.69%	85.29% 89.83%
Positive predictive value	Pr(D| +)	90.48%	88.58% 92.15%
Negative predictive value	Pr(~D| -)	26.51%	24.88% 28.19%

Assay Ratio vs. Adherent by the ARMS: Receiver Operating Characteristics

The c-statistic for the assay ratio versus adherent by the ARMS was moderate in strength (c-statistic 0.60, 95% CI 0.54 to 0.66; Figure 4). Detailed report of sensitivity and specificity for adherence of the assay are reported in the Chapter 3 Appendix. When examining this relationship by individual antihypertensive medications, the ROC AUC for amlodipine was highest, although relationships were weak to moderate in strength for all medications (Figure 5). Detailed reports of sensitivity and specificity for each drug and ROC curves for adherent defined by ARMS <15 (median ARMS score) are reported in the Chapter 3 Appendix.

Figure 4: Population A, ROC Curve of Assay for Adherent by ARMS

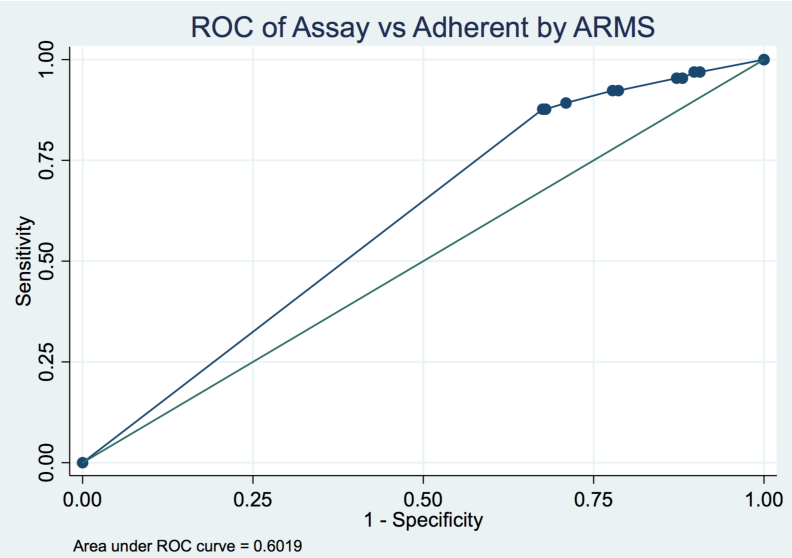


Figure 5: Population A, ROC Curves of the Assay Ratio for Adherent by the ARMS

For: lisinopril (N = 132), metoprolol (N = 106), hydrochlorothiazide (HCTZ; N = 90), amlodipine (N = 76), and losartan (N = 36).

Aim 2: Brief Summary

As anticipated given that the assay ratio and ARMS measure different aspects of medication adherence, the associations between these measures was weak to moderate in strength. Population A Aim 2 results provided sufficient evidence to proceed with Aim 3 analyses using the assay ratio as a measure of antihypertensive adherence. Distribution of the assay ratio was skewed; altering the threshold to classify adherent behavior to an assay ratio ≤0.80 reclassified only one person. Therefore, Aim 3 analyses were conducted using the dichotomized assay ratio (adherent = assay ratio of 1.0; non-adherent = assay ratio <1.0) as the primary measure of antihypertensive adherence.

Aim 3 Results: Adherence vs. SBP

Aim 3: Determine the relationship between adherence measured and SBP.

Hypothesis 3A: *Lower antihypertensive adherence is associated with higher SBP.*
Hypothesis 3B: *The assay provides meaningful information about antihypertensive adherence in the ED beyond that obtained from patient characteristics or an adherence survey.*

Population A was also used for Aim 3 analyses. Overall demographics and clinical characteristics for Population A are found in the Chapter 3 Appendix; Table 8 presents these characteristics stratified by adherent/non-adherent according to the assay ratio.

Patients who were classified as non-adherent by the assay ratio were on average slightly younger, more likely to be female, non-white, and to have diabetes. Non-adherent patients had on average a lower comorbidity index but were prescribed more medicines (by self report) and antihypertensive medications (by medication reconciliation). Education and health literacy were similar between the two groups; those who were non-adherent had slightly lower numeracy and had been diagnosed with hypertension more recently.

Table 8: Aim 3 Population A Characteristics

Variable*	Adherent* N = 215	Non-Adherent* N = 84
Age, mean (sd) years median (Q_1, Q_3)	59.9 (10.8) 59 (52, 67)	56.9 (12.0) 57 (49.5, 65)
Female, no. (%)	112 (52.1)	49 (58.3)
White, no. (%)	143 (66.5)	43 (51.2)
Non-Hispanic, no. (%)	212 (99.1)	82 (97.6)
Insurance, no. (%)		
Private	88 (40.9)	35 (41.7)
Other (Medicare/ Medicare/Federal/No Insurance)	127 (59.1)	49 (58.3)
Atrial Fibrillation, no. (%)	26 (12.1)	9 (10.7)
Diabetes, no. (%)	79 (36.7)	34 (40.5)
Chronic Renal Insufficiency, no. (%)	54 (25.1)	19 (22.6)
Elixhauser sum, mean (sd) median (Q_1, Q_3)	13.5 (11.0) 12 (4, 21)	13.0 (12.3) 11.5 (3.5, 21)
BMI (kg/meter squared), mean (sd) median (Q_1, Q_3)	 31.7 (9.3) 29.5 (25.1, 35.9)	 34.4 (9.5) 33.5 (27.4, 38.9)
Total number of medications, per patient report mean (sd) median (Q_1, Q_3)	 8.4 (5.1) 8 (5, 11)	 9.1 (5.4) 7 (6, 12)
Total number of antihypertensives, per patient report mean (sd)	 1.9 (1.1)	 2.1 (1.7)

median (Q_1, Q_3)	2 (1, 2)	2 (1, 3)
Highest Level of Education mean (sd) years median (Q_1, Q_3)	 12.3 (1.8) 13 (12, 14)	 12.4 (1.7) 13 (12, 14)
Health Literacy Level mean (sd) median (Q_1, Q_3)	 13.2 (2.8) 15 (12, 15)	 13.4 (2.6) 15 (12, 15)
Numeracy mean (sd) median (Q_1, Q_3)	 32.3 (8.0) 34 (27, 38)	 29.8 (7.8) 32 (23, 35)
Hypertension >10 years no. (%)	 133 (62.2)	 48 (57.1)
* adherent: assay ratio = 1.0; non-adherent: assay ratio<1.0		

Exposure: Medication Adherence

Based on results of Aim 2, the assay ratio and ARMS were dichotomized for main Aim 3 analyses, (Tables 4 and 9). In planned secondary analyses, the assay ratio and ARMS were modeled as continuous measures; for consistency, the ARMS was reverse scored throughout so that higher ARMS indicated higher patient-reported medication adherence.

According to the assay ratio, 71.9% of patients were adherent; in contrast, only 21.7% of patients were classified as adherent according to the ARMS.

Table 9: Aim 3 Population A Adherence Measures (N = 299)	
Adherence: Assay Ratio	
Adherent (Assay ratio = 1.0), no. (%)	215 (71.9)
Assay Ratio, mean (sd) median (Q_1, Q_3)	0.83 (0.31) 1 (0.67, 1)
Adherence to Refills and Medications Scale (ARMS)	
Adherent (ARMS = 12), no. (%)	65 (21.7)
Reverse-scored ARMS (range 1-37) mean (sd) median (Q_1, Q_3)	 33.8 (3.2) 35 (23, 36)

Outcome: ED Systolic Blood Pressure

Mean ED SBP was used as the primary measure of SBP in the ED. Mean ED SBP was computed using up to 10 SBP's recorded during clinical care and excluded both triage SBP and any SBP measured after administration of vasoactive medications. Of the 299 patients in Population A, 38 were given blood pressure lowering vasoactive medication prior to a SBP measurement; of these 38 who received vasoactive medication, 19 were given nitroglycerin. Therefore, mean ED SBP was available for 261 of the 299 subjects in Population A; the mean of this measure of ED SBP was 137.2 mmHg (sd 23.5 mmHg). The average number of BPs used to compute mean ED SBP was 3.2 (sd 1.8). Mean ED SBP was slightly higher, <1 mmHg, than research SBP.

Mean research SBP was 136.7 mmHg (sd 24.2 mmHg). Research SBP was available for 297 of the 299 subjects in Population A, and 245 of these were measured before administration of vasoactive

medication. Summary statistics for research SBP and research SBP prior to administration of vasoactive medication are reported in the Chapter 3 Appendix; given the small difference between these, the research SBP for 297 subjects was used as the secondary measure of ED SBP.

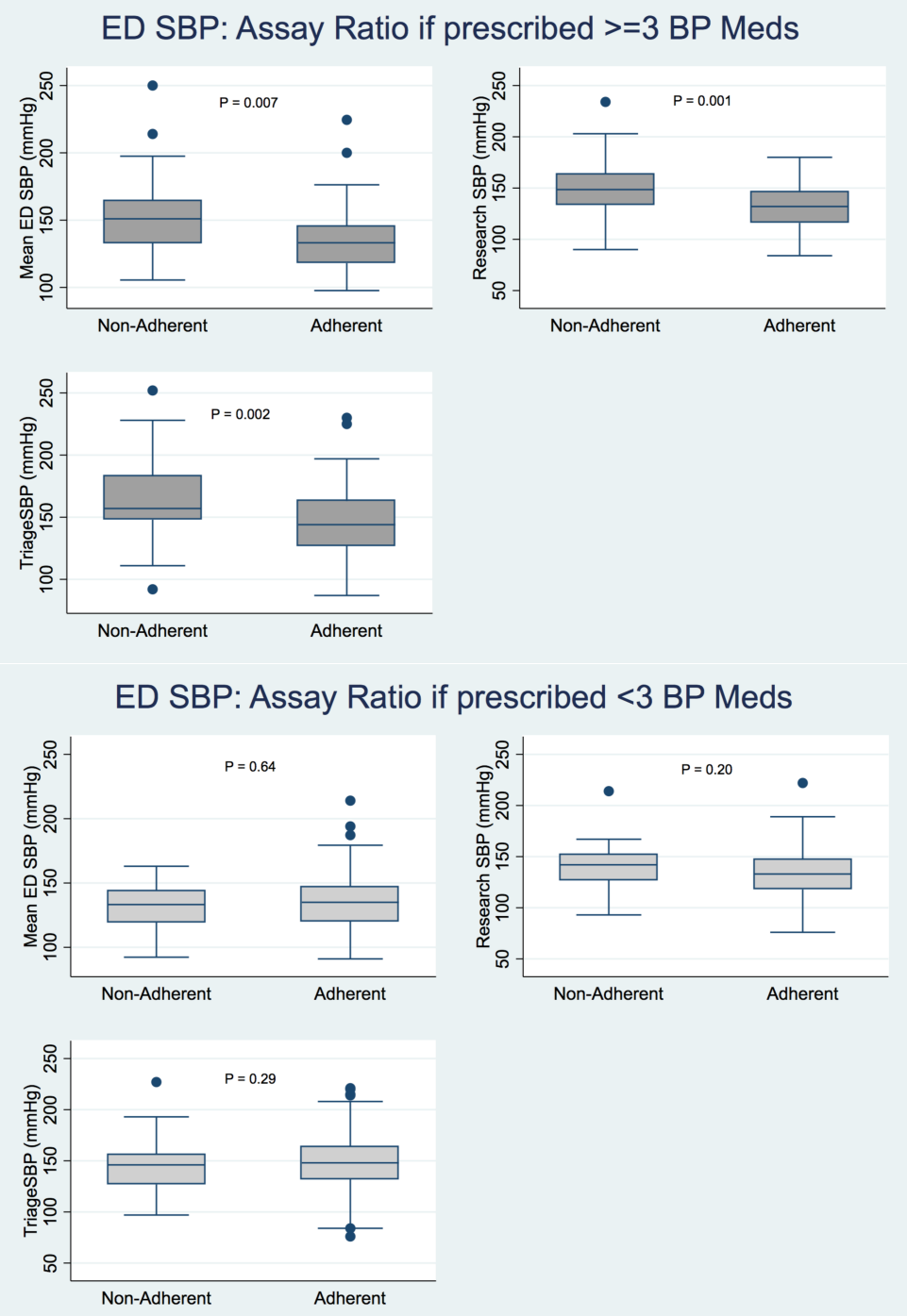
Triage SBP, reported in the Chapter 3 Appendix for completeness, was available for all 299 patients in Population A; given concerns regarding accuracy of measurement methods, this was not used in analyses. By triage SBP, 31.1% of patients had SBP≥160 mmHg, though this proportion was only 12.6% according to mean ED SBP, and 15.1% by research SBP.

Univariate Associations of Medications Adherence with ED SBP

Box plots for ED SBP by adherent/non-adherent stratified by the number of prescribed BP medications are found in Figure 6 (< 3 BP medications, N = 198; ≥3 BP medications, N = 101). Similar boxplots using the ARMS to classify adherent/non-adherent are reported in the Chapter 3 Appendix. Regardless of the measure of ED SBP and adherence used, non-adherent patients had higher SBP compared to adherent patients.

For completeness, univariate associations between of patient characteristics with medication adherence (the exposure) and ED SBP (the outcome) are reported in the Chapter 3 Appendix. Medication adherence was associated with both age and race; there was evidence for associations with BMI, numeracy, duration of hypertension, and number of hypertensive medications for adherence measured by the assay, by not by the ARMS. Race and number of prescribed hypertensives were associated with all measures of ED SBP. BMI was associated with mean ED SBP and with triage SBP but not with research SBP. Having a history of atrial fibrillation and health literacy were associated with only triage SBP. Numeracy and duration of hypertension were associated with research SBP.

Figure 6: Population A, ED SBP by Adherent/Non-Adherent, Stratified by Number of Prescribed Antihypertensives*
* P-values from Spearman rank order tests



Adjusted Associations of Adherence with ED SBP

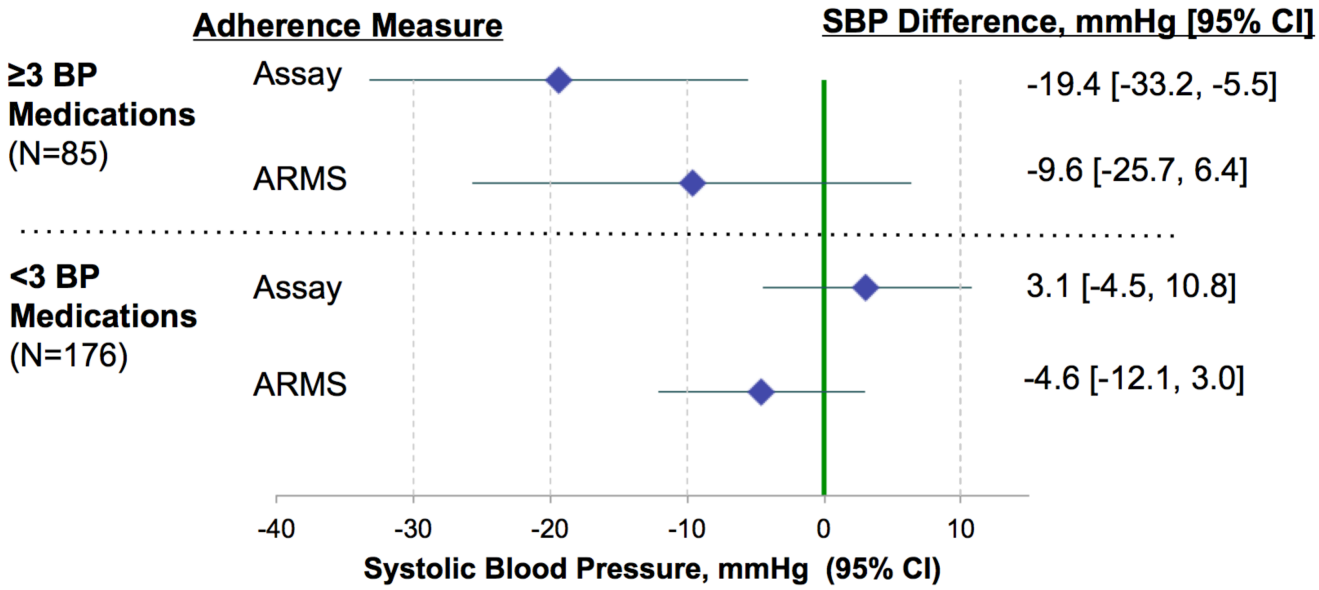
Following multiple imputation of numeracy for 18 subjects, unadjusted and adjusted linear regression were performed to evaluate the relationship between medication adherence and ED SBP. Analyses were stratified by the number of prescribed BP medications (<3/≥3). The decision to stratify by >= 3 antihypertensive medications was made *a priori* based on clinical significance. Use of three antihypertensives and an elevated BP value constitutes the definition for resistant hypertension.

Thus determining which patients who were at risk for being categorized as resistant hypertension due to non-adherence would be an important distinction in this cohort.

Medication adherence was measured by the assay ratio and the ARMS in separate models; both measures of adherence were examined as dichotomous (adherent/nonadherent) and continuous variables. Results of adjusted models, which were marginally different from unadjusted models (not presented), are presented in Table 10. Results of adjusted analyses are also visualized in Figure 7.

Table 10: Adjusted Associations Between Adherent and SBP in the ED*				
	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)
Prescribed ≥3 BP Medications				
	Adherent By Assay	Assay (continuous, per 10% increase)	Adherent By ARMS	ARMS (continuous)
Mean ED SBP, mmHg (N = 85)	-19.4 (-33.2 to -5.5)	-5.1 (-8.0 to -2.2)	-9.6 (25.7 to 6.4)	-3.4 (-5.8 to -1.1)
Research SBP, mmHg (N = 99)	-22.2 (-33.2 to -11.2)	-4.2 (-6.3 to -2.1)	-15.3 (-29.4 to -1.3)	-2.5 (-4.3 to 0.7)
Prescribed <3 BP Medications				
	Adherent By Assay	Assay (continuous, per 10% increase)	Adherent By ARMS	ARMS (continuous)
Mean ED SBP, mmHg (N = 176)	3.1 (-4.5 to 10.8)	0.6 (-0.4 to 1.5)	-4.6 (-12.1 to 3.0)	-0.5 (-1.6 to 0.6)
Research SBP, mmHg (N = 198)	-3.0 (-11.2 to 5.2)	0.02 (-1.0 to 1.0)	-2.3 (-10.0 to 5.4)	-0.8 (-1.9 to 0.3)
*Adjusted for: age, sex, race, insurance status, health literacy, numeracy, BMI, chronic renal insufficiency, comorbidity index, and duration of hypertension diagnosis				

Figure 7: Difference in mean ED SBP* for Completely Adherent Subjects Compared to Partially/Completely Non-Adherent Subjects, *stratified by number of prescribed antihypertensive medications*



* Adjusted for age, pain, sex, race, health insurance, health literacy, numeracy, BMI, chronic renal insufficiency, comorbid conditions, and duration of hypertension diagnosis
Abbreviations: BP, blood pressure; ARMS, adherence to refills and medications scale; BMI, body mass index

Assay Ratio vs. ARMS

The assay ratio explained a significant amount of variance in ED SBP beyond that explained by the ARMS among patients prescribed ≥3 BP medications. This was true for both mean ED and research SBP, regardless of whether adherence was modeled as a dichotomous or continuous variable (Table 11). There was not evidence that the assay ratio explained a significant, independent component of variance in ED SBP beyond that of the ARMS among patients who were prescribed <3 BP medications. This suggests that although the relationship between medication adherence and ED SBP was similar in direction when adherence was measured by the assay ratio versus the ARMS, the assay ratio was a better measure of medication adherence in terms of its relationship with ED SBP, at least among patients prescribed ≥3 BP medications.

Table 11: Population A - Wald Test P-values for Assay Ratio vs. ARMS (Prescribed ≥3 BP Medications)*

	Mean ED SBP (N = 85)	Research SBP (N = 99)
P-value for Assay Ratio (continuous)	0.01	0.001
P-value Adherent By Assay Ratio	0.01	<0.001
P-value for ARMS (continuous)	0.19	0.09
P-value for Adherent by ARMS	0.51	0.09
* model includes both the assay ratio and ARMS		

Subgroups: Raw Chromatograph Output and SBP

Among patients prescribed ≥3 BP medications, there was only evidence for an association between standardized raw chromatograph output with ED SBP for lisinopril (Table 12); there was not, however, evidence for relationships for the other four BP medications evaluated. There was no evidence for associations between raw chromatograph output and ED SBP for patients prescribed <3 BP medications.

Table 12: Unadjusted Associations Between Standardized Chromatograph Raw Output and Mean ED SBP Among Patients Prescribed ≥3 Antihypertensive Medications, by Individual BP Medications

	Mean ED SBP	Research SBP	Triage SBP
	Beta* (95% CI)	*Beta (95% CI)	*Beta (95% CI)
Lisinopril	**-24.0 (-43.7 to -4.4)** (N = 37)	-15.7 (-37.3 to 5.9) (N = 41)	**-34.4 (-60.4 to -8.4)** (N =42)
Metoprolol	-3.2 (-14.7 to 8.4) (N = 31)	-4.4 (-15.8 to 7.1) (N = 36)	1.9 (-13.0 to 16.9) (N = 37)
HCTZ	-3.2 (-12.4 to 6.1) (N = 32)	3.1 (-4.4 to 10.7) (N = 34)	4.4 (-6.8 to 15.6) (N = 35)
Amlodipine	-6.9 (-15.6 to 1.8) (N = 39)	-5.4 (-14.5 to 3.7) (N = 41)	-6.0 (-15.5 to 3.5) (N = 42)
Losartan	-3.1 (-15.6 to 9.4) (N = 18)	-4.0 (-14.5 to 6.5) (N = 20)	-4.8 (-16.9 to 7.2) (N = 21)
*Standardized beta coefficients			

Aim 3: Brief Summary

After accounting for multiple patient demographics and clinical characteristics, higher medication adherence measured by either the assay ratio or ARMS was associated with significantly lower ED SBP in Population A, although this relationship was statistically significant only for the assay ratio and among patients prescribed ≥3 antihypertensive medications. This was the case regardless of whether ED SBP was measured as the mean of clinically measured BPs or by research staff. The assay ratio performed better as a measure of medication adherence than the ARMS, in terms of explaining variance in ED SBP.

We sought to determine whether our findings regarding the assay's test characteristics and its relationship with SBP were true in other settings and patient populations. Aim 2 and 3 analyses were repeated in Population B, as described in the following sections.

Population B: External Validation of the Assay Ratio

Population B analyses were conducted to examine the validity of assay ratio as a measure of antihypertensive adherence in a different setting and patient population . Patients in Population B were recruited in the ED but their adherence and SBP data was collected 16 weeks later during the course of a randomized control trial; these patients were all Black, very few had primary care access, and their enrollment ED SBP was much higher than that of Population A. Our goal was to examine whether the overall conclusions from Population A analyses were confirmed in Population B.

Study Population and Setting

Population B consisted of outpatients enrolled in a randomized trial that was designed to evaluate the impact of Vitamin D supplementation on BP control among African American patients (Adjunct Vitamin D Therapy as a Means to Reduce the Disparity in Subclinical Target Damage, AdDReaCH). For this trial, 111 subjects were enrolled, and of these 99 had Week 16 follow up samples available for analysis. These 99 subjects are included in the subset of Aim 2 and 3 analyses as Population B.

Population B subjects were recruited from the ED at the Detroit Receiving Hospital, which is an inner-city, tertiary care institution in Detroit, MI that is affiliated with the Wayne State University (WSU) School of Medicine and has ~ 102,000 adult visits per year. The primary outcome of the parent study was change in left ventricular mass/left ventricular hypertrophy (LV mass indexed to body surface area) as determined by cardiac magnetic resonance (CMR) imaging at baseline, week 16, and week 52. Samples drawn at Week 16 were used for analyses in Aim 2 and 3. Patients who self-identified as African Americans and resided in the Detroit metropolitan area were recruited. Those with known hypertension (defined by self-report or documented diagnosis in a previous ED, clinic, or electronic health record report) and poorly controlled BP (initial ED SBP ≥ 160 mmHg) were screened using the following inclusion and exclusion criteria:

Population B inclusion criteria included the following:

- African-American race (by self-report)
- At least one other SBP ≥ 160 mmHg within 1 hour of arrival
- Age 30-74 years
- Asymptomatic elevated BP (class I as defined by Goldman Specific Activity Scale[37])
- Serum vitamin D level < 20 ng/dl
- Increased left ventricular mass by CMR (> 89 g/m^2 in men, and > 73 g/m^2 in women)

Population B exclusion criteria included the following:

- Dyspnea (exertional, rest or nocturnal) or chest pain as a primary or secondary chief complaint
- Prior history of heart failure, coronary artery disease, myocardial infarction, any cardiomyopathy, any valvular heart disease, renal failure with current, previous, or planned future dialysis, or stroke
- Acute illness or injury requiring hospitalization
- Acute alcohol or cocaine intoxication; chronic alcohol abuse or cocaine (self-reported) abuse
- Acute or decompensated psychiatric disorder or any underlying psychiatric disorder or cognitive deficit that prevented effective on-going communication or ability to follow-up
- Cancer (other than skin), HIV, or any other medical condition that might limit life expectancy
- Hepatitis or liver enzyme elevations > 1.5 times normal
- Plans move > 50 miles in the next 9 months
- History of kidney stones

- Serum calcium > 10.5 mg/dl or known history of hypercalcemia
- Renal insufficiency (eGFR <60)
- History of or known primary hyperparathyroidism
- Sarcoidosis or other granulomatous disease
- Pregnant or planning to become pregnant
- Allergy or known hypersensitivity to gadolinium contrast
- Severe claustrophobia

At enrollment, research assistants recorded demographics including self-reported income, insurance status, and zip code, medical and social history, and current medications and collected initial serum samples. BP was measured using the BP Tru device, which provides a standardized automated method of brachial cuff oscillometric measurement. Using the BP Tru device, six readings in the seated position were obtained over 7 minutes, and the average of the final five BP readings is reported. Patients were then randomized to receive adjunct vitamin D therapy, 50,000 IU of cholecalciferol every other week or placebo.

A complete list of variables collected for Population B are found in the Chapter 3 Appendix. Briefly, age, sex, ethnicity, education, employment status, health insurance status, and whether the patient had a primary care provider were collected at the time of enrollment in the parent study. Smoking status, alcohol intake, BMI, and exercise were also collected.

Blood Pressure Management Protocol

All medications for manangement of blood pressure and comorbidities such as diabetes, and hyperlipidemia were provided by the study team using a standardized algorithm:

1) Initial treatment with a diuretic (for those in whom combination drug therapy was not otherwise indicated) appropriate for the level of kidney function: HCTZ used only when eGFR > 45 ml/min/1.73 m^2; chlorthalidone when eGFR > 35;
2) Two drug combination therapy when BP was 15 mmHg systolic and/or 10 mmHg diastolic above goal (> 140/90 mmHg); and 3) addition of a calcium channel blocker when a third drug was needed. Drugs doses were at least at the mid-point of their maximal FDA approved dosing range. When BP remained above goal, BP medications were intensified at 4-week intervals until BP goal was achieved. Patients were on, at most, 4 medications at a time, with a median of 2 medications (Q_1 to Q_3: 2, 3).

Table 13: Population B Prescribed Blood Pressure Medications Prescribed (N=99)

Medication	Number (%)
Amlodipine	42 (42.4%)
Chlorthalidone	82 (82.8%)
Lisinopril	62 (62.6%)
Losartan	12 (12.1%)
Metoprolol	12 (12.1%)
Spironolactone	2 (2.0%)

Measures of Medication Adherence

Medication adherence, the focus of Aim 2 analyses and the exposure in Aim 3, was measured by three tools at Week 16 - the mass spectrometry assay, the Morisky scale, and pill count ratios – as outlined in Table 14.

Table 14: Population B Measures of Adherence

Measure of Adherence	Modeling Approaches
Assay* N = 99	Dichotomized (adherent: assay ratio = 1.0, nonadherent: assay ratio <1.0) Continuous Subgroups: Continuous (raw chromatograph output) for lisinopril, metoprolol, chlorthalidone, amlodipine, losartan
Morisky N = 99	Dichotomous (Adherent = 0; Nonadherent>0) Continuous
Pill Count Ratio* N = 67	Dichotomous (Adherent ≥0.80; Nonadherent <0.80) Continuous

Mass Spectrometry Assay

In Population B, the mass spectrometry assay was performed on plasma samples drawn during the Week 16 study visit. As in Population A, the assay adherence ratio was computed as follows: (# detected antihypertensive medications / # of prescribed antihypertensive medications). This was then dichotomized: adherent: assay ratio = 1.0; non-adherent: assay ratio<1.0), and this dichotomized covariate was used as the primary measure of medication adherence in Population B. Because antihypertensive medications for Population B were prescribed according to a pre-specified protocol (see above, Section 5.b.), only the following medications were used to compute the assay ratio: amlodipine, chlorthalidone, lisinopril, losartan, and metoprolol. Spironolactone was not included the assay ratio computation in because it was prescribed for only two patients.

Morisky

The ARMS used in Population A as a measure of adherence was derived from the Morisky, which also utilizes patient-reported adherence to medication taking and medication refill behaviors. The Morisky administered to patients in Population B consisted of 4 yes/no items. The summed 4-item scale is typically categorized as follows: 0 = high adherence, 1-2 = medium adherence, >2 = low adherence,[38] and dichotomized to adherent/non-adherent as follows: adherent = 0; non-adherent > 0. For consistency across adherence measures, the continuous Morisky score for each subject was reverse-scored so that higher scores indicated higher patient-reported adherence behaviors. The Morisky was measured at enrollment, Week 2, and Week 16. One subject did not completely the Morisky at the Week 16 visit; for this patient, the Week 2 Morisky was carried forward and used as the Week 16 Morisky. Patients were asked the Morisky items about their BP medication and study medication separately.

Pill Count Ratio

As part of the parent study all antihypertensive medications were provided free of charge, prescribed and titrated according to protocol. At Week 16, subjects were asked to bring in all of their pill bottles;

when available, pills were counted for each prescribed medication, and this was used to compute the pill count ratio as a measure of antihypertensive adherence for each patient.

For each medication, a pill count ratio was computed as follows:

(# of pills dispensed - # of pills remaining in pill bottle)/ [(prescription fill date – date of pill count) x frequency],

where the frequency was daily, twice daily, or three times daily. For patients prescribed more than one antihypertensive medication, a summary pill count adherence measure was computed as follows:

(Sum of each medication pill count ratio, computed as above)/ (number of medications for which there were pill counts available)

The summary pill count ratio was used primarily as a dichotomous ratio (adherent: pill count ratio ≥ 0.80; nonadherent: pill count ratio < 0.80); in secondary analyses, it was also examined as a continuous measure.

Systolic Blood Pressure

In Population B, BP was measured by a BPTru machine, which computed the mean of the last 2 of 3 BP measurements taken one minute apart. BP was measured at the time of randomization and at Week 16 follow up visit. At the Week 16 visit, 98 of the 99 subjects had BP measured; these subjects are included in Aim 3 analyses, which examined the relationship between medication adherence and SBP.

Statistical Analyses: Aims 2 and 3

In Aim 2 analyses, we compared test characteristics of the assay ratio against two other, referent measures of medication adherence: the Morisky and pill count ratios. In Aim 3 analyses, we evaluated the relationship between each of the three measures of medication adherence and Week 16 SBP. Of 101 subjects enrolled in the study, 99 attended the Week 16 visit, had blood available to perform the assay, and completed the Morisky for Aim 2 analyses. Of these, 98 of these had SBP measured at Week 16 and were included in Aim 3 analyses.

Aim 2: Assay Ratio vs. Morisky and Pill Count Ratio

As in Population A Aim 2, we examined the mass spectrometry assay as a measure of antihypertensive adherence by comparing the assay ratio's distribution and non-parametric correlations with the reference standards of previously validated measures of medication adherence, the Morisky-8 and pill count ratio. The three measures of medication adherence were compared using scatter plots with locally weighted scatterplot smoothing (LOWESS) lines and Spearman's correlation coefficients with 95% confidence intervals (CI). Correlations within individual medications were examined using raw chromatograph output.

Test characteristics of the assay ratio were evaluated with receiver operating characteristic (ROC) curves, with computation of sensitivity, specificity, positive predictive value, and negative predictive value of the assay against the adherent/non-adherent referent standard of the Morisky and pill count ratios. The odds of being non-adherent, with 95% CI, were computed for adherent/non-adherent classified by the Morisky and pill count ratio.

In planned secondary analyses, we examined the assay ratio's performance by drug: lisinopril, metoprolol, chlorthalidone, amlodipine, and losartan. For each of these drugs, ROC curves examined the test characteristics of the assay ratio against adherent/non-adherent according to the Morisky-8 and pill count ratio. Results of similar analyses using the assay ratio as the referent standard are reported in the Chapter 3 Appendix.

As was done for Population A, a 4-level measure of adherence combining the assay ratio and Morisky was also used to examine the relationship between adherence and SBP; these results are included in the Chapter 3 Appendix.

Aim 3: Week 16 Adherence vs. SBP

Demographics and clinical characteristics for patients classified as adherent versus non-adherent by the assay ratio were examined. Analyses were stratified by number of prescribed antihypertensives (<3, ≥ 3 prescribed BP medications). Because of the small sample size in Population B, only unadjusted models were performed. The relationships between adherent/non-adherent (by assay, Morisky, and pill count ratio) with Week 16 SBP were examined using boxplots and linear regression. The likelihood ratio test was performed to examine the relative contribution of the assay ratio, Morisky-8, and pill count ratio in explaining Week 16 SBP variance. In planned secondary analyses, unadjusted linear regression was performed to examine the relationship between Week 16 SBP and standardized raw chromatograph output for individual BP medications.

Aim 2 Results: Assay Ratio vs. Morisky and Pill Count Ratio

Results for Aims 2 and 3 for Population B are reported separately. Aim 2 analyses compared the assay ratio to the Morisky and pill count ratio, while Aim 3 analyses examine the relationship between adherence with Week 16 SBP, comparing the assay ratio to the Morisky and pill count ratio.

Demographics and Clinical Characteristics

Full details of Population B patients are included in the Chapter 3 Appendix. Overall, population B subjects included in Aim 2 analyses were all Black and 95% were Non-Hispanic. On average, patients in Population B were younger, more likely to have no health insurance and had completed less schooling than Population A. Only 1/3 of Population B reported having a primary care provider, 58.6% reported having no health insurance, and 41.4% reported that they were unemployed.

Measures of Medication Adherence

Of the six antihypertensive medications on the treatment protocol for Population B, chlorthalidone was prescribed most frequently, followed by lisinopril and amlodipine (Table 15). As in Population A, the number of prescribed antihypertensives was on average higher than the number detected (detailed reported in Chapter 3 Appendix). The number of prescribed blood pressure medications per patient ranged from 1 to 4, with a mean of 2.2 (sd 0.7)

Table 15: Antihypertensives Prescribed in Population B (N = 99)

Medication	No. (%)
Lisinopril	63 (63.6)
Metoprolol	12 (12.1)
Chlorthalidone	82 (82.3)
Amlodipine	42 (42.4)
Losartan	12 (12.1)
Spironolactone	2 (2.0)

The proportion of subjects with detected antihypertensive medication varied by the prescribed antihypertensive (Table 16) and was lowest for spironolactone, losartan, and chlorthalidone. I Population B, antihypertensive presence was detected among ≥ 80% of those prescribed only for lisinopril and amlodipine.

Table 16: Population B - Prescribed and Detected Antihypertensive Medications, for the Six Antihypertensives Included in the Assay Ratio (N = 99)

	Prescribed	Detected	Percent Detected
Lisinopril	63	52	82.5%
Metoprolol	12	9	75.0%
Chlorthalidone	82	57	69.5%
Amlodipine	42	36	85.7%
Losartan	12	8	66.7%
Spironolactone	2	1	50.0%

Distributions of the measures of adherence for Population B are reported in Table 17. As in Population A, the measures of medication adherence were skewed, and the majority of subjects were

categorized as adherent (histograms are included in the Chapter 3 Appendix). The pill count ratio classified the highest proportion of patients as adherent, followed by the assay ratio and then the Morisky. Of note, however, only 67 (68%) of patients brought their pill bottles to the Week 16 visit.

Table 17: Population B Adherence Measures	
Week 16 Assay Ratio (N = 99)	
Assay Ratio, mean (sd) median (Q_1, Q_3)	0.75 (0.38) 1 (0.5, 1)
Adherent (Assay ratio = 1.0), no. (%)	63 (63.6)
Week 16 reverse-coded Morisky (N = 99)	
Morisky (range, 0 to 4), mean (sd) median (Q_1, Q_3)	0.87 (0.79) 1 (0, 1)
Morisky, reverse-coded (range 1 to 5), mean (sd) median (Q_1, Q_3)	8.1 (0.79) 8 (8, 9)
Morisky Adherence Categories, no. (%) High Medium Low	 33 (33.7) 62 (63.3) 3 (3.1)
Week 16 Pill Count Ratio (N = 67)	
Pill Count Ratio, mean (sd) median (Q_1, Q_3)	0.86 (0.16) 0.91 (0.80, 0.98)
Proportion with Pill Count Ratio ≥0.80, no. (%)	52 (77.6)

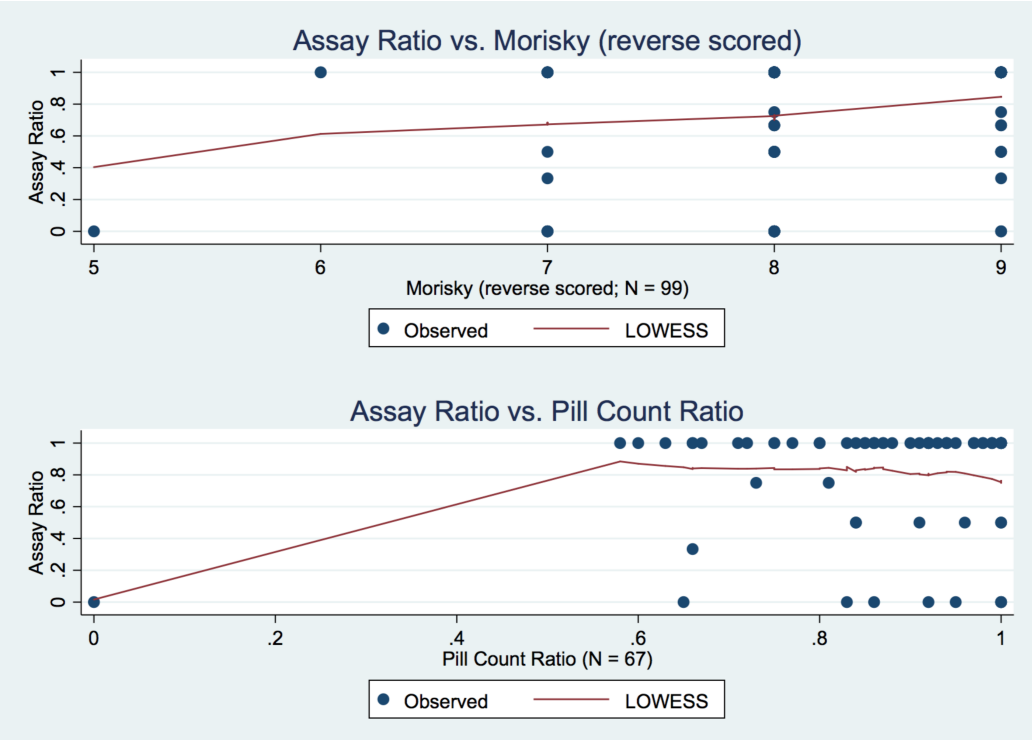
Continuous Assay Ratio vs. Morisky and Pill Count

The relationship between adherence measured by the assay ratio compared to the Morisky and pill count ratio are illustrated in Figure 8. The relationship between the assay and the Morisky is approximately linear, similar to the relationship with the ARMS for Population A; across the range of both the assay ratio and Morisky, there were patients with an adherence assay ratio of 1.0 who had evidence of non-adherence by the Morisky, and visa versa. The relationship of the assay ration with pill counts was not linear and appeared to have a threshold at approximately a pill count ratio of 0.60.

In the small sample size available in Population B, there was not evidence for statistically significant correlation between the assay ratio and Morisky or pill count ratio, globally or for drug subgroups (full results reported in the Chapter 3 Appendix). The point estimate for the global correlation coefficient for the assay ratio versus the Morisky (rho 0.18) was similar to that found in Population A (rho 0.23); point estimates for correlations by individual BP medications were also similar across the two study populations, with the exception of metoprolol, which was negative in Population B. There was no evident correlation between the assay ratio and pill count ratio, globally or by individual medications.

There were also no evident associations between standardized raw chromatograph output by individual antihypertensive medications, with either the Morisky (reverse-scored) or the pill count ratio (full results reported in the Chapter 3 Appendix). Of note, however, there was evidence for correlation between pill counts and the Morisky (reverse-scored), as has been found in prior work,[39,40] with a Spearman's rho of 0.60 (95% CI 0.38 to 0.71, P<0.001).

Figure 8: Population B Scatterplot and LOWESS of Assay Ratio versus the Morisky (Reverse Scored) and Pill Count Ratio



Dichotomous: Assay Ratio vs. Morisky and Pill Count Ratio

Nonadherence identified by the assay ratio had a PPV of 75.0% for non-adherence classified by the Morisky, in a population where 66.7% of subjects were classified as non-adherent by the reference standard (Table 18). Of the 63 patients classified adherent by the assay ratio, 39 (62%) were classified non-adherent by the Morisky. Of note, patients had been instructed to take their morning dose of BP medication prior to their Week 16 study visit.

Table 18: Non-Adherent, by Assay Ratio and Morisky (Referent: Morisky)

	Non-Adherent by Morisky (Morisky > 0)	Adherent by Morisky (Morisky = 0)	
Non-Adherent by Assay Ratio (assay ratio < 1.0)	27	9	36
Adherent by Assay Ratio (assay ratio = 1.0)	39	24	63
	66	24	99

OR 1.8 (95% CI 0.7 to 5.2)

Sensitivity	Pr(+| D)	40.91%	28.95%	53.71%
Specificity	Pr(-|~D)	72.73%	54.48%	86.70%
Positive predictive value	Pr(D| +)	75.00%	57.80%	87.88%
Negative predictive value	Pr(~D| -)	38.10%	26.15%	51.20%

Nonadherence identified by the assay ratio had a PPV of 23.5% for non-adherence classified by the pill count ratio; this was not statistically significant (Table 19).

Table 19: Non-Adherent, by Assay Ratio and Pill Count Ratio (Referent: Pill Count Ratio ≥0.80)

	Non-Adherent by Pill Count Ratio (ratio <0.80)	Adherent by Pill Count Ratio (ratio ≥0.80)	
Non-Adherent by Assay Ratio (assay ratio < 1.0)	4	13	18
Adherent by Assay Ratio (assay ratio = 1.0)	11	38	49
	15	52	67

OR 1.0 (0.2 to 4.1)

Sensitivity	Pr(+| D)	26.67%	7.79%	55.10%
Specificity	Pr(-|~D)	74.51%	60.37%	85.67%
Positive predictive value	Pr(D| +)	23.53%	6.81%	49.90%
Negative predictive value	Pr(~D| -)	77.55%	63.38%	88.23%

Results comparing the Morisky and pill count ratios to the assay ratio using the assay ratio as the reference standard are reported in the Chapter 3 Appendix.

The c-statistics comparing the assay ratio to the Morisky (c-statistic 0.52) and pill count ratios (c-statistic 0.50) were statistically no better than chance. When restricting analyses by prescribed antihypertensive medication, slight differences were noted; for lisinopril and amlodipine, c-statistics were similar to those in Population A (0.67 and 0.61, respectively), while c-statistics for chlorthalidone and losartan were less than 0.50, or worse than chance. All ROC curves are reported in the Chapter 3 Appendix.

Aim 2 Brief Summary

As in Population A, we anticipated that because the three Population B measures of medication adherence focused on different aspects of medication adherence their associations would be weak-to-moderate at best. The point estimate for correlation between the assay ratio and reverse-scored Morisky (0.18, 95% CI -0.021 to 0.36) were similar to that for the assay ratio with the ARMS (Spearman's rho 0.23, 95% CI 0.11 to 0.33), although the correlation between the assay ratio and Morisky were not statistically significant (N = 99). The large proportion of patients missing Week 16 pill counts hampers the ability to draw firm conclusions regarding its relationship with the assay ratio.

Aim 3 Results: Medication Adherence and Week 16 SBP

In Aim 3, Population B was examined to determine whether the relationship between medication adherence and SBP was similar in direction and strength to those found in Population A. Analyses were stratified, as in Population A, by the number of prescribed BP medications (<3, ≥3 BP medications), and given the small sample size in Population B, were unadjusted.

For 98 subjects in Population B, Week 16 SBP and the assay ratio were available; one subject for whom blood was drawn did not have BP measured during the visit. Thus, 98 subjects were included in Aim 3 Population B analyses. Population B demographics, stratified by adherence, are reported in Table 20. Patients who were adherent according to the assay ratio were more likely to be male, have health insurance, have a primary care provider, and have completed at least a high school education. Adherent patients were also more likely to be employed full time and not smoke; their BMI was slightly higher and their medication therapeutic intensity score was slightly lower than patients who were classified as non-adherent by the assay ratio.

Table 20: Population B, Aim 3 Demographics and Clinical Characteristics

Variable*	Adherent by Assay Ratio (N = 63)	Non-Adherent by Assay Ratio (N = 35)
Age at randomization, years		
mean (sd)	46.9 (8.0)	45.3 (7.5)
median (Q_1, Q_3)	47.6 (40.7, 53.4)	45.2 (40.1, 52.0)
Female, no. (%)	28 (44.4)	24 (68.6)
Health Insurance, no. (%)		
No insurance	35 (55.6)	22 (62.9)
Medicare/Medicaid/Other government insurance	15 (23.8)	6 (17.1)
HMI/PPO/Other Private Insurance	13 (20.6)	7 (20.0)
Has a Primary Care Provider, no. (%); 2.0% missing	21 (33.9)	8 (26.5)
Annual Income in US dollars	(N = 34)	(N = 22)
mean (sd)	16,502 (13,398)	22,684 (18,848)
median (Q_1, Q_3)	16,000 (5,000, 25000)	20,000 (6800, 30,000)
Highest Level of Education, no. (%)		
<High School	8 (12.7)	7 (20.0)
High School/GED	40 (63.5)	19 (54.3)
> High School	15 (23.8)	9 (25.7)
Employment Status, no. (%)		
Full-Time	22 (34.9)	8 (22.9)
Unemployed	28 (44.4)	13 (37.1)
Ever Smoked Cigarettes, no. (%)	34 (54.0)	27 (77.1)
Exercises Regularly, no. (%)	28 (44.4)	17 (48.6)
Has diabetes, no. (%)	7 (11.1)	5 (14.3)
BMI at CMR visit; kilograms per meter-squared		
mean (sd)	34.1 (8.0)	32.1 (9.6)
median (Q_1, Q_3)	34.8 (30.8, 37.4)	29.8 (23.8, 39.0)
Total Therapeutic Intensity Score, mean (sd)	0.73 (0.61)	0.84 (0.68)
median (Q_1, Q_3)	0.75 (0.11, 1.25)	0.75 (0.36, 1.5)
Group A Randomization, no. (%)	27 (42.9)	19 (54.3)
*No missing data unless otherwise noted		

Exposure: Medication Adherence

Based on results of Population B Aim 2 analyses, the three measures of medication adherence were modeled as dichotomous variables, adherent/non-adherent (Table 21). Among the 67 patients for whom pill count ratios were available, 77.6% were classified as adherent, compared to 64.9% by the assay ratio and 33.7% by the Morisky.

Table 21: Population B, Aim 3 Medication Adherence	
Adherent by assay (ratio = 1.0), no. (%) N = 98	63 (64.9)
Adherent by Morisky (Morisky = 0), no. (%) N = 98	33 (33.7)
Adherent by pill count ratio (ratio ≥0.80), no. (%) N = 67	52 (77.6)

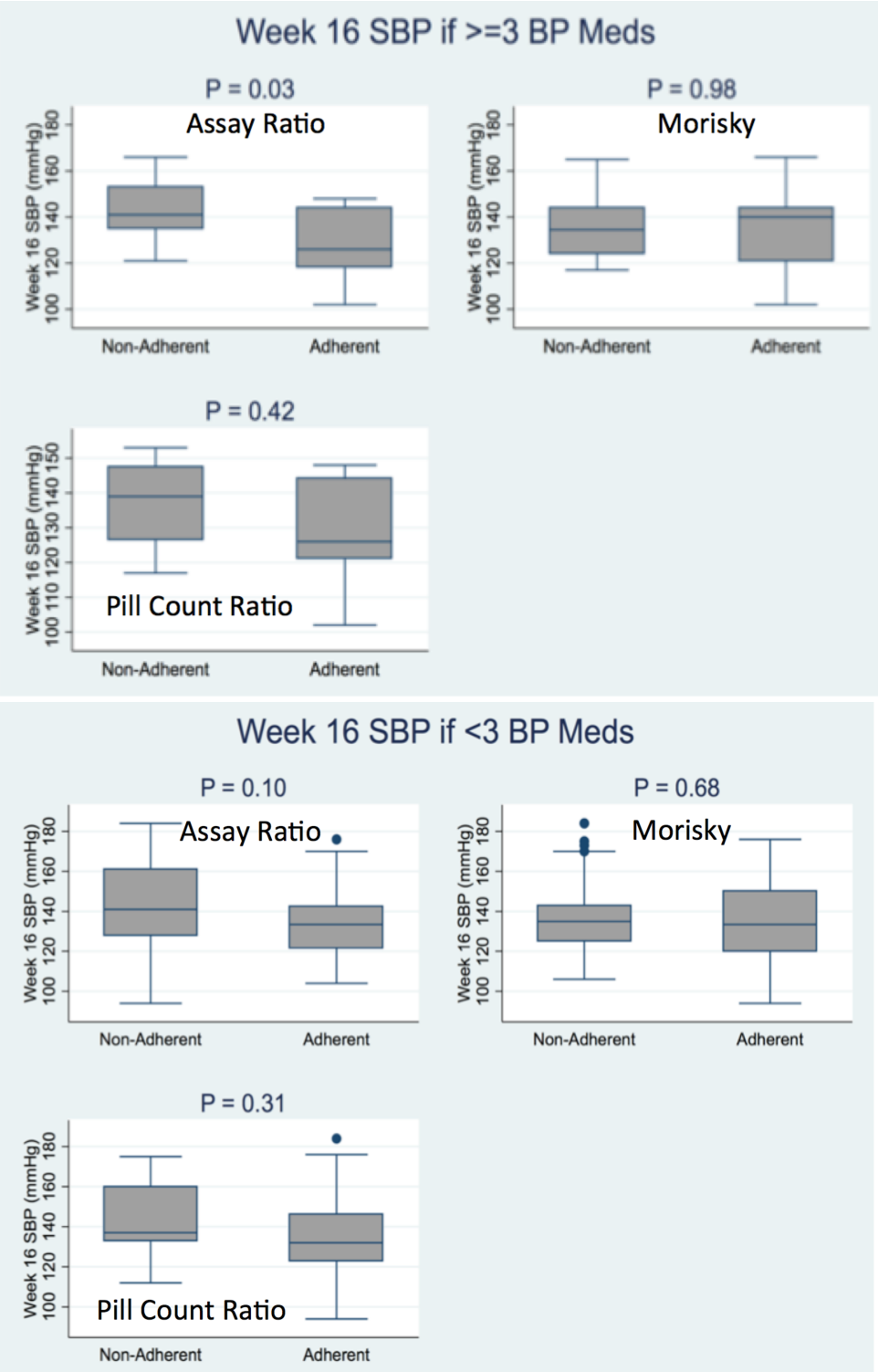
Outcome: Week 16 SBP

Distribution of Week 16 SBP in Population B was similar to the distribution of mean ED SBP for Population A (Chapter 3 Appendix), with a mean SBP of 136.0 mmHg and standard deviation of 18.8 mmHg. Median Week 16 SBP was 135.0 mmHg (Q_1, Q_3: 124.0, 144.0 mmHg). The mean decrease in SBP from enrollment to Week 16 was 58.2 mmHg.

Boxplots: Medication Adherence vs. SBP

Boxplots show the distribution of Week 16 SBP, comparing adherent to non-adherent patients according to each of the three measures of medication adherence (Figure 9). By the rank sum test, Week 16 SBP was statistically different only among patients prescribed ≥3 BP medications when adherent/non-adherent was defined by the assay ratio. Although not statistically significant in this small sample size, overall, point estimates were consistent with higher Week SBP among patients classified as non-adherent, with the exception of non-adherence classified by the Morisky among patients prescribed ≥3 BP medications.

Figure 9: Population B Week 16 SBP by Adherent/Non-Adherent (Classified by the Assay Ratio, Morisky, and Pill Count Ratio), Stratified by Number of Prescribed Antihypertensive Medications



Regressions Models: Medication Adherence vs. SBP

Unadjusted linear regression was performed to evaluate the magnitude of the difference in Week 16 SBP between adherent and non-adherent patients, by each measure of medication adherence (Table 22). In Population B, patients who were adherent according to the assay ratio had Week 16 SBP that

was approximately 17 mmHg lower than patients who were non-adherent; this is similar to the difference in SBP of approximately 19 mmHg found in Population A.

Table 22: Population B - Unadjusted Linear Regression of Medication Adherence with Week 16 SBP, Stratified by Number of Prescribed BP Medications			
	Difference in Week 16 SBP (mmHg)		
Measures of Adherence	Beta	95% CI	Adjusted R-squared for Model
Prescribed ≥3 BP Medications			
Adherent by assay ratio (N = 25)	-17.2	-29.3 to -5.0	0.24
Adherent by Morisky (N = 25)	-1.9	-34.3 to 9.5	-0.04
Adherent by pill count ratio (N = 19)	-9.3	-26.4 to 7.8	0.02
Prescribed <3 BP Medications			
Adherent by assay ratio (N = 73)	-8.6	-18.1 to 0.9	0.03
Adherent by Morisky (N = 73)	-2.2	-12.2 to 7.9	-0.01
Adherent by pill count ratio (N = 48)	-6.3	-20.9 to 8.3	-0.01

Comparison of Adherence Measures

The likelihood ratio test was performed to determine whether there was detectable evidence that the additional variance in Week 16 SBP was explained by the assay ratio, beyond that explained by either the Morisky or pill count ratio. R-squared statistics for separate models by adherence measure are included in Table 22. Among the 25 patients who were prescribed ≥3 BP medications, the assay ratio explained significantly more variance than that explained by the Morisky (P = 0.004). Among the 19 patients prescribed ≥3 BP medications and for whom pill counts were available, the P-value of the likelihood ratio test was 0.33. For patients prescribed <3 BP medications, the P-value for the likelihood ratio test was 0.08 for the 73 patients for whom the assay ratio and Morisky were available; the P-value was 0.06 for the 48 patients for whom the assay ratio and pill count ratio were both available.

Raw Chromatograph Output vs. SBP by Medication

Unadjusted linear regression was used to examine the relationship between standardized raw chromatograph output with Week 16 SBP (full results are included in the Chapter 3 Appendix). Sample sizes for detected medications stratified by the number of prescribed medications were small, less than 40. Point estimates for the associations among patients prescribed ≥3 BP medications were consistent with lower SBP for higher raw chromatograph output. Only the relationship between chlorthalidone and SBP among patients prescribed <3 BP medications was statistically significant.

Aim 3: Brief Summary

In this second patient population, with a diverse demographic background and in an outpatient setting, overall patterns of results were similar to those found in Population A. The assay ratio was loosely related to the other, indirection measures of adherence, the Morisky and pill count ratios. Point estimates for the relationship between the assay ratio and Week 16 SBP were similar to those identified in Population A, although they were not statistically significant. Samples sizes were too small to decipher clear patterns within individual antihypertensive medications. We found evidence in Population B to support the findings in Population A that assay ratio is an important, independent predictor of SBP, beyond indirect measures of medication adherence.

Discussion

Aims 2 and 3 examined the construct and predictive validity of the assay ratio as a measure of antihypertensive medication adherence. The assay ratio is derived from a liquid chromatography mass spectrometry blood assay that has been validated to detect 35 cardiovascular drugs; this mass spectrometry assay meets FDA recommendations for quantification, i.e., calculation of drug levels, for 14 of the 35 cardiovascular medications. The questions Aims 2 and 3 sought to answer were:

1) What are the test characteristics of the assay ratio (number of BP medications detected by the mass spectrometry assay / number of prescribed BP medications) as a measure of medication adherence compared to other, validated measures of medication adherence?
2) Is the assay ratio associated with SBP?

If so,

3) Is the relationship between the assay ratio and SBP consistent in multiple clinical settings and patient populations?
4) What is the value of performing the assay instead of using the other, previously validated measures of medication adherence?

To answer these questions, we utilized two diverse patient populations in different clinical settings: Population A, which consisted of 299 primary care patients who were prescribed any one or more of 15 BP medications detected by the assay during an ED visit; and Population B, which consisted of 99 African American patients in an urban setting who had treated or untreated hypertension at the time of their recruitment into a clinical trial; Population B measures were collected at the Week 16 study visit.

In Population A, medication adherence was measured by the assay ratio (computed from a total of 14 BP medications) and the ARMS, and SBP measures were obtained by clinical and research staff; all measures were obtained during an ED visit. In Population B, medication adherence was measured by the assay ratio (computed from five BP medications that were prescribed according to study protocol), the Morisky, and when available, pill counts; SBP was measured by research staff and was obtained using the BPTru device, which computes an average of multiple BP measurements that are taken 1 minute apart.

Assay Ratio Test Characteristics

Overall, the assay ratio performed as a sensitive measure of antihypertensive for the antihypertensive medications detected by the assay. Nonadherence identified by the assay ratio had a PPV of 91% for nonadherence identified by the ARMS in Population A and PPV of 75% for nonadherence identified by the Morisky in Population B; PPV was 24% for nonadherence identified by pill count ratios in Population B. The point estimate for the global, nonparametric correlation coefficient for the assay ratio versus the Morisky (rho 0.18) was similar to that found in Population A (rho 0.23). The AUC for ROC for the assay versus the ARMS was 0.60 in Population A, compared to a c-statistic for the Morisky of 0.52 in Population B. Point estimates for correlations by individual BP medications were also similar across the two study populations, with the exception of metoprolol, which had a negative correlation coefficient in Population B. There was no evident correlation between the assay ratio and pill count ratio, globally or by individual medications.

For Population A, the assay ratio was restricted to 14 specific antihypertensive medications, and for Population B it was restricted to five medications. The nature of mass spectrometry drug detection and quantification using blood also contributes to the assay's performance sensitive, rather than specific, measure of antihypertensive adherence; patients can miss several doses, take too much or too little medication, or take medication at the wrong time and still have sufficient measureable drug to be classified as adherent by the assay ratio.

The ARMS, an indirect measures of general medication adherence, classified more patients as non-adherent than the assay ratio. The Morisky classified 67% of patients as non-adherent, compared to 64% according to the assay ratio; for 48 out of 99 patients, the Morisky and assay ratio classified adherence differently. The ARMS and Morisky are global measures of medication adherence, not limited to antihypertensive medications or to a specified time frame. Patients were left to interpret whether survey items about medication taking and refill behavior referred to short or long-term behaviors. In addition, the ARMS and Morisky focus on multiple domains of general medication adherence, namely medication taking and medication refill behavior, and rely on patient report of these behaviors. Patient report is subject to recall and social desirability bias, which may influence report of behaviors in either direction.

Pill counts are a proxy for medication taking behavior that can be manipulated by pill dumping or storing in other locations. Prior work found that pill counts consistently overestimate adherence.[41] In our study, the only factor that correlated with pill counts was self-reported exercise, another behavior subject to recall and social-desirability bias.

Relationships between the assay ratio and indirect measures of adherence were weak-to-moderate in strength. This is consistent with prior work that revealed weak associations among multiple measures of medication adherence.[42] Keeping in mind the small sample size and large proportion of missing data, we did not find evidence for an association between the assay ratio and pill count ratios. The correlation (rho 0.50) between the two indirect adherence measures, the Morisky and pill count ratio, was similar to that found in other studies, however, suggesting that our findings were otherwise similar to prior work.[39,40]

Relationship Between Medication Adherence and SBP

In both Population A and B, we found that among patients who were prescribed ≥3 BP medications, patients classified as adherent by assay ratio had approximately 19 mmHg lower SBP when compared to patients who were classified as non-adherent by the assay ratio. Relationships between medication adherence and SBP among patients prescribed <3 BP medications were not statistically significant in these small patients populations. When measured by the ARMS, the relationship between medication adherence and ED SBP had similar point estimates, though they were not statistically significant. When measured by the Morisky, the point estimate for the difference in SBP between adherent and non-adherent patients was only 1.9 mmHg and was not statistically significant.

Based on evidence for effect modification, we stratified analyses by number of prescribed medications: <3 BP medications, ≥3 BP medications. This stratification reflects the current definition of resistant hypertension, which is an area of growing research interest; in particular with regards to the role that medication non-adherence may play in apparent resistant hypertension.

In Population A, models included adjustment for multiple patient factors (age, sex, race, insurance status, comorbid conditions, BMI) after imputing numeracy for 18 patients who had missing numeracy. These final, adjusted models were only slightly different from the unadjusted models.

Of the three medication adherence measures collected in Population B, the assay ratio was most closely related to Week 16 SBP, particularly among patients prescribe ≥3 BP medications.

Assay Ratio Performance in Multiple Settings

Despite differences in demographics, clinical characteristics, and clinical settings, the assay ratio test characteristics and the relationship with SBP were, overall, consistent between Population A and B. Population A consisted of primary care patients with hypertension who were recruited during an ED visit; these patients were older, had received more education, had higher health literacy/numeracy skills, and were more likely to have health insurance compared to patients in Population B. Patients in Population B were all Black; more than 1/3 did not have a primary care provider, and some patients were not receiving treatment for hypertension at their entry into the study. BP and medication adherence were measured in Population B at the Week 16 follow up visit. The difference in timing (during an ED visit vs. at a study follow up visit) and difference in prescribed BP medications (no protocol vs. strict study protocol using a limited range of medications) may account for some of the differences in relationships between the assay and indirect measures of adherence in the two populations, particularly among individual BP medications.

Assay Ratio vs. Other Measures of Medication Adherence

We found evidence that the assay ratio was a better measure of medication adherence than indirect measures such as the ARMS, Morisky, or pill count ratios alone. In Population A, among patients who were prescribed ≥3 BP medications the assay ratio explained an important amount of variance in SBP beyond that explained by the ARMS. In Population B, the assay ratio also explained more variance in Week 16 SBP than the Morisky or pill count ratio among patients who were prescribed ≥ 3 BP medications; by the likelihood ratio test, these differences were not statistically significant, although power was hampered by the sample size of 25 patients.

Although the assay ratio provided more information than indirect measures of medication adherence, measurement of both offers the advantage of providing a more complete, nuanced picture of adherence patterns. The assay ratio provides a snap shot, a short window of measurement of adherence and does not capture nuances of adherence such as precise dose or timing, nor does it capture persistence; surveys and pill counts provide a different perspective on these domains of medication adherence and can be generalized to medications not detected by the assay. Particularly given the different aspects of adherence that are measured by the assay ratio versus indirect measures such as surveys and/or pill counts, there may be significant benefit in measuring both.

Limitations

The assay ratio is a snap-shot of antihypertensive adherence for a limited number of BP medications that does not account for potential interactions between and among multiple medications, nor does the assay ratio account for other factors, such as diet, exercise, acute illness, other medications, etc., may influence BP. Therefore, there may be a relationship between adherence and ED SBP among patients who are prescribed one or two BP medications that was not detectible in this population.

Population B Aim 2 analyses were limited by the very small sample size, particularly for pill counts (total N = 67) and given that analyses were stratified by number of prescribed BP medications: 25 patients were prescribed ≥ 3 BP medications, and 73 were prescribed <3 BP medications. This limits the ability to detect influences in BP that are small in magnitude but that may be clinically important on a population level. Regarding pill counts, it is possible that patients who were more adherent to their medications would also be more likely to bring the pill bottles to the Week 16 study visit;

therefore, the available pill count ratios may overestimate medication adherence. In addition, potentially important factors such as numeracy and health literacy were not available in this patient population. Timing of last medication dose ingestion, e.g., just prior to Week 16 follow up visit, is not known; this may play a role is the discrepancy between non-adherence detected by the Morisky versus by the assay ratio. Despite these limitations, the patterns in Population B analyses were similar to those in Population A, lending credence to assay ratio as a valid measure of antihypertensive adherence.

Assay Ratio and Medication Adherence Considerations

Medication adherence is composed of multiple domains. Complete medication adherence requires taking the correct medicine at the correct dose and frequency at the correct time, and continuing to take the medication as prescribed for as long as directed. Adherence to one medication may not necessary be tightly related to adherence to other medications. Therefore, as anticipated given that the assay ratio and ARMS measure different types and aspects of medication adherence, the associations between medication adherence measured by the assay ratio and the ARMS were weak to moderate in strength.

Medication absorption, metabolism, elimination, excretion, drug and diet interactions, smoking, body fat content, genetic influences, and acute illness (e.g., fever) all play a role in serum, plasma, and urine drug levels. Drug characteristics also play a role in assay interpretation. As Gordis et al noted in 1984, “A person may be a poor complier but obtain an adequate blood level if he takes the medication at all. Conversely, a person may be a very good complier but not achieve a good serum level for a variety of reasons.”[43] Not only do drug levels vary widely between patients, but they can also vary widely within a single individual over time. These are important considerations when interpreting results of the mass spectrometry assay; these factors also suggest that, in general, use of assay results as “detected/not detected” for individual medications may be appropriate in most cases, given the many factors that influences the absolute value of raw chromatograph output.

Aim 2 and 3 were cross sectional, rather than longitudinal analyses. Ideally, adherence assays should be used to establish the *pattern* of adherence, which is more informative than a single summary measure, or snapshot, of adherence. A summary measure of adherence of 50% over a two week time may accurately describe a patient who took no medication for one week and then took all medication the following week, but it also describes the patient who took medication every other day, or a patient who took only morning doses or who alternated between taking and not taking medication two days in a row. Effective interventions to improve medication adherence may be different for each pattern of adherence.

Lastly, the assay is not available for clinical practice and for the foreseeable future will only be available for research purposes.

Distribution of medication adherence measured by the assay ratio was highly skewed towards a ratio of 1.0; altering the threshold to classify adherent behavior to an assay ratio ≤0.80 reclassified only one person. Given this, the assay ratio was used primarily as a dichotomized measure (adherent = assay ratio of 1.0; non-adherent = assay ratio <1.0).

Conclusions

Validated by comparison against the indirect measures of adherence of the ARMS, Morisky, and pill count ratios, the assay ratio is a valid measure of antihypertensive medication adherence, taking note of the special considerations of interpretation of assay results described above. In two diverse patient

populations and clinical settings, SBP was approximately 19 mmHg higher among patients prescribed ≥3 BP medications who were classified as adherent by the assay ratio, compared to patients who were classified as non-adherent. The assay may be a reasonable option to measure antihypertensive adherence in both the ED and outpatient clinic research settings. Because the assay ratio measures different aspects of medication adherence than surveys or pill counts, multiple measures of medication adherence should be considered.

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CHAPTER 4: CONCLUSIONS AND FUTURE WORK

Aims 1, 2, and 3 of this work lay the foundation for future work understanding the potential role of the emergency department (ED) in the management of chronic conditions such as hypertension. As more Americans seek care in the ED each year and the prevalence of hypertension and other chronic conditions continue to rise, the role of the ED as a lynchpin between outpatient and inpatient care, another touchpoint and opportunity to impact long term healthcare, will continue to grow in importance. Evidence to guide this expanding and changing role will be vital to ensure the most health benefit for our patients.

In Aim 1, which examined the relationship between the lowest systolic blood pressure (SBP) recorded during an ED visit, we found that this conservative measure of ED SBP was closely related to elevated SBP over the year after the ED visit. Patients without evidence of diagnosed hypertension were more likely to have elevated mean follow up SBP (≥140 mmHg) compared to patients with evidence of diagnosed hypertension; this suggests that patients without diagnosed hypertension but who have elevated ED SBP may warrant close post-ED follow up to determine whether they may have undiagnosed hypertension. This suggests two potential explanations. First, that patients without diagnosed hypertension but who have elevated ED SBP may actually have hypertension but have not 'officially' received the diagnosis or treatment. Second, it suggests that the trajectory of BP among those with a hypertension diagnosis may more often be acted upon in the outpatient setting during the year after their ED visit. This preliminary work adds to the growing body of evidence that under some clinical circumstances ED intervention may be appropriate and even necessary in the management of chronic conditions such as hypertension. Limitations of Aim 1 analyses – use of administrative data, inability to adjust for interventions such as medication administration, initiation, titration, and defining follow up SBP simply as the mean SBP over the 52 weeks after an ED visit – will be addressed in the following planned future work:

<u>Planned Future Work Related to Aim 1:</u>

- Longitudinal analyses of the relationship between ED and follow up SBP
- Examine the relationship between ED and follow up SBP among patients with multiple ED visits
- Expand accounting for potential confounders, including administered/initiated/titrated medications, intervening health events (e.g., stroke)
- Evaluation of alternative measures of follow up SBP, e.g., proportion of time spent with follow up SBP <140 mmHg
- Examine whether ED chief complaint impact BP trajectory
- Examine the impact of initiation and titration of BP medication in the ED
- Examine these relationships for diastolic BP and mean arterial blood pressure
- Examine the relationship between ED SBP and post-ED healthcare utilization and mortality
- Evaluate the relationship between ED and chronic SBP in other populations

This additional work will provide more complete evidence to guide healthcare providers in decisions regarding management of hypertension in the ED setting.

In Aim 2, the construct validity of a mass spectrometry blood assay was examined as a measure of medication adherence. For use as a measure of antihypertensive adherence, the assay was used to compute the ratio of number of detected antihypertensive medications to number of prescribed antihypertensive medications; the resulting assay ratio test characteristics were determined by comparing it to existing, indirect measures of antihypertensive adherence (the Adherence to Refills

and Medications Survey, Morisky, and pill count ratio) in 2 distinct patient populations (primary care patients with hypertension during an ED visit; patients with elevated SBP during an ED visit who participated in a randomized control trial).

As anticipated given the differences between the assay ratio and the indirect measures of adherence used as comparators, correlations, c-statistics, and positive/negative predictive value of the assay ratio were moderate in strength. The primary exception was the comparison between the assay ratio and pill count ratio; with a sample size of only 67 patients and concern that patients with missing pill count ratio may have been more likely to be nonadherent to their antihypertensive medications; there was no evident relationship between the assay ratio and pill count ratio.

The relationships with the assay ratio were strong enough to move forward to evaluate the assay ratio as a measure of adherence in Aim 3 for predictive validity to systolic BP. Overall, the assay ratio classified patients as adherent more often than the indirect measures; this also was not surprising given the mechanism of the assay compared to measurement by the ARMS or Morisky. The assay, which uses plasma or serum, detects drug presence near the therapeutic range for each antihypertensive medication; drug presence does not guarantee that the correct dose of medication was taken, nor that it was taken at the correct time, or that the medication has been taken for more than the past 24-36 hours, depending on the drug half life. The ARMS and Morisky, on the other hand, are more global measures of adherence that ask patients about a range of adherence-related behaviors over a broader time frame. Given these and other considerations related to interpretation of the assay ratio as a measure of antihypertensive adherence, planned work related to the assay includes the following:

Planned Future Work Related to Aim 2:

- Examination of adherence measured by the assay ratio over time, within and among individual patients
- Evaluate optimal methods for interpretation and communication of results of the assay ratio for patients and healthcare providers
- Examine the impact of provision of these results of the patient-provider relationship
- Determine methods for combining the assay ratio with other measures of adherence to gain a complete picture of adherence patterns

This work will provide greater detail regarding the validity of the assay ratio as a measure of antihypertensive adherence *patterns* and provider greater insights into when and how the assay ratio may be best used as a measure of antihypertensive adherence.

Aim 3 examined the predictive validity of the assay ratio, that is, its relationship with a clinically important outcome, in this case SBP. First, we found evidence for effect modification by the number of prescribed antihypertensive medications; in other words, among patients who were prescribed more antihypertensive medications, the relationship between adherence and SBP was stronger than among patients prescribed fewer BP medications. We used a threshold of ≥3 antihypertensive medications, which approximates the current definition of resistant hypertension. In these cross sectional analyses, it was not possible to distinguish patients who were prescribed more antihypertensive medications because their BP remained elevated because the medication was not sufficiently effective to reduce BP, or if they were prescribed more antihypertensives because their BP remained elevated due to non-adherence.

Second, in the ED setting, among 299 primary care patients with diagnosed hypertension who were prescribed ≥3 antihypertensive medications, patients classified as adherent by the assay ratio had substantially lower ED SBP, approximately 20 mmHg lower, compared to patients who were non-adherent. A similar pattern in the relationship between adherence and SBP was found in the secondary population of 99 patients enrolled in the randomized control trial. In both populations, the assay ratio was more closely related to SBP than indirect measures of adherence, suggesting that the assay provides value beyond that obtained from the ARMS, Morisky, or pill counts.

Following this preliminary work examining the predictive validity of the assay ratio, the following additional research is planned:

Planned Future Work Related to Aim 3:

- Longitudinal analysis of the relationship between the assay ratio and SBP
- Examine the relationship between medication adherence by the assay ratio in the ED with:
  - follow up (chronic) SBP
  - resource utilization
  - mortality after the ED visit

  and determine whether these relationships may be influenced by trust in healthcare providers
- Determine whether the relationship between numeracy and mortality among ED patients is mediated by adherence
- Evaluate the predictive validity of the assay ratio against diastolic and mean arterial pressures
- Examination of a measure of adherence that combined direct and indirect measures

These planned analyses and studies more fully examine the potential role that the ED visit and providers may play in identifying and potentially addressing medication adherence, and it begins expansion of the assay ratio into other clinical settings such as the primary care clinic. These findings will also help guide future work aimed at improving antihypertensive adherence more broadly among the high risk group of patients who seek ED care, providing a framework on which to build similar interventions for other chronic conditions such as diabetes or heart failure.

CHAPTER 1 APPENDIX

Blood pressure in the Emergency Department

ED BP and Chronic BP

Chapter 1 Appendix Table 1: Prior Work Evaluating the Relationship Between ED BP and Chronic BP

Study	Study Design	Location BP Measurement	Sample Size	Measures and Analyses	Findings	Limitations
Backer et al. (2003)[1]	•Limited to patients with elevated BP during ED visit or minor injury visit •2-month enrollment period •6-month follow up period •Patients without hypertension •EHR, letter, phone follow up	ED, Primary care, and occupational health clinic. BP by nurses in triage; repeated twice if elevated BP measurement method not stated	407 consented 201 with follow up BP	McNemar's test for correlated proportions Chi-squared test to compare un-paired proportion	70% had elevated f/u BP No evidence for difference in BP by location (ED vs. minor injury clinic), pain, or degree of elevation at the initial visit. Higher BP associated with greater proportion with elevated follow up BP	Patients without hypertension "Elevated BP" not defined. 65% follow up. Patient race not recorded
Chernow et al. (1987)[2]	•ED SBP>159 mmHg or DBP >94 mmHg; •Included patients with and without hypertension •Follow up by letter (self-addressed, stamped survey card); 2nd letter mailed if no response	ED only; BP by triage nurse, repeated if BP>159/94 mmHg; only those with repeat elevated BP were followed Sphygmomanometer	239 consented 107 with follow up BP	No formal analyses	35% had BP>159/95 mmHg; 33% with SBP 140-159 mmHg/DBP 90-94 mmHg; 32% SBP <140/90 mmHg 70% in each category with painful complaints	Follow up by letter only; 55% lost to follow up
Slater et al. (1985)[3]	•No h/o of HTN •Excluded those hospitalized from ED •Follow up BP obtained by contacting primary care	A&E, England BP by doctor, semi-recumbent, both arms; repeated at 10 min intervals "until	60 with elevated A&E BP called back to ED; 53 returned, BP re-measured, found to	No formal analyses	15 with DBP >95 mmHg; 14 treated for hypertension by primary care	Small sample size; Limited patient info

	provider	consistent readings" Sphygmomanometer	have consistently elevated BP, told to seek primary care			
Shiber-Ofer et al. (2015)[4]	• No h/o diagnosed HTN • At least two ED BP >= 140/90 mmHg • Follow up by hospital record or community registry • Outcome: development of hypertension (clinic BP>140/90 mmHg, mean ambulatory BP>135/85 mmHg), or treatment with BP medication	ED, Israel BP measured by nurse, sitting, 5 minutes of rest; if elevated, measured a second time Single arm Sphygmomanometer	195 patients enrolled and followed 142 (73%) were diagnosed with hypertension following the index ED	Generalized multiple linear model	Follow up mean of 30 months (sd 16 months). No evidence for difference in BP by chief complaint. DBP and pain score higher among those not later diagnosed with hypertension	BP prior to ED visit not available; BP not re-measured during ED visit

Number of Blood Pressure Readings

According to JNC 7, at least 2 measurements of blood pressure should be obtained in the office setting after the patient has been sitting quietly in a chair for at least 5 minutes[5]; this is supported by clinic-based research that found that a single measurement of BP in clinic may overestimate the prevalence of hypertension by as much as 12.6%.[6] The American College of Emergency Physician guidelines suggest outpatient follow-up for elevated BP based on the following three studies; these guidelines defer to the JNC 7 recommendations for a minimum of 2 measurements in the ED setting, to confirm elevated BP.

Pain and Blood Pressure

Appendix Table 2 outlines prior studies that examined the relationship between pain or anxiety with vital signs prior to or during an ED visit. No prior studies have evaluated potential differences in relationships between pain and BP among patients with versus those without hypertension; each of these studies used only a single measure of pain.

Chapter 1 Appendix Table 2: Prior Work Evaluating the Relationship Between Vital Signs and Pain, Anxiety in Emergency Patients

Study	Study Design	Location	Sample Size	Measures and Analyses	Findings
Bendall 2011[7]	EMS records of patients with complaints of pain;	Pre-hospital	> 53,000	Spearman's correlations; ordinal	For age 16-64, a heart rate of 100 beats/min or more was

	2004 – 2006			logistic regression	associated with 18% increased odds of severe pain (P<0.0001). Aged 65 to 100, systolic BP >139 mmHg were associated with 14% increased odds of more severe pain (P<0.0001). Simple correlation: no clinically important associations.
Marco 2006[8]	Chart review; ED patients, >17 years with verifiable painful diagnoses; 2004-2005	Adult ED	1,063 subjects nephrolithiasis (25%; n = 267) and fracture (23%; n = 249)	Self-reported pain Correlations	No clinically significant associations between self-reported triage pain scores and heart rate, blood pressure, or respiratory rate
Tanabe 2008[9]	Prospective cohort. No history of hypertension and 2 blood pressure measurements >139/89 mm Hg; provided with home blood pressure monitors, and asked to take their blood pressure twice a day for 1 week	Adult ED and home	189 patients were enrolled; 156 returned the monitors and completed the protocol	ED anxiety (Spielberger State Anxiety Scale) and pain (10-point scale)	Difference between home and ED systolic blood pressures was not associated with anxiety (r=-.03; P=.69); association with pain was in the opposite direction from expected (r=.18; P=.03).

Chapter 1 Appendix Table 3: Sensitivity and specificity of cardiovascular assay among plasma samples

						Sensitivity		Specificity		Accuracy	
		TN	TP	FN	FP		0.95 CL		0.95 CL		0.95 CL
1	Acetylsalicylic.Acid	39	11	0	1	1.000	(1.000, 1.000)	0.975	(0.919, 1.000)	0.980	(0.941, 1.000)
2	Aliskiren	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
3	Amlodipine	43	8	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
4	Atenolol	50	1	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
5	Atorvastatin	48	3	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
6	Canrenone.Spironalctone	47	4	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
7	Captopril	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
8	Carvedilol	49	2	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
9	Clonidine	50	1	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
10	Clopidogrel	50	1	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
11	Digoxin	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
12	Diltiazem	49	1	0	1	1.000	(1.000, 1.000)	0.980	(0.939, 1.000)	0.980	(0.941, 1.000)
13	Enalapril	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
14	Fenofibrate	43	8	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
15	Furosemide	39	12	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
16	HCTZ	50	1	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
17	Hydralazine	48	3	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
18	Isosorbide	47	2	2	0	0.500	(0.000, 1.000)	1.000	(1.000, 1.000)	0.961	(0.902, 1.000)
19	Lisinopril	49	1	0	1	1.000	(1.000, 1.000)	0.980	(0.939, 1.000)	0.980	(0.941, 1.000)
20	Losartan	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
21	Lovastatin	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
22	Methyldopa	50	1	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
23	Metoprolol	39	12	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
24	Niacin	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
25	Nifedipine	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
26	Pravastatin	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
27	Propranolol	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
28	Ramipril	47	4	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
29	Simvastatin	46	5	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
30	Triamterene	50	1	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
31	Telmisartan	51	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
32	Valsartan	27	23	0	1	1.000	(1.000, 1.000)	0.964	(0.885, 1.000)	0.980	(0.941, 1.000)
33	Verapamil	49	2	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
34	Warfarin	45	6	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)

Chapter 1 Appendix Table 4: Sensitivity and specificity of cardiovascular assay among serum samples

						Sensitivity		Specificity		Accuracy	
		TN	TP	FN	FP		0.95 CL		0.95 CL		0.95 CL
1	Acetylsalicylic.Acid	69	160	8	6	0.952	(0.918, 0.982)	0.920	(0.851, 0.974)	0.942	(0.909, 0.971)
2	Aliskiren	241	2	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
3	Amlodipine	198	41	1	3	0.976	(0.919, 1.000)	0.985	(0.966, 1.000)	0.984	(0.967, 0.996)
4	Atenolol	214	29	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
5	Atorvastatin	191	49	2	1	0.961	(0.902, 1.000)	0.995	(0.984, 1.000)	0.988	(0.971, 1.000)
6	Canrenone.Spironalctone	185	56	0	2	1.000	(1.000, 1.000)	0.989	(0.973, 1.000)	0.992	(0.979, 1.000)
7	Captopril	239	1	3	0	0.250	(0.000, 1.000)	1.000	(1.000, 1.000)	0.988	(0.971, 1.000)
8	Carvedilol	176	67	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
9	Clonidine	216	24	0	3	1.000	(1.000, 1.000)	0.986	(0.968, 1.000)	0.988	(0.971, 1.000)
10	Clopidogrel	169	67	7	0	0.905	(0.835, 0.968)	1.000	(1.000, 1.000)	0.971	(0.951, 0.992)
11	Digoxin	213	28	1	1	0.966	(0.880, 1.000)	0.995	(0.985, 1.000)	0.992	(0.979, 1.000)
12	Diltiazem	212	29	0	2	1.000	(1.000, 1.000)	0.991	(0.976, 1.000)	0.992	(0.979, 1.000)
13	Enalapril	228	15	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
14	Fenofibrate	225	17	1	0	0.944	(0.812, 1.000)	1.000	(1.000, 1.000)	0.996	(0.988, 1.000)
15	Furosemide	135	107	1	0	0.991	(0.970, 1.000)	1.000	(1.000, 1.000)	0.996	(0.988, 1.000)
16	HCTZ	197	45	0	1	1.000	(1.000, 1.000)	0.995	(0.984, 1.000)	0.996	(0.988, 1.000)
17	Hydralazine	211	31	1	0	0.969	(0.897, 1.000)	1.000	(1.000, 1.000)	0.996	(0.988, 1.000)
18	Isosorbide	205	24	4	10	0.857	(0.706, 0.968)	0.953	(0.925, 0.978)	0.942	(0.914, 0.971)
19	Lisinopril	154	87	0	2	1.000	(1.000, 1.000)	0.987	(0.967, 1.000)	0.992	(0.979, 1.000)
20	Losartan	211	32	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
21	Lovastatin	242	1	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
22	Methyldopa	243	0	0	0			1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
23	Metoprolol	143	99	1	0	0.990	(0.966, 1.000)	1.000	(1.000, 1.000)	0.996	(0.988, 1.000)
24	Niacin	234	8	1	0	0.889	(0.625, 1.000)	1.000	(1.000, 1.000)	0.996	(0.988, 1.000)
25	Nifedipine	219	24	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
26	Pravastatin	215	28	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
27	Propranolol	236	7	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
28	Ramipril	239	4	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
29	Simvastatin	179	58	4	2	0.935	(0.867, 0.985)	0.989	(0.972, 1.000)	0.975	(0.955, 0.992)
30	Triamterene	237	6	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
31	Telmisartan	241	2	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)
32	Valsartan	228	12	0	3	1.000	(1.000, 1.000)	0.987	(0.970, 1.000)	0.988	(0.971, 1.000)
33	Verapamil	226	15	0	2	1.000	(1.000, 1.000)	0.991	(0.978, 1.000)	0.992	(0.979, 1.000)
34	Warfarin	178	65	0	0	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)	1.000	(1.000, 1.000)

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CHAPTER 2 APPENDIX

Chapter 2 Appendix Table 1: Aim 1 Variable definitions. Earliest date of extraction January 1, 2007		
Variables	**Definition**	
Age	Years, at the time of the ED visit	
Race	White, non-white	
ED disposition	dispo_cat (1 = discharged; 2 = admitted; 3 = other)	
Sex	Female, Male	
Arrival Mode	Ambulance/aeromedical transportation Personal Vehicle	
ED Chief Complaint	Text describing the patient's reported reason for seeking ED care	
Insurance Status	At the time of the ED visit (Private/Medicare vs. Federal/Medicaid/Other vs. Self-Pay)	
BP Medications	Number of BP medication classes prescribed as of 3 months prior to the ED visit. To identify medications 3 months prior to the ED visit, data was abstracted for the year prior to the 3 months before the ED visit. Medications were categorized as 7 classes: beta blocker, calcium channel blocker, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, loop diuretics, thiazide diuretics, alpha adrenergic blockers, and other (e.g., vasodilators). Data was extracted from outpatient and inpatient prescription orders and natural language processing (NLP) of clinical notes.	
BMI	Median BMI from all BMIs prior to the ED visit; where the 5-year median BMI was lower than the overall median BMI, this was used.	
Follow Up BP Measurement Frequency	Number of BP values measured during follow-up	
Follow up time	Weeks between ED and subsequent BP measurements	
Comorbid Conditions	**Definition***	
Hypertension	ICD-9 CM diagnosis codes: 401.X-405.X	
Diabetes	ICD-9 CM diagnosis code 250*	
Cerebrovascular disease	Carotid revascularization	ICD 9-CM procedure codes: 38.12, 38.11, 00.61, 00.63, 39.28 CPT procedure codes: 35301
	TIA	ICD-9 CM diagnosis codes: 435.X
	Stroke	ICD-9 CM diagnosis codes: 430.X, 431.X. 434.X, 436.X, 433.1
Cardiovascular disease	MI	ICD-9 CM diagnosis codes: 410, 412,429.7
	Obstructive coronary disease	ICD-9 CM diagnosis codes: 411; 413 or 414.X ICD-9 procedure codes: 36.01,

		36.02, 36.03, 36.05, 36.09, 36.10-36.19 CPT codes: 33533-36, 33510-23, 30, 92980-82, 84, 92995-6
Congestive Heart failure	ICD-9 CM diagnosis codes: 428, 402.02, 402.11, 402.91, 425.xx	
	DRG: 127	
Cancer	ICD-9 CM diagnosis codes: 140-208, except for 173	
Organ transplant (kidney, heart, lung, liver, bone marrow, pancreas)	ICD-9 CM diagnosis codes: V42.0, V42.1, V42.6, V42.7, V42.81, V42.83) ICD-9 CM procedure codes 33.5, 33.6 37.5, 41.0, 50.5, 52.8, 55.6 CPT procedure codes: 50320, 50360, 50365, 50370, 50380, 33935, 33940, 33945, 32851, 32852, 32853, 323854, 47135, 47136, 38240, 38241, 48554, 48556	
Renal Disease	End stage renal disease on dialysis	ICD-9 CM diagnosis code: 585.6
	Dialysis treatment	CPT procedure codes: 3993, 5498, 90935, 90937, 90945, 90947, 90989, 90993, 90921, and 90925.
	Encounter for dialysis & dialysis catheter care	ICD-9 CM diagnosis code: V56.X, V45.1
HIV	042, 079.53	

* A single mention was required for all conditions. ICD-9 CM and CPT codes were extracted from billing and procedure codes after January 1, 2007.

Classification	Medications
ACE/ ARB	aliskiren, benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril, candesartan, irbesartan, losartan, olmisartan, telmisartan, valsartan
Thiazide diuretics/ Potassium-sparing diuretics alone and in combination	chlorothiazide, chlorthalidone, hydrochlorothiazide, methyclothiazide, trichlormethiazide, metolazone, indapamide, eplerenone, amiloride, spironolactone, triamterene, hydrochlorothiazide–triamterene, hydrochlorothiazide–spironolactone
Calcium Channel Blockers	amlodipine, isradipine, felodipine, nifedipine, nicardipine; diltiazem (regular and sustained release), verapamil (regular and sustained release), nimodipine, nisoldipine, bepridil, amlodipine–atorvastatin
Beta Blockers	acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol tartrate, metoprolol succinate, propranolol, penbutolol, pindolol, nadolol, sotalol, timolol
Alpha adrenergic antagonists	doxazosin, prazosin, terazosin

Loop Diuretics	furosemide; ethacrynic acid; bumetanide; torsemide
Centrally acting agents and other antihypertensive agents	clonidine, guanabenz, guanfacine, hydralazine, methyldopa, metyrosine, reserpine, minoxidil

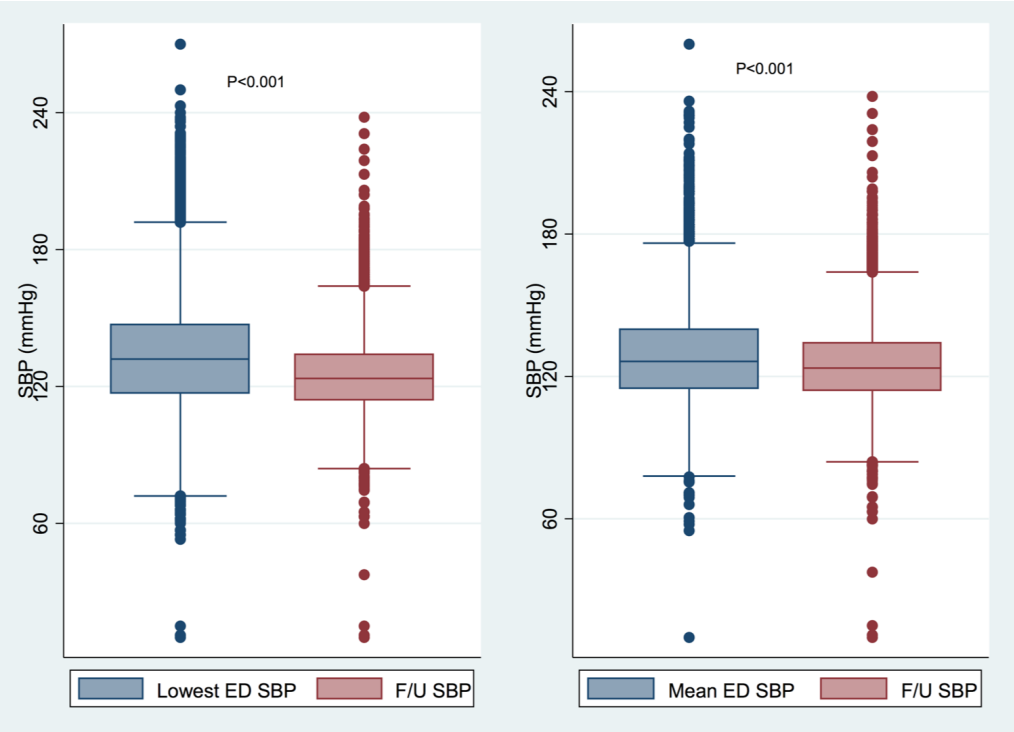
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CPT = Current Procedural Terminology; ICD-9 CM= International Classification of Diseases, Ninth Revision; MI = myocardial infarction; TIA = transient ischemic attack.

Chapter 2 Appendix Table 2: Aim 1 Demographics of Excluded Patients (N = 28,325 patients, among 83,775 ED visits). Demographics are for the first ED visit during the study period.	
Age in years, mean (sd) median (Q_1, Q_3)	53.7 (18.0) 55 (41, 67)
Female, no. (%)	14,675 (51.8)
White, no. (%)	21,989 (78.1)
Insurance, no. (%)	
Private	5,385 (19.0)
Medicare/Federal/Medicaid	20,726 (73.2)
Self-Pay/unknown	2,214 (7.8)
Discharged from the ED, no. (%)	25,498 (90.0)
Admitted to an ICU, no. (%)	1,677 (5.9)
Comorbid Conditions, %	
Hypertension	12,876 (45.5)
Diabetes	7,133 (35.3)
Heart Failure	1,533 (5.4)
HIV	672 (2.4)
Organ Transplant	1,619 (5.7)
Total Number of Comorbidities, mean (sd) median (Q_1, Q_3)	 1.0 (0.9) 1 (0, 2)
BMI, kg/m^2, mean (sd) median (Q_1, Q_3)	29.2 (7.7) 27.8 (23.8, 33.0)
Prescribed BP Medications (at the time of the ED visit) ,no. (%)	
ACE/ARB	7,422 (26.2)
Beta blocker	6,055 (21.4)
Calcium channel blocker	3,792 (13.4)
Loop diuretic	4,420 (15.60)
Thiazide diuretic	5,110 (18.0)
Alpha adrenergic blocker	508 (1.8)
Other	2,440 (8.6)
Total BP Medication Classes, mean (sd) median (Q_1, Q_3)	 1.1 (1.4) 0 (0, 2)
Number of ED BP's measured during ED visit, excluding triage mean (sd) median (Q_1, Q_3)	 2.9 (13.3) 2 (1, 2)
Number of BP's measured after the ED visit mean (sd) median (Q_1, Q_3)	 81.5 (175.0) 24 (7, 77)

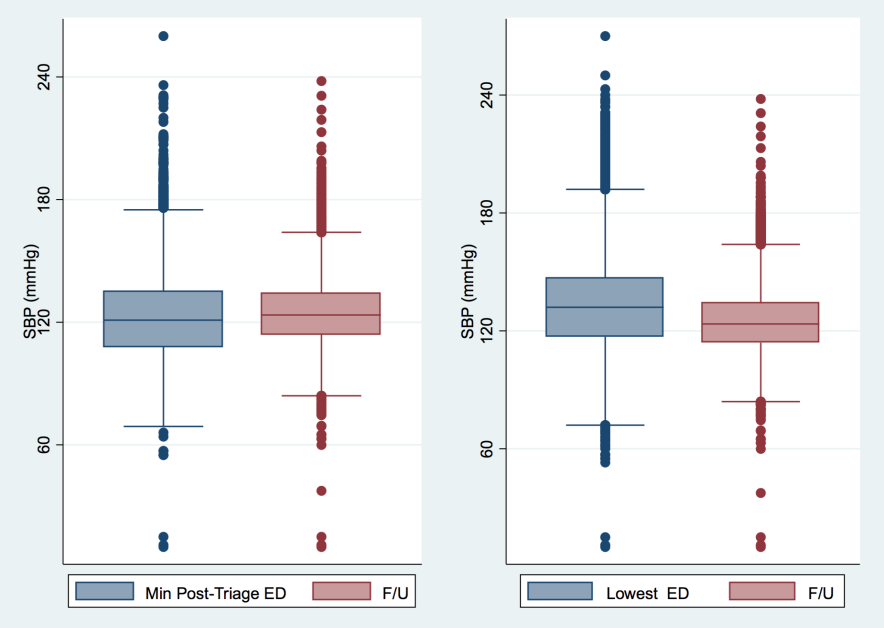
Chapter 2 Appendix Table 3: Aim 1 Cohort demographics by Evidence of Diagnosed Hypertension (N = 26,769)		
Variable	Evidence of Diagnosed Hypertension	No Evidence of Diagnosed Hypertension
Demographics	N = 9,873	N = 16,896
Age in years, mean (sd) median (Q_1, Q_3)	60.4 (15.5) 60 (50, 71)	39.3 (16.3) 37 (25, 51)
Female, no. (%)	4,675 (47.4)	9,854 (58.3)
Race, no. (%)		
White	1,931 (19.6)	13,613 (80.6)
Insurance, no. (%)		
Private	1,503 (15.2)	4,382 (25.9)
Medicare/Federal/Medicaid	7.838 (79.4)	10,942 (64.8)
Self-Pay/unknown	532 (5.4)	1,572 (9.3)
Discharged	4.075 (41.3)	10,738 (63.6)
Admitted to an ICU, no. (%)	466 (4.7)	326 (1.9)
Comorbid Conditions, %		
Diabetes	2,959 (70.0)	842 (5.0)
Heart Failure	845 (8.6)	52 (0.3)
HIV	155 (1.6)	256 (1.5)
Organ Transplant	142 (1.4)	69 (0.4)
Total Number of Comorbidities, mean (sd) median (Q_1, Q_3)	 1.4 (0.6) 1 (1, 2)	 0.1 (0.3) 0 (0, 0)
BMI, kg/m^2, mean (sd) median (Q_1, Q_3)	30.6 (7.6) 29.3 (25.4, 34.5)	26.6 (6.5) 25.2 (22.1, 29.7)
Prescribed BP Medications (at the time of the ED visit), no. (%)		
ACE/ARB	3,617 (36.6)	600 (3.6)
Beta blocker	2,486 (25.2)	713 (4.2)
Calcium channel blocker	1,456 (14.8)	217 (1.3)
Loop diuretic	1,336 (13.5)	347 (2.1)
Thiazide diuretic	2,256 (22.9)	468 (2.8)
Alpha adrenergic blocker	165 (1.7)	54 (0.3)
Other	810 (8.2)	243 (1.4)
Number of ED BP's measured during ED visit, excluding triage mean (sd) median (Q_1, Q_3)	 2.7 (3.8) 2 (1, 3)	 2.5 (2.9) 2 (1, 3)
Number of BP's measured after the ED visit mean (sd) median (Q_1, Q_3)	 18.7 (23.2) 10 (4, 24)	 10.2 (16.6) 4 (2, 11)

Chapter 2 Appendix Table 4: Aim 1 Cohort demographics by race and sex				
	White = 21,484		Non-White = 4,972	
	Male	Female	Male	Female
	N = 9,613	N = 11,871	N = 1,961	N = 3,011
Age in years, mean (sd) median (Q_1, Q_3)	48.1 (18.8) 49 (32, 62)	48.3 (19.4) 48 (32, 62)	41.3 (17.3) 40 (25, 40)	43.6 (17.6) 42 (28, 56)
Insurance, no. (%)				
Private	1,805 (18.8)	2,517 (21.2)	487 (24.8)	982 (32.6)
Medicare/Federal/Medicaid	6,984 (72.7)	8,678 (73.1)	1,159 (59.1)	1,776 (59.0)
Self-Pay/unknown	824 (8.6)	676 (5.7)	315 (16.1)	253 (8.4)
Discharged from the ED, no. (%)	4,662 (48.5)	6,817 (57.4)	1,115 (56.9)	2,003 (66.5)
Admitted to an ICU, no. (%)	359 (3.7)	312 (2.6)	55 (2.8)	62 (2.1)
Comorbid Conditions, %				
Hypertension	3,909 (40.7)	3,962 (33.4)	729 (39.9)	1,202 (39.9)
Diabetes	1,494 (15.5)	1,448 (12.2)	308 (15.7)	508 (16.9)
Heart Failure	518 (5.4)	260 (2.2)	58 (3.0)	56 (1.9)
HIV	206 (2.4)	35 (0.3)	127 (6.5)	42 (1.4)
Organ Transplant	99 (1.0)	77 (0.7)	14 (0.7)	17 (0.6)
Total Number of Comorbidities, mean (sd) median (Q_1, Q_3)	 0.7 (0.8) 0 (0, 1)	 0.5 (0.7) 0 (0, 1)	 0.6 (0.8) 0 (0, 1)	 0.6 (0.8) 0 (0, 1)
Patients with >1 Comorbid Condition, no. (%)	1,688 (17.6)3	1,310 (11.0)	327 (16.7)	490 (16.3)
BMI, kg/m^2, mean (sd) median (Q_1, Q_3)	28.3 (7.3) 26.9 (23.1, 31.9)	28.3 (6.3) 26.1 (24.0, 31.3)	28.1 (7.4) 26.8 (23.2, 31.4)	30.8 (8.8) 29.2 (24.1, 35.7)
Prescribed BP Medications (at the time of the ED visit) ,no. (%)				
ACE/ARB	1,819 (18.9)	1,564 (13.2)	314 (16.0)	488 (16.2)
Beta blocker	1,364 (14.2)	1,335 (11.3)	177 (9.0)	305 (10.1)
Calcium channel blocker	632 (6.6)	644 (5.4)	139 (7.1)	249 (8.3)
Loop diuretic	674 (7.0)	706 (6.0)	104 (5.3)	193 (6.4)
Thiazide diuretic	912 (9.5)	1,206 (10.2)	187 (9.5)	404 (13.4)
Alpha adrenergic blocker	139 (1.5)	45 (0.4)	139 (1.5)	45 (0.4)
Other	402 (4.2)	431 (3.6)	88 (4.5)	125 (4.2)
Total BP Medication Classes, mean (sd) median (Q_1, Q_3)	 0.6 (1.2) 0 (0, 1)	 0.5 (1.0) 0 (0, 1)	 0.5 (1.1) 0 (0, 1)	 0.6 (1.1) 0 (1, 0)
Number of ED BP's measured during ED visit, excluding triage mean (sd) median (Q_1, Q_3)	 2.7 (3.3) 2 (1, 3)	 2.6 (3.5) 2 (1, 2)	 2.4 (2.1) 2 (1, 3)	 2.5 (2.6) 2 (1, 3)
Number of BP's measured after the ED visit mean (sd) median (Q_1, Q_3)	 15.1 (21.2) 6 (2, 18)	 13.1 (19.4) 5 (2, 15)	 11.8 (18.4) 4 (2, 13)	 10.0 (16.5) 4 (2, 10)

Chapter 2 Appendix Figure 1: Boxplots of Lowest ED SBP and Mean ED SBP Versus Mean Follow Up SBP



Chapter 2 Appendix Figure 2: Boxplots of Lowest Post-Triage ED SBP and Lowest (Overall) ED SBP Versus Mean Follow Up SBP



Chapter 2 Appendix Table 5: ROC Curve c-statistics (area under the curve, AUC) of measures of ED SBP for mean follow up SBP ≥ 140 mmHg and ≥160 mmHg		
	AUC	95% CI
For Mean Follow Up SBP ≥ 140 mmHg		
Lowest ED SBP (N = 26,769)	0.74	0.74-0.75
Post-Triage ED SBP (N = 9,571)		
Mean	0.82	0.81-0.83
Median	0.82	0.81-0.83
90th Percentile	0.82	0.81-0.83
Minimum	0.78	0.78-0.79
Maximum	0.81	0.80-0.82
Triage ED SBP (N = 26,624)	0.76	0.76-0.77
For Mean Follow Up SBP ≥ 160 mmHg		
Post-Triage ED SBP (N = 9,571)	0.78	0.78-0.79
Lowest ED SBP (N = 26,769)		
Mean	0.87	0.86-0.87
Median	0.87	0.86-0.88
90th Percentile	0.86	0.86-0.87
Minimum	0.84	0.84-0.85
Maximum	0.86	0.85-0.86
Triage ED SBP (N = 26,624)	0.81	0.81-0.82

Chapter 2 Appendix Table 6: Elevated ED SBP (by *lowest Post-Triage* ED SBP ≥140 mmHg, ≥150 mmHg, or ≥ 160 mmHg) versus elevated mean follow up SBP (≥ 140 mmHg); N = 9,571

Lowest ED SBP ≥ 140 mmHg versus mean follow up SBP ≥ 140 mmHg

	Follow Up SBP ≥ 140 mmHg	Follow Up SBP < 140 mmHg	
ED SBP ≥ 140 mmHg	785	1,010	1,795
ED SBP < 140 mmHg	738	7,038	7,776
	1,523	8,048	9,571

OR 7.4 (95% CI 6.6 to 8.4)

Sensitivity	Pr(+| D)	51.54%	49.00% 54.08%
Specificity	Pr(-|~D)	87.45%	86.71% 88.17%
Positive predictive value	Pr(D| +)	43.73%	41.42% 46.06%
Negative predictive value	Pr(~D| -)	90.51%	89.84% 91.15%

Lowest ED SBP ≥ 150 mmHg versus mean follow up SBP ≥ 140 mmHg

	Follow Up SBP ≥ 140 mmHg	Follow Up SBP < 140 mmHg	
ED SBP ≥ 150 mmHg	513	422	935
ED SBP < 150 mmHg	1,010	7,626	8,636
	1,523	8,048	9,571

OR 9.2 (95% CI 7.9 to 10.6)

Sensitivity	Pr(+| D)	33.68%	31.31% 36.12%
Specificity	Pr(-|~D)	94.76%	94.25% 95.23%
Positive predictive value	Pr(D| +)	54.87%	51.61% 58.09%
Negative predictive value	Pr(~D| -)	88.30%	87.61% 88.98%

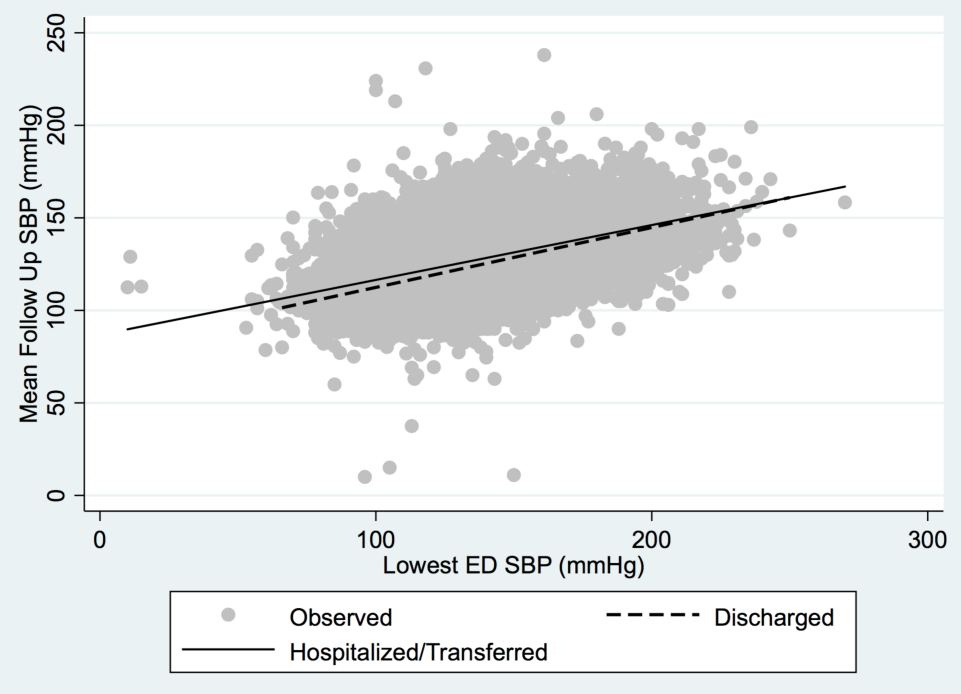
Lowest ED SBP ≥ 160 mmHg versus mean follow up SBP ≥ 140 mmHg

	Follow Up SBP ≥ 140 mmHg	Follow Up SBP < 140 mmHg	
ED SBP ≥ 160 mmHg	289	173	462
ED SBP < 160 mmHg	1,234	7,875	9,109
	1,523	8,048	9,571

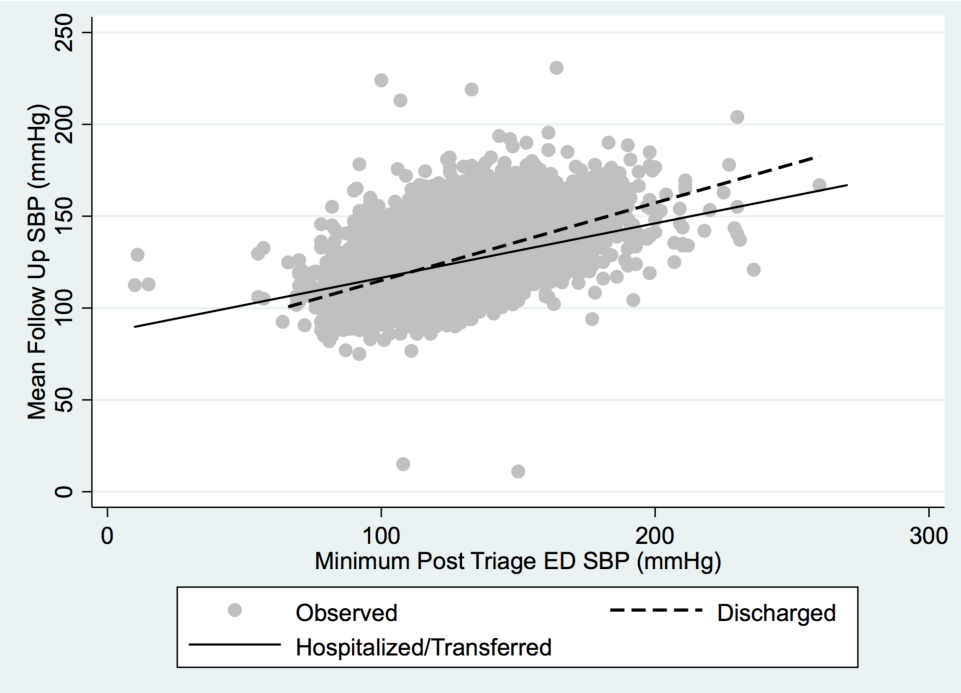
OR 10.7 (95% CI 8.7 to 13.01)

Sensitivity	Pr(+| D)	18.98%	17.03% 21.04%
Specificity	Pr(-|~D)	97.85%	97.51% 98.16%
Positive predictive value	Pr(D| +)	62.55%	57.96% 66.98%
Negative predictive value	Pr(~D| -)	86.45%	85.73% 87.15%

Chapter 2 Appendix Figure 3: Scatterplot of observed values (lowest (overall) ED SBP vs. mean follow up SBP), comparing fitted lines for patients discharged



Chapter 2 Appendix Figure 4: Scatterplot of observed values (lowest *Post Triage* ED SBP vs. mean follow up SBP), comparing fitted lines for patients discharged

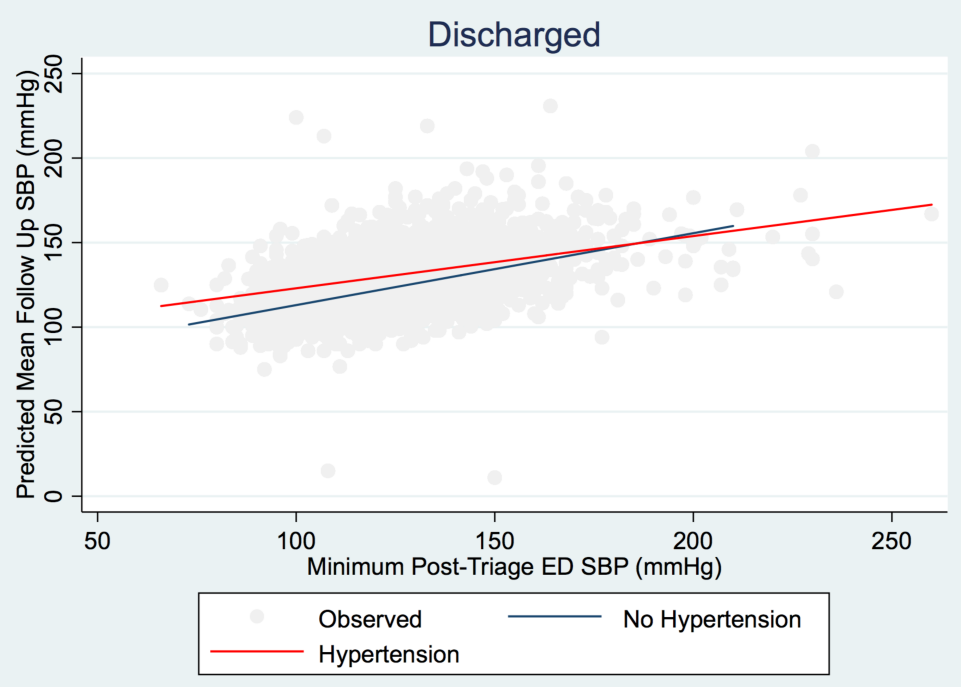


Chapter 2 Appendix Table 7: Aim 1 multiple logistic regression of categorized ED SBP (lowest *post triage* ED SBP; <140 mmHg referent) for elevated mean follow up SBP (≥ 140 mmHg)*				
	Discharged: Adjusted OR (95% CI)	Interaction Coefficient and P-value	Not Discharged Adjusted OR (95% CI)	Interaction Coefficient and P-value
Lowest Post Triage ED SBP 140-159 mmHg	4.0 (2.8 to 5.7)	-0.3 (P = 0.3)	6.9 (5.1 to 9.4)	-0.5 (P = 0.004)
Lowest Post Triage ED SBP ≥ 160 mmHg	11.0 (5.7 to 21.0)	- 0.5 (P = 0.3)	14.1 (8.1 to 24.4)	-0.2 (P = 0.47)
*Adjusted for number of post-ED discharge BPs measured, age, sex, race, insurance status, comorbid conditions, number of prescribed antihypertensive classes, and included an interaction term for evidence of diagnosed hypertension; BMI imputed				

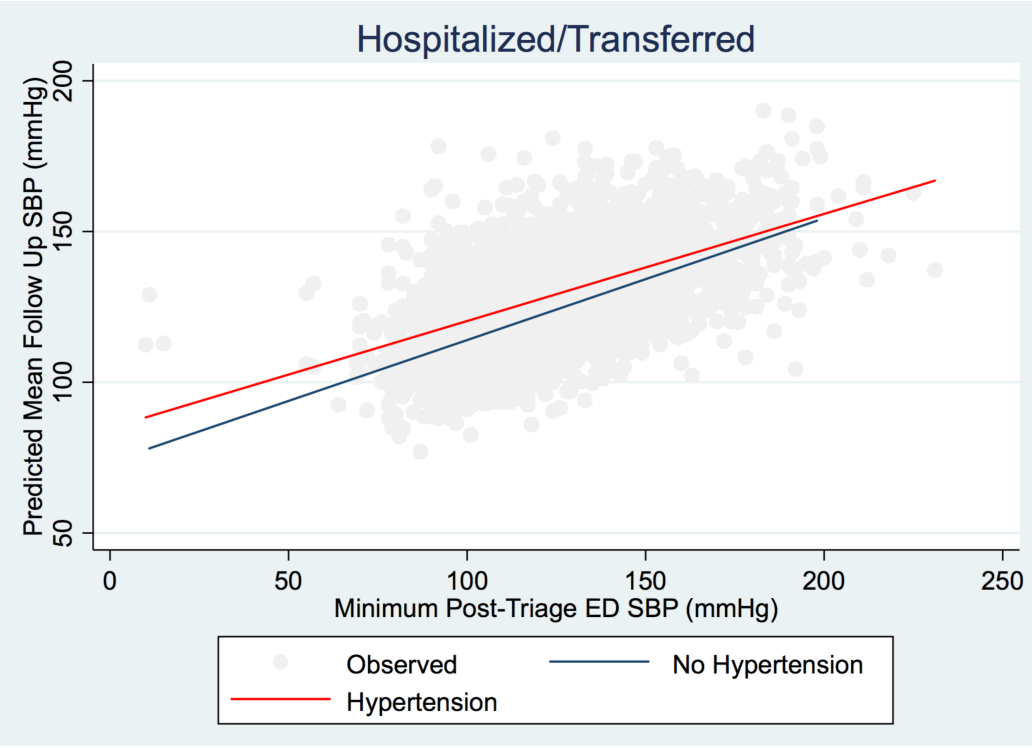
Analyses using alternate definition of elevated follow up SBP:

Chapter 2 Appendix Table 8: Aim 1 multiple logistic regression* of categorized ED SBP (lowest ED SBP; <140 mmHg referent) for elevated follow up SBP**				
	Discharged: Adjusted OR (95% CI)	Interaction OR and P-value	Not Discharged Adjusted OR (95% CI)	Interaction OR and P-value
Lowest Post Triage ED SBP 140-159 mmHg	3.4 (2.7 to 4.2)	0.7 (P = 0.03)	3.4 (2.5 to 4.5)	0.6 (P = 0.003)
Lowest Post Triage ED SBP ≥ 160 mmHg	8.9 (6.9 to 11.4)	0.5 (P < 0.001)	10.0 (7.1 to 14.1)	0.4 (P<0.001)
* Elevated follow up SBP was defined as either ≥3 follow up SBP ≥140mmHg or ≥1 follow up SBP ≥160 mmHg ** Adjusted for number of post-ED discharge BPs measured, age, sex, race, insurance status, comorbid conditions, number of prescribed antihypertensive classes, and included an interaction term for evidence of diagnosed hypertension; BMI imputed				

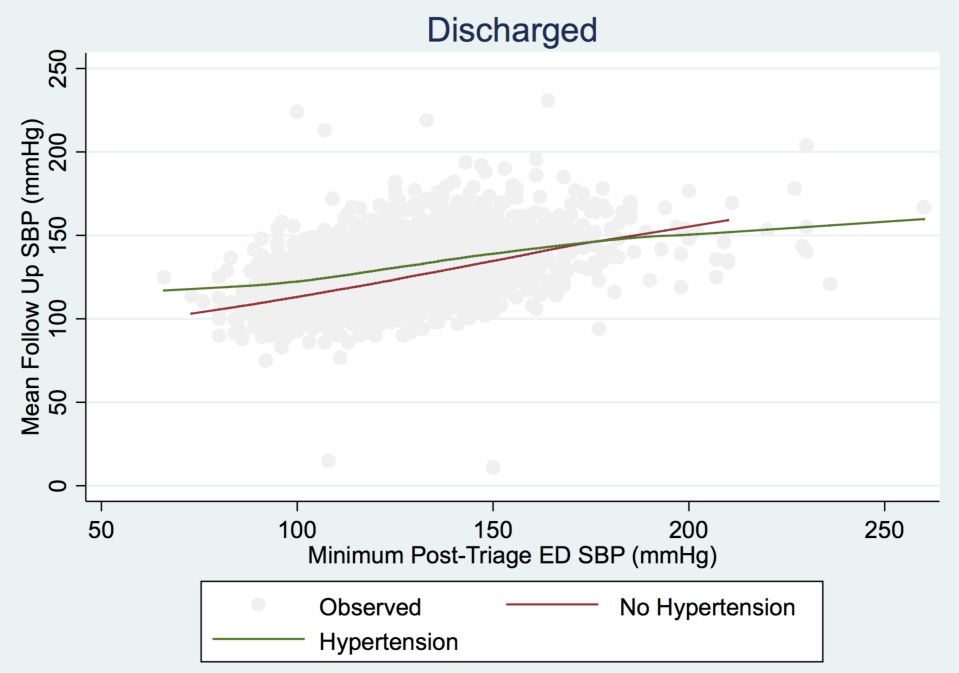
Chapter 2 Appendix Figure 5: Scatterplot of observed values (Lowest ED SBP vs. Mean Follow Up SBP), comparing fitted lines for patients with and without diagnosed hypertension among patients who were discharged from the ED



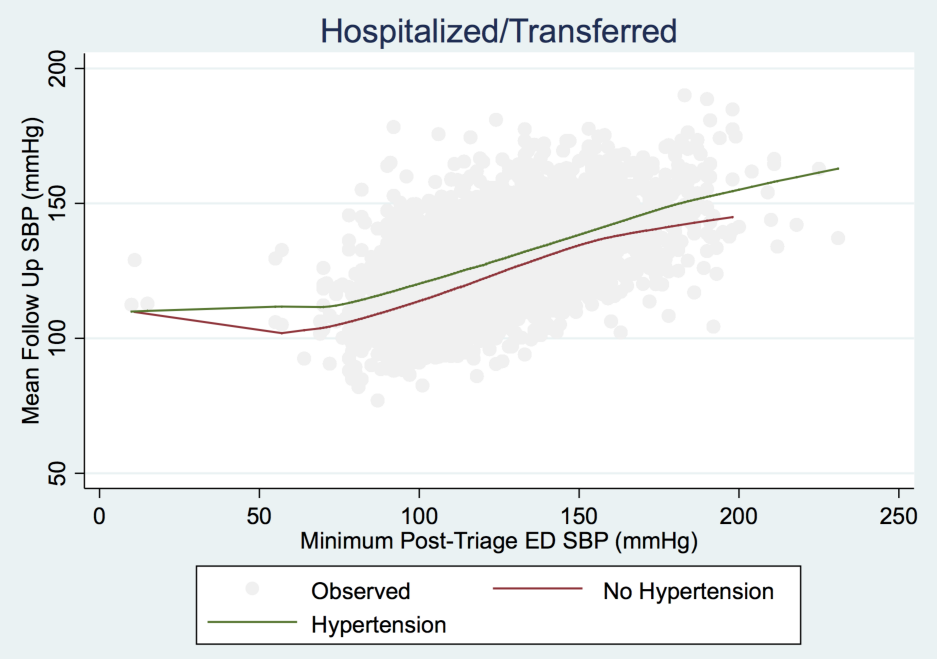
Chapter 2 Appendix Figure 6: Scatterplot of observed values (Lowest ED SBP vs. Mean Follow Up SBP), comparing fitted lines for patients with and without diagnosed hypertension among patients who were hospitalized or transferred from the ED



Chapter 2 Appendix Figure 7: Scatterplot of observed values (Lowest ED SBP vs. Mean Follow Up SBP), comparing LOWESS lines for patients with and without diagnosed hypertension among patients who were discharged from the ED



Chapter 2 Appendix Figure 8: Scatterplot of observed values (Lowest ED SBP vs. Mean Follow Up SBP), comparing LOWESS lines for patients with and without diagnosed hypertension among patients who were hospitalized or transferred from the ED



CHAPTER 3 APPENDIX

Mass Spectrometry Assay Acceptance Criteria

Chapter 3 Appendix Table 1: Acceptance Criteria for each of the 35 drugs in the mass spectrometry cardiovascular drug assay

Isosorbide: A retention time between 0.6 and 0.68 minutes, a minimum response of 100, and a ratio between the transitions between 10 and 70.
Niacin: A retention time around 0.61 minutes, a minimum response of 500, and a ratio between 75 and 150. A response between 100 and 499 is typical of a patient on multivitamins or supplemental B-vitamins but not specifically niacin.
Methyldopa: A retention time around .86 minutes, typical response is unknown but expected around 500, with a ratio around 85. There is an interfering peak at 1 minutes tentatively identified as L-dopa with a minimum peak around 1000. Be certain not to pick the L-dopa peak as methyldopa.
Hydralazine: A retention time between 1 and 1.1 minutes, a minimum response of 100, with a ratio around 35. Peaks less than 100 but with a clear peak are typically from doses greater than 24 hours prior.
Atenolol: A retention time between 1.9 and 2.1 minutes, with a minimum response of 1000, and a ratio around 70. Responses below 1000 are typically either endogenous compounds or unrelated to atenolol. If BQL, qualitative==0 because it quantifies so well.
Clonidine: A retention time around 2.2minutes, a response above 150, with a ratio around 9.
Hydrochlorothiazide (HCTZ): A retention time around 2.4 minutes, a typical response is 50 or above, with a ratio between 40 and 80.
Lisinopril: A retention time between 2.87 and 3.1 minutes, a minimum response of 100, and a ratio of 15-30. Lisinopril also has a signature peak shape, which can be used to distinguish a true peak from a false one.
Metoprolol: A retention time around 4.3, with a minimum response of 100, and a ratio of 35-60. Metoprolol is also confirmed by monitoring it's acid metabolite at a retention time around 2.9 a minimum response of 1000 and a ratio between 6 and 12.
Triamterene: A retention time around 3.4, with a typical minimum response around 1000, and a ratio around 60.
Enalapril: A retention time between 5.5 and 5.7, with a minimum response of 50, and a ratio between transitions of 38-70. Enalapril has a distinctive peak shape which can aid in the identification as well as a metabolite which should be present if enalapril were prescribed, but the metabolite Enalaprilat can also be prescribed itself. If both Enalapril and Enalaprilat are low or borderline, consider negative.
Enalaprilat: A retention time between 3.7 and 3.85, a minimum response of 100, and a ratio between 30 and 50. Enalaprilat has a distinctive peak shape like enalapril, and can be used to distinguish between true peaks and interferences. If both Enalapril and Enalaprilat are low or borderline, consider negative.
Captopril: A retention time around 4 minutes, a response above 50, and a ratio between 80 and 160. There is known to be crosstalk between Metoprolol and Captopril so be certain to check the retention times. The method for captopril is still being refined.
Acetylsalicylic acid: A retention time between 4.79 and 4.95 minutes, any response with decent signal to noise is considered positive, a typical ratio between transitions is around 40±10. ASA rapidly metabolizes to salicylic acid so that is used to call positives and negatives if the transitions for ASA are not conclusive.
Salicylic acid: A retention time around 5 minutes, with a response over 1000, and a ratio

between 5 and 7. Check to be certain the instrument is not integrating more than it should in order to avoid false positives.
Propranolol: A retention time between 5.4 and 5.5 minutes, a typical response of around 1000, with a ratio between 65 and 80.
Ramipril: A retention time between 6 and 6.15 minutes, a minimum response of 100, and a ratio between transitions in the range of 1-5. Ramipril can be confirmed by the presence of Ramiprilat it's major metabolite.
Ramiprilat: A retention time between 5.4 and 5.5 minutes, a minimum response of 200, and a ratio between 50 and 75. Ramiprilat has a distinctive peak shape that will differentiate between true positive and other peaks.
Diltiazem: A retention time between 5.85 and 6.25 minutes, a response over 1000, and a ratio between 27 and 47. Peaks below 1000 counts are not confirmed to be related to diltiazem, even if the retention time and ratio and peak shape are correct.
Carvedilol: A retention time between 6.05 and 6.35 minutes, a response over 100, and a ratio between 45 and 55.
Aliskiren: A retention time between 6.1 and 6.2 minutes, a response over 100, and a ratio between 35 and 55.
Amlodipine: A retention time between 6.15 and 6.41, a minimum response of 100, and a ratio between 60 and 90.
Digoxin: A retention time between 6.2 and 6.4, a response of 10 or more but typically less than 100, with a ratio between 9 and 90.
Furosemide: A retention time between 6.2 and 6.4 minutes, a minimum response of 100, and a ratio between 30 and 75.
Verapamil: A retention time between 6.27 and 6.5 minutes, a minimum response of 1000, and a ratio between 25 and 40.
Pravastatin: A retention time between 6.24 and 6.37 minutes, a minimum response of 9 counts, with a ratio between 55 and 140. Pravastatin has a typical pattern of two peaks are present in both ion traces about 0.2 minutes apart or with baseline separation, this is most noticeable in low abundance samples and can help in identifying true positives.
Telmisartan: A retention time between 6.39 and 6.5 minutes, with a minimum response of 200, and a ratio between 60 and 70.
Losartan: A retention time between 6.7 and 6.85 minutes, with a minimum response of 100, and a typical ratio between 20 and 30. This is more accurate in plasma samples. If BQL, qualitative results = 0.
Nifedipine: A typical retention time of 7.315 minutes, a response over 100, and a ratio between 15 and 35.
Valsartan: A retention time between 7.55 and 7.7, a minimum response of 800, a ratio between 45 and 80.
Warfarin: A retention time between 7.59 and 7.7 minutes, a response over 50,000 counts, and a ratio between 40 and 50.
Spironolactone (Canrenone): A retention time between 7.72 and 7.96 minutes, a minimum response of 100, and a ratio between 50 and 150. Canrenone is the metabolite of Spironolactone, since Spironolactone is metabolized so quickly we are only monitoring its metabolite. If close to 100 but BQL, consider 0; around 100 it is no longer reliable for quantification.
Clopidogrel: A retention time between 7.85 and 8.05 minutes, a minimum response of 10 counts, and a ratio between 55 and 125.
Atorvastatin: A retention time between 8.04 and 8.15 minutes, with a minimum response of 30, and a ratio between 29 and 50.
Fenofibric acid: A retention time between 8.05 and 8.15 minutes, an estimated minimum response of 20,000 counts, and a ratio between 60 and 75. Fenofibric acid is the main

metabolite of Fenofibrate since in all the samples that should be positive for fenofibrate we have no response we began monitoring this metabolite.
Lovastatin: A retention time around 9.05 minutes, a minimum response of 100, and a ratio between 50 and 75.
Simvastatin: A retention time around 9.4, there is no minimum response required, and the ratio between the transitions is unimportant. In order to confirm that the response for simvastatin is genuine we are using three ion transitions, and the retention time must be the same in all three transitions for it to be considered a positive.
Chlorthalidone:
Retention time is (between 5.0 min and 5.2 min most likely) around 5.1, the response should be above 3000 (some variability with each batch, according to the low QC sample) and the ratio between 22-24.

Population A, Appendix Materials

Chapter 3 Appendix Table 2: Population A variable definitions

Variable	Definition/Details
Age	Years
Sex	Female = 0; Male = 1
Race	White = 0; Non-White = 1
Insurance Status	0 = Private, 1 = Government, 2 = Self-Pay
BMI	Continuous Categorized: 1 = underweight (BMI<19) 2 = optimum (BMI 19-24) 3 = overweight (BMI 25-29) 4 = obese (BMI 30-34) 5= morbidly obese (BMI >34)
Highest Level of Education	Number of years of schooling, per patient report
Health Literacy Level	Brief Health Literacy Survey[10]; continuous (3-15); higher indicates better literacy
Numeracy	Subjective Numeracy Scale[11]; continuous (8-48); higher indicates better numeracy
Number of years with hypertension	Per patient report: categorized <1, 1-4, 5-10, >10
Number of antihypertensive medications	Continuous; per patient report
Medication Adherence	ARMS[12]: Dichotomized: adherent =12, non-adherent >12; continuous (reverse-scored)
Adherence (assay)	# BP medications detected/# BP medications prescribed; dichotomized (ratio = 1.0, ratio <1.0) and continuous
Elixhauser Comorbidity Index[13,14]	Van Walraven modification; weighted sum of 30 comorbidities
Charlson-Deyo Comorbidity Index[15]	Weighted sum of 17 comorbidities
Vital Signs (BP, heart rate, respiratory rate, temperature, oxygen saturation)	Mean ED SBP: mean SBP measured during clinical care, excluding Triage SBP and any BPs measured after administration of vasoactive medication Research Vital Signs: single measure of BP, using oscillatory method, performed by a trained research

	assistant Triage SBP: single measure of SBP performed by nurses during initial, brief ED evaluation Clinical Vital Signs: As they occurred and were recorded during the course of routine clinical care; by protocol, all patients are required to undergo measurement of vital signs every two hours while under ED care

Chapter 3 Appendix Table 3: Aim 3 Population A demographics and clinical characteristics

Variable*	N = 299
Age, mean (sd) years median (Q_1, Q_3)	59.1 (11.2) 59 (52, 66)
Female, no. (%)	161 (53.9)
White, no. (%)	186 (62.2)
Non-Hispanic, no. (%)	294 (98.7)
Insurance, no. (%)	
Private	123 (41.1)
Other (Medicare/ Medicare/Federal/No Insurance)	176 (58.9)
Atrial Fibrillation, no. (%)	35 (11.7)
Diabetes, no. (%)	113 (37.8)
Chronic Renal Insufficiency, no. (%)	73 (24.4)
Elixhauser sum, mean (sd) median (Q_1, Q_3)	 13.3 (11.4) 12 (4, 21)
BMI (kg/meter squared), mean (sd) median (Q_1, Q_3)	 32.5 (9.4) 30.9 (25.7, 37.2)
Total number of medications, per patient report mean (sd) median (Q_1, Q_3)	 8.6 (5.2) 8 (5, 11)
Total number of antihypertensives, per patient report mean (sd) median (Q_1, Q_3)	 1.9 (1.3) 2 (1,2)
Highest Level of Education mean (sd) years median (Q_1, Q_3)	 12.4 (1.8) 13 (12, 14)
Health Literacy Level mean (sd) median (Q_1, Q_3)	 13.3 (2.8) 15 (12, 15)
Numeracy (6% missing) mean (sd) median (Q_1, Q_3)	 31.6 (8.0) 33 (26, 38)
Hypertension >10 years no. (%) (4% missing)	 181 (60.7)
* unless otherwise indicated, no missing data	

Chapter 3 Appendix Table 4: Aim 2 Population A Cardiovascular Medications Prescribed (n=299)	
Drug	**Number (%)**
Amlodipine	**76 (25.4%)**
Atenolol	21 (7.0%)
Captopril	0 (0.0%)
Carvedilol	48 (16.1%)
Clonidine	25 (8.4%)
Diltiazem	24 (8.3%)
Enalapril	3 (1.0%)
Lasix	76 (25.0%)
Plavix	36 (12.0%)
Fenofibrate	7 (2.3%)
HCTZ	**90 (30.1%)**
Hydralazine	20 (6.7%)
Isosorbide	22 (7.3%)
Lisinopril	**132 (44.2%)**
Losartan	**36 (12.0%)**
Lovastatin	8 (2.7%)
Metoprolol	**106 (35.5%)**
Nifedipine	37 (12.4%)
Pravastatin	24 (8.0%)
Propranolol	3 (1.3%)
Ramipril	8 (2.7%)
Simvastatin	70 (23.3%)
Telmisartan	3 (1.0%)
Valsartan	13 (4.3%)
Verapamil	10 (3.3%)
Warfarin	14 (4.7%)
Bold indicates medication of interest in sub-group analyses	

Chapter 3 Appendix Table 5: Number of Prescribed BP Medications	
Number of Prescribed Antihypertensives	No. (%)
1	94 (31.4%)
2	104 (34.8%)
3	68 (22.7%)
4	24 (8.4%)
5	8 (2.7%)

Chapter 3 Appendix Table 6: Prescribed and detected antihypertensive medications, for patients prescribed **1 BP medication**			
	Prescribed	Detected	Percent Detected
Amlodipine	13	12	92.3
Atenolol	5	5	100
Carvedilol	7	7	100
Diltiazem	4	4	100
Clonidine	--	--	--
Hydrochlorothiazide	9	8	88.9
Hydralazine	-	-	-
Lisinopril	31	26	83.4
Losartan	-	-	-
Metoprolol	17	14	82.4
Nifedipine	5	4	80.0
Ramipril	1	0	0.0
Valsartan	1	1	100
Verapamil	1	0	0.0
Bold indicates <80% of expected medications were detected by the assay			

Chapter 3 Appendix Table 7: Prescribed and detected antihypertensive medications, for patients prescribed **2 BP medications**			
	Prescribed	Detected	Percent Detected
Amlodipine	14	12	85.7
Atenolol	4	4	100
Carvedilol	19	18	94.7
Diltiazem	6	6	100
Clonidine	**8**	**5**	**62.5**
Hydrochlorothiazide	**28**	**17**	**60.7**
Hydralazine	6	5	83.3
Lisinopril	51	43	84.3
Losartan	9	8	88.9
Metoprolol	42	5	88.1
Nifedipine	13	11	84.6
Ramipril	**2**	**1**	**50.0**
Valsartan	3	1	75.0
Verapamil	2	2	100
Bold indicates <80% of expected medications were detected by the assay			

Chapter 3 Appendix Table 8: Prescribed and detected antihypertensive medications, for patients prescribed **3 BP medications**			
	Prescribed	Detected	Percent Detected
Amlodipine	29	27	93.1
Atenolol	**9**	**7**	**77.8**
Carvedilol	14	14	100.0
Diltiazem	4	4	100.0
Clonidine	**8**	**6**	**75.0**
Hydrochlorothiazide	**30**	**21**	**70.0**
Hydralazine	5	4	80.0

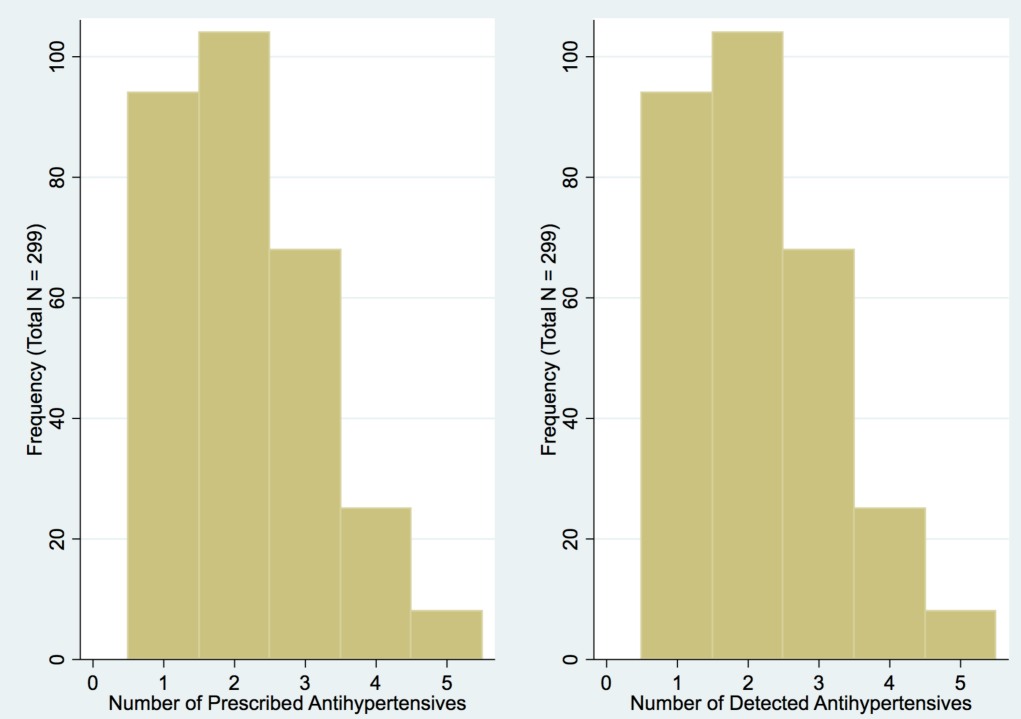
Lisinopril	33	29	87.9
Losartan	16	13	81.3
Metoprolol	29	24	82.8
Nifedipine	**13**	**9**	**69.2**
Ramipril	**4**	**3**	**75.0**
Valsartan	5	4	80.0
Verapamil	5	5	100.0
Bold indicates <80% of expected medications were detected by the assay			

Chapter 3 Appendix Table 9: Prescribed and detected antihypertensive medications, for patients prescribed **4 BP medications**			
	Prescribed	Detected	Percent Detected
Amlodipine	14	13	92.9
Atenolol	2	2	100
Carvedilol	6	5	83.3
Diltiazem	8	7	87.5
Clonidine	**5**	**1**	**20.0**
Hydrochlorothiazide	**17**	**13**	**76.5**
Hydralazine	6	6	100.0
Lisinopril	**13**	**10**	**76.9**
Losartan	8	7	87.5
Metoprolol	**13**	**10**	**76.9**
Nifedipine	**2**	**1**	**50.0**
Ramipril	**1**	**0**	**0.0**
Valsartan	3	3	100.0
Verapamil	2	2	100.0
Bold indicates <80% of expected medications were detected by the assay			

Chapter 3 Appendix Table 10: Prescribed and detected antihypertensive medications, for patients prescribed **5 BP medications**			
	Prescribed	Detected	Percent Detected
Amlodipine	**6**	**3**	**50.0**
Atenolol	**1**	**0**	**0.0**
Carvedilol	2	2	100.0
Diltiazem	2	2	100.0
Clonidine	**4**	**1**	**25.0**
Hydrochlorothiazide	**6**	**2**	**33.3**
Hydralazine	3	3	100.0
Lisinopril	**4**	**3**	**75.0**
Losartan	**3**	**1**	**33.3**
Metoprolol	**5**	**3**	**60.0**
Nifedipine	**4**	**1**	**25.0**
Ramipril	-	-	-
Valsartan	-	-	-
Verapamil	-	-	-
Bold indicates <80% of expected medications were detected by the assay			

Chapter 3 Appendix Table 11: Population A - Number of prescribed and detected antihypertensive medications, N =299	
Number of *prescribed* antihypertensive medications mean (sd) median (Q_1, Q_3)	 2.2 (1.0) 2.0 (1.0, 3.0)
Number of *detected* antihypertensive medications mean (sd) median (Q_1, Q_3)	 1.8 (1.0) 2.0 (1.0, 2.0)

Chapter 3 Appendix Figure 1: Population A – Distribution of number antihypertensive medications that were prescribed versus the number detected by the mass spectrometry assay (N = 299)



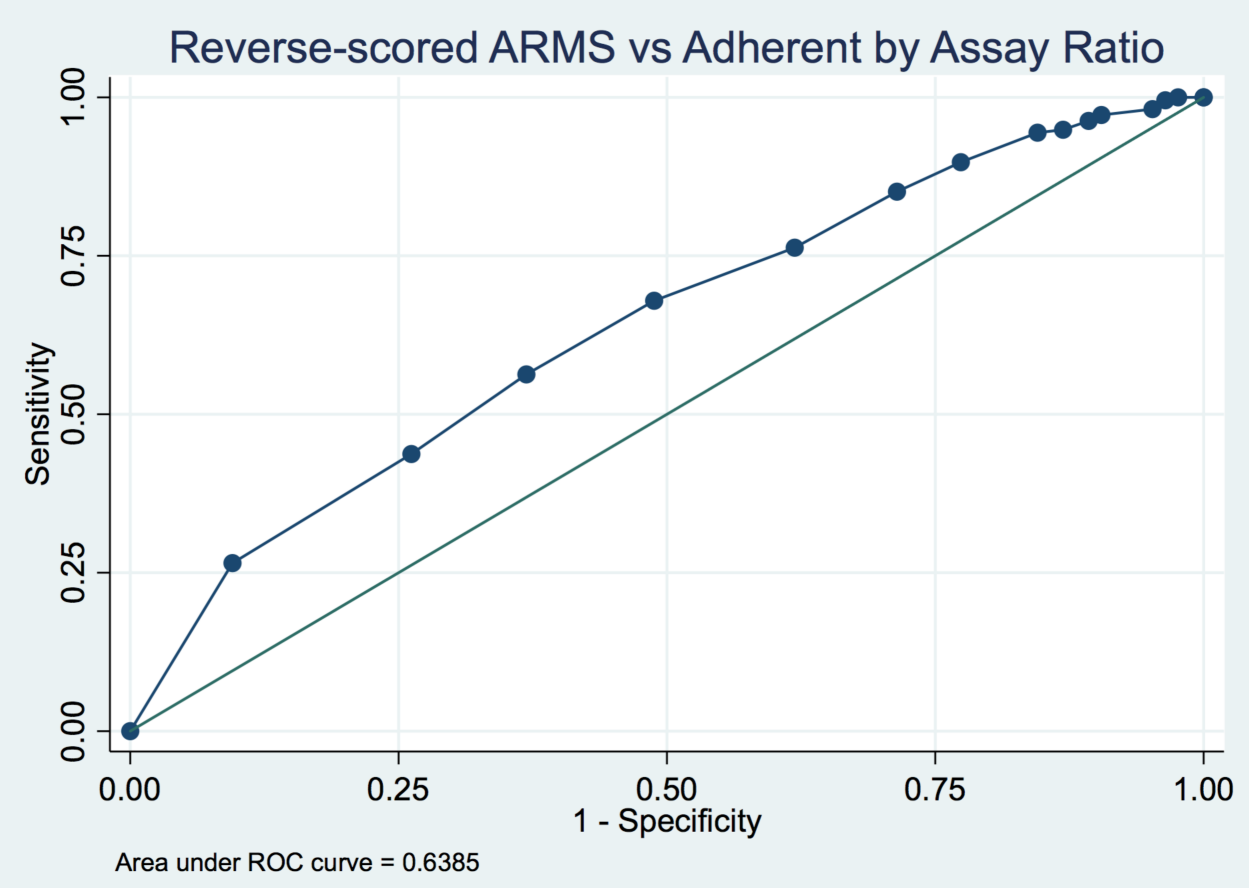
Population A, Aim 2 Results: ARMS vs. adherent by Assay Ratio

Chapter 3 Appendix Table 12: Non-Adherent, by Assay and ARMS			
	Non-Adherent (assay ratio < 1.0)	Adherent (assay ratio = 1.0)	
Non-Adherent by ARMS (ARMS > 12)	76	158	234
Adherent by ARMS (ARMS = 12)	8	57	65
	84	215	299
Odds ratio (OR) for a subject being nonadherent by the assay ratio if he/she was nonadherent by the ARMS: 3.4 (95% CI 1.5, 8.7)			
Sensitivity	Pr(D| +) 90.48%	(95% CI 82.09%, 95.80%)	
Specificity	Pr(~D| -) 26.51%	(95% CI 20.74%, 32.94%)	
Positive predictive value	Pr(+| D) 32.48%	(95% CI 26.52%, 38.89%)	
Negative predictive value	Pr(-|~D) 87.69%	(95% CI 77.18%, 94.53%)	

The alternative ARMS threshold for defining adherent (ARMS<15, or median ARMS score) had higher PPV and specificity for adherent by the assay ratio and lower NPV and sensitivity (Table 13), as expected.

Chapter 3 Appendix Table 13: Non-Adherent, by Assay and ARMS (ARMS adherent <15)			
	Non-Adherent by Assay (ratio < 1)	Adherent by Assay (ratio = 1)	
Non-Adherent by ARMS (ARMS ≥15)	53	94	147
Adherent by ARMS (ARMS <15)	31	121	152
	84	215	299
OR for a subject being nonadherent by the assay ratio if he/she was nonadherent by the ARMS (ARMS>14): 2.2 (95% CI 1.3, 3.9)			
Sensitivity	Pr(D| +) 63.10%	(95% CI 51.87%, 73.37%)	
Specificity	Pr(~D| -) 56.28%	(95% CI 49.37%, 63.01%)	
Positive predictive value	Pr(+| D) 36.05%	(95% CI 28.31%, 44.38%)	
Negative predictive value	Pr(-|~D) 79.61%	(95% CI 72.32%, 85.70%)	

Chapter 3 Appendix Figure 2: Population A - ROC curve of reverse-scored ARMS for adherent by assay ratio



Defining adherent by the assay as an assay ratio ≥80% reclassified 1 subject and did not result in a change in the AUC of the ROC for the ARMS.

Population A, Sensitivity and Specificity

Detailed report of sensitivity and specificity of ARMS for adherent by the assay ratio

Population A, Aim 2: ARMS, reverse-scored, vs. Adherent by assay

Detailed report of sensitivity and specificity (corresponding to ARMS 12 to 21)

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 21)	100.00%	0.00%	71.91%	1.0000	
(>= 22)	100.00%	2.38%	72.58%	1.0244	0.0000
(>= 25)	99.53%	3.57%	72.58%	1.0322	0.1302
(>= 26)	98.14%	4.76%	71.91%	1.0305	0.3907
(>= 27)	97.21%	9.52%	72.58%	1.0744	0.2930
(>= 28)	96.28%	10.71%	72.24%	1.0783	0.3473
(>= 29)	94.88%	13.10%	71.91%	1.0918	0.3907
(>= 30)	94.42%	15.48%	72.24%	1.1171	0.3606
(>= 31)	89.77%	22.62%	70.90%	1.1601	0.4524
(>= 32)	85.12%	28.57%	69.23%	1.1916	0.5209
(>= 33)	76.28%	38.10%	65.55%	1.2322	0.6227
(>= 34)	67.91%	51.19%	63.21%	1.3913	0.6269
(>= 35)	56.28%	63.10%	58.19%	1.5250	0.6929
(>= 36)	43.72%	73.81%	52.17%	1.6693	0.7625
(>= 37)	26.51%	90.48%	44.48%	2.7837	0.8122
(> 37)	0.00%	100.00%	28.09%		1.0000

Obs	ROC Area	Std. Err.	-- Binomial Exact -- [95% Conf.	Interval]
299	0.6385	0.0348	0.58151	0.69330

Population A, Aim 2: ARMS vs. Adherent by assay

Detailed report of sensitivity and specificity - ARMS without reverse scoring

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 12)	100.00%	0.00%	71.91%	1.0000	
(>= 13)	73.49%	9.52%	55.52%	0.8122	2.7837
(>= 14)	56.28%	26.19%	47.83%	0.7625	1.6693
(>= 15)	43.72%	36.90%	41.81%	0.6929	1.5250
(>= 16)	32.09%	48.81%	36.79%	0.6269	1.3913
(>= 17)	23.72%	61.90%	34.45%	0.6227	1.2322
(>= 18)	14.88%	71.43%	30.77%	0.5209	1.1916
(>= 19)	10.23%	77.38%	29.10%	0.4524	1.1601
(>= 20)	5.58%	84.52%	27.76%	0.3606	1.1171
(>= 21)	5.12%	86.90%	28.09%	0.3907	1.0918
(>= 22)	3.72%	89.29%	27.76%	0.3473	1.0783
(>= 23)	2.79%	90.48%	27.42%	0.2930	1.0744
(>= 24)	1.86%	95.24%	28.09%	0.3907	1.0305
(>= 27)	0.47%	96.43%	27.42%	0.1302	1.0322
(>= 28)	0.00%	97.62%	27.42%	0.0000	1.0244
(> 28)	0.00%	100.00%	28.09%		1.0000

Obs	ROC Area	Std. Err.	-- Binomial Exact -- [95% Conf.	Interval]
299	0.3615	0.0348	0.30670	0.41849

Population A, Aim 2: Detailed report of sensitivity and specificity of the assay ratio to detect adherent by the ARMS (ARMS = 12)

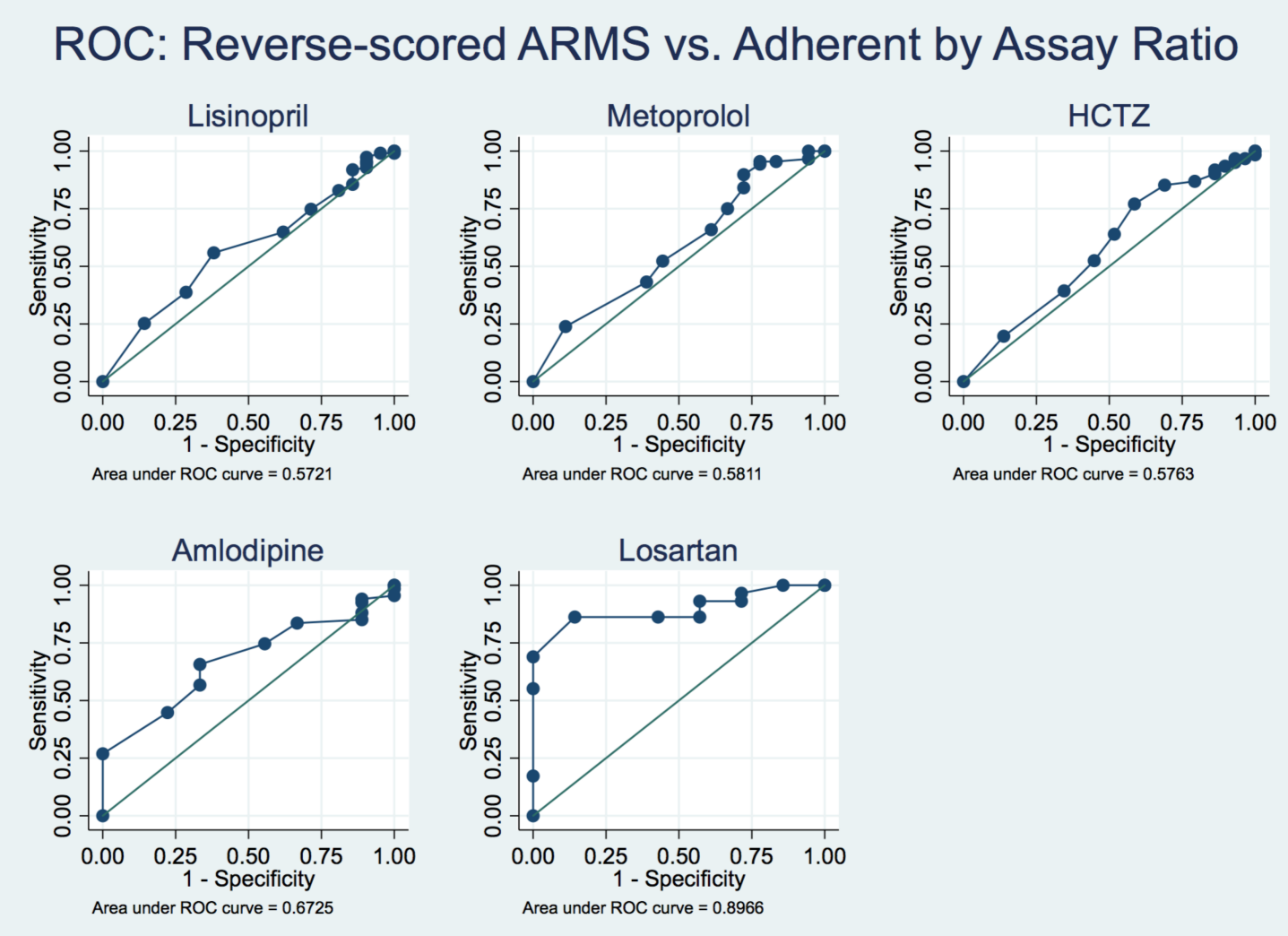
Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 0)	100.00%	0.00%	21.74%	1.0000	
(>= .2)	96.92%	9.40%	28.43%	1.0698	0.3273
(>= .3333)	96.92%	10.26%	29.10%	1.0800	0.3000
(>= .4)	95.38%	11.97%	30.10%	1.0835	0.3857
(>= .5)	95.38%	12.82%	30.77%	1.0941	0.3600
(>= .6)	92.31%	21.37%	36.79%	1.1739	0.3600
(>= .6666)	92.31%	22.22%	37.46%	1.1868	0.3462
(>= .75)	89.23%	29.06%	42.14%	1.2578	0.3706
(>= .8)	87.69%	32.05%	44.15%	1.2906	0.3840
(>= 1)	87.69%	32.48%	44.48%	1.2987	0.3789
(> 1)	0.00%	100.00%	78.26%		1.0000

Obs	ROC Area	Std. Err.	-- Binomial Exact -- [95% Conf.	Interval]
299	0.6019	0.0258	0.54407	0.65790

Population A, Aim 2: Subgroup Analyses by Separate Medications - Referent: Assay ratio

Within subgroups by antihypertensive medication, c-statistics of the ARMS for adherent by the assay ratio were overall weak in strength, with the exception of losartan, which had an ROC AUC of 0.90 (Figure 3). Detailed reports of sensitivity and specificity for each drug are reported in the Chapter 3 Appendix.

Chapter 3 Appendix Figure 3: Population A - ROC curves for reverse-score ARMS versus adherent by the assay (assay ratio = 1.0) for lisinopril (N = 132), metoprolol (N = 106), hydrochlorothiazide (HCTZ; N = 90), amlodipine (N = 76), and losartan (N = 36).



Sensitivity and specificity of the ARMS (reverse-scored) to correctly classify adherent measured by the assay (assay ratio = 1), for lisinopril, metoprolol, hydrochlorothiazide, amlodipine, and losartan.

Lisinopril: Detailed report of sensitivity and specificity (corresponding to ARMS scores 12 to 28)

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 21)	100.00%	0.00%	84.09%	1.0000	
(>= 22)	99.10%	0.00%	83.33%	0.9910	
(>= 25)	99.10%	4.76%	84.09%	1.0405	0.1892
(>= 26)	97.30%	9.52%	83.33%	1.0754	0.2838
(>= 27)	95.50%	9.52%	81.82%	1.0555	0.4730
(>= 28)	94.59%	9.52%	81.06%	1.0455	0.5676
(>= 29)	92.79%	9.52%	79.55%	1.0256	0.7568
(>= 30)	9189%	14.29%	79.55%	1.0721	0.5676
(>= 31)	85.59%	14.29%	74.24%	0.9985	1.0090
(>= 32)	82.88%	19.05%	72.73%	1.0238	0.8986
(>= 33)	74.77%	28.57%	67.42%	1.0468	0.8829
(>= 34)	64.86%	38.10%	60.61%	1.0478	0.9223
(>= 35)	55.86%	61.90%	56.82%	1.4662	0.7131
(>= 36)	38.74%	71.43%	43.94%	1.3559	0.8577
(>= 37)	25.23%	85.71%	34.85%	1.7658	0.8724
(> 37)	0.00%	100.00%	15.91%		1.0000

Obs	ROC Area	Std. Err.	-Asymptotic Normal- [95% Conf.	Interval]
132	0.5721	0.0659	0.44294	0.70120

Metoprolol: Detailed report of sensitivity and specificity (corresponding to ARMS scores 12 to 28)

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 21)	100.00%	0.00%	83.02%	1.0000	
(>= 25)	100.00%	5.56%	83.96%	1.0588	0.0000
(>= 26)	96.59%	5.56%	81.13%	1.0227	0.6136
(>= 28)	95.45%	16.67%	82.08%	1.1455	0.2727
(>= 29)	95.45%	22.22%	83.02%	1.2273	0.2045
(>= 30)	94.32%	22.22%	82.08%	1.2127	0.2557
(>= 31)	89.77%	27.78%	79.25%	1.2430	0.3682
(>= 32)	84.09%	27.78%	74.53%	1.1643	0.5727
(>= 33)	75.00%	33.33%	67.92%	1.1250	0.7500
(>= 34)	65.91%	38.89%	61.32%	1.0785	0.8766
(>= 35)	52.27%	55.56%	52.83%	1.1761	0.8591
(>= 36)	43.18%	61.11%	46.23%	1.1104	0.9298
(>= 37)	23.86%	88.89%	34.91%	2.1477	0.8565
(> 37)	0.00%	100.00%	16.98%		1.0000

Obs	ROC Area	Std. Err.	-Asymptotic Normal- [95% Conf.	Interval]
106	0.5811	0.0762	0.43176	0.73049

HCTZ: Detailed report of sensitivity and specificity (corresponding to ARMS scores 12 to 28)

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 21)	100.00%	0.00%	67.78%	1.0000	
(>= 22)	98.36%	0.00%	66.67%	0.9836	
(>= 25)	96.72%	3.45%	66.67%	1.0018	0.9508
(>= 26)	96.72%	6.90%	67.78%	1.0389	0.4754
(>= 27)	95.08%	6.90%	66.67%	1.0213	0.7131
(>= 28)	93.44%	10.34%	66.67%	1.0422	0.6339
(>= 29)	91.80%	13.79%	66.67%	1.0649	0.5943
(>= 30)	90.16%	13.79%	65.56%	1.0459	0.7131
(>= 31)	86.89%	20.69%	65.56%	1.0955	0.6339
(>= 32)	85.25%	31.03%	67.78%	1.2361	0.4754
(>= 33)	77.05%	41.38%	65.56%	1.3144	0.5546
(>= 34)	63.93%	48.28%	58.89%	1.2361	0.7471

(>= 35)	52.46%	55.17%	53.33%	1.1702	0.8617
(>= 36)	39.34%	65.52%	47.78%	1.1410	0.9258
(>= 37)	19.67%	86.21%	41.11%	1.4262	0.9318
(> 37)	0.00%	100.00%	32.22%		1.0000

Obs	ROC Area	Std. Err.	-Asymptotic Normal-- [95% Conf.	Interval]
90	0.5763	0.0664	0.44621	0.70642

Amlodipine: Detailed report of sensitivity and specificity (corresponding to ARMS scores 12 to 28)

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 21)	100.00%	0.00%	88.16%	1.0000	
(>= 25)	98.51%	0.00%	86.84%	0.9851	
(>= 26)	95.52%	0.00%	84.21%	0.9552	
(>= 27)	94.03%	11.11%	84.21%	1.0578	0.5373
(>= 28)	92.54%	11.11%	82.89%	1.0410	0.6716
(>= 30)	88.06%	11.11%	78.95%	0.9907	1.0746
(>= 31)	85.07%	11.11%	76.32%	0.9571	1.3433
(>= 32)	83.58%	33.33%	77.63%	1.2537	0.4925
(>= 33)	74.63%	44.44%	71.05%	1.3433	0.5709
(>= 34)	65.67%	66.67%	65.79%	1.9701	0.5149
(>= 35)	56.72%	66.67%	57.89%	1.7015	0.6493
(>= 36)	44.78%	77.78%	48.68%	2.0149	0.7100
(>= 37)	26.87%	100.00%	35.53%		0.7313
(> 37)	0.00%	100.00%	11.84%		1.0000

Obs	ROC Area	Std. Err.	-Asymptotic Normal-- [95% Conf.	Interval]
76	0.6725	0.0823	0.51126	0.83368

Losartan: Detailed report of sensitivity and specificity (corresponding to ARMS scores 12 to 23)

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 26)	100.00%	0.00%	80.56%	1.0000	
(>= 28)	100.00%	14.29%	83.33%	1.1667	0.0000
(>= 29)	96.55%	28.57%	83.33%	1.3517	0.1207
(>= 30)	93.10%	28.57%	80.56%	1.3034	0.2414
(>= 31)	93.10%	42.86%	83.33%	1.6293	0.1609
(>= 32)	86.21%	42.86%	77.78%	1.5086	0.3218
(>= 33)	86.21%	57.14%	80.56%	2.0115	0.2414
(>= 34)	86.21%	85.71%	86.11%	6.0345	0.1609
(>= 35)	68.97%	100.00%	75.00%		0.3103
(>= 36)	55.17%	100.00%	63.89%		0.4483
(>= 37)	17.24%	100.00%	33.33%		0.8276
(> 37)	0.00%	100.00%	19.44%		1.0000

Obs	ROC Area	Std. Err.	-Asymptotic Normal-- [95% Conf.	Interval]
36	0.8966	0.0523	0.79407	0.99903

Population A, Aim 2 – Subgroup Analyses by Separate Medications; ARMS = referent standard

Sensitivity and specificity of the assay to correctly classify adherent/non-adherent according to the ARMS (ARMS =12), for lisinopril, metoprolol, hydrochlorothiazide, amlodipine, and losartan.

Lisinopril: Detailed report of sensitivity and specificity

Detailed report of sensitivity and specificity

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 0)	100.00%	0.00%	23.48%	1.0000	
(>= .2)	96.77%	10.89%	31.06%	1.0860	0.2962
(>= .3333..)	96.77%	11.88%	31.82%	1.0982	0.2715
(>= .4)	93.55%	13.86%	32.58%	1.0860	0.4654
(>= .5)	93.55%	14.85%	33.33%	1.0986	0.4344
(>= .6666..)	90.32%	21.78%	37.88%	1.1548	0.4443
(>= .75)	90.32%	29.70%	43.94%	1.2849	0.3258
(>= .8)	87.10%	32.67%	45.45%	1.2936	0.3949
(>= 1)	87.10%	33.66%	46.21%	1.3130	0.3833
(> 1)	0.00%	100.00%	76.52%		1.0000

Obs	ROC Area	Std. Err.	-Asymptotic Normal-- [95% Conf.	Interval]
132	0.6040	0.0392	0.52719	0.68073

Metoprolol: Detailed report of sensitivity and specificity

Detailed report of sensitivity and specificity

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 0)	100.00%	0.00%	21.70%	1.0000	
(>= .2)	95.65%	6.02%	25.47%	1.0178	0.7217
(>= .3333..)	95.65%	7.23%	26.42%	1.0311	0.6014
(>= .4)	91.30%	10.84%	28.30%	1.0241	0.8019
(>= .5)	91.30%	13.25%	30.19%	1.0525	0.6561
(>= .6666..)	86.96%	18.07%	33.02%	1.0614	0.7217
(>= .75)	82.61%	26.51%	38.68%	1.1240	0.6561
(>= .8)	82.61%	30.12%	41.51%	1.1822	0.5774
(>= 1)	82.61%	31.33%	42.45%	1.2029	0.5552
(> 1)	0.00%	100.00%	78.30%		1.0000

Obs	ROC Area	Std. Err.	-Asymptotic Normal-- [95% Conf.	Interval]
106	0.5642	0.0501	0.46600	0.66234

HCTZ: Detailed report of sensitivity and specificity

Detailed report of sensitivity and specificity

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 0)	100.00%	0.00%	17.78%	1.0000	
(>= .2)	100.00%	8.11%	24.44%	1.0882	0.0000
(>= .3333..)	100.00%	10.81%	26.67%	1.1212	0.0000
(>= .4)	93.75%	13.51%	27.78%	1.0840	0.4625
(>= .5)	93.75%	14.86%	28.89%	1.1012	0.4205
(>= .6)	81.25%	29.73%	38.89%	1.1563	0.6307
(>= .6666..)	81.25%	31.08%	40.00%	1.1789	0.6033
(>= .75)	75.00%	39.19%	45.56%	1.2333	0.6379
(>= .8)	68.75%	43.24%	47.78%	1.2113	0.7227
(>= 1)	68.75%	44.59%	48.89%	1.2409	0.7008
(> 1)	0.00%	100.00%	82.22%		1.0000

Obs	ROC Area	Std. Err.	-Asymptotic Normal-- [95% Conf.	Interval]
90	0.5802	0.0650	0.45292	0.70755

Amlodipine: Detailed report of sensitivity and specificity

Detailed report of sensitivity and specificity

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 0)	100.00%	0.00%	23.68%	1.0000	
(>= .2)	100.00%	6.90%	28.95%	1.0741	0.0000
(>= .3333..)	100.00%	8.62%	30.26%	1.0943	0.0000
(>= .4)	100.00%	10.34%	31.58%	1.1154	0.0000
(>= .5)	100.00%	13.79%	34.21%	1.1600	0.0000
(>= .6)	100.00%	15.52%	35.53%	1.1837	0.0000
(>= .6666..)	100.00%	18.97%	38.16%	1.2340	0.0000
(>= .75)	100.00%	36.21%	51.32%	1.5676	0.0000
(>= 1)	100.00%	44.83%	57.89%	1.8125	0.0000
(> 1)	0.00%	100.00%	76.32%		1.0000

Obs	ROC Area	Std. Err.	-Asymptotic Normal-- [95% Conf.	Interval]
76	0.7241	0.0329	0.65959	0.78869

Losartan: Detailed report of sensitivity and specificity

Detailed report of sensitivity and specificity

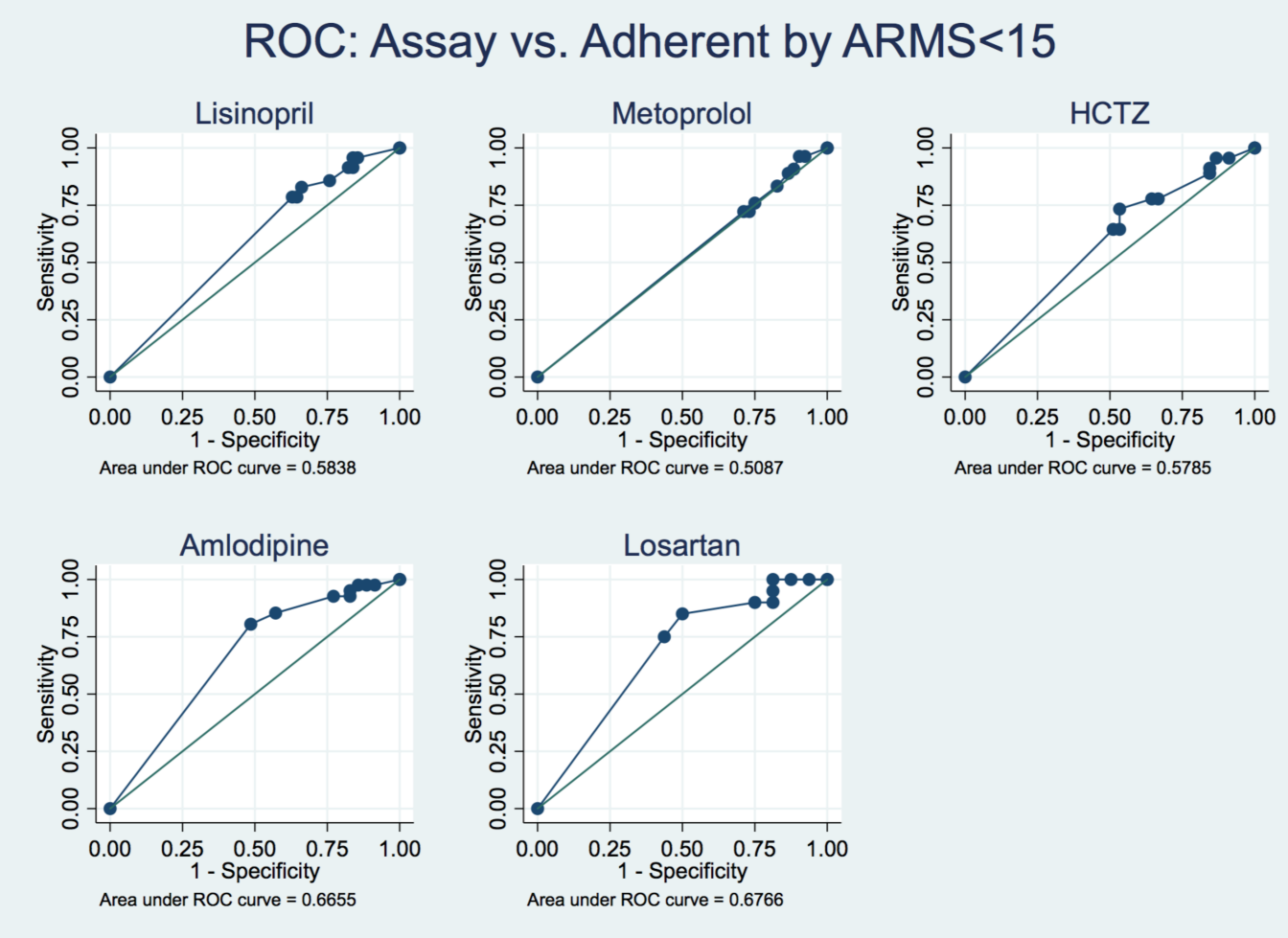
Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 0)	100.00%	0.00%	13.89%	1.0000	
(>= .2)	100.00%	3.23%	16.67%	1.0333	0.0000
(>= .3333..)	100.00%	6.45%	19.44%	1.0690	0.0000
(>= .4)	100.00%	9.68%	22.22%	1.1071	0.0000
(>= .5)	100.00%	12.90%	25.00%	1.1481	0.0000
(>= .6)	100.00%	16.13%	27.78%	1.1923	0.0000
(>= .6666..)	100.00%	19.35%	30.56%	1.2400	0.0000
(>= .75)	80.00%	32.26%	38.89%	1.1810	0.6200
(>= 1)	80.00%	41.94%	47.22%	1.3778	0.4769
(> 1)	0.00%	100.00%	86.11%		1.0000

Obs	ROC Area	Std. Err.	-Asymptotic Normal-- [95% Conf.	Interval]
36	0.6194	0.1023	0.41882	0.81989

Population A, Aim 2: Alternative threshold for adherent by ARMS: ARMS<15

The AUC curves are smaller when adherent was defined as ARMS <15 (Figure 4).

Chapter 3 Appendix Figure 4: Population A - ROC curves for the assay ratio compared to adherent by the ARMS (ARMS <15) for lisinopril (N = 132), metoprolol (N = 106), hydrochlorothiazide (HCTZ; N = 90), amlodipine (N = 76), and losartan (N = 36).



Aim 3 Population A Univariate Associations with Medication Adherence

Chapter 3 Appendix Table 14: Population A – Univariate Relationships of Patient Characteristics with Measures of Adherence*				
Variable	**Adherence – by Assay**	**P-value**	**Adherence – by ARMS**	**P-value**
Age	0.139	**0.02**	-0.18	**0.004**
Sex		0.55		0.47
Race (White, Non-White)		**0.01**		**0.0002**
Insurance		0.82		0.50
History of Atrial Fibrillation		0.53		0.15
Diabetes		0.62		0.96
Chronic Renal Insufficiency		0.67		0.30
Elixhauser Index		0.70		0.17
Charlson-Deyo Index		0.84		0.13
BMI (kg/meter squared)	-0.14	**0.01**	0.06	0.34
Highest Level of Education, years	-0.005	0.93	-0.008	0.89
Health Literacy Level	-0.02	0.68	-0.09	0.11
Numeracy Level, (4% missing)	0.15	**0.01**	-0.05	0.36
Hypertension Duration, (0.3%) missing		**0.04**		0.08
Number of antihypertensive medications, mean (sd), (3% missing)	-0.24	**<0.001**	0.008	0.89
* Spearman's rho for continuous variables; Kruskal-Wallis test for categorical variables				

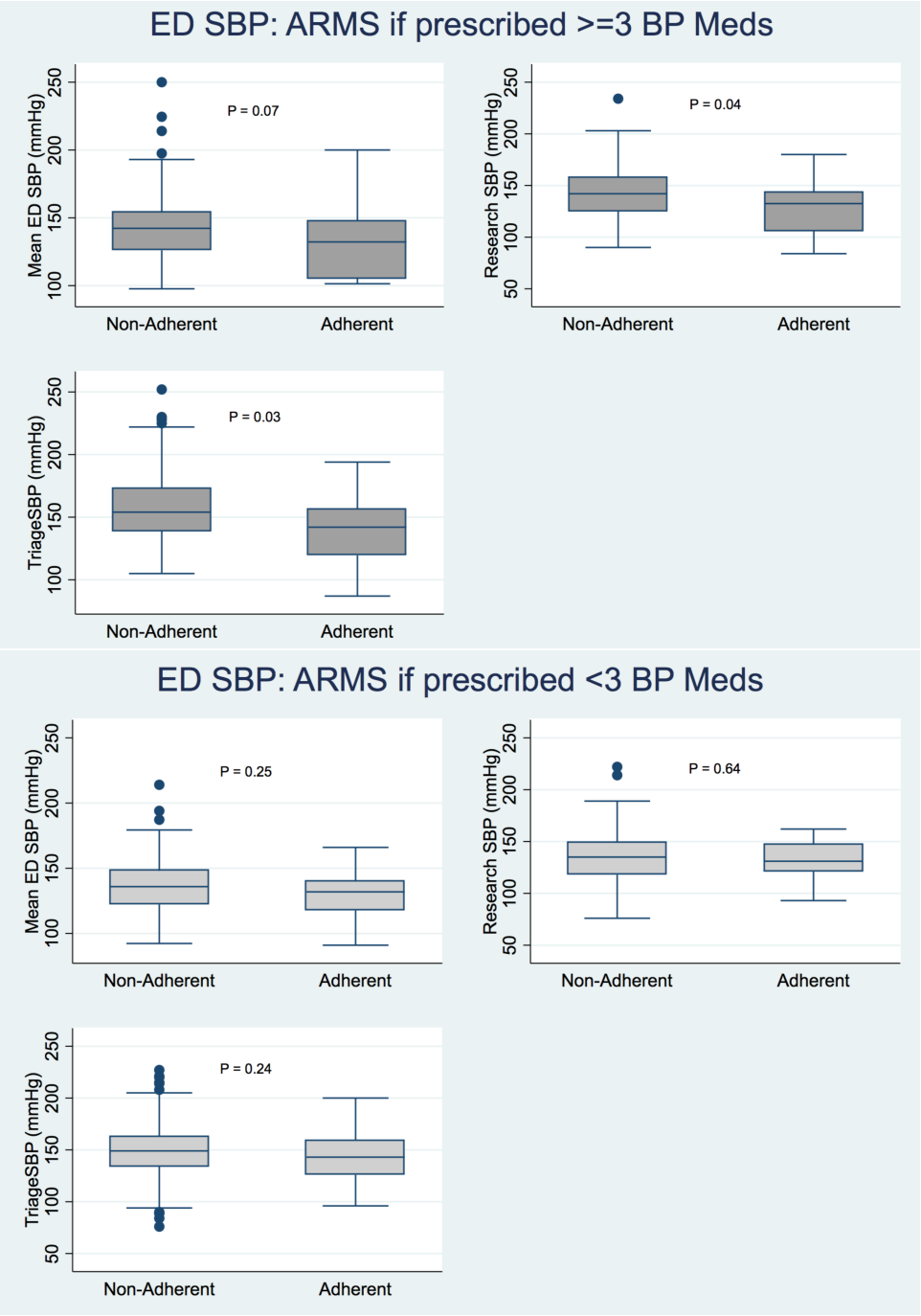
Aim 3 Population A Univariate Associations with SBP

By the assay ratio, ED SBP was higher (visibly and by Spearman rank order test) among non-adherent patients prescribed ≥3 BP medications, regardless of how ED SBP was measured (Table 15). The trend was similar when adherence was measured by the ARMS, although it was statistically significant only for research and triage ED SBP. These relationships are visualized in box plots as well, stratified by number of prescribed medications, for the assay ratio and ARMS in.

Chapter 3 Appendix Table 15: ED SBP by adherent/nonadherent*		
	P-value, Prescribed ≥3 BP Medications	P-value, Prescribed <3 BP Medications
Adherent by Assay Ratio		
Mean ED SBP	0.007	0.64
Research SBP	0.001	0.20
Triage SBP	0.002	0.29
Adherent by ARMS		
Mean ED SBP	0.07	0.25
Research SBP	0.04	0.64
Triage SBP	0.03	0.24
* by Spearman rank order test		

Chapter 3 Appendix Table 16: Population A – Univariate Relationships of Patient Characteristics with ED Blood Pressure Measures						
Variable	**Mean ED SBP, Excluding Triage (N = 262)**	**P-value**	**Research SBP (N = 298)**	**P-value**	**Triage SBP (N = 300)**	**P-value**
Age	-0.02	0.98	-0.04	0.49	-0.003	0.96
Sex		0.86		0.55		0.16
Race (White, Non-White)		**0.02**		**0.02**		**0.02**
Insurance		0.89		0.41		0.14
History of Atrial Fibrillation		0.18		0.20		**0.04**
Diabetes		0.73		0.35		0.84
Chronic Renal Insufficiency		0.47		0.06		0.75
BMI (kg/meter squared)	**0.14**	**0.03**	0.11	0.06	**0.14**	**0.02**
Elixhauser Index	-0.06	0.34	-0.07	0.25	-0.09	0.12
Charlson-Deyo Index	-0.09	0.16	-0.10	0.09	-0.10	0.09
Highest Level of Education, years	0.03	0.67	0.02	0.77	0.05	0.39
Health Literacy Level	0.01	0.87	0.04	0.44	**0.13**	**0.03**
Numeracy Level, (4% missing)	-0.1	0.12	-0.12	**0.05**	-0.03	0.62
Hypertension Duration, (0.3%) missing		0.87		**0.03**		0.41
Number of antihypertensive medications, mean (sd), (3% missing)	**0.15**	**0.01**	**0.14**	**0.01**	**0.16**	**0.007**
* Spearman's rho for continuous variables; Kruskal-Wallis test for categorical variables						

Chapter 3 Appendix Figure 5: Population A, ED SBP comparing adherent to non-adherent measured by the ARMS, among patients prescribed ≥ 3 BP medications



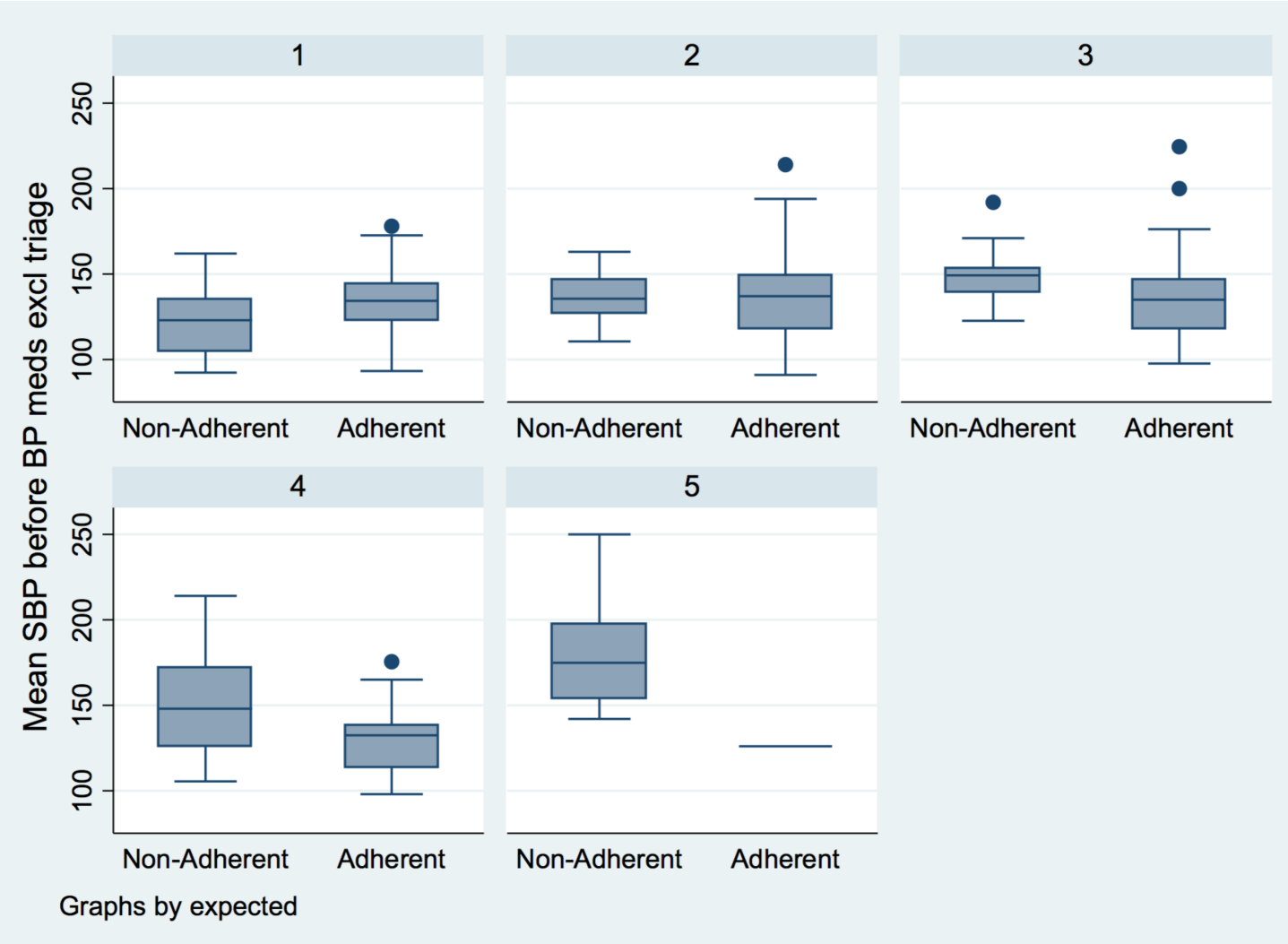
Population A: ED SBP

Chapter 3 Appendix Table 17: Aim 3 Population A – Measures of Systolic Blood Pressure in the ED		
Blood Pressure	Summary Statistic	Missing N (%)
Mean ED SBP - *Primary* mean (sd) median (Q_1, Q_3)	 137.3 (23.5) 135.8 (122.7, 150.0)	38 (12.7)
Number of ED BPs, excluding Triage mean (sd) median (Q_1, Q_3)	 3.2 (1.8) 3 (2, 4)	38 (12.7)
Research SBP - *Secondary* mean (sd) median (Q_1, Q_3)	 136.7 (24.2) 136.0 (121.0, 150.0)	2 (0.7)
Research SBP, prior to vasoactive medication mean (sd) median (Q_1, Q_3)	 137.0 (24.5) 136.0 (121.0, 150.0)	54 (18.0)
Triage SBP mean (sd) median (Q_1, Q_3)	 150.1 (29.5) 150.0 (133.0, 164.0)	0

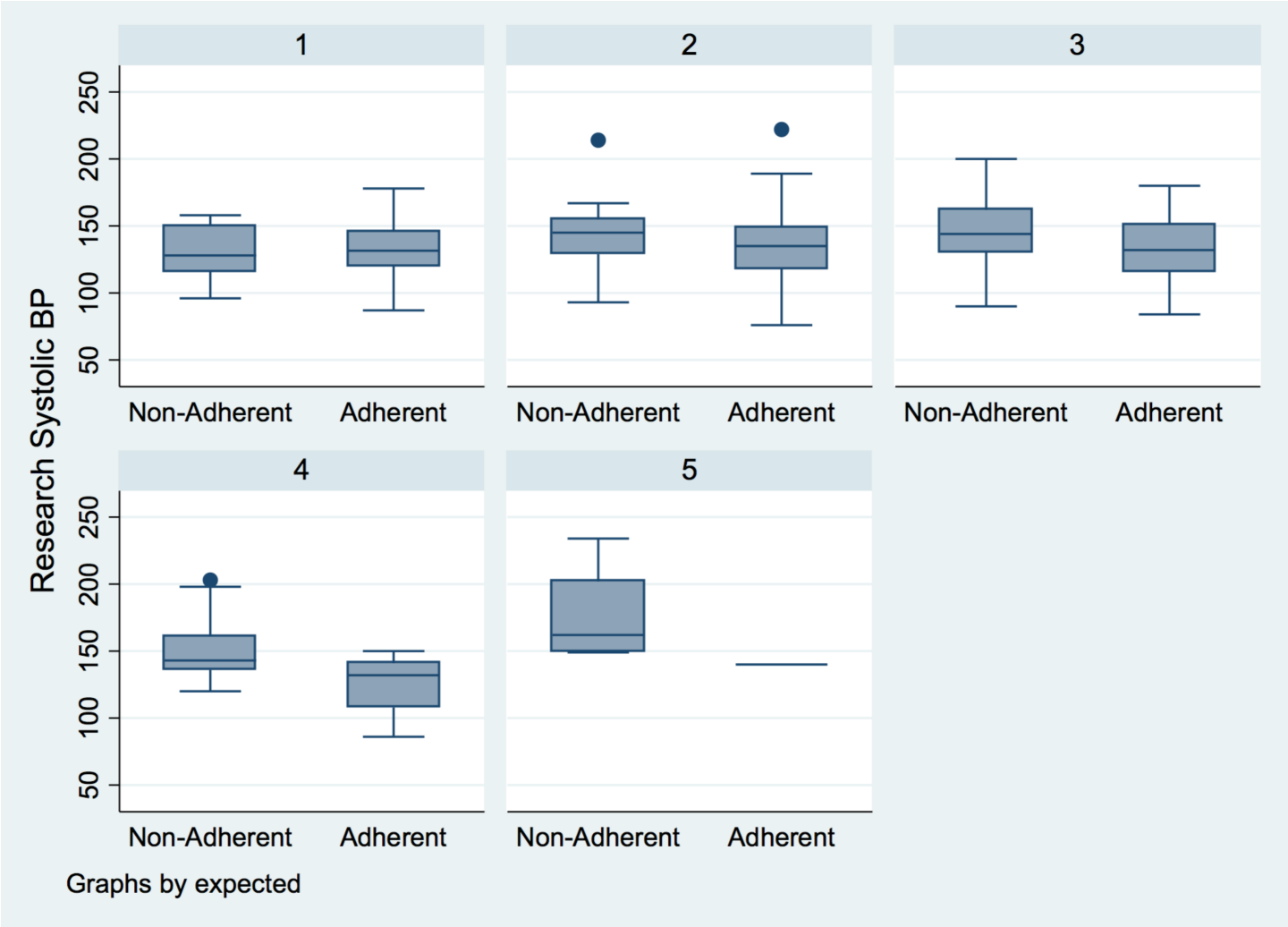
Chapter 3 Appendix Table 18: Aim 3 Population A – Categories of Systolic Blood Pressure in the ED	
Mean ED SBP Categories (N = 261)	No. (%)
SBP <140 mmHg	155 (59.4)
≥140, <160 mmHg	73 (28.0)
SBP>160 mmHg	33 (12.6)
Research SBP Categories (N = 297)	
SBP <140 mmHg	166 (55.9)
≥140, <160 mmHg	86 (29.0)
SBP>160 mmHg	45 (15.2)
Triage SBP Categories (N = 299)	
SBP <140 mmHg	101 (33.8)
≥140, <160 mmHg	105 (35.1)
SBP>160 mmHg	93 (31.1)

Aim 3 - SBP by Adherent, by number of prescribed BP medications

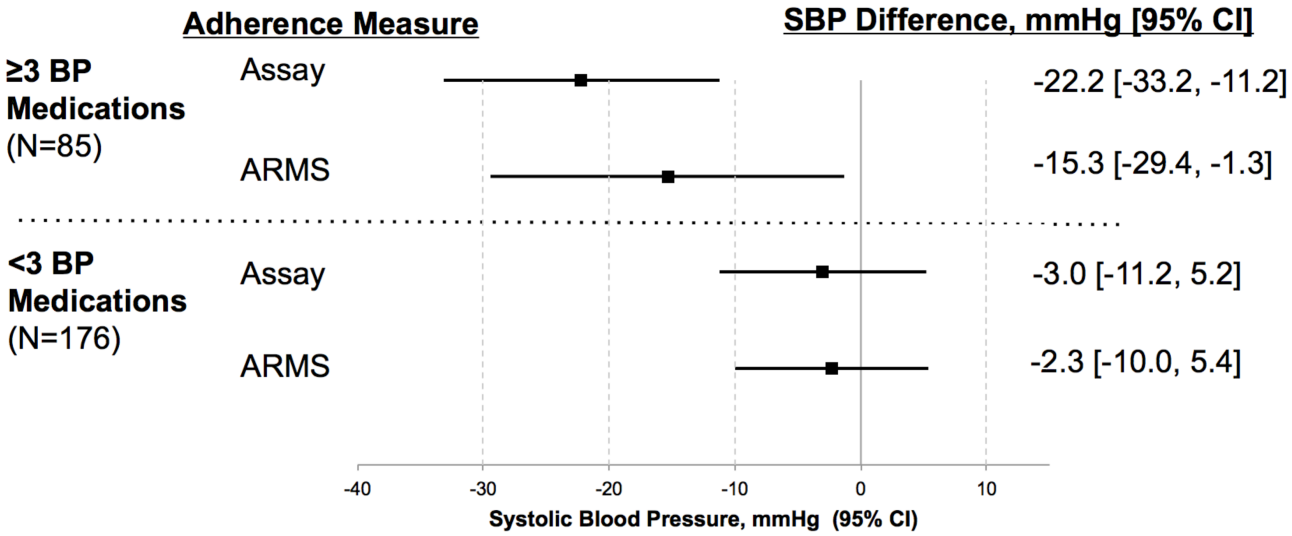
Chapter 3 Appendix Figure 6: Adherent by Mean ED SBP, by Number of Prescribed Antihypertensives



Chapter 3 Appendix Figure 7: Adherent by *Research* SBP, by Number of Prescribed Antihypertensives



Chapter 3 Appendix Figure 8: Difference in research SBP* for Completely Adherent Subjects Compared to Partially/Completely Non-Adherent Subjects, *stratified by number of prescribed antihypertensive medications*



* Adjusted for age, pain, sex, race, health insurance, health literacy, numeracy, BMI, chronic renal insufficiency, comorbid conditions, and duration of hypertension diagnosis

Abbreviations: BP, blood pressure; ARMS, adherence to refills and medications scale; BMI, body mass index

Adherence Variable Combining the Assay Ratio and ARMS:

Examining the distribution of adherence according to both the assay ratio and ARMS, the proportion of patients in each category was as follows:

Non-adherent by both assay ratio and ARMS: 76 (25.4%)
Adherent by assay ratio, non-adherent by ARMS: 8 (2.7%)
Non-adherent by assay ratio, adherent by ARMS: 158 (52.8%)
Adherent by both assay ratio and ARMS: 57 (19.1%)

Table 19: Adjusted Associations Between 4-level Adherent Variable (Assay Ratio and ARMS) with SBP in the ED*		
	Beta (95% CI)	Beta (95% CI)
Prescribed ≥3 BP Medications		
	Mean ED SBP, mmHg (N = 85)	Research SBP, mmHg (N = 99)
Assay Ratio: Non-Adherent ARMS: Non-Adherent	(referent)	(referent)
Assay Ratio: Non-Adherent ARMS: Adherent	-22.5 (-54.4 to 9.4)	-17.8 (-42.5 to 7.0)
Assay Ratio: Adherent ARMS: Non-Adherent	-23.1 (-39.2 to -6.9)	-22.4 (-35.0 to -10.0)
Assay Ratio: Adherent ARMS: Adherent	-22.5 (-41.4 to -3.6)	-31.1 (-47.2 to -15.0)
Prescribed <3 BP Medications		
	Mean ED SBP, mmHg (N = 175)	Research SBP, mmHg (N = 197)
Assay Ratio: Non-Adherent ARMS: Non-Adherent	(referent)	(referent)
Assay Ratio: Non-Adherent ARMS: Adherent	-14.9 (-39.5 to 9.7)	-13.3 (-40.2 to 13.6)
Assay Ratio: Adherent ARMS: Non-Adherent	3.1 (-5.0 to 11.2)	-3.7 (-12.3 to 4.9)
Assay Ratio: Adherent ARMS: Adherent	-1.2 (-11.2 to 8.8)	-4.6 (-15.1 to 5.9)
*Adjusted for: age, sex, race, insurance status, health literacy, numeracy, BMI, chronic renal insufficiency, comorbidity index, and duration of hypertension diagnosis; s/p MI for SNS		

Population B Appendix Materials

Chapter 3 Appendix Table 20: Population B – Variable Definitions	
Variable	**Definition/Details**
Age (calculated)	Years, on day of randomization (calculated from date of randomization – DOB)
Sex (f08_gender)	1 = Female 2 = Male (recode: Female = 0; Male = 1)
Race – n/a	(all subjects were African American; by patient report of geneology)
Ethnicity (f08_ethnicity)	1 = Hispanic 2 = Non-Hispanic 9 = Unknown/refused
Insurance Status (f08_insurance_status)	1 = No insurance 2 = Medicare/Medicaid/Other government insurance 3 = HMO/PPO 4 = Traditional insurance 5 = Unknown/refused
Household Yearly Income (f08_household_yearly_income)	Dollars; 9 = unknown/refused Measured at ED visit
Highest level of Education (f08_education_level)	1 = < high school 2 = HS/GED 3 = Associate Degree 4 = Bachelor Degree 5 = Masters Degree 6 = PhD/Doctorate
Employment status (f08_employment_status)	1 = Full-time 2 = Part-time 3 = Disabled/unable to work 4 = Unemployed/actively seeing employment 5 = Unknown/refused
Smoking Status (f08_ever_smoked_cigarettes)	1 = Yes 2 = No (recode: 0 = No, 1 = Yes)
Alcohol intake (f08_alcoholic_beverages)	1 = Yes 2 = No (recode: 0 = No, 1 = Yes)
Regular Exercise (f08_exercise_regular_basis)	1 = Yes 2 = No (recode: 0 = No, 1 = Yes)
BMI (f13_calculated_bmi_2)	CMR visit Continuous Categorized: (<18.5, 18.5-24.9, 25.0-29.9,≥30)
History of Diabetes (f02_hx_diabetes)	1 = Yes 2 = No (recode: 0 = No, 1 = Yes)
Estimated Glomerular Filtration Rate (eGFR) (f07_egfr_1)	Measured at ED visit (week 16 eGFR also available); in milliliters per minute per 1.73 meters squared. Computed using the MDRD equation.

ALT (f07_serum_alt_1)	Measured at ED visit (international units per liter)
AST (f07_serum_ast_1)	Measured at ED visit (international units per liter)
Urine Albumin to Creatinine Ratio (f07_urine_alb_cre_2)	Measured at ED visit (ratio)
Central Pulse Pressure (f15_central_pulse_press_2)	Measured at CMR visit; in mmHg
Pulse wave velocity (f15_pulse_wave_velocity_2)	Measured at CMR visit; in milliseconds
Augmentation index (f15_augmentation_index_2)	Measured at CMR visit; in percentage
Ejection duration (f15_ejection_duration_2)	Measured at CMR visit; in milliseconds
Left ventricular mass index (LVMI) (f16_lvmi_2)	Measured at CMR visit; in grams per meter-squared
Number of prescribed antihypertensive medications, as of Week 16 visit	From the following 6 medications, maximum of 4: Amlodipine 10mg Chlorthalidone 25mg Lisinopril 20/40mg Losartan 25/50mg Metoprolol 50mg Spironolactone 25mg
Medication Adherence: Morisky items, Week 16*	Morisky: 1 = Yes 2 = No (Recode: 1 = Yes; 0 = No) Continuous Dichotomized: adherent =0, non-adherent >0 Categorized: high adherence = 0; medium adherence = 1-2; Low adherence = 3-4 *Where missing but available at Week 2, carried forward
Pill Count Ratio, Week 16	For each medication: (# of pills dispensed - # of pills remaining in pill bottle)/ [(script fill date - day pill count was preformed) * frequency] Summary Pill Count Ratio: (Sum of all individual medication % compliance per pill count)/ (total number of individual medications for which there are pill counts) Continuous Dichotomized: <0.80 (non-adherent), greater than or equal to 0.80 (adherent)
Summary Therapeutic Intensity Score (Week 16)	Computed for each medication as the current dose/maximum dose; summary measure for each patient at each visit computed from separate medication scores Individual medication TIS scores: 0 to 1 Summary TIS: add TIS scores for each prescribed medication
Antihypertensive adherence assay ratio	Continuous: ratio of number of medications detected to number of medications prescribed

(o_e)	Dichotomized: adherent: assay ratio = 1.0; non-adherent: assay ratio <1
Dates	Date of ED visit Date of Randomization Date of 16 week study visit
Vital Signs (f03_sbp_1 f03_sbp_post_triage_1 f13_sbp_2 f13_sbp_3 f13_sbp_4 f13_sbp_5 f13_sbp_6 f13_sbp_7 f13_sbp_8 f13_sbp_9)	SBP, DBP – measured by BPTrue device: - average of 5 oscillatory measures, 1 minute apart - at ED (triage, post triage), CMR, randomization, and at each follow up (weeks 2, 8, 16, 28, 40, 52)
Randomization	1 = Group A 2 = Group B

Therapeutic intensity scores (TIS) were calculated for each subject at each follow up visit.[16,17] TIS was calculated by dividing the current antihypertensive medication doses by the maximal FDA approved dose for each medication (Table 20). A summary TIS was computed for each patient at each follow up visit and reflected the medication prescription at the time of arrival to the visit; changes made to prescriptions at each visit were reflected in the TIS for the following visit.

Chapter 3 Appendix Table 21: Population B Therapeutic Intensity Scores

	Maximum Doses for TIS Scores	Examples TIS Scores
Amlodipine	10 mg	Amlodipine 10 mg = 1.0
Chlorthalidone	50 mg	Chlorthalidone 25 mg = 0.50
Lisinopril	80 mg	Lisinopril 40 mg = 0.50
Losartan	100 mg	Losartan 25 mg = 0.25
Metoprolol	450 mg	Metoprolol 50 mg BID = 0.22 Metoprolol 25 mg BID or 50 mg QD = 0.11
Spironolactone	100 mg	Spironolactone 25 mg = 0.25

Population B Characteristics

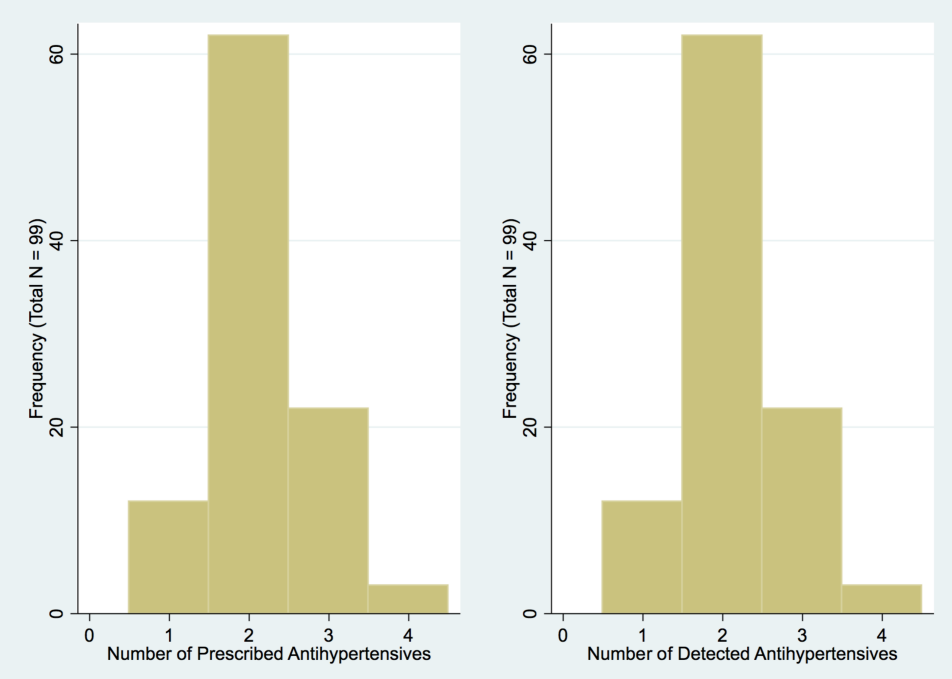
Chapter 3 Appendix Table 22: Population B Characteristics

Variable*	Population B N = 99
Age at randomization, years mean (sd) median (Q_1, Q_3)	 46.2 (7.8) 47.5 (40.5, 53.2)
Female, no. (%)	53 (53.5%)
Ethnicity – Non-Hispanic, no. (%); 1.0% missing	94 (95.0%)
Health Insurance, no. (%)	
No insurance	58 (58.6%)
Medicare/Medicaid/Other government insurance	21 (21.2%)
HMO/PPO	8 (8.1%)
Other Private Insurance	12 (12.1%)
Has a Primary Care Provider, no. (%); 2.0% missing	30 (30.3%)

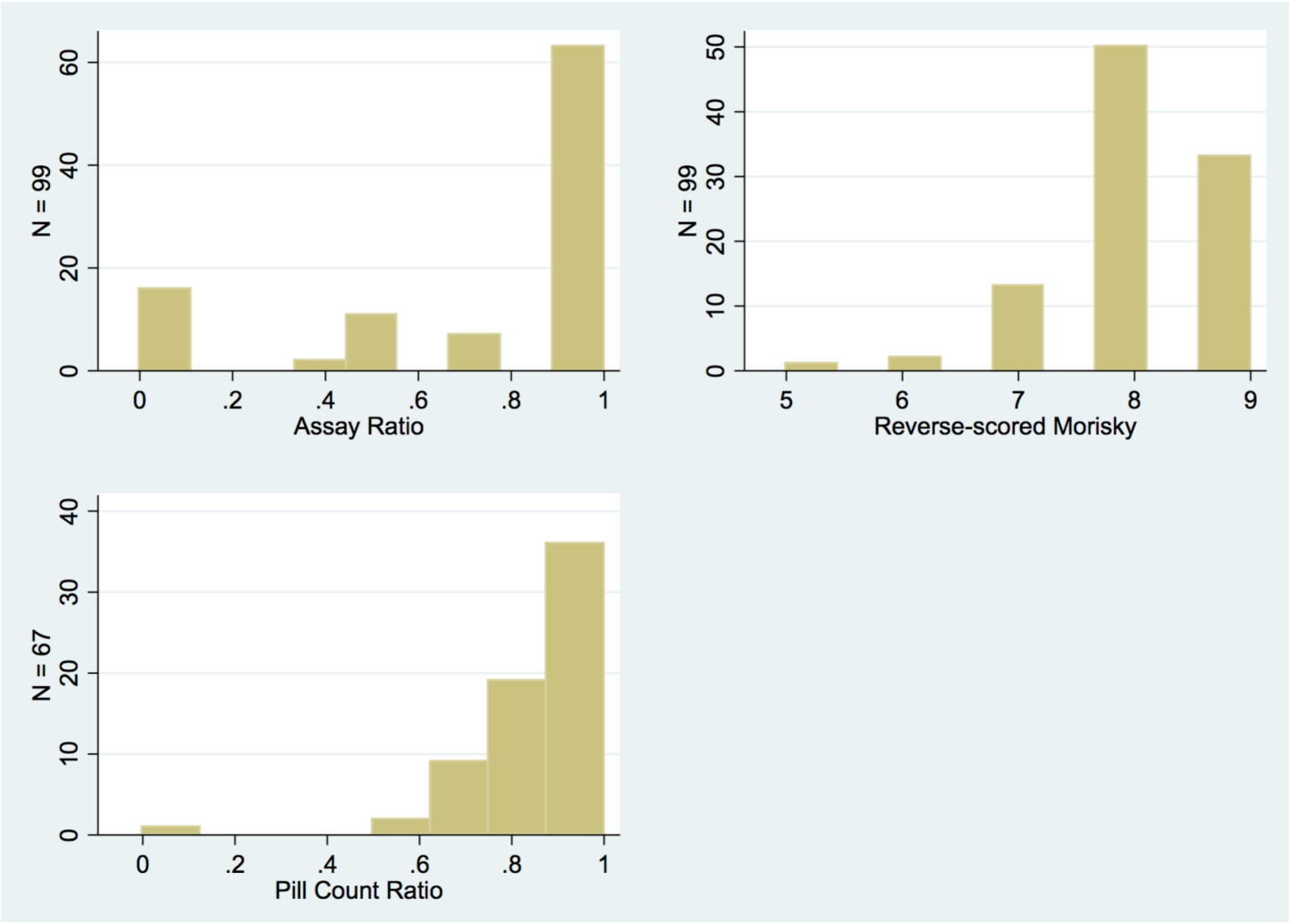
Annual Income in US dollars (43.4% missing) mean (sd) median (Q_1, Q_3)	 $18,931 ($15,894.65) $17,500 ($5,600, $30,000)
Highest Level of Education, no. (%)	
<High School	15 (15.2%)
High School/GED	60 (60.6%)
Associates Degree	18 (18.2%)
Bachelors Degree	5 (5.1%)
Masters Degree	1 (1.0%)
Employment Status, no. (%)	
Full-Time	31 (31.3%)
Part-Time	24 (24.2%)
Disabled	1 (1.0%)
Retired	2 (2.0%)
Unemployed	41 (41.4%)
Ever Smoked Cigarettes, no. (%)	62 (62.6%)
Still Smokes Cigarettes, no. (%); 1.0% missing	46 (75.4%)
Ever Drank Alcohol, no. (%); 1.0% missing	50 (50.5%)
Still Drinks Alcohol, no. (%); 2.0% missing	37 (74.0%)
Exercises Regularly, no. (%)	45 (45.5%)
Has diabetes, no. (%)	12 (12.1%)
BMI at CMR visit; kilograms per meter-squared mean (sd) median (Q_1, Q_3)	 33.6 (8.8) 34.2 (28.6, 38.8)
ALT (at ED visit; units per Liter) mean (sd) median (Q_1, Q_3)	 27.6 (12.1) 25 (19, 33)
AST (at ED visit; units per Liter) mean (sd) median (Q_1, Q_3)	 20.3 (9.9) 18 (13, 24)
Estimated Glomerular Filtration Rate (at ED visit, milliliters per minute per 1.73 meters-squared; 20.0% missing) mean (sd) median (Q_1, Q_3)	 85.6 (15.8) 85 (70, 96)
Urine albumin to creatinine ratio (at CMR visit); 10.1% missing mean (sd) median (Q_1, Q_3)	 61.6 (136.0) 15.7 (7.4, 47.5)
Total Therapeutic Intensity – Week 16; 1.0% missing mean (sd) median (Q_1, Q_3)	 0.77 (0.64) 0.75 (0.11, 1.25)
Randomization, no. (%) Group A Group B	 47 (47.5) 52 (52.5)
*No missing data unless otherwise noted	

Chapter 3 Appendix Table 23: Population B, Number of prescribed and detected antihypertensive medications at Week 16, N = 99	
Number of Prescribed BP Medications mean (sd) median (Q_1, Q_3)	 2.2 (0.7) 2 (2, 3)
Number of detected antihypertensive medications mean (sd) median (Q_1, Q_3)	 1.7 (0.9) 2 (1, 2)

Chapter 3 Appendix Figure 9: Population B - Number of prescribed and detected antihypertensive medications (N = 99)



Chapter 3 Appendix Figure 10: Population B – Distribution of assay ratio, Morisky, and pill count ratio



Chapter 3 Appendix Table 24: Population B Spearman rank correlations for adherence measured by the assay and Morisky, globally and by medication.			
	Spearman's rho	(95% CI)	P-value
Assay Ratio vs. Morisky (N = 99)	0.18	-0.021 to 0.36	0.08
By medication:			
Lisinopril (N = 63)	0.16	-0.09 to 0.39	0.45
Metoprolol (N = 12)	-0.24	-0.72 to 0.39	0.45
Chlorthalidone (N = 82)	0.12	-0.10 to 0.32	0.30
Amlodipine (N = 42)	0.24	-0.06 to 0.56	0.12
Losartan (N = 12)	-0.02	-0.59 to 0.56	0.95
Spironolactone (n = 2)	--	--	--
Assay Ratio vs. Pill Count Ratio (N = 67)	0.003	-0.24 to 0.24	0.98
By medication:			
Lisinopril (N = 44)	-0.02	-0.31 to 0.28	0.91
Metoprolol (N = 9)	0.33	-0.43 to 0.82	0.38
Chlorthalidone (N = 52)	-0.03	-0.30 to 0.24	0.81
Amlodipine (N = 33)	0.09	-0.26 to 0.42	0.62
Losartan (N = 5)	--	--	--
Spironolactone (N = 1)	--	--	--
-- too few to evaluate association			

Chapter 3 Appendix Table 25: Population B – Spearman's correlations of standardized raw chromatograph output with Morisky and pill count ratio, by individual medications			
	Spearman's rho	95% CI	P-value
Correlations with Morisky			
Lisinopril detected (N = 52)	0.05	-0.23 to 0.32	0.72
Metoprolol detected (N = 9)	-0.38	-0.83 to 0.38	0.32
Chlorthalidone detected (N = 57)	0.01	-0.25 to 0.27	0.92
Amlodipine detected (N = 36)	0.20	-0.14 to 0.50	0.25
Losartan detected (N = 8)	0.26	-0.54 to 0.82	0.53
Correlations with Pill Count Ratio			
Lisinopril detected (N = 39)	-0.04	-0.35 to 0.28	0.82
Metoprolol detected (N = 6)	-0.09	-0.84 to 0.78	0.87
Chlorthalidone detected (N = 40)	0.005	-0.32 to 0.31	0.98
Amlodipine	0.04	-0.33 to 0.39	0.86

detected (N = 30)			
Losartan detected (N = 4)	0.80	-0.70 to 1.0	0.20

Adherent/Non-adherent: Assay Ratio Compared to Morisky (reverse-scored) and Pill Count Ratios

Of the 36 subjects who were non-adherent by the assay ratio (assay ratio < 1.0), 9 (25%) were classified as adherent by the Morisky (Table 25). Of the 63 patients identified as being completely adherent by assay (assay ratio = 1.0), 39 (62%) were classified as being non-adherent by the Morisky.

Chapter 3 Appendix Table 26: Non-Adherent, by assay ratio and Morisky (Referent: assay ratio)

	Non-Adherent by Assay Ratio (assay ratio < 1.0)	Adherent by Assay Ratio (assay ratio = 1.0)	
Non-Adherent by Morisky (Morisky > 0)	27	39	66
Adherent by Morisky (Morisky = 0)	9	24	33
	36	63	99

Sensitivity	Pr(+| D) 40.91%	28.95%	53.71%
Specificity	Pr(-|~D) 72.73%	54.48%	86.70%
Positive predictive value	Pr(D| +) 75.00%	57.80%	87.88%
Negative predictive value	Pr(~D| -) 38.10%	26.15%	51.20%

Non-adherence identified by the Morisky was not statistically associated with non-adherence identified by the assay ratio: OR for being non-adherent by the assay for patients who were non-adherent by the Morisky: 0.54 (95% CI 0.19 to 1.45).

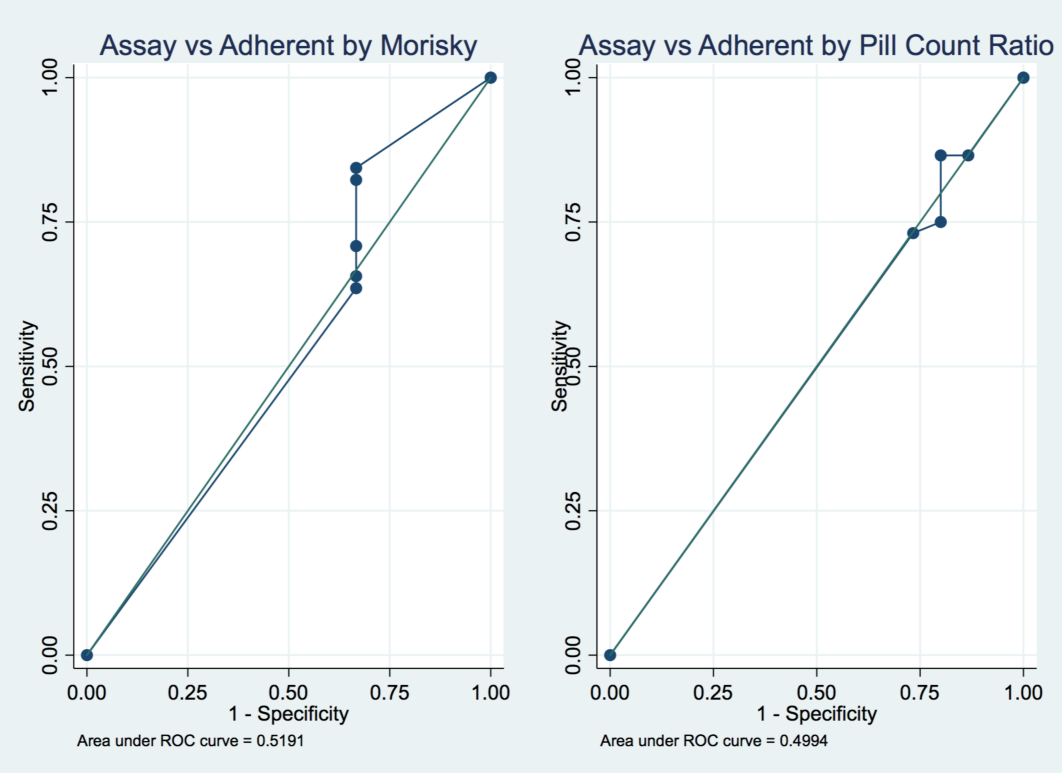
Of the 18 subjects classified as non-adherent by the assay, 14 (78%) were classified as adherent by the pill count ratio (Table 26). Of the 49 patients identified as adherent by the assay ratio, 11 (22%) were classified as being non-adherent by the pill count ratio.

Chapter 3 Appendix Table 27: Non-Adherent, by assay ratio and pill count ratio (Referent: assay ratio)			
	Non-Adherent by Assay Ratio (assay ratio < 1.0)	Adherent by Assay Ratio (assay ratio = 1.0)	
Non-Adherent by Pill Count Ratio (Pill Count Ratio ≥0.80)	4	11	15
Adherent by Pill Count Ratio (Pill Count Ratio<0.80)	14	38	52
	18	49	67

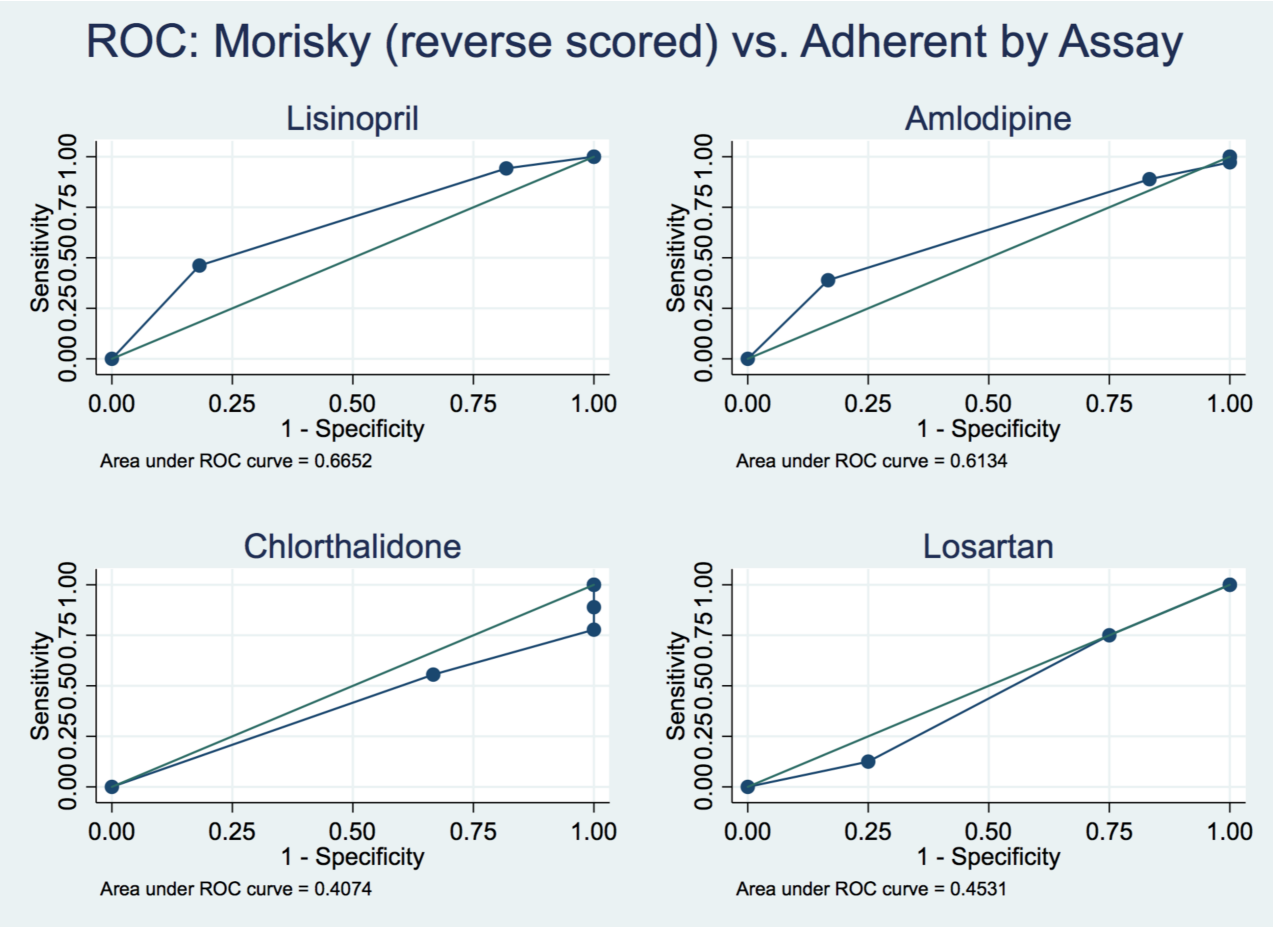
Sensitivity	Pr(+| D)	26.67%	7.79%	55.10%
Specificity	Pr(-|~D)	73.08%	58.98%	84.43%
Positive predictive value	Pr(D| +)	22.22%	6.41%	47.64%
Negative predictive value	Pr(~D| -)	77.55%	63.38%	88.23%

Non-adherence identified by pill count ratios was not statistically associated with non-adherence identified by the assay ratio: OR for being non-adherent by the assay for patients who were non-adherent by pill count ratios: 1.01 (95% CI 0.24 to 5.09).

Chapter 3 Appendix Figure 11: ROC Curve for assay compared to adherent, defined by the Morisky (N = 99) and pill count ratio (N = 67)



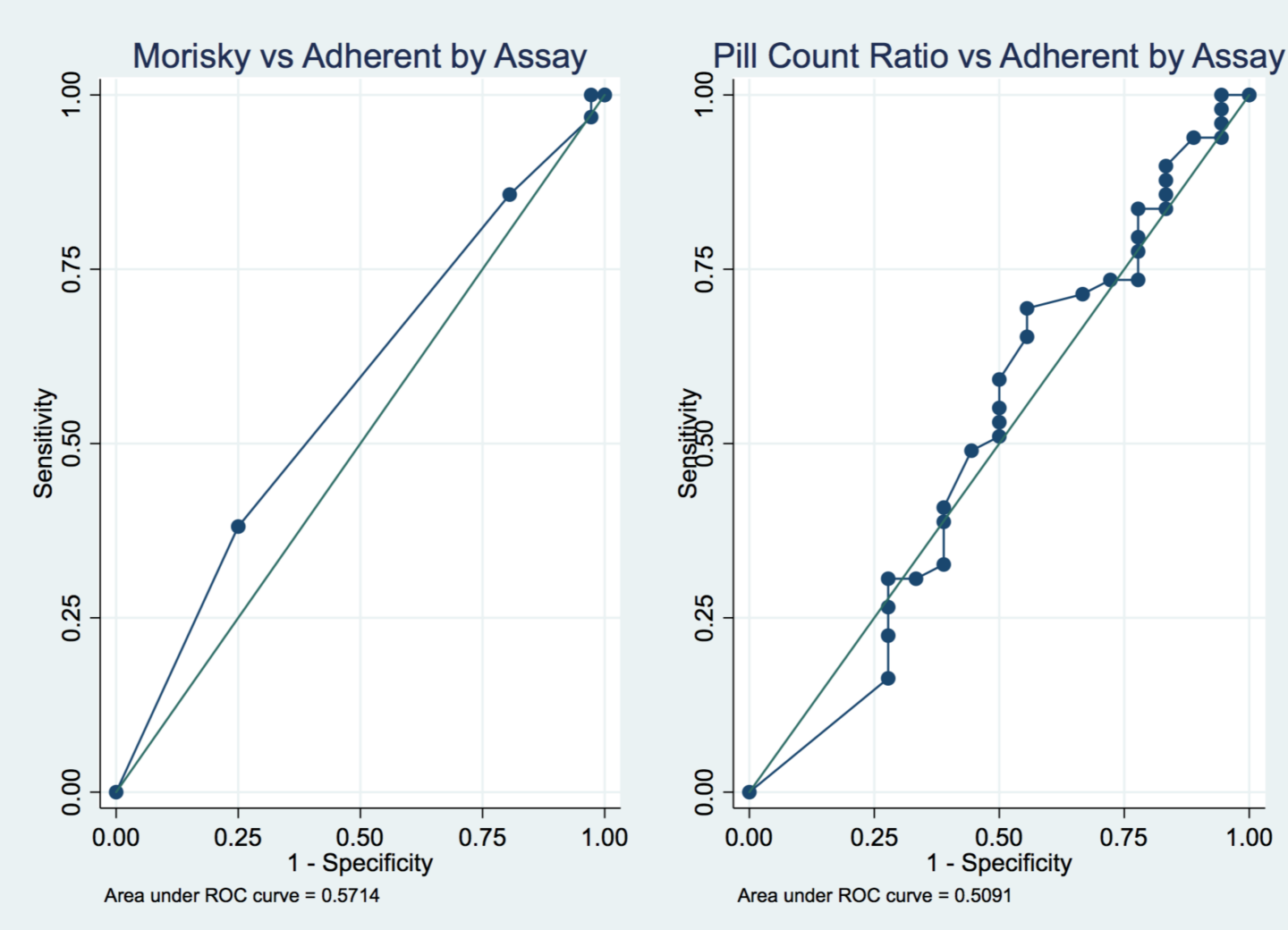
Chapter 3 Appendix Figure 12: Population B - ROC curves for the reverse-scored Morisky for adherent by assay ratio for lisinopril, metoprolol, chlorthalidone, amlodipine, and losartan



Receiver operating curve characteristics: Morisky (reverse-scored) and pill count ratios compared to adherent by the assay ratio

ROC curves of the Morisky (reverse-scored) and pill count ratio for adherent defined by the assay ratio (assay ratio = 1.0), the relationships were not statistically significant (Figure 13).

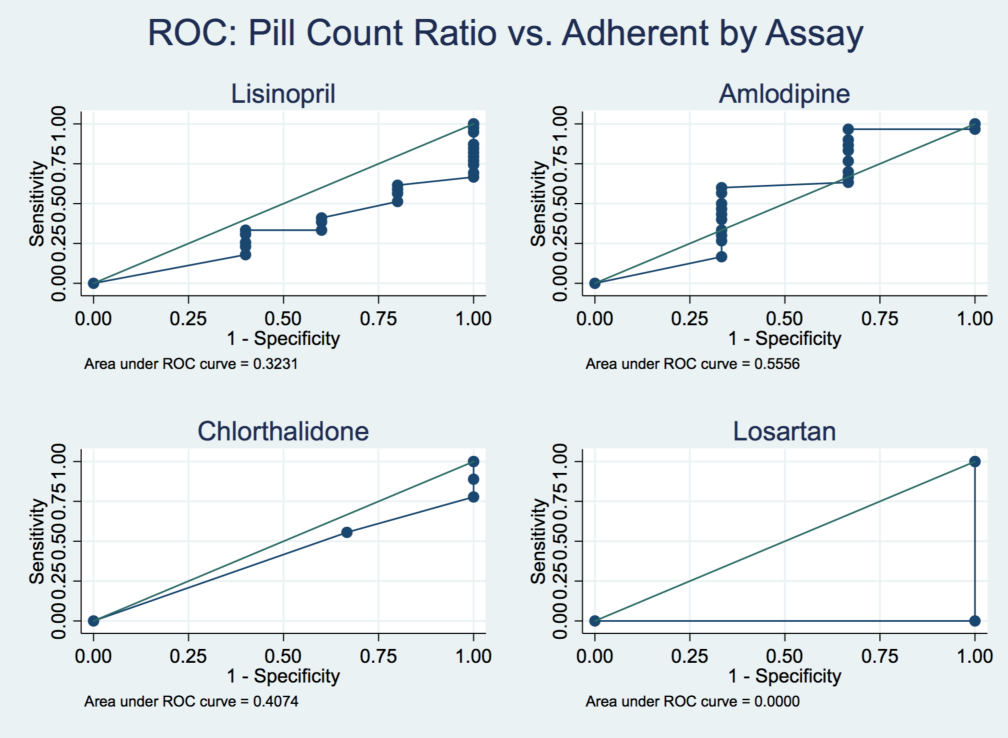
Chapter 3 Appendix Figure 13: Population B - ROC Curve for Morisky (reverse-scored; N = 99) and pill count ratios (N = 67) for adherent/non-adherent by the assay ratio.



Receiver operating curve characteristics: Pill count ratios compared to adherent by assay ratio

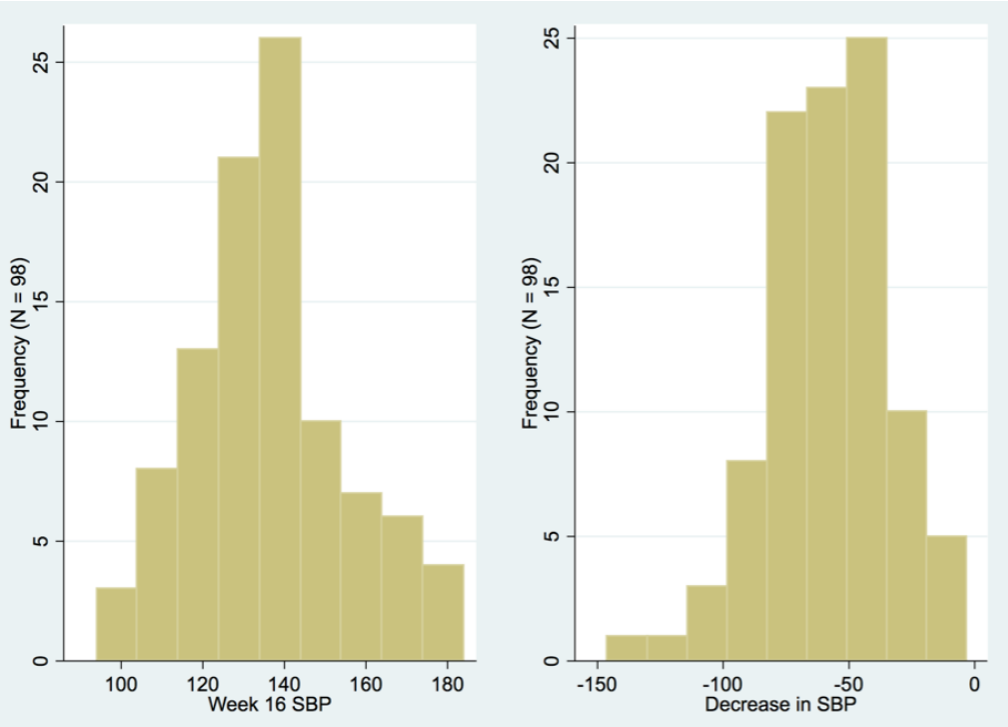
In Population B, among the 67 patients with pill counts available at week 16, there was no evident relationship between pill counts and adherent by the assay ratio (Figure 14).

Chapter 3 Appendix Figure 14: Population B - ROC curves of pill count ratios for adherent by the assay ratio, for lisinopril, metoprolol, chlorthalidone, amlodipine, and losartan



Population B, Aim 3 Outcome: Week 16 SBP

Chapter 3 Appendix Figure 15: Distribution of Week 16 SBP and change in SBP from ED to Week 16



Aim 3 Population B Univariate Associations with Medication Adherence

Chapter 3 Appendix Table 28: Population B – Univariate Relationships of Patient Characteristics with Measures of Adherence						
Variable	**Adherence – by Assay (N = 99)**	**P-value**	**Adherence – by Morisky (N = 99)**	**P-value**	**Adherence – by Pill Counts (N = 67)**	**P-value**
Age* (years, at randomization)	0.15	0.13	-0.19	0.07	**0.32**	**0.008**
Female**		**0.005**		0.08		0.62
Ethnicity – Non-Hispanic**		0.19		0.37		0.88
Health Insurance**		0.762		0.79		0.35
No insurance						
Medicare/Medicaid/Other government insurance						
HMO/PPO						
Traditional insurance						
Has a PCP		0.46		0.52		0.89
Annual Income* (N = 56)	-0.15	0.27	0.24	0.08	-0.16	0.34
Highest Level of Education**		0.57		0.87		**0.29**
<High School						
High School/GED						
Associates Degree						
Bachelors Degree						
Masters Degree						
Employment Status**		0.26		0.49		0.87
Full-Time						
Part-Time						
Disabled						
Unemployed						
Unknown/Refused						
Ever Smoked Cigarettes**		**0.02**		**0.02**		0.57
Drinks Alcohol**		0.24		0.91		0.41
Exercises Regularly**		0.56		0.20		**0.001**
BMI (at CMR visit; kilograms per meter-squared)*	0.16	0.11	-0.05	0.69	-0.008	0.95
Has Diabetes		0.41		0.05		0.15
ALT (at ED visit; units per Liter)*	0.07	0.48	-0.03	0.78	-0.11	0.37
AST (at ED visit; units per Liter)*	0.01	0.88	0.01	0.89	-0.18	0.14
Estimated Glomerular Filtration Rate (at ED visit, milliliters per minute per 1.73 meters-squared)*	-0.09	0.40	0.13	0.22	-0.03	0.83
Urine albumin to creatinine	-0.06	0.55	0.002	0.98	0.08	0.52

ratio (at CMR visit)*						
Therapeutic Intensity – Week 16	-0.008	0.94	-0.07	0.50	0.05	0.68
MRI Data (Week 2)* **						
Central Pulse Pressure (at CMR visit, N = 96)	0.07	0.47	-0.10	0.33	-0.02	0.87
Augmentation index (at CMR visit, N = 94)	**-0.22**	**0.03**	-0.05	0.60	0.06	0.62
Pulse wave velocity (at CMR visit, N = 80)	-0.08	0.49	-0.02	0.87	0.009	0.95
Ejection duration (at CMR visit, N = 96)	-0.08	0.46	-0.10	0.35	0.13	0.29
Left ventricular mass index (LVMI, grams per meter-squared; at CMR visit, N = 98)	0.05	0.62	-0.06	0.58	-0.18	0.15
Myocardial Fibrosis		0.75		0.72		0.24
* Spearman's rho ** Kruskal-Wallis test ***N for pill counts = 65, 65, 52, 65, 65, 66						

Aim 3 Population B Univariate Associations with SBP

Chapter 3 Appendix Table 29: Population B – Univariate Relationships of Patient Characteristics with Week 16 Systolic Blood Pressure and Change in SBP from Enrollment to Week 16				
Variable	**Week 16 SBP**	**P -value**	**SBP Change (Enrollment to Week 16)**	**P- value**
Age* (years, at randomization)	0.03	0.79	0.10	0.34
Female**		0.32		0.39
Ethnicity – Non-Hispanic**		0.10		0.59
Health Insurance**		0.89		0.21
No insurance				
Medicare/Medicaid/Other government insurance				
HMO/PPO				
Traditional insurance				
Has a PCP		0.39		0.59
Annual Income* (N = 56)	0.03	0.81	-0.21	0.12
Highest Level of Education**		0.20		0.59
<High School				
High School/GED				
Associates Degree				
Bachelors Degree				
Masters Degree				
Employment Status**		0.41		0.39
Full-Time				
Part-Time				
Disabled				
Unemployed				
Unknown/Refused				
Ever Smoked Cigarettes**		0.06		**0.002**
Drinks Alcohol**		0.33		0.43
Exercises Regularly**		0.72		0.23
BMI (at CMR visit; kilograms per meter-squared)*	-0.16	0.11	0.07	0.51
Has Diabetes		0.86		0.74
ALT (at ED visit; units per Liter)*	0.03	0.74	-0.19	0.06
AST (at ED visit; units per Liter)*	-0.04	0.69	-0.05	0.65
Estimated Glomerular Filtration Rate (at ED visit, milliliters per minute per 1.73 meters-squared)*	-0.13	0.19	-0.14	0.17
Urine albumin to creatinine ratio (at CMR visit)*	-0.10	0.34	0.10	0.37
Therapeutic Intensity – Week 16	0.13	0.20	0.05	0.63
MRI Data				

Central Pulse Pressure (at CMR visit; N = 95)	0.17	0.10	0.04	0.71
Augmentation index (at CMR visit, N = 93)	0.003	0.98	-0.04	0.69
Pulse wave velocity (at CMR visit, N = 79)	0.14	0.22	0.02	0.84
Ejection duration (at CMR visit, N 95)	-0.06	0.55	-0.03	0.85
Left ventricular mass index (LVMI, grams per meter-squared; at CMR visit, N = 97)	**0.33**	**0.001**	-0.04	0.70
Myocardial Fibrosis (N = 98)		0.99		0.45
* Spearman's rho ** Kruskal-Wallis test				

Population B Regression Appendix Results

Chapter 3 Appendix Table 30: Population B – Unadjusted linear regression of standardized, raw chromatograph output with Week 16 SBP, by individual BP medication

	Difference in Week 16 SBP (mmHg) (standardized beta coefficient)	95% CI	P-Value
Prescribed ≥3 BP Medications			
Lisinopril (N = 20)	-3.0	-9.0 to 3.0	0.30
Metoprolol (N = 5)	-14.0	-38.0 to 10.1	0.16
Chlorthalidone (N = 19)	-1.5	-7.3 to 4.4	0.60
Amlodipine (N = 19)	-2.9	-12.2 to 6.5	0.52
Losartan (N = 1)	--	--	--
Prescribed <3 BP Medications			
Lisinopril (N = 32)	-5.0	-17.6 to 7.6	0.42
Metoprolol (N = 4)	1.3	-19.4 to 22.0	0.81
Chlorthalidone (N = 38)	-6.3	-11.7 to -1.0	0.02
Amlodipine (N = 17)	-7.7	-15.7 to 0.3	0.06
Losartan (N = 7)	2.7	-11.4 to 16.8	0.66

Population B Regression Appendix Results – 4-level Adherence Variable

Table 31: Unadjusted Associations Between 4-level Adherent Variable (Assay Ratio and Morisky) with Week 16 SBP	
	Beta (95% CI)
Prescribed ≥3 BP Medications	
	Week 16 SBP, mmHg (N = 25)
Assay Ratio: Non-Adherent Morisky: Adherent	(referent)
Assay Ratio: Non-Adherent Morisky: Adherent	-7.8 (-27.3 to 11.7)
Assay Ratio: Adherent Morisky: Non-Adherent	-20.8 (-38.1 to -3.6)
Assay Ratio: Adherent Morisky: Adherent	-21.4 (-40.1 to -2.7)
Prescribed <3 BP Medications	
	Week 16 SBP, mmHg (N = 74)
Assay Ratio: Non-Adherent Morisky: Adherent	(referent)
Assay Ratio: Non-Adherent Morisky: Adherent	-3.8 (-25.1 to 17.5)
Assay Ratio: Adherent Morisky: Non-Adherent	-9.5 (-20.6 to 1.6)
Assay Ratio: Adherent Morisky: Adherent	-8.6 (-21.2 to 3.9)