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Modeling Antihypertensive Therapeutic Inertia And Intensification To Support Clinical Action Toward Hypertension Control

Benjamin Martin
bmarti6@clemson.edu

MODELING ANTIHYPERTENSIVE THERAPEUTIC INERTIA AND INTENSIFICATION TO SUPPORT CLINICAL ACTION TOWARD HYPERTENSION CONTROL

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by
Benjamin Martin
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Presented to:
Dr. Ronald Gimbel, Ph.D., Committee Chair
Dr. Brent Egan, M.D.
Dr. Xia Jing, Ph.D.
Dr. Jihad Obeid, M.D.
Dr. Lior Rennert, Ph.D.

ABSTRACT

Background

Hypertension is the leading modifiable risk factor for cardiovascular disease and consequent mortality worldwide. In the U.S., more than half of hypertension cases remain uncontrolled, despite availability of effective pharmaceutical treatment options. Evidence suggests that therapeutic inertia, defined as clinician failure to initiate or increase therapy when treatment goals are unmet, is the most influential barrier to improving hypertension control. Substantial rates of therapeutic inertia have been reported in ambulatory primary care settings where hypertension is typically treated and managed. Understanding and overcoming the forces driving therapeutic inertia in hypertension management is a critical strategy to reach population health goals for blood pressure control and cardiovascular disease prevention.

Objectives

Three embedded studies within this dissertation that include: (1) descriptive and predictive modeling of antihypertensive therapeutic inertia, (2) a model of antihypertensive treatment selection, and (3) a propensity-score matched model of observed reductions in blood pressure after increasing dose or adding new classes of antihypertensive medication using electronic health record (EHR) data generated from real-world clinical practice.

Materials and Methods

Data for defining and modeling antihypertensive therapeutic inertia comes from five health care organizations; four located in the Southeast and one in the Midwest U.S. EHR data

extracted from each system used in these analyses include patient demographic information, diagnoses, procedures, medications, vital signs, and laboratory measurements. Mixed-effects regression, classification trees, and ensemble learning, and propensity-score matching are applied to produce descriptive and predictive models of antihypertensive therapeutic inertia and intensification, treatment selection, and treatment effectiveness.

Results

For 120,755 patients with hypertension, therapeutic inertia was indicated at 84.1% of 168,222 visits where BP was uncontrolled (>140/>90mmHg). Therapeutic intensification occurred via dose increase of existing medication at 6.6% of visits, and addition of a new medication class at 9.2% of visits with uncontrolled BP. Mixed-effects modeling of patient and clinical variables extracted from the electronic health record accounted for 13.2% of the variance in therapeutic inertia vs. intensification among visits with uncontrolled BP. Gradient boosted classification trees produced the strongest predictive model of therapeutic inertia (test AUC: 0.748). Mixed-effects modeling explained 38.5% of the variance between treatment selection options. Propensity-score matched cases of treatment selection groups found a 1.31 mmHg greater reduction in SBP when a new class of medication was added.

Discussion

Patient, clinical, and encounter related variables extracted from the EHR did not account for a significant proportion of the observed variance in antihypertensive therapeutic inertia vs. intensification and increasing dose vs. adding a new medication. Consequently, predictive modeling using these variables was limited in performance. However, modeling of the

relationship between EHR derived variables and therapeutic inertia/intensification and treatment selection was sufficiently robust to determine the contribution of patient and visit related clinical factors to likelihood of antihypertensive treatment action, and to evaluate the best methods for prediction of hypertension treatment events.

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I. INTRODUCTION

Hypertension is a modifiable risk factor with the highest attributable risk to cardiovascular disease.[1-4] Specifically, heart disease and stroke are the first and fifth most common causes of death in the United States.[5] Controlling elevated blood pressure (BP) in patients with hypertension is paramount to reducing the substantial morbidity and mortality caused by heart disease, stroke, and other cardiovascular diseases.[1-18]

Clinical trials have demonstrated the safety and efficacy of more than a dozen classes of blood pressure-reducing drugs.[14-22] Despite the well-documented risks attributed to uncontrolled hypertension, defined at BP ≥140/≥90 or BP ≥130/≥80 mmHg depending on the guidelines referenced,[23, 24] and the availability of effective options for antihypertensive therapy, hypertension control rates remain well below goals set by national population health initiatives.[1, 3, 12, 13, 25-28] The AHA and American Medical Association's (AMA) Target: BP Program encourages health systems and physician practices to raise hypertension control among their patients to 70%, while the Centers for Disease Control's (CDC) Million Hearts 2027 program aims to improve hypertension by 20% or to 80%, of all adults receiving health care.[29, 30] According to 2015-2016 data from the National Health and Nutrition Examination Survey, 75 million U.S. adults have hypertension (29%), and only 48% are controlled. Furthermore, only 72% among those already taking antihypertensive medications have their hypertension under control.[28]

Data from the National Health and Nutrition Examination Survey (NHANES) show that prevalence of hypertension among adults in the U.S., defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, was 31.5% during 2009-2012, 32.0% during 2013-2016, and 32.9% during 2017-2020.[28] Of those with hypertension, 48.2% had controlled BP in 2017-2020, a 4.6% decrease in control from 2009-2012.[28] Furthermore, only 67.7% of hypertensive adults taking antihypertensive medication were controlled in

2017 to 2020.[28] Disparities among subgroups are also important to consider. Hypertension control was lower among adults 75+ years of age (-9.2%), women (-8.4%), and non-Hispanic black adults (-11.5%) compared to the overall hypertension control rate of 48.2% in 2017-2020.[28] Current trends of increasing hypertension prevalence, declining BP control, especially among those already taking antihypertensive medication, calls attention to the importance of addressing factors contributing to these trends and the need for informed strategies to reverse them.[26-28]

Problem Statement

"Achieving standard-of-care goals in only limited numbers of treated patients must be attributed either to therapeutic ineffectiveness or to clinical inertia." – Phillips et al. [31]

Evidence suggests that therapeutic inertia, defined as clinician failure to initiate or increase therapy when treatment goals are unmet, is the single most influential barrier to improving hypertension control.[32, 33] Therapeutic inertia rates exceeding 80% have been reported in ambulatory primary care settings where hypertension is typically treated and managed. Understanding and overcoming the forces driving therapeutic inertia in hypertension management is critical to reach population health goals for blood pressure control and cardiovascular disease prevention.

This will require an informed strategy that utilizes informatics to best understand and break down the problem of therapeutic inertia in hypertension care. Starting with the providing insight into the nature of the problem, further analysis of previously studied factors associated with therapeutic inertia and intensification and hypothesized factors not previously studied for their relationship with therapeutic inertia and intensification is needed to better quantify and explain the variance in observed rates of therapeutic inertia and intensification. Furthermore, there is a lack of evidence for prediction of therapeutic inertia instances in ambulatory primary care. Validation of an accurate predictive model for

anticipating therapeutic inertia in clinical care will be vital for proactive intervention on clinician action in treating hypertension. To build on the insight into therapeutic inertia and form a comprehensive strategy for informing antihypertensive clinician action, the same approach is needed to better understand the factors driving decision making in therapeutic intensification. Modeling the relationship between patient and clinical variables and likelihood of adding a new medication or increasing dose of an existing medication and comparing the effectiveness of these two therapeutic intensification strategies on subsequent reduction in blood pressure will be valuable to guide clinician decision making toward the most effective action when therapeutic inertia is overcome and clinical action is taken.

II. COMPREHENSIVE LITERATURE REVIEW

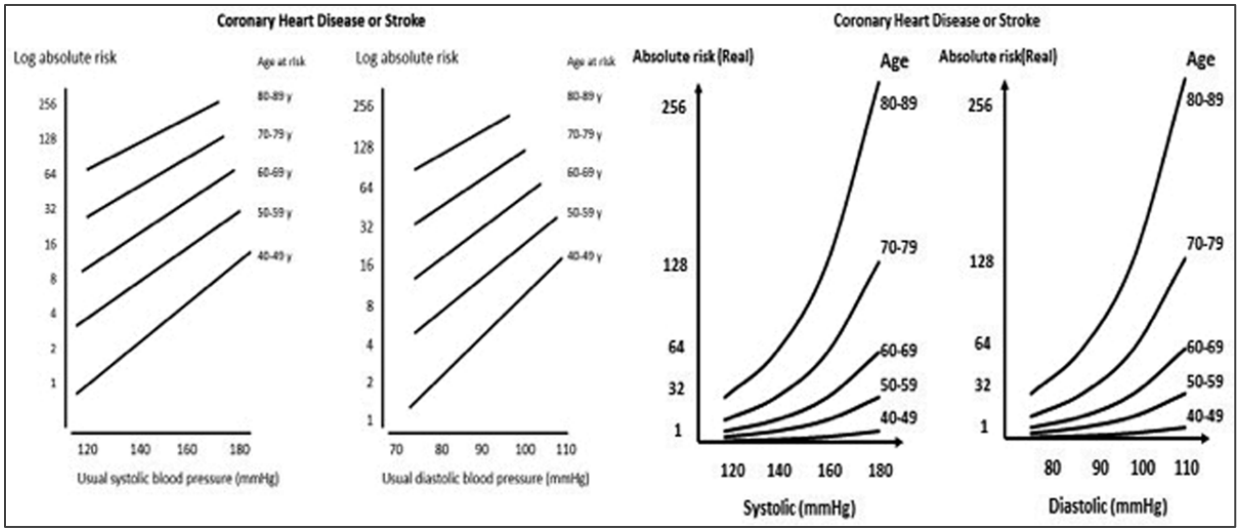
Hypertension and Cardiovascular Disease

Since the development of the sphygmomanometer in the late 19th century, extensive evidence has been published demonstrating the association between high blood pressure (BP) and cardiovascular disease (CVD). A decade after the device was introduced in the U.S., the relationship between high BP and CVD was first documented, with a systolic blood pressure of 160 mm Hg or higher identified as pathological.[34, 35] It wasn't until decades later that the consideration of selection bias due to a majority of humans having higher than normal blood pressure, and the examination of blood pressure in isolated, unacculturated populations, led researchers to redefine what biologically normal blood pressure should be and at what point elevated blood pressure starts to increase risk of CVD.[36] In the century since, large-scale observational studies,[37-39] and randomized controlled trials (RCTs)[14-22] have provided a solid and progressive understanding of CVD risk mitigation from treating elevated BP and hypertension, including the 1967 Veterans Administration (VA) Cooperative Study Group on

Antihypertensive Agents, the 1991 Systolic Hypertension in the Elderly Program (SHEP), and the 2015 Systolic Blood Pressure Intervention Trial (SPRINT).[14-16].

Some of the most formative observational evidence for hypertension's contribution to CVD comes from the Oxford Population Health Prospective Studies Collaboration. Their 2002 collaborative meta-analysis of data from 61 prospective cohort studies with nearly 13 million person-years of follow-up shows that higher levels of SBP and DBP are strongly and directly related to higher risk of CVD and mortality. For all BP values above 115/75 mm Hg, the risk of CVD doubled for every 20 mm Hg increase in SBP and 10 mm Hg increase in DBP (Figure 1, below).[2]

Figure 1. Log-transformed absolute risk (left) and untransformed absolute risk (right) of coronary heart disease or stroke in adults, by SBP and DBP, stratified by age.[2]



The Prospective Studies Collaboration estimated the attributable risk for BP above 115/75 mm Hg to be 49% for CHD and 62% for stroke.[2] The most recent reports from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), another set of highly comprehensive observational epidemiological analyses, estimate high blood pressure to be the leading risk factor globally for attributable deaths, accounting for 10.8 million deaths or 19.2% of all deaths in 2019.[1] In terms of hazard ratio, a study linking the Third National Health and Nutrition Examination Survey (1988-1994) and the 2011 National Death Index files showed a higher risk of all-cause (HR = 1.62, 95%CI = 1.35–1.95), CVD-specific (HR = 2.23, 95%CI = 1.66–2.99), heart disease-specific (HR = 2.19, 95%CI = 1.57–3.05) and cerebrovascular disease-specific (HR = 3.01, 95%CI = 1.91–4.73) mortality for treated but uncontrolled hypertensive patients compared to normotensive patients, and a higher risk of all-cause (HR = 1.40, 95%CI = 1.21–1.62), CVD-specific (HR = 1.77, 95%CI = 1.34–2.35), heart disease-specific (HR = 1.69, 95%CI = 1.23–2.32) and cerebrovascular disease-specific death (HR = 2.53, 95%CI = 1.52–4.23) for untreated hypertensive patients compared to normotensive patients.[3] Hazard ratios estimated from more than 3 million adult patients in the UK Biobank (UKB) and Korean National Health Insurance Service (KNHIS) cohorts show an elevated risk of major adverse cardiac and cerebrovascular events (MACCEs) and all-cause mortality among patients with controlled hypertension compared to normotensive patients; UKB: 1.73 (95% CI 1.55 to 1.92); KNHIS: 1.46 (95% CI 1.43 to 1.49) for MACCEs and UKB: 1.28 (95% CI 1.18 to 1.39) KNHIS: 1.29 (95% CI 1.26 to 1.32) for all-cause mortality.[40] While residual risk of adverse outcomes for controlled hypertension is still elevated compared to normotension, there is extensive evidence showing significant reduction in risk going from uncontrolled, to treated but uncontrolled, to treated and controlled hypertension.[1, 4, 11, 40] The opportunity for substantial decreases in risk of major cardiovascular and cerebrovascular adverse events and mortality should put secondary prevention in hypertension through BP lowering treatments at a very high priority in chronic disease management.

Several RCTs have been pivotal to the development of clinical guidelines for diagnosis, treatment, and management of hypertension to reduce the risk of CVD.[14-22, 41] Among these key trials are the 1967 Veterans Administration (VA) Cooperative Study Group on Antihypertensive Agents, the 1991 Systolic Hypertension in the Elderly Program (SHEP), and the 2015 Systolic Blood Pressure Intervention Trial (SPRINT).[14-16] The VA trial looked at patients with an average DBP between 115 and 129 mm Hg and found that 24 months of active treatment with a triple combination regimen of hydrochlorothiazide, reserpine, and hydralazine resulted in an average reduction of 43 mm Hg systolic and 29.7 mm Hg diastolic BP and a significant decrease in subsequent morbid cardiovascular events compared to placebo. Treating hypertension according to the VA trial would prevent one major CVD event per year for every six patients with an average DBP between 115 and 129 mm Hg.[15] Since the VA study focused on DBP as an indicator of uncontrolled hypertension, many physicians still considered isolated systolic hypertension a natural and benign consequence of aging until the publication of the SHEP trial results.[42] This trial evaluated persons aged 60 years and over with SBP ranging from 160-219 mm Hg and DBP less than 90 mm Hg. SHEP showed that antihypertensive treatment with chlorthalidone and add on treatment as required to decrease SBP by 20 mm Hg or below 160 mm Hg reduced the incidence of stroke by 36%.[16] SPRINT found that after a median follow-up of 3.26 years, participants randomized to an SBP goal of less than 120 mm Hg (intensive treatment) had a 25% lower incidence of CVD (specifically: myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) compared with those randomized to an SBP goal of less than 140 mm Hg (standard treatment), where the mean SBP after one year was 121.4 mm Hg in the intensive treatment group and 136.2 mm Hg in the standard treatment group.[14]

Additionally, robust meta-analyses of RCTs and observational studies have provided strong evidence to verify the relationship between blood pressure and CVD risk.[17, 18, 21, 22] Two such studies by Law et al., one looking at 364 RCTs and another including 147 RCTs, determined the average reduction in BP

from active treatment with a single antihypertensive medication to be 9.1 mm Hg systolic and 5.5 mm Hg diastolic at standard dose and calculated a 62% reduction in stroke risk and 46% reduction in CHD risk.[17, 18] This reduction in risk of CVD from active antihypertensive treatment assessed by the Law et al. meta-analyses is nearly equivalent to the expected reduction of CVD risk for a 10 mm Hg difference in SBP observed by the Prospective Studies Collaboration meta-analysis.[2] The parallelism between the risk reduction determined from RCTs and risk calculations from observational is mutually supportive and further indicates the direct effect of elevated blood pressure on CVD risk.

While the safety and effectiveness of BP-lowering drugs in primary and secondary prevention of cardiovascular disease have been repeatedly established by comprehensive meta-analyses and randomized controlled trials,[14-22] large quasi-experimental observational studies have proven useful in filling evidence gaps in medicine due to limitations in speed and scale of formal randomized controlled trials.[37-39, 43, 44] Particularly where large, integrated sets of observational data are available for analysis, the limited scope of controlled trials can be supplemented with extensive subgroup analysis and head to head comparisons for which there is not enough data within the RCTs to address. Observational effectiveness studies are necessary to determine the extent to which RCT evidence applies to patient populations seen in practice.[45] Furthermore, certain clinical conditions like therapeutic inertia (absence of guideline-recommended treatment initiation or intensification) would not be ethical to assign patients with uncontrolled hypertension. Observational studies with quasi-experimental design elements provide the best available methods for generating evidence for clinical conditions that would be inappropriate or impractical to assign in a randomized trial.[45-48]

There is an emphasis on employing "real-world data" (RWD) and “real-world evidence” (RWE) to support regulatory and clinical decision-making in health care stemming from the 21st Century Cures Act

passed in 2016, where the U.S. Congress called for the development a formal Real-World Evidence Program by the U.S. Food & Drug Administration (FDA).[49] A primary objective of the FDA's RWE program is to evaluate the role of evidence generated from observational studies in contributing to regulatory decisions moving forward.[50] Rigorously designed observational studies are needed to support the FDA RWE program and the larger movement toward utilization of real-world data that is becoming increasingly abundant from integrated EHRs, claims, and clinical registries.

More rigorous observational studies like the Large-Scale Evidence Generation and Evaluation (LEGEND) are needed to help address gaps in the RCT evidence-base for treatment guidelines and to support the FDA's focus on incorporating real-world evidence in pharmacological regulation and decision-making. The LEGEND framework was first applied to hypertension treatment evidence, and provided results that are equable with existing RCT and meta-analysis results.[38]

Antihypertensive Treatment Guidelines

Based on the 2017 American College of Cardiology (ACC) and American Heart Association (AHA) guideline for prevention, detection, evaluation, and management of high blood pressure, initiation of antihypertensive medication is recommended for all patients with an SBP and DBP greater than 140 mmHg or 90 mmHg, respectively. Patients with SBP 130-139 mmHg or DBP of 80-89 mmHg are considered to have "stage 1 hypertension." Patients with stage 1 hypertension who are also considered at high risk for CVD events based on 10-year atherosclerotic CVD risk of 10% or higher are recommended to receive pharmacological treatment. Furthermore, the guidelines emphasize that most patients with BP above the threshold for recommendation of pharmacological therapy will require at least two medications to achieve BP control, advising initial treatment to begin with two drugs for patients with average BP more than 20/10 mmHg above their treatment goal.[23]

The 2018 European Society of Cardiology and European Society of Hypertension guidelines for managing arterial hypertension make recommendations that are generally more conservative in their indications to initiate or intensify treatment than the ACC/AHA guidelines. The ESC/ESH defines Stage 1 hypertension as SBP between 140-159 and/or DBP between 90-99 mm Hg and only recommends medication for patients with BP 130-139/85-89 mmHg that are very high-risk and have CVD. The European guidelines also point out that monotherapy is usually insufficient to achieve BP control for most patients with hypertension, especially with lower BP treatment targets compared to previous guidelines. The ESC/ESH 2018 guidelines have a stronger recommendation for initiating treatment with a single-pill combination of two drugs compared to the ACC/AHA 2017 guidelines.[23, 24] The ESC/ESH guidelines recommend all instances of uncontrolled hypertension prompting pharmacological therapy be initiated with a single-pill combination of two antihypertensive drugs, with exceptions being frail older patients and those with SBP <150 mmHg, where monotherapy may be sufficient to reach control or necessary to avoid side effects. [23, 24]

Therapeutic Inertia in Hypertension Management

Phillips et al. were the first to use the term “clinical inertia” in their 2001 perspective article by that title. They defined the phenomenon as the “failure of health care providers to initiate or intensify therapy when indicated.”[31] Based on the premise that good management of patients with hypertension, dyslipidemia, or diabetes is dependent on both accurate diagnosis and initiating and intensifying treatment until treatment goals are achieved, they argued that causes of clinical inertia include an overestimation of care provided, use of “soft reasoning” to avoid intensification of therapy and lack of focus on achieving treatment goals.[31] The identification of clinical inertia as a problem in hypertension management was brought to light by a seminal study published three years earlier by investigators

looking at hypertension control in the Department of Veteran Affairs clinics. This examination by Berlowitz et al. found that even with an average of more than six hypertension-related visits per year over two years, 40% of hypertensive patients had a BP above 160/90 mm Hg, and antihypertensive therapy was initiated or intensified at only 6.7% of visits.[32] The VA study results from Berlowitz et al. provided a strong rationale to further investigate the newly identified problem of inadequate treatment intensification in hypertension management.[32]

Using the homologous term “therapeutic inertia,” Okonofua and colleagues provided the first findings estimating the quantitative impact of therapeutic inertia in hypertension. The authors of this paper defined “therapeutic inertia” as more specifically referring to pharmacotherapy whereas the preceding term includes non-pharmacological or lifestyle recommendations to treat hypertension. Therapeutic inertia was observed for 86.9% of ambulatory office visits where BP was greater than or equal to 140/90 mm Hg, and multivariate analysis determined that therapeutic inertia accounted for 19% of the variance in BP control. Furthermore, they estimated that improving antihypertensive medication intensification to 30% of visits would increase the observed BP control rate by more than 20 percentage points in one year.[33]

A study using the Blood Pressure Control Model[51] to simulate usual care for hypertensive patients determined that BP control would improve from 46% to 80% over three years if treatment intensification rates were improved from 13% to 62%, even when other important drivers of hypertension control (medication adherence and follow-up visit frequency) remained the same. Improving intensification to perfect care (100%) would increase BP control to 87.2%, much more than perfect adherence or perfect follow-up time which would increase BP control to 57.0% and 67.8%, respectively.[52] This highlights therapeutic inertia as the single, most impactful barrier to improving hypertension control.

Several studies have focused on identifying the driving forces behind therapeutic inertia. Nearly all of these studies have determined higher SBP/DBP to be the most significant predictor of antihypertensive treatment intensification or SBP/DBP close to treatment goal thresholds to be the most significant predictor of therapeutic inertia.[32, 33, 53-62] Many of these studies have also identified older age, sex, existing medications, visit frequency, BMI, and comorbidities as significant factors associated with antihypertensive therapeutic intensification or inertia. Older age is the only patient-level variable consistently associated with antihypertensive therapeutic inertia.[33, 55, 57, 58, 60-64] Variables associated with inertia in some studies and with intensification in others, include visit frequency, sex, BMI, comorbidities, and existing medications. [32, 33, 53-58, 60-62, 64] The inconsistency of findings in the literature for these variables related to antihypertensive therapeutic inertia or intensification needs further study to establish clinical and patient related factors predictive of opportunities for improving pharmacological treatment of uncontrolled hypertension.

Antihypertensive Therapeutic Intensification

Although hypertension guidelines recommend initiating pharmacological therapy with two drugs in single-pill combination form, there is less guidance around intensifying treatment after initiation.[23, 24] Specifically, physicians can enact two options for antihypertensive treatment intensification: increasing the prescribed dose of existing medication and adding a new drug to the treatment regimen. Two meta-analyses evaluating pharmacological options for lowering blood pressure and preventing cardiovascular disease determined that, on average, adding an antihypertensive medication at ½ standard, standard, and twice standard dose results in a BP decrease of 7, 9, and 11 mmHg, respectively, compared to a 2-3 mmHg BP reduction for doubling dose of an existing antihypertensive medication.[18, 41] In a recent observational study evaluating hypertensive patients at the Veterans Health Administration, a direct

comparison of adding a new medication versus maximizing the dose of an existing drug to control hypertension found that adding a new drug resulted in a slightly larger reduction in mean SBP (-0.8 mm Hg at three months, and -1.1 mm Hg at 12 months). Furthermore, maximizing dose was more likely amongst older patients and three times more common than adding a new medication among all patients. [65]

III. GAPS IN LITERATURE, RESEARCH QUESTIONS AND OBJECTIVES

Gaps in Literature

Many opportunities exist to build on the current literature and address gaps in our understanding of antihypertensive therapeutic inertia. Few studies have identified factors associated with therapeutic inertia using longitudinal EHR data (mostly cross-sectional surveys, manual chart review, or RCT data). Evidence for predictive modeling of therapeutic inertia with cross-validation is severely lacking (only Berlowitz 1998, Redon 2010) [32, 58] Ensemble methods have not been used to improve the performance of modeling therapeutic inertia. In response, the first study of this dissertation employs ensemble methods to model antihypertensive therapeutic inertia in using clinical and patient variables extracted from longitudinal EHR data to ~~address these gaps~~ build upon previous studies investigating therapeutic inertia and to provide deeper insight into factors contributing to the observed rates of therapeutic inertia and the expected impact of improving rates of therapeutic intensification on blood pressure reduction and hypertension control.

There is one published study evaluating the likelihood of antihypertensive medication intensification by adding a new medication or increasing dose (Aubert et al. 2021). This study examines patients at the Veterans Health Administration – almost all male (>98%), older population (65 years or older; mean age 76 years) [65] The only patient-related variables examined for association with the type of therapeutic intensification included age, baseline comorbid chronic conditions, baseline number of medications, baseline medication classes, and baseline SBP baseline visits. Other patient variables (e.g., sex, BMI, visit frequency, and proportion of visits with uncontrolled BP) have not been investigated for association with the type of therapeutic intensification. The second study within this dissertation builds upon the models of antihypertensive therapeutic inertia developed in the first study, to model treatment selection in antihypertensive therapeutic intensification strategies using clinical variables extracted from observational EHR data.

The effect of increasing dose compared to adding a new medication for BP lowering treatment has been measured in numerous RCTs[14, 17, 18, 41, 66-68], but only one observational study using EHR data to compare these two methods of antihypertensive treatment intensification has been published in the literature.[65] Furthermore, this study examines patients at the Veterans Health Administration – almost all male (>98%), older population (65 years or older; mean age 76 years). [65] There is little evidence using observational data to derive expected effect in SBP/DBP from incremental additions of medication classes, medication combinations with known additive effects vs. combinations with known less than additive effects and increasing dose by less than half max vs. half max or greater. The final study in this dissertation will model effectiveness of antihypertensive therapeutic intensification from observational EHR data. Specifically, this study will compare the effect on BP from increasing dose vs. adding new medication vs. no change in medication, increasing dose by less than half max vs. half max or greater, incremental additions of medication classes, and between medication combinations with known additive effects vs. combinations with known less than additive effects.

Research Questions:

1. How much do previously studied factors associated with therapeutic inertia impact the likelihood of therapeutic inertia and explain the observed variance in therapeutic inertia? How much do hypothesized factors not previously studied for their relationship with therapeutic inertia impact the likelihood of and explain observed variance in therapeutic inertia? Previously unexamined factors with hypothesized effects on therapeutic inertia include percent of visits where BP controlled, average BP across visits, BP variability, visit frequency, and ASCVD risk.
2. How much do previously studied and not previously studied factors impact the likelihood and explain the variance in time to therapeutic initiation or intensification?
3. Can a reliable predictive model for therapeutic inertia in hypertension care that improves upon the accuracy and validity of previously developed models for therapeutic inertia published in the literature?
4. How much do previously studied and not previously studied factors impact the likelihood and explain the variance of increasing dose vs. adding a new medication when antihypertensive therapy is intensified?
5. Are greater reductions in BP observed subsequent to instances of therapeutic intensification where dose of an existing medication is increased or where a new class of medication is added?
6. Do the observed reductions in BP after incremental increases in dose differ between key patient characteristics (race/ethnicity, sex, and age) among specific classes of antihypertensive drugs?

7. Do the observed reductions in BP after prescribing a new medication differ between key patient characteristics (race/ethnicity, sex, and age) among specific combinations of antihypertensive drugs?

Research Objectives:

STUDY 1: Modeling therapeutic inertia in hypertension management using clinical patient characteristics extracted from longitudinal EHR data

- Build a *descriptive model* of therapeutic inertia using EHR data to better understand drivers of therapeutic inertia and barriers to therapeutic intensification
- Train and validate a *predictive model* to estimate the probability of therapeutic inertia during a given visit.

STUDY 2: Modeling selection of antihypertensive therapeutic intensification using patient clinical variables extracted from longitudinal EHR data

- Identify patient variables significantly associated (and quantify strength of association) with the two types of antihypertensive therapeutic intensification: adding a new medication and increasing dose of an existing medication
- Calculate *propensity scores* for treatment selection based on these patient variables

STUDY 3: Comparing effectiveness of antihypertensive therapeutic intensification from observational data – increasing dose vs. adding new medication

- Compare systolic blood pressure changes following different approaches/levels of therapeutic intensification for uncontrolled hypertensive patients: Adding a new medication class vs. increasing dose of existing medication vs. no change in medication
    - Compare SBP changes after increasing dose by less than half max vs. half max or greater
    - Compare SBP changes after incremental additions of medication classes, and between medication combinations with known additive effects vs. combinations with known less than additive effects
- Determine variation and standard deviation in systolic blood pressure changes following different approaches/levels of therapeutic intensification; quantify range of observed response to therapeutic intensification

IV. MATERIALS & METHODS

The proposed set of three studies will explore the value and reliability of descriptive and predictive modeling techniques applied to antihypertensive therapeutic inertia and intensification.

Study 1: The first study will use mixed effects logistic regression to build a descriptive model of therapeutic inertia from previously studied and hypothesized factors related to therapeutic inertia. The same set of variables will then be used to train a predictive classification model using logistic regression, decision trees, and ensemble methods including bagging and boosting.

Study 2: The second study will use mixed effects logistic regression to model therapeutic intensification and calculate propensity scores for selection of two treatment strategies: adding a new medication or increasing dose of an existing medication.

Study 3: The third study will use linear regression modeling and propensity score matching to estimate and compare the effectiveness of adding a new medication or increasing dose of an existing medication to lower blood pressure. All model construction and statistical analysis will be performed using the R statistical programming language (version 4.0.2).[69]

Human Subjects Research Determination

The study protocol for all three analyses in this dissertation were reviewed by the American Medical Association's IRB of record (University of Illinois Chicago) and Clemson University's IRB office. Both IRB offices determined that the proposed studies do not involve human subjects as defined in the federal regulations governing the protection of human subjects in research, 45 CFR 46.102(e), therefore full IRB review and approval were not required.

Data Sources

The data used in this project is an aggregated, limited dataset of extracted EHR data from multiple health care organizations (HCOs) participating in the American Medical Association's (AMA) Measure Accurately, Act Rapidly, and Partner with Patients (MAP) blood pressure (BP) control quality improvement (QI) program. Some of the participating health systems work with AMA software engineers to extract comprehensive electronic health record data for the AMA MAP team to provide relevant information to support clinicians and care managers in their blood pressure control efforts. The full datasets from each health system are stored separately for use in AMA MAP QI reports that utilize protected health information (PHI). A limited dataset containing data from five participating health care organizations, with all PHI removed except for elements of date, will be used for all analyses in this project.

Study Setting

Data from five health care organizations are included in the limited data set. Four are located in South Carolina and one is located in the Chicago, Illinois area. Three are federally qualified health centers (FQHCs); one with more than 600k patients and two with less than 75k patients in their respective EHR systems over the last three years. The other two HCOs are larger, each with more than 400k patients in their EHR over the last three years; a comprehensive academic medical center and a single-hospital medical complex. Attributes for each participating HCO are summarized in *Table 1* below. The full aggregated limited dataset includes data for a total of 1.6 million patients and 12 million encounters. The variety present among the five study sites included in the aggregated dataset provides a context that is more representative of the diversity of health care settings across the national system.

Table 1. Health Care Organizations included in the limited data set.

HCO Participants	Description	Location	Patients (2020-2022)	Encounters (2020-2022)
HCO A	Academic medical center	Southeast	530,094	3,342,443
HCO B	FQHC	Southeast	22,276	253,046
HCO C	FQHC	Southeast	75,627	1,175,740
HCO D	FQHC	Midwest	665,868	2,962,630
HCO E	Single-hospital medical complex	Southeast	416,827	4,300,036
Total (Aggregated Dataset)			**1,710,692**	**12,033,895**

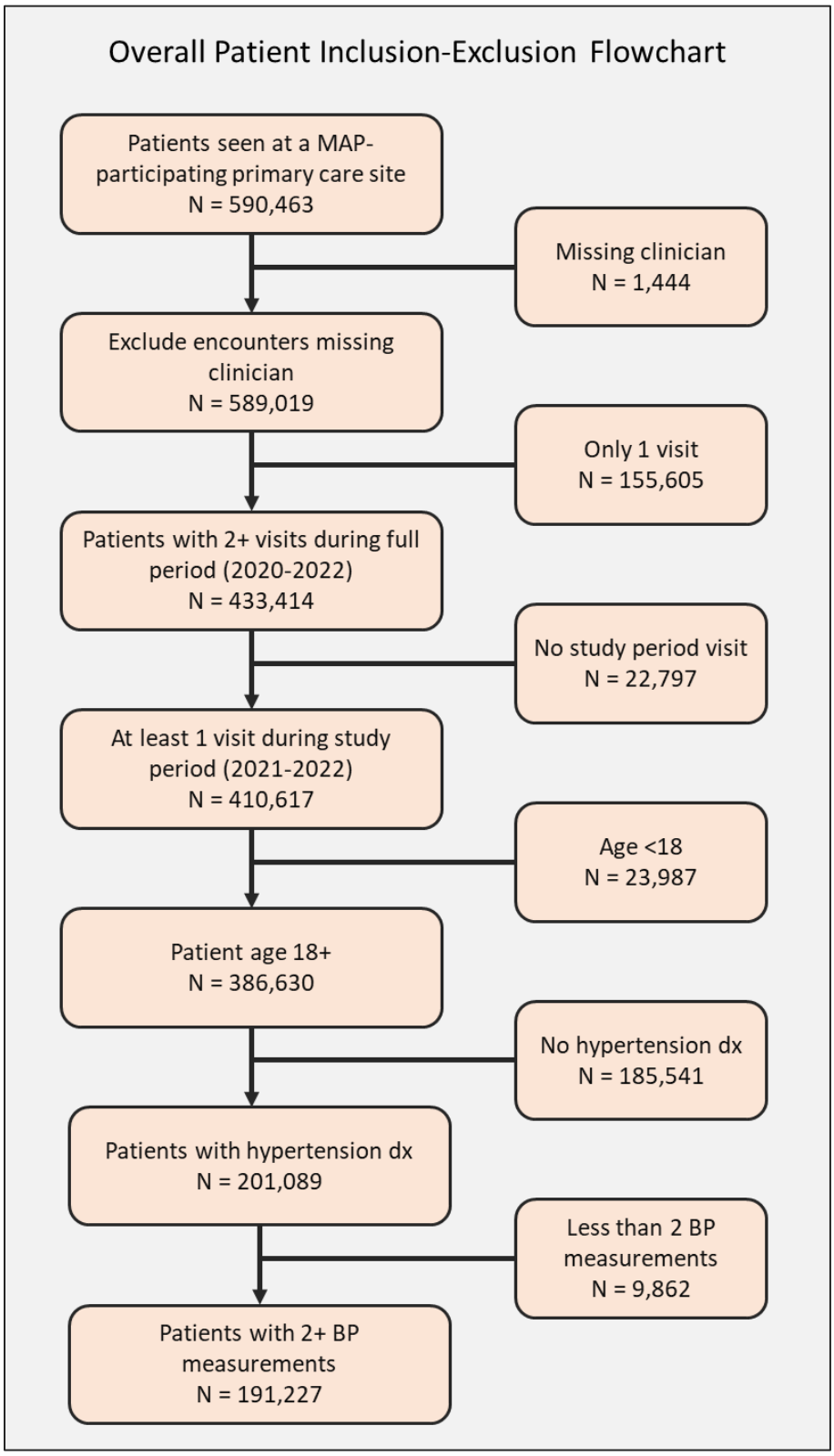
Table 2. MAP Patients, Encounters, Clinicians and Sites by HCO

HCO Participants	MAP Patients (2020-2022)	MAP Encounters (2020-2022)	MAP Sites (2020-2022)	MAP Clinicians (2020-2022)
HCO A	116,851	549,455	26	633
HCO B	13,477	86,283	3	52
HCO C	66,510	898,596	8	158
HCO D	109,087	559,804	25	679
HCO E	230,403	1,473,326	28	454
Total	**536,328**	**3,567,464**	**90**	**1,976**

Inclusion/Exclusion Criteria

The study sample for each analysis included in this dissertation was drawn from a base set of adult patients diagnosed with hypertension that had at least two primary care visits and two blood pressure measurements recorded in the EHR during the two-year study period (11/1/2019 – 10/31/2021). All five health care organizations participating in the AMA MAP quality improvement program detailed above were included in the aggregated dataset. Of the 386,630 patients that met the age criteria (18+ years old) and had at least two visits and BP measurements at a participating MAP primary care site, 201,089 patients had a diagnosis of hypertension. *Figure 1* shows the inclusion/exclusion criteria applied to extract the base dataset used for all three analyses in this dissertation.

Figure 1. AMA LDS Patient Inclusion-Exclusion Flow Diagram



Summary of Analyses

The overarching purpose of all analyses in this project is to better understand factors contributing to the prevalence of antihypertensive therapeutic inertia and to inform antihypertensive treatment intensification and selection in ambulatory clinical settings. Each proposed model included in this project will help provide evidence for implementing a strategy that utilizes EHR derived information and informatics tools to target the problem of therapeutic inertia and maximize therapeutic intensification in hypertension treatment. By modeling therapeutic inertia incidence, treatment selection, and SBP change after therapeutic intensification, all three studies in this project will help provide insight into factors contributing to the observed rates of therapeutic inertia and the expected impact of improving rates of therapeutic intensification on blood pressure reduction and hypertension control.

Table 3. EHR-derived clinical variables used for model consideration.

Variable Type	**Variable Name**
Processed	Sex Gender Race Height Weight Body Mass Index (BMI) Systolic Blood Pressure (SBP) Diastolic Blood Pressure (DBP) Blood Glucose Hemoglobin A1C (HbA1C) Total Cholesterol High-density Lipoprotein Cholesterol (HDL) Low-density Lipoprotein Cholesterol, Estimated (LDL_C) Low-density Lipoprotein Cholesterol, Direct (LDL_D) Triglycerides Very-low-density Lipoprotein (VLDL)

	Medications ~~Serum Creatinine~~ ~~Serum Potassium~~
	Encounters Medications Comorbidities
Calculated	Age at encounter Visit Frequency Baseline antihypertensive medication classes Baseline number of medications Clinician Continuity (2) Number of days since previous visit Number of days since previous change in antihypertensive med Proportion of visits with BP ≥140/≥90 Baseline BP Previous visit BP

STUDY 1: MODELING THERAPEUTIC INERTIA IN HYPERTENSION MANAGEMENT USING CLINICAL PATIENT CHARACTERISTICS EXTRACTED FROM EHR DATA

Abstract

Background: This study aims to explore the factors that contribute to therapeutic inertia and intensification in the management of uncontrolled hypertension. Despite the availability of effective antihypertensive therapies, hypertension control rates have remained stagnant for over a decade, with rates ranging from 66% to 87% for therapeutic inertia in ambulatory hypertension management. Higher blood pressure at the current visit has been consistently found to be the most significant predictor of antihypertensive treatment intensification, while many other patient and clinical factors have inconsistent results in the literature. This study seeks to identify both previously studied and unexamined factors associated with therapeutic inertia and intensification to develop a predictive model for anticipating therapeutic inertia instances. The research findings can inform antihypertensive clinician action and improve the accuracy and validity of previously developed models for therapeutic inertia published in the literature.

Methods: The data used in this study is an aggregated set of data from five healthcare organizations: three federally qualified health centers and two large integrated health systems. Mixed-effects logistic regression is used to build descriptive models of therapeutic inertia for inference. Classification trees using different ensemble methods and resampling techniques are used to train and test predictive models of antihypertensive therapeutic inertia versus intensification.

Results: : For 120,755 patients with hypertension, therapeutic inertia was indicated at 84.1% of 168,222 visits where BP was uncontrolled (>140/>90mmHg). Therapeutic intensification occurred via dose increase of existing medication at 6.6% of visits, and addition of a new medication class at 9.2% of visits with uncontrolled BP. Mixed-effects modeling of patient and clinical variables extracted from the electronic health record accounted for 13.2% of the variance in therapeutic inertia vs. intensification among visits with uncontrolled BP. Gradient boosted classification trees produced the strongest predictive model of therapeutic inertia (test AUC: 0.683).

Discussion: The predictive models had moderate performance and suggested potential use in helping guide clinician decision-making regarding therapeutic inertia vs. intensification. However, further research is needed to validate the models on larger and more diverse datasets, as well as to determine the factors influencing therapeutic inertia and intensification, especially regarding provider and patient-level factors. This study provides valuable insights into the factors influencing therapeutic intensification for patients with uncontrolled hypertension but suggests that still further research is needed to identify the factors influencing therapeutic inertia and intensification, particularly regarding provider and patient-level factors. Healthcare providers should be aware of the potential impact of these factors and take steps to minimize barriers to optimal hypertension management.

Conclusion: The study provides insights on factors affecting treatment intensification for patients with uncontrolled hypertension. The study emphasizes the significance of SBP and DBP as predictors of therapeutic intensification and suggests further research to identify the reasons behind therapeutic inertia and intensification. Healthcare providers should consider these factors and reduce barriers to achieve optimal hypertension management.

Background

Therapeutic inertia, the term used to describe the absence of action from healthcare providers to initiate or intensify therapy when indicated, was first defined by Phillips et al. in 2001,[31] but first identified as a significant problem in hypertension management by Berlowitz et al. in 1998.[32] Qualitative studies have found common themes in reported reasons for therapeutic inertia: overestimation of care provided, soft reasoning to avoid intensification of therapy, and a lack of focus on achieving treatment goals.[31, 70] The reporting of inadequate treatment intensification in hypertension management among VA health care clinics by Berlowitz et al. found that 40% of hypertensive patients had a BP above 160/90 mm Hg, and antihypertensive therapy was initiated or intensified at only 6.7% of visits, despite more than six hypertension-related visits per year over two years.[32] Okonofua and colleagues further specified the term therapeutic inertia to strictly refer to pharmacotherapy, reporting findings where 86.9% of ambulatory office visits had therapeutic inertia when BP was greater than or equal to 140/90 mm Hg.[33] More recent analyses of therapeutic inertia in ambulatory hypertension management report rates ranging from 66% to 87%, with most findings around 80%.[56, 58-61, 64, 71]

For more than a decade now, hypertension control rates have been stagnant and even falling for some demographic groups,[26-28] and continue to remain below national goals[29, 30] – all despite the well-documented risks attributed to uncontrolled hypertension,[1-18] treatment actions recommended outlined by international recognized guidelines,[23, 24] and the availability more than a dozen distinct classes of safe, effective pharmacological options for antihypertensive therapy.[14-22] Okonofua et al. estimated that improving antihypertensive medication intensification to 30% of visits would increase the observed BP control rate by more than 20 percentage points in one year.[33] By developing a Markov-chain simulation model of usual care for hypertensive patients, Bellows et al. determined that BP control

would improve from 46% to 80% over three years if treatment intensification rates were improved from 13% to 62%.[52]

The 1998 study from Berlowitz et al. found variables predictive of decisions to increase therapy for hypertension to be increased levels of both systolic and diastolic blood pressure at the visit, a change in therapy at the preceding visit, the presence of coronary artery disease (among patients with a blood pressure of <165/90 mm Hg), and a scheduled visit. Blood pressure recorded during previous visits and cardiovascular risk factors other than hypertension were not identified as predictors by the model. Increases in therapy were most common during visits with a diastolic blood pressure of ≥90 mm Hg and a change in therapy at the preceding visit.[32]

More than a dozen studies looking at variables associated with antihypertensive therapeutic inertia and intensification have since been published; analyzing patient and clinical variables collected from:

- Manual chart review [32, 53, 56, 58, 63, 72-74]
- EHR data extraction [33, 54, 55, 57, 61, 64]
- RCT primary and secondary analyses [62, 75]
- Quantitative and qualitative surveys [60, 76, 77]
- Administrative claims [59]

Higher SBP and DBP at the current visit was consistently found to be the most significant predictor of antihypertensive treatment intensification in all previous studies, with elevated SBP/DBP close to treatment goal thresholds being associated with therapeutic inertia.[32, 33, 53-62, 72] Blood pressure at previous visits and average BP were only examined by a few studies, finding a similar relationship with therapeutic inertia as current visit BP.[53, 56, 57] Reports of age and sex are inconsistently significant but consistent in their relationship with TI; older age and female sex being associated with therapeutic

inertia.[33, 53, 57, 58, 60-62, 64] No statistically significant relationship between race/ethnicity and TI has been reported.[60, 62, 64, 72] Previous therapeutic intensification events have been found to be associated with higher likelihood of therapeutic intensification at the current visit,[32, 53] while number of AH medications currently prescribed is associated with both therapeutic inertia and intensification.[33, 55, 57, 58, 60] Cardiovascular related comorbidities including congestive heart failure (CHF) and coronary artery disease (CAD) are most often linked to greater therapeutic inertia,[32, 33, 61] while diabetes, hyperlipidemia, and depression are associated with therapeutic inertia.[33, 54, 60, 61, 63, 74] However, some studies have reported the reverse relationship for cardiovascular disease (CVD), CHF, and diabetes.[33, 55, 57] Harle et al. looked at total number of comorbidities rather than specific conditions and found higher rates of therapeutic intensification with greater number of comorbidities.[64] Visit frequency was found to be a predictor of therapeutic inertia,[58] though visits with a patient's primary physician is correlated with therapeutic intensification compared visits with a different or covering physician.[56] Patient BMI has reported relationships with both greater therapeutic inertia and intensification.[62, 64] Other factors found to contribute to reluctance to intensify AH treatment, include concerns about medication side effects,[78-80] workflow constraints (e.g., time),[81] dosing uncertainty (especially when cardiovascular comorbidities are present),[81] discrepancies and uncertainty in BP readings (due to measurement error and/or "white coat" hypertension),[82, 83] and medication costs.[25]

Previous studies have only examined a subset of all of the potentially relevant factors related to therapeutic inertia and intensification. Furthermore, many findings are conflicting regarding some key variables like comorbid CVD, CHF, diabetes, BMI, and number of AH medications. Additionally, relevant variables that can be ascertained from data available in the EHR, including proportion of visits where BP controlled, BP variability, confirmatory blood pressure measurement, and clinician continuity, have not

been examined for their relationship with AH treatment action. Further study is needed to establish clinical and patient-related factors and predictive of opportunities for improving pharmacological treatment of uncontrolled hypertension through the conversion of therapeutic inertia to intensification. Overcoming therapeutic inertia is critical to reach population health goals, and an informed strategy utilizing informatics is necessary to understand and address this issue. Comprehensive analysis of previously studied and unexamined factors and hypothesized factors associated with therapeutic inertia and intensification is needed. Developing an accurate predictive model for anticipating therapeutic inertia instances would be a powerful tool for proactive intervention. Understanding the factors driving decision-making in therapeutic intensification is critical, and modeling the relationship between patient and clinical variables can guide clinician decision-making toward the most effective action for improving hypertension control. The purpose of this study is to inform antihypertensive clinician action through descriptive and predictive modeling of a comprehensive set of patient and clinical variables extracted from EHRs for secondary analysis.

Study Objectives & Research Questions

Research Questions:

1. How much do previously studied factors associated with therapeutic inertia impact the likelihood of therapeutic inertia and explain the observed variance in therapeutic inertia? How much do hypothesized factors not previously studied for their relationship with therapeutic inertia impact the likelihood of and explain observed variance in therapeutic inertia? Previously unexamined factors with hypothesized effects on therapeutic inertia include proportion of visits where BP controlled, BP variability, confirmatory blood pressure measurement, and clinician continuity.

2. How much do previously studied and not previously studied factors impact the likelihood and explain the variance in time to therapeutic initiation or intensification?

3. Can a reliable predictive model for therapeutic inertia in hypertension care that improves upon the accuracy and validity of previously developed models for therapeutic inertia published in the literature?

Objectives:

The purpose of the first analysis is to model therapeutic inertia using clinical data that are associated with therapeutic inertia and therapeutic intensification in hypertension management.

- Build a *descriptive model* of therapeutic inertia using EHR data to better understand drivers of therapeutic inertia and barriers to therapeutic intensification.
- Train and validate a *predictive model* to estimate the probability of therapeutic inertia during a given visit, and
- Evaluate different ensemble methods and resampling techniques to determine the most robust method for modeling antihypertensive therapeutic inertia vs. intensification.

Methodology

Extensive descriptive modeling of therapeutic inertia will be constructed using the mixed effects logistic regression function from the generalized linear mixed-effects models package (lme4) in R.[84, 85] Time to therapeutic initiation or intensification will be modelled with linear regression using the Linear Mixed-Effects Models package (lme4).[84, 85] Descriptive modeling of both therapeutic intensification and time to intensification will consist of univariate regression models for each variable listed in *TableX* and adjusted multivariate regression models for variables determined to be statistically significant from the univariate analysis. Random intercepts for multiple observations for each patient and clinician will be included in all descriptive models. The logistic regression models of therapeutic inertia will be evaluated by computing a pseudo-R^2 formulated for evaluating generalized linear mixed models (GLMMs).[86, 87] The linear regression models for time to therapeutic initiation or intensification will be evaluated with R^2 and mean square error calculations to assess the variability in outcome explained by the models.[88]

Using the same set of variables, predictive models for classification of therapeutic inertia vs. intensification will be trained and validated using decision trees and two types of ensemble learning: bagging and boosting.[89-92] Resampling methods of oversampling, SMOTE, ROSE, and undersampling will are applied to adjust for the imbalance in outcome frequency between inertia and intensification.[93-97] The models will be estimated using the Random Forests package and the XGBoost gradient boosting algorithm in R.[98, 99] All trained classification models for predicting antihypertensive therapeutic inertia will be evaluated using holdout set cross-validation, calculation of area under the receiver operating characteristic curve (AUC) and balanced accuracy, and generation of confusion matrices to assess prediction error and predictive utility.[100]

Study Data and Setting

The project uses a limited dataset from multiple health care organizations (HCOs) participating in the American Medical Association's blood pressure control quality improvement program. The dataset contains data from five healthcare organizations, four in the southeast and one in the Midwest U.S., including three federally qualified health centers and two large health systems. The dataset contains EHR data for 1.6 million patients and 12 million encounters before applying study inclusion/exclusion criteria. The dataset's diversity provides a context that is more representative of the diversity of healthcare settings across the national system (see *Table 1* for patient demographic and clinical characteristics by HCO).

Inclusion and Exclusion Criteria

The study included 590,463 patients who were seen at a MAP-participating primary care site. Encounters missing clinician were excluded, leaving 589,019 encounters. Patients with at least two visits during the full study period (2020-2022) totaled 433,414, while 410,617 had at least one visit during the study period (2021-2022). Patients were required to be 18 years or older (386,630). Additionally, patients with a hypertension diagnosis (201,089) and those with at least two blood pressure measurements (191,227) were included. Patients with all antihypertensive medications verified (120,755) were also included. Uncontrolled blood pressure visits (73,974) were included in the study, while patients with at least one visit during the baseline period in 2020 (56,963) were included as well. Figure 2 provides an overview of all inclusion/exclusion criteria for this study as they were applied to the full dataset.

Figure 2. Patient Inclusion-Exclusion Flowchart for Therapeutic Intensification Event Analysis

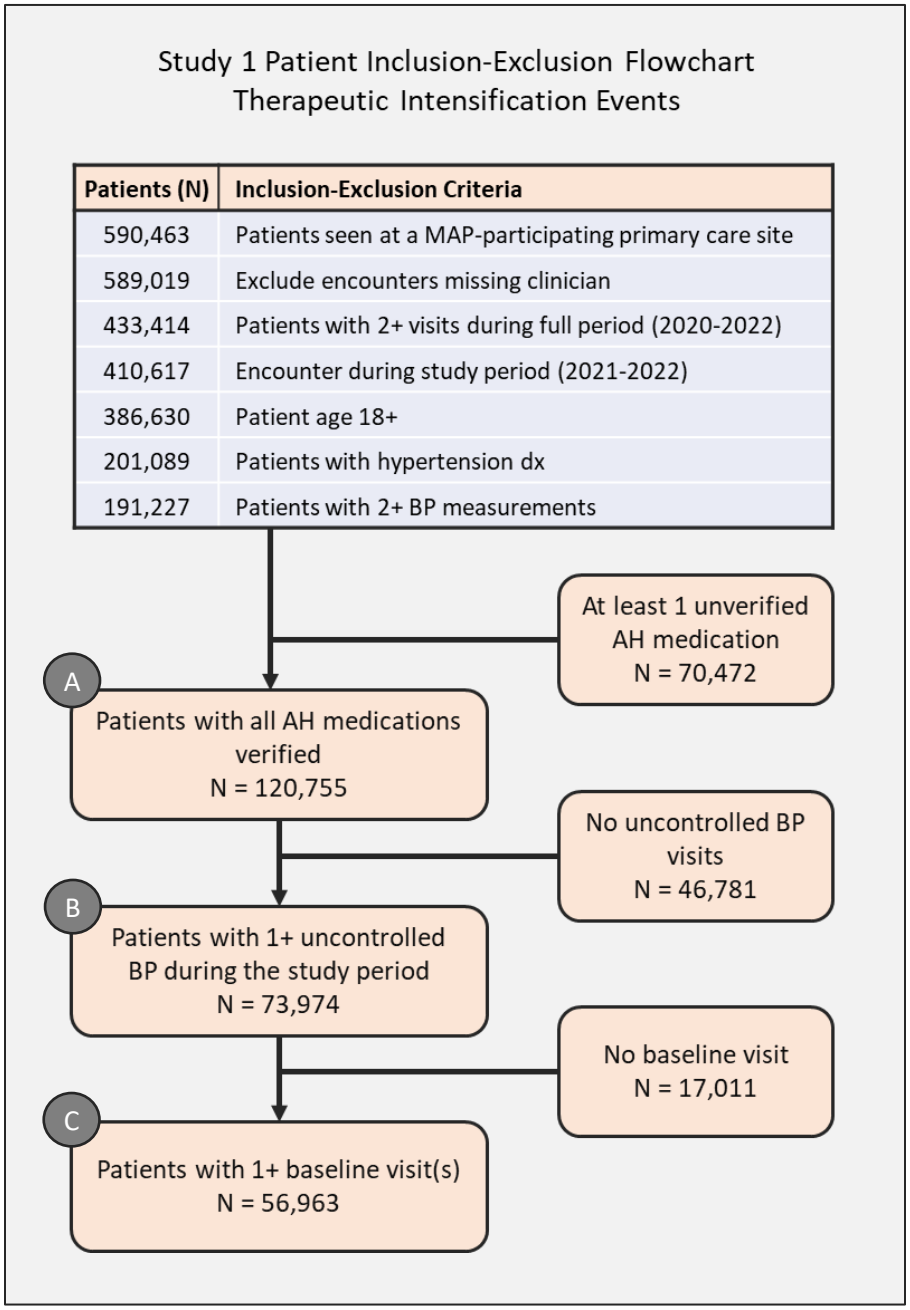


Figure 3. Patient Inclusion-Exclusion Flowchart for Time to Therapeutic Intensification Analysis

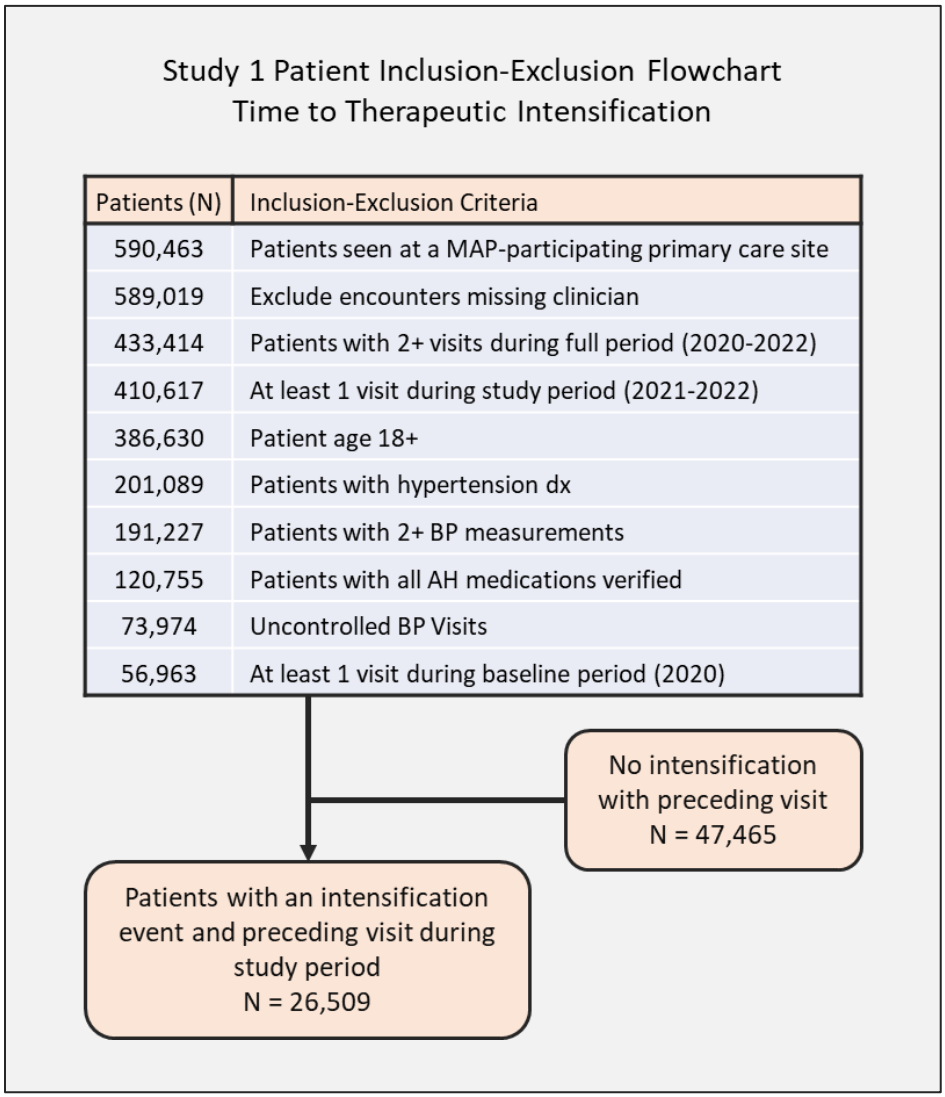


Table 4. Summary of Patients and Encounters for Therapeutic Intensification Event Analysis

HCO	Patients	Encounters	Encounters per Patient
A	11,174	22,251	1.99
B	2,637	6,913	2.62
C	7,035	19,568	2.78
D	11,123	25,535	2.30
E	24,994	56,544	2.26
Total	**56,963**	**130,811**	**2.30**

Table 5. Summary of Patients and Encounters for Time to Therapeutic Intensification Analysis

HCO	Patients	Encounters	Encounters per Patient
A	4,971	9,275	1.87
B	1,156	2,914	2.52
C	3,236	8,429	2.60
D	5,494	11,723	2.13
E	11,652	23,811	2.04
Total	**26,509**	**56,152**	**2.12**

Data Processing

All data processing to prepare the raw data for analysis was completed using the the R statistical programming language (version 4.0.2) and the Tidyverse suite of packages for data science.[69, 101] As is often required when using EHR data for secondary analyses, many processing steps were performed before running the models produced in this study. After limiting the data set to ambulatory primary care visits at MAP sites, unique encounters were defined by date, under the assumption that only one visit

per day would be made by a patient at a particular site. Encounters by a patient on the same day at two different sites would have been kept with separate encounter IDs for distinction, but no cases like this were observed in the data after filtering the encounters to only those that occurred at a MAP-participating primary care clinic. However, two key encounter level variables had numerous cases where different values were attached to the same encounter: clinician and blood pressure. To condense these cases with multiple instances of a single encounter in the data, a clinician was chosen based on frequency and the BP with the lowest SBP and corresponding or "paired" DBP reading. Attribution of clinician was done by assigning the most frequently seen clinician by each patient as their designated "primary clinician." Secondary and tertiary clinicians were also determined for each patient as their second and third most visited, respectively. For cases where multiple clinicians were listed for a single encounter:

- If one of the clinicians listed with the encounter corresponded with the patient's assigned "primary clinician," that clinician was kept and others removed.
- If one of the clinicians listed with the encounter corresponded with the patient's assigned "secondary clinician," that clinician was kept and others removed.
- If one of the clinicians listed with the encounter corresponded with the patient's assigned "tertiary clinician," that clinician was kept and others removed.
- If none of the clinicians listed were the patient's primary, secondary, or tertiary clinician, the first clinician listed was kept and others removed.

Medications are manually validated by the team of data acquisition specialists, analysts, and software engineers at the AMA's Improving Health Outcomes (IHO) division on a separate server where the identifiable data is loaded and processed for calculation of MAP program dashboard metrics. The validation process utilizes a combination of an internally developed string parsing function with manual

review of each generic drug name and dose derived from the drug description and prescription instructions extracted from medication orders in the EHR.

Therapeutic Inertia and Intensification

Classification of therapeutic inertia is dependent on the accurate determination of therapeutic intensification events. Classification of increases in dose of an existing medication and additions of a new class of medication were handled separately. First all medication orders were consolidated to one line for each combination of patient/drug/dose, and the first and last order date were kept in different columns to retain when the specific drug/dose was first and last seen in the data. For dose increases, all unique combinations of patient/drug/dose were ordered chronologically by the first date listed the data for each. Then an if, else statement was used to determine two consecutive patient/drug/dose combinations were for the same patient and the same drug, and if the dose was higher for the more recent instance. If so, that date of first instance for the new dose was marked as a dose increase for that patient. For additions of new medication classes, unique combinations of patient/class were ordered by first date listed in the data. The baseline period was used to provide a 12-month window to pick all currently prescribed AH medications for each patient (AH medication prescriptions need to be renewed every 12 months at the most). Two conditions had to be met for a class addition to be indicated:

- The AH class must not be present in the baseline period for a patient
- There must be a visit on record for a patient at least 12 months prior to the first date listed for the AH class (to eliminate new patients or patients not seen for over a year from being falsely identified as having a new medication added when they are just receiving an overdue renewal or a renewal with a new provider)

Mixed-Effects Modeling

Mixed effects modeling is a statistical technique used to analyze data that have both fixed and random effects. Fixed effects are factors that are known or measured, while random effects are factors that are not known or unmeasured but can still have an impact on the outcome. Mixed effects modeling provides a solution to the challenge of modeling clustered data in longitudinal analysis. In datasets where there may be multiple observations for a single individual or distinct group, introducing random effects allows the model to adjust for implicit differences in variation of explanatory and outcome variables that exist between individual subjects or distinct groups.[102, 103] The dataset analyzed in this study has multiple observations per patient and per clinician. Random intercepts were added to all descriptive models, for each patient and clinician included in the dataset, to adjust for implicit differences between individual treating and being treated, as well as the clustering of biological variables (i.e. vitals and laboratory tests) measured at different time points for the same patients over the course of the longitudinal cohort study. The specific implementation used for all descriptive models in this study is the Linear Mixed-Effects Models package (lme4) in R.[84, 85]

Regression Model Evaluation

A Pseudo R-squared measure developed and validated by Nakagawa and Schielzeth[86, 87] specifically for mixed-effects logistic regression is used to evaluate the fit and explanation of variance in each logit model of therapeutic inertia. Pseudo R-squared is a measure of the goodness of fit of a statistical model that can be used to evaluate the performance of mixed-effects logistic regression models. It is a modification of the traditional R-squared used in linear regression models that considers the complexity of the model and the variability in the data. The interpretation of pseudo R-squared in mixed-effects logistic regression models is similar to that in linear regression models. A higher value of pseudo R-

squared indicates a better fit of the model to the data, with values ranging from 0 to 1.[104] For linear mixed-effects models, a regular adjusted-R^2 is used to evaluate model fit for descriptive models of time to therapeutic intensification,[88] but using the Nakagawa and Schielzeth method for estimating variance explained by fixed effects alone vs. fixed and random effects together.[86, 87]

Bootstrap Aggregation

Bootstrap aggregation, or "bagging," is an ensemble method of machine learning that aims to improve the stability and accuracy of predictions by combining multiple models trained on different subsets of the dataset. In bagging, a large number of random subsets of the training data are sampled with replacement, and a separate model is trained on each subset. These models are then combined to make predictions by taking the average or majority vote of their outputs. By reducing the variance of the individual models, bagging can often lead to better performance and generalization.[92, 105, 106] To predict therapeutic inertia vs. intensification, this study employs the *Random Forest* algorithm,[107] which uses bagging to build a large number of decision trees and aggregate their predictions to make a final prediction. Random Forest has been successfully applied to a wide range of tasks, including image classification, speech recognition, and drug discovery.[92, 105, 106, 108]

Boosting

Boosting is another ensemble learning technique where models are trained sequentially, with each new model trying to correct the errors made by the previous models. This study also tests the XGBoost algorithm[99] for prediction of therapeutic inertia vs. intensification. XGBoost works by training decision

trees using gradient boosting, where, at each iteration, a new decision tree is trained to fit the residual errors of the previous iteration. The XGBoost algorithm for gradient boosting includes several parameters that must be tuned through experimentation and cross-validation to find the optimal settings for maximizing accuracy while avoiding overfitting to the training data. The *nrounds* parameter of XGBoost specifies the number of boosting rounds, which is the number of decision trees that will be trained in the ensemble. The *nrounds* parameter controls the number of iterations of the boosting algorithm. Increasing the number of rounds allows the model to learn more complex relationships between the input features and the output variable. However, setting *nrounds* too high can lead to overfitting, where the model fits the training data too closely and performs poorly on new, unseen data. The *scale_pos_weight* parameter allows for adjustment of training on imbalanced data, as in the case of this study where therapeutic inertia is much more frequently observed than therapeutic inertia.[92, 98, 99, 109]

Resampling

Since the Random Forests algorithm does not have a built-in parameter to handle class imbalance like XGBoost, several resampling methods are tested to see which techniques best adjusts for the low ratio of therapeutic inertia to intensification in the data. Oversampling, Synthetic Minority Over-sampling Technique (SMOTE), Random Over-sampling Examples (ROSE), and undersampling were all tested in combination with random forest classification using the Caret package in R.[97]

Oversampling involves duplicating instances from the minority class to balance the classes. This method can lead to overfitting and reduced model performance, especially if the minority class is heavily oversampled. However, oversampling can be effective if the dataset is small and the minority class has important instances that should not be missed.[94, 96]

SMOTE (Synthetic Minority Over-sampling Technique) is a more advanced form of oversampling that involves creating synthetic instances in the minority class by interpolating between existing instances. This method can be more effective than simple oversampling because it generates new instances that are different from the existing instances and can improve the model's ability to generalize.[93]

ROSE (Random Over-Sampling Examples) is another oversampling method that generates synthetic instances by interpolating between existing instances, but it uses a different approach to select the instances to be oversampled. ROSE uses a heuristic approach to identify the most informative instances to be oversampled, which can improve the model's performance.[95]

Undersampling involves removing instances from the majority class to balance the classes. This method can lead to loss of information and reduced model performance, especially if the majority class is heavily undersampled. However, undersampling can be effective if the dataset is very large and the majority class contains many instances that are not relevant to the problem.[94, 96]

Cross-validation

Cross-validation was used to evaluate the performance of each predictive model in this study. Specifically, we used hold-out set cross-validation, randomly dividing the data into two sets: a training set and a validation set, with 70% of observations allocated to the training set and 30% of observations allocated to the test set for performance estimation. This approach provides a more realistic estimate of the model's performance on data not seen by the model during training. The measures used to evaluate the performance of each predictive model in this study were accuracy, sensitivity, specificity, balanced accuracy, precision, recall, F1 score, and area under the receiver operating characteristic curve (AUC-ROC).[110, 111]

Comorbidity Indices

This study utilized two validated methods of measuring the burden of comorbid conditions in patients the Charlson Comorbidity Index (CCI) and Elixhauser Comorbidity Index (ECI). The Charlson Comorbidity Index is a scoring system that assigns a numerical value to 19 different medical conditions, each with a corresponding weight, based on the potential impact on patient mortality.[112] The Elixhauser Comorbidity Index is a more recently developed scoring system that includes 31 different medical conditions, each with a corresponding weight, that have been associated with increased mortality and resource utilization. The ECI also includes a set of comorbidity categories, such as obesity, drug abuse, and alcohol abuse, that do not correspond to specific medical conditions.[113] This study used the "comorbidity" package,[114] an R-language rewrite of the coding algorithms developed by Quan et al.[115] to map ICD-10 diagnosis codes to the medical condition categories defined in the CCI and ECI indices. The scoring systems for each index were not utilized in this analysis. The indices were simply used to categorize clinically relevant comorbid conditions, specifically: diabetes (with and without complications), congestive heart failure (CHF), cardiac arrhythmia, peripheral vascular disease (PVD), renal failure, liver disease, solid tumor cancers, metastatic cancers from the Elixhauser index and myocardial infarction, cerebrovascular disease, and dementia from the Charlson index.[112, 113]

RESULTS

Table 1 provides a summary of patient demographics and clinical characteristics for the 120,755 patients meeting the study inclusion criteria through criteria A, outlined in Figure 1. The number of patients meeting study inclusion criteria at each HCO included in this analysis ranges substantially, with HCO E having the most patients (51,069) and HCO B having the fewest patients (4,613). The mean age of all patients is 61.3 years, with HCO C having the lowest mean age (57.2 years) and HCO D having the highest mean age (62.0 years). The total patient set is majority female, making up 56% of the 53,104 total patients, and ranging from 53.3% female at HCO E to 59.5% female at HCO C. In terms of race, 56.6% are white compared to 38.0% black. The proportion of white patients compared to black patients for each HCO ranged from 72.6% and 23.3% black to 30.7% white and 67.1% black.

The table also shows clinical characteristics such as baseline and final antihypertensive medications per patient, mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP), mean body mass index (BMI), mean hemoglobin A1C (HbA1C), mean glucose level, mean low-density lipoprotein (LDL) cholesterol, mean high-density lipoprotein (HDL) cholesterol, and mean total cholesterol. Additionally, the table shows the number and percentage of patients with certain health conditions, such as diabetes, congestive heart failure (CHF), arrhythmia, renal failure, and liver disease, with HCO E having the highest percentage of patients with diabetes (50.6%) and HCO C having the highest percentage of patients with renal failure (19.6%). The most prevalent comorbidity overall was diabetes at 31.8%, followed by chronic pulmonary disease at 18.5%.

Table 1. Summary of Patient Demographics and Clinical Characteristics

		Total		HCO A		HCO B		HCO C		HCO D		HCO E	
Patients	N	120,755		28,847		4,613		13,915		22,311		51,069	
Age	mean, SD	61.3	14.1	62.3	14.8	57.2	13.9	58.0	14.3	61.6	11.7	62.0	14.4
Male	N, %	53,104	44.0%	12,051	41.8%	1,884	40.8%	5,632	40.5%	9,680	43.4%	23,857	46.7%
Female	N, %	67,650	56.0%	16,796	58.2%	2,729	59.2%	8,283	59.5%	12,630	56.6%	27,212	53.3%
White	N, %	68,407	56.6%	18,185	63.0%	1,417	30.7%	4,490	32.3%	7,240	32.5%	37,075	72.6%
Black	N, %	45,939	38.0%	9,640	33.4%	3,095	67.1%	8,920	64.1%	12,396	55.6%	11,888	23.3%
Other	N, %	4,203	3.5%	628	2.2%	53	1.1%	420	3.0%	1,614	7.2%	1,488	2.9%
Baseline AH meds per pt	mean	1.5		1.5		1.9		1.8		2.1		1.2	
Final AH meds per pt	mean	1.9		1.8		2.2		2.1		2.3		1.7	
SBP	mean, SD	130.9	15.5	129.8	15.0	132.5	17.9	131.5	16.5	135.1	17.4	129.7	14.5
DBP	mean, SD	76.7	10.5	77.1	10.3	80.8	12.9	79.7	9.9	71.9	10.8	77.6	9.7
BMI	mean, SD	31.7	8.0	31.2	7.9	32.8	8.9	32.6	9.0	31.6	7.9	31.6	7.6
HbA1C	mean, SD	6.6	1.6	6.3	1.5	6.7	1.7	6.8	1.8	6.8	1.8	6.6	1.5
Glucose	mean, SD	117.3	52.5	113.8	47.8	116.0	59.7	116.8	60.7	128.4	64.8	114.5	44.8
LDL	mean, SD	100.9	36.5	102.1	36.6	104.9	36.2	104.9	36.8	103.5	37.7	98.1	35.7
HDL	mean, SD	54.9	17.1	55.9	18.0	52.5	16.0	51.7	14.9	49.7	13.3	57.4	18.1
Cholesterol	mean, SD	165.5	50.6	124.9	52.5	180.6	44.1	181.6	43.6	172.0	45.0	178.2	42.5
Diabetes	N, %	38,386	31.8%	7,790	27.0%	1,457	31.6%	3,953	28.4%	11,298	50.6%	13,888	27.2%
CHF	N, %	7,635	6.3%	2,320	8.0%	376	8.2%	657	4.7%	2,235	10.0%	2,047	4.0%
Arrhythmia	N, %	18,196	15.1%	5,872	20.4%	488	10.6%	1,057	7.6%	3,124	14.0%	7,655	15.0%
Renal Failure	N, %	13,043	10.8%	3,150	10.9%	902	19.6%	1,369	9.8%	3,491	15.6%	4,131	8.1%
Liver Disease	N, %	7,548	6.3%	2,148	7.4%	191	4.1%	505	3.6%	2,540	11.4%	2,164	4.2%
Valvular Disease	N, %	4,794	4.0%	1,500	5.2%	48	1.0%	151	1.1%	700	3.1%	2,395	4.7%
CEVD	N, %	9,436	7.8%	2,794	9.7%	277	6.0%	701	5.0%	1,962	8.8%	3,702	7.2%
MI	N, %	3,047	2.5%	1,255	4.4%	54	1.2%	150	1.1%	849	3.8%	739	1.4%
PVD	N, %	8,955	7.4%	2,870	9.9%	257	5.6%	596	4.3%	2,055	9.2%	3,177	6.2%
CPD	N, %	22,326	18.5%	6,351	22.0%	881	19.1%	2,862	20.6%	4,839	21.7%	7,393	14.5%
Metastatic Cancer	N, %	2,240	1.9%	609	2.1%	7	0.2%	61	0.4%	900	4.0%	663	1.3%
Solid Tumor	N, %	10,053	8.3%	2,830	9.8%	160	3.5%	472	3.4%	2,946	13.2%	3,645	7.1%

Table 2 and table 3 summarize the distribution of SBP and DBP overall and across the different HCOs for the 569,966 blood pressure encounters that met all study criteria through criteria A in Figure 1. On average 26.5% of all visits had an SBP of 140 or higher. All of the HCOs had the highest proportion of visits in the 130-140 mmHg, except for HCO E which had a slightly higher proportion of patients in the 120-130 mmHg group. HCO C had the highest proportion of visits with SBP above 140 mmHg at 38%, while all other HCOs had between 22-30% of visits above 140. HCO B had the highest proportion of visits above 160 mmHg at 10.7%, with all other HCOs reporting between 4-9% of visits above 160. The majority of visits for all sites saw DBP between 70-90 mmHg, except for HCO D where 42.0% had a reported DBP 70 mmHg or lower. HCO B had the highest proportion of visits above 90 mmHg at 22.4%, and all other HCOs had between 10-11% of visits above 90, except for HCO which had the lowest percent of uncontrolled DBP visits at 7.3%.

Table 2. Systolic Blood Pressure Distribution

	Total		**HCO A**		**HCO B**		**HCO C**		**HCO D**		**HCO E**	
SBP	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%
<120	114,144	20.0%	24,476	20.7%	4,899	20.5%	20,481	23.6%	12,819	14.5%	51,469	20.4%
120-130	145,634	25.6%	31,101	26.3%	5,212	21.8%	20,299	23.4%	16,257	18.4%	72,765	28.8%
130-140	159,158	27.9%	36,421	30.8%	6,634	27.8%	23,790	27.4%	25,771	29.1%	66,542	26.3%
140-150	80,722	14.2%	14,215	12.0%	3,301	13.8%	10,352	11.9%	16,290	18.4%	36,564	14.5%
150-160	36,889	6.5%	6,831	5.8%	1,815	7.6%	6,289	7.3%	7,827	8.8%	14,127	5.6%
160-170	18,529	3.3%	3,124	2.6%	953	4.0%	3,027	3.5%	4,388	5.0%	7,037	2.8%
170+	14,890	2.6%	1,948	1.6%	1,046	4.4%	2,486	2.9%	5,150	5.8%	4,260	1.7%

Table 3. Diastolic Blood Pressure Distribution

Total	**HCO A**	**HCO B**	**HCO C**	**HCO D**	**HCO E**

DBP	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%
<70	123,789	21.7%	25,267	21.4%	4,027	16.9%	13,416	15.5%	37,628	42.5%	43,451	17.2%
70-80	192,388	33.8%	39,737	33.6%	6,313	26.5%	31,478	36.3%	28,191	31.9%	86,669	34.3%
80-90	191,928	33.7%	40,802	34.5%	8,184	34.3%	31,911	36.8%	16,192	18.3%	94,839	37.5%
90-100	47,018	8.2%	9,237	7.8%	3,459	14.5%	7,383	8.5%	5,128	5.8%	21,811	8.6%
100-110	11,316	2.0%	2,389	2.0%	1,263	5.3%	1,758	2.0%	1,017	1.1%	4,889	1.9%
110+	3,527	0.6%	684	0.6%	614	2.6%	778	0.9%	346	0.4%	1,105	0.4%

Encounter summaries and descriptive statistics for the aggregated dataset and by HCO are included in Table 4. For 813,465 total encounters in the dataset, BP was measured at 569,966 encounters. On average, each patient had 4.7 BP encounters, which ranged from 4.0-6.2 by HCO. There were 168,222 encounters where the patient's BP was uncontrolled (29.5% of all BP encounters). Before the applying study criteria B (minimum of 1 uncontrolled visit), each patient had 1.4 encounters with uncontrolled BP readings. Only 9.7% of encounters with uncontrolled BP readings had confirmatory BP measurements taken, with HCO B having the highest percentage of confirmatory BP measurements taken (26.3%). Most of the encounters included in this analysis were with the patient's primary clinician 79.8%. This was consistent across all HCOs with 72-86% of visits being with the patient's primary clinician. Clinician continuity was also high; 71.7% of all encounters were with the same clinician as the patient's previous encounter.

Table 4. Summary of Blood Pressure Encounters

	Total	HCO A	HCO B	HCO C	HCO D	HCO E
Total Patients	120,755	28,847	4,613	13,915	22,311	51,069
Total Encounters	813,465	146,431	28,814	233,542	129,560	275,118
BP Encounters	569,966	118,116	23,860	86,724	88,502	252,764
BP Encounters per patient	4.7	4.1	5.2	6.2	4.0	4.9
Uncontrolled BP Encounters	168,222	30,002	9,028	24,263	34,863	70,066

Uncontrolled BP Encounters (%)	29.5%	25.4%	37.8%	28.0%	39.4%	27.7%
Uncontrolled BP per Patient	1.4	1.0	2.0	1.7	1.6	1.4
Confirmatory BP Measurements (%)	9.7%	19.0%	26.3%	7.9%	9.4%	4.7%
Encounters with Primary Clinician (%)	79.8%	73.8%	76.8%	80.9%	72.0%	85.9%
Encounters with Same Clinician as Previous (%)	71.7%	61.2%	70.9%	76.0%	62.2%	78.2%

Table 5 presents rates of therapeutic intensification and therapeutic inertia, and intensification type (dose increase or class addition) overall and by HCO. Cases where patients receive a new medication class are labeled “first class additions” and are subtracted from class additions to provide a distinct rate of “class intensifications” for direct comparison to dose increases that can only occur for patients that are already on at least one medication. Average therapeutic intensification rate was 15.9%, with the highest rate occurring in HCO D (19.5%) and lowest at HCO E (13.3%). This corresponds to an overall therapeutic intensification rate of 84.1%. Therapeutic inertia was fairly consistent between all five HCOs. Observed therapeutic inertia rate ranged from 86.7% (HCO E) to 80.5% (HCO D). Dose increase rate was 6.6%, with the highest rate occurring in HCO E (12.6%). Class addition rate was 12.0%, with the highest rate occurring in HCO A (14.6%). However, 24% of class additions were for a patients first recorded AH medication. Removing first class additions left an overall class intensification rate of 9.2% for comparison with the 6.6% dose increase rate.

Table 5. Summary of Therapeutic Intensification and Therapeutic Inertia

	Total	**HCO A**	**HCO B**	**HCO C**	**HCO D**	**HCO E**
Uncontrolled Encounters	168,222	30,002	9,028	24,263	34,863	70,066
Therapeutic Intensification Events	26,669	5,496	1,631	3,417	6,798	9,327
Therapeutic Intensification Rate	15.9%	18.3%	18.1%	14.1%	19.5%	13.3%
Therapeutic Inertia Events	141,553	24,506	7,397	20,846	28,065	60,739
Therapeutic Inertia Rate	84.1%	81.7%	81.9%	85.9%	80.5%	86.7%

Dose Increases	11,059	2,010	743	1,592	4,396	2,318
Dose Increase Rate	6.6%	6.7%	8.2%	6.6%	12.6%	3.3%
Class Additions	20,158	4,371	1,138	2,347	3,814	8,488
Class Addition Rate	12.0%	14.6%	12.6%	9.7%	10.9%	12.1%
First Class Additions	4,757	1,050	168	453	543	2,543
First Class Addition Rate	2.8%	3.5%	1.9%	1.9%	1.6%	3.6%
Class Intensifications	15,401	3,321	970	1,894	3,271	5,945
Class Intensification Rate	9.2%	11.1%	10.7%	7.8%	9.4%	8.5%

Therapeutic Intensification Modeling

Univariate and multiple variables logistic regression results for modeling therapeutic intensification events are included in Tables 6-8. The odds ratios and p-values for each variable are presented, along with the marginal R^2 (variance explained by fixed effects only) and conditional R^2 values (variance explained by fixed and random effects together). Since separate blood pressure thresholds for SBP and DBP were used to define "uncontrolled visits" as part of the inclusion criteria for visits that could be considered either therapeutic inertia or intensification (SBP>140 or DBP>90), Table 6 provides the

results of univariate analysis of SBP and DBP at the current visit before limiting the dataset to only include uncontrolled visits. This provides an unbiased interpretation of the effect of SBP/DBP measurements on likelihood of therapeutic intensification because all visits with SBP<140 must have a DBP>90 and all visits with DBP<90 must have an SBP>140 to meet the inclusion criteria for the modeling uncontrolled visits. The bias is most present for the BP groups below and right above the threshold (SBP<120, SBP 120-130, SBP 130-140, and SBP 140-150 / DBP <70, DBP 70-80, and DBP 80-90) in Table 7A and Table 8. The adjusted multiple linear regression model results for time to therapeutic intensification are presented in Table 9. The full regression outputs for each univariate and multiple variable models produced for therapeutic intensification events and time to therapeutic intensification analyses are included in Appendix II and Appendix III, respectively.

Table 6 shows the results of univariate mixed-effects modeling of therapeutic intensification with systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the current visit, for all visits whether controlled or uncontrolled. The table shows the odds ratio and p-values for each SBP and DBP category, as well as the marginal and conditional R2 values. The results indicate that as SBP increases from <120 to 170+, the odds of therapeutic intensification increase from 0.79 to 2.93 in reference to the 130-140 group, with a significant p-value of <2E-16 for each SBP group. Similarly, as DBP increases from <70 to 110+, the odds of therapeutic intensification increase from 0.86 to 1.85 in reference to the 80-90 mmHg group. All DBP groups were statistically significant to <1E-12. These findings indicate that SBP and DBP at the current visit are important predictors of therapeutic intensification in this population. Table 7A presents the results of univariate and multiple regression mixed-effects modeling of therapeutic intensification with SBP and DBP at current and previous visits. For current visit SBP, odds ratios were statistically significant and increased as SBP increased, ranging from 0.60133 for SBP <120 to 2.34966 for SBP 170+, in reference to SBP 130-140. For current visit DBP, odds ratios were statistically significant and increased as DBP increased, ranging from 0.84835 for DBP <70 to 1.81223 for DBP 110+. For previous

visit SBP and DBP, odds ratios were statistically significant and increased as SBP/DBP increased, in reference to DBP 80-90. Multiple regression analysis showed that the inclusion of both current and previous SBP/DBP improved the model's R^2 values, indicating that both current and previous BP values are considered by clinicians when deciding whether or not to increase therapy. Table 7B presents the results of univariate and multiple regression mixed-effects modeling of therapeutic intensification with cumulative average and standard deviation of SBP and DBP. cumulative SBP average and cumulative DBP average were both significantly associated with therapeutic intensification with odds ratios of 1.02 for both SBP and DBP when adjusting for standard deviation of each. Additionally, cumulative SBP and DBP had a similar R2 (0.086) to that of the current SBP and DBP (0.089).

Table 7C presents the results of univariate mixed-effects modeling of therapeutic intensification with patient demographics. The reference categories for sex and age were male sex and age 30-40. The results show that being female is associated with a slightly higher odds ratio for therapeutic intensification, while being of a non-white race is associated with a lower odds ratio. Age is also a significant factor, with increasing age being associated with a lower odds ratio for therapeutic intensification. While the odds ratios were statistically significant for sex, race, and age, the marginal R^2 values were very small, ranging from 0.00062 to 0.00742, with age explaining the most variance in intensification of the three demographic variables.

Table 7D shows the results of univariate mixed-effects modeling of therapeutic intensification with encounter attributes and AH medications. Visit related variables explained the most amount of variance and therapeutic intensification with BP visit frequency, days since last BP visit, and total BP visits having the highest marginal R-squared values (0.044, 0.0209, and 0.0204, respectively). Greater BP visits frequency and counts were associated with lower odds of intensification (0.535 and 0.945), while longer intervals since the most previous visit with BP was linked to greater odds of intensification. Confirmatory blood pressure measurement explained the third most variance in intensification (0.011) followed by

proportion of uncontrolled visits (0.0103). The odds of therapeutic intensification decreased incrementally as patients were on increasing counts of AH medications. Patients currently on 1 AH medication were associated with 0.12 less odds of intensification compared to patients on no AH medications. Patients with four or more current AH medications had 0.35 lower odds of intensification compared to patients on no AH medications. The marginal R^2 for current AH medication count was 0.0053.

Table 7E presents the results of univariate mixed-effects modeling of therapeutic intensification with patient comorbidities and lab measurements. The comorbidities with a statistically significant association with therapeutic intensification from the univariate analysis included diabetes with complications, congestive heart failure, cardiac arrhythmia, peripheral vascular disease, renal failure, solid tumor cancer, myocardial infarction, cerebral vascular disease, and dementia. All of the comorbidities had an odds ratio of less than one indicating that the presence of each of these comorbidities decreased the odds of therapeutic intensification. The total sum count of comorbidities included in this analysis explained more variance in therapeutic intensification than any single comorbidity on its own and was associated with 3.2% lower odds of intensification (marginal R^2 = 0.0017, OR = 0.968)

Table 8 presents the results of the multiple variable mixed-effects modeling of therapeutic intensification. The variables analyzed included those that were found statistically significant and had a marginal R^2 greater than 0.0001: SBP , DBP , Previous Visit SBP , Previous Visit DBP , Cumulative SBP Average , Cumulative DBP Average , Cumulative SBP Std. Deviation , Cumulative DBP Std. Deviation , Current AH Meds , Proportion of Uncontrolled Visits , Previous TI Event , Visit with Primary Physician , Encounter BP Count , BP Visits Frequency , Congestive Heart Failure , Peripheral Vascular Disease , Cardiac Arrhythmia , Cerebral Vascular Disease , Renal Failure , Age , Sex , White vs. Non-white , LDL , BMI , and Total Comorbidities. After the model adjust for the effect of each of these variables through

multiple regression, the following variables remained significant: SBP , DBP , Previous Visit SBP , Previous Visit DBP , Cumulative SBP Average , Cumulative SBP Std. Deviation , Cumulative DBP Std. Deviation , Current AH Meds , Proportion of Uncontrolled Visits , Previous TI Event , Visit with Primary Physician , Encounter BP Count , BP Visits Frequency , Congestive Heart Failure , Cerebral Vascular Disease , Renal Failure , Age 80+ , White vs. Non-white race, BMI , and Total Comorbidities. The final multiple variable model was able to explain 12.7% of the variance in therapeutic intensification from the fixed effects and 13.2% by including random intercepts for both patient and clinician clustered observations.

Table 9 presents the results of a multiple variable mixed-effects modeling analysis of time to therapeutic intensification for a range of variables. The results are comparable to the TI event analysis in statistical significance and variance explained, but this model used multiple linear regression as opposed to logistic regression since the outcome of days until TI was a continuous variable, so the magnitude of the coefficients is on a different scale. Like in the previously described logit model, SBP, previous SBP, cumulative DBP, current AH medications of two or more, proportion of uncontrolled visits, previous TI event encounter BP confirmatory measurement, BP visit frequency, age 80-90 and 90+, and total comorbidities were all found to be statistically significant in relation to time to intensification. In contrast to the TI event multiple variable model, current or previous DBP were not statistically. The presence of specific comorbidities, age, sex, race, and laboratory measurements were also not significant in this model. Expectedly, greater current and previous SBP was associated with less time until intensification. As the number of currently prescribed AH medications went up so did the time to intensification. Interestingly, the proportion of uncontrolled visits and BP visit frequency were associated with more time to intensification. Finally, while total comorbidities was associated with a slightly lower odds of intensification in the previous multiple variable model, total comorbidities in this model was associated with less time to intensification.

Table 6. Univariate Mixed-Effects Modeling of Therapeutic Intensification with SBP and DBP at Current Visit (All visits; controlled or uncontrolled)

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
SBP <120	0.78666	<2E-16	0.019047	0.107559
SBP 120-130	0.87283	<2E-16		
SBP 140-150	1.58911	<2E-16		
SBP 150-160	2.15168	<2E-16		
SBP 160-170	2.51207	<2E-16		
SBP 170+	2.92578	<2E-16		
DBP <70	0.85835	<2E-16		
DBP 70-80	0.91648	9.13E-13		
DBP 90-100	1.33763	<2E-16		
DBP 100-110	1.65802	<2E-16		
DBP 110+	1.85226	<2E-16		

Table 7A. Univariate and Multiple Regression Mixed-Effects Modeling of Therapeutic Intensification with SBP and DBP at Current and Previous Visits

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
SBP <120	0.60133	0.00098	0.02815	0.08902
SBP 120-130	0.79331	0.00028		
SBP 130-140 (Reference)	1.00000	--		
SBP 140-150	1.25880	3.45E-11		
SBP 150-160	1.71536	<2E-16		
SBP 160-170	2.01162	<2E-16		
SBP 170+	2.34966	<2E-16		
DBP <70	0.84835	1.13E-08		
DBP 70-80	0.93849	0.00247		
DBP 80-90 (Reference)	1.00000	--		

DBP 90-100	1.25241	<2E-16		
DBP 100-110	1.60413	<2E-16		
DBP 110+	1.81223	<2E-16		
Previous Visit SBP <120	0.81141	2.22E-10	0.01584	0.07769
Previous Visit SBP 120-130	0.85965	5.50E-10		
Previous Visit SBP 130-140 (Reference)	1.00000	--		
Previous Visit SBP 140-150	1.15987	6.60E-12		
Previous Visit SBP 150-160	1.28501	<2E-16		
Previous Visit SBP 160-170	1.28191	1.49E-15		
Previous Visit SBP 170+	1.37308	<2E-16		
Previous Visit DBP <70	0.88000	1.16E-07		
Previous Visit DBP 70-80	0.93246	0.00028		
Previous Visit DBP 80-90 (Reference)	1.00000	--		
Previous Visit DBP 90-100	1.21989	<2E-16		
Previous Visit DBP 100-110	1.37656	<2E-16		
Previous Visit DBP 110+	1.35313	1.48E-06		
Multiple Variable Regression: Current & Previous SBP / DBP	See Appendix 1	See Appendix 1	0.03573	0.09877

Table 7B. Univariate and Multiple Regression Mixed-Effects Modeling of Therapeutic Intensification with Cumulative Average and Standard Deviation of SBP and DBP

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
Cumulative SBP Average	1.01824	<2E-16	0.02323	0.08628
Cumulative DBP Average	1.01679	<2E-16		
Cumulative SBP Std. Deviation	1.01322	1.47E-10	0.00488	0.06324
Cumulative DBP Std. Deviation	1.02131	9.54E-10		
Cumulative SBP Average	1.01625	<2E-16	0.02508	0.07718
Cumulative DBP Average	1.02019	<2E-16		
Cumulative SBP Std. Deviation	1.00674	0.00190		
Cumulative DBP Std. Deviation	1.00925	0.00935		

Table 7C. Univariate Mixed-Effects Modeling of Therapeutic Intensification with Patient Demographics

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
Sex (Reference: Male)	1.09965	1.05E-09	0.00062	0.06918
Race (Reference: White)	0.84599	<2E-16	0.00198	0.06949
Age <30	0.88715	0.12053	0.00742	0.07310
Age 30-40 (Reference)	1.00000	--		
Age 40-50	0.98216	0.63947		
Age 50-60	0.91667	0.01581		
Age 60-70	0.84293	1.36E-06		
Age 70-80	0.73960	<2E-16		
Age 80-90	0.59114	<2E-16		
Age 90+	0.46008	<2E-16		

Table 7D. Univariate Mixed-Effects Modeling of Therapeutic Intensification with Encounter Attributes and AH Medications

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
Proportion of Uncontrolled Visits	1.99896	<2E-16	0.01033	0.07671
Current AH Meds 0 (Reference)	1.00000	--	0.00529	0.08213
Current AH Meds 1	0.88752	1.51E-07		
Current AH Meds 2	0.78887	<2E-16		
Current AH Meds 3	0.73035	<2E-16		
Current AH Meds 4+	0.64778	<2E-16		
BP Visits	0.94545	<2E-16	0.02038	0.06813
BP Visits Per 100 Days	0.53526	<2E-16	0.04394	0.08994
Days Since Previous BP	1.00205	<2E-16	0.02087	0.07528
Days Since Previous Uncontrolled BP	1.00051	<2E-16	0.00246	0.07286
Encounter BP Count	1.55642	<2E-16	0.01109	0.07443
Same Previous Clinician	1.20766	<2E-16	0.00212	0.06993
Proportion of Visits with Primary Physician	1.24171	7.05E-10	0.00065	0.06907
Visit with Primary Physician	1.55850	<2E-16	0.00981	0.07798
Previous TI Event	1.04282	0.01402	0.00009	0.06405

Days Since Previous TI	0.99907	1.42E-15	0.00417	0.06991

Table 7E. Univariate Mixed-Effects Modeling of Therapeutic Intensification with Patient Comorbidities and Lab Measurements

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
Diabetes	0.97795	0.16738	0.00003	0.06910
Diabetes with Complications	0.96483	0.06139	0.00006	0.06905
Congestive Heart Failure	0.82764	3.17E-08	0.00057	0.06929
Cardiac Arrhythmia	0.80454	<2E-16	0.00159	0.06943
Peripheral Vascular Disease	0.81000	1.82E-11	0.00085	0.06933
Renal Failure	0.89150	2.16E-06	0.00040	0.06944
Liver Disease	0.95078	0.13533	0.00004	0.06903
Solid Tumor	0.93489	0.02554	0.00009	0.06916
Metastatic Cancer	0.95652	0.50783	0.00001	0.06908
Myocardial Infarction	0.84113	0.00182	0.00018	0.06913
Cerebral Vascular Disease	0.81219	1.05E-11	0.00086	0.06925
Dementia	0.64365	7.91E-11	0.00093	0.06957
Total Comorbidities	0.96771	<2E-16	0.00173	0.06893
BMI (kg/m^2)	1.00826	<2E-16	0.00134	0.07068
HbA1c (mmols/mol)	0.99708	0.60137	0.00001	0.06825
Glucose (mg/dL)	1.00001	0.95582	0.00000	0.07057
LDL (mg/dL)	1.00213	<2E-16	0.00175	0.06820
HDL (mg/dL)	0.99816	0.00103	0.00024	0.06685
Total Cholesterol (mg/dL)	0.99981	0.25535	0.00003	0.06913

Table 8. Multiple Variable Mixed-Effects Modeling of Therapeutic Intensification

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
SBP <120	0.60806	0.08622	0.12749	0.13237
SBP 120-130	0.96791	0.76022		
SBP 140-150	1.29555	2.80E-05		
SBP 150-160	1.71655	2.59E-16		
SBP 160-170	1.82953	7.62E-16		
SBP 170+	1.98925	1.38E-14		
DBP <70	0.98317	0.79676		
DBP 70-80	0.98363	0.69076		
DBP 90-100	1.20794	2.70E-06		
DBP 100-110	1.41276	1.02E-07		
DBP 110+	1.82126	2.25E-07		
Previous Visit SBP <120	0.85813	0.01466		
Previous Visit SBP 120-130	0.87572	0.00183		
Previous Visit SBP 140-150	1.22860	1.07E-06		
Previous Visit SBP 150-160	1.33259	2.42E-08		
Previous Visit SBP 160-170	1.17547	0.01233		
Previous Visit SBP 170+	1.16835	0.05076		
Previous Visit DBP <70	0.89641	0.05929		
Previous Visit DBP 70-80	0.97345	0.46812		
Previous Visit DBP 90-100	1.10562	0.02534		
Previous Visit DBP 100-110	1.27599	0.00114		
Previous Visit DBP 110+	1.07298	0.60839		
Cumulative SBP Average	1.01041	0.00035		
Cumulative DBP Average	0.99648	0.34945		
Cumulative SBP Std. Deviation	1.00571	0.04346		
Cumulative DBP Std. Deviation	1.00958	0.03428		
Current AH Meds 1	0.81739	1.56E-07		
Current AH Meds 2	0.67291	<2E-16		
Current AH Meds 3	0.59452	<2E-16		
Current AH Meds 4+	0.47822	<2E-16		
Proportion of Uncontrolled Visits	0.58862	7.38E-08		
Previous TI Event	1.26122	2.06E-12		
Visit with Primary Physician	1.80886	<2E-16		
Encounter BP Count	1.58365	<2E-16		

BP Visits Per 100 Days	0.47035	<2E-16
Congestive Heart Failure	0.76606	0.00133
Peripheral Vascular Disease	0.95704	0.48997
Cardiac Arrhythmia	0.92927	0.09930
Cerebral Vascular Disease	0.85277	0.00893
Renal Failure	1.03516	0.49888
Age <30	1.20820	0.22358
Age 40-50	1.14613	0.07023
Age 50-60	1.11004	0.14784
Age 60-70	0.99980	0.99778
Age 70-80	0.89374	0.14523
Age 80-90	0.70493	0.00011
Age 90+	0.50453	8.78E-05
Male Sex	1.01724	0.54334
Percent White Race	0.85818	1.09E-07
LDL	1.00048	0.20483
BMI	1.00864	2.33E-06
Total Comorbidities	1.02666	0.00534

Table 9. Multiple Variable Mixed-Effects Modeling of Time to Therapeutic Intensification

Variable	Estimate	p-value	R^2 Marginal	R^2 Conditional
SBP <120	50.6885	0.00840	0.10292	0.14881
SBP 120-130	4.4538	0.56659		
SBP 140-150	-8.4889	0.06400		
SBP 150-160	-23.5082	1.94E-06		
SBP 160-170	-26.3562	2.61E-06		
SBP 170+	-36.8449	4.71E-08		
DBP <70	-16.9715	0.00067		
DBP 70-80	-6.1234	0.04921		
DBP 90-100	-7.3266	0.01493		
DBP 100-110	-8.9631	0.06586		
DBP 110+	-18.4382	0.03442		

Previous Visit SBP <120	8.4149	0.06655
Previous Visit SBP 120-130	7.3958	0.01857
Previous Visit SBP 140-150	-21.1349	1.74E-11
Previous Visit SBP 150-160	-25.8601	1.66E-11
Previous Visit SBP 160-170	-25.8222	8.34E-08
Previous Visit SBP 170+	-24.9594	2.95E-05
Previous Visit DBP <70	0.2116	0.96094
Previous Visit DBP 70-80	-2.1074	0.44794
Previous Visit DBP 90-100	-2.2192	0.50469
Previous Visit DBP 100-110	3.0662	0.58475
Previous Visit DBP 110+	-10.4542	0.32496
Cumulative SBP Average	-0.2977	0.18072
Cumulative DBP Average	-0.6442	0.02558
Cumulative SBP Std. Deviation	0.0518	0.81890
Cumulative DBP Std. Deviation	0.0335	0.92594
Current AH Meds 1	4.2310	0.13394
Current AH Meds 2	7.0770	0.02294
Current AH Meds 3	13.6612	0.00031
Current AH Meds 4+	9.2316	0.04830
Proportion of Uncontrolled Visits	96.6283	<2E-16
Previous TI Event	-72.8344	<2E-16
Encounter BP Count	-23.4712	<2E-16
BP Visits Per 100 Days	45.4068	<2E-16
Congestive Heart Failure	2.3751	0.73201
Cardiac Arrhythmia	-2.3685	0.50096
Peripheral Vascular Disease	3.0759	0.54447
Cerebral Vascular Disease	0.6839	0.88521
Renal Failure	-0.1378	0.97334
Age <30	-10.6837	0.37989
Age 40-50	-6.5316	0.24992
Age 50-60	-0.5225	0.92331
Age 60-70	8.8865	0.10637
Age 70-80	10.7750	0.06418
Age 80-90	17.2286	0.01244
Age 90+	40.4256	0.00184
Sex: Male	-0.4815	0.82586
Race: White	3.8462	0.08451
LDL	-0.0333	0.26147
BMI	0.1218	0.39628
Total Comorbidities	-6.0983	8.26E-16

Cox Regression for Time to Therapeutic Intensification

Cox regression was used to model the likelihood of therapeutic intensification over time since each patient's first uncontrolled BP measurement. Time was calculated as the number days between each patient's first uncontrolled BP measurement and the first subsequent therapeutic intensification (event) or the patient's last recorded visit in the study period if no TI was observed (censored). The covariates that explained the most variance in time to therapeutic intensification through univariate analysis were cumulative number of visits with BP measurement, previous therapeutic intensification event, SBP and DBP at the current visit, BP visit frequency, current number of AH medications, average SBP and DBP, visits with the patient's primary physician, total comorbidities, and patient age. All other covariates explained less than 1% of the variance in odds of therapeutic intensification over time. Only SBP greater than 140 and DBP greater than 90 were associated with higher likelihood of intensification over time. Only previous visit SBP of 170+ and DBP of 90+ were associated with higher odds of TI over time, with much less magnitude and variance explained compared to current visit BP. Greater visit frequency, cumulative number of visits, previous therapeutic intensification, number of existing AH medications, total comorbidities, and patient age were all associated with a lower likelihood of intensification over time. Hazard ratios and R2 estimates for the univariate analysis of significant covariates of therapeutic intensification over time are included in *Table 1*. Adjustment for statistically significant covariates in a multivariable cox regression model explained 38.1% of the variance in TI over time. Adjusted hazard ratios from multivariable model estimation are included in *Table 2*. The density plot of therapeutic intensification events over the number of days since the first uncontrolled BP measurement in the study period is illustrated in *Figure 1*.

Table 1. Univariate Estimation of Covariate Relationship with Likelihood of TI Over Time.

Covariate	Hazard Ratio	p-value	R2
Cumulative Visit Count	-0.17	<2E-16	0.2595

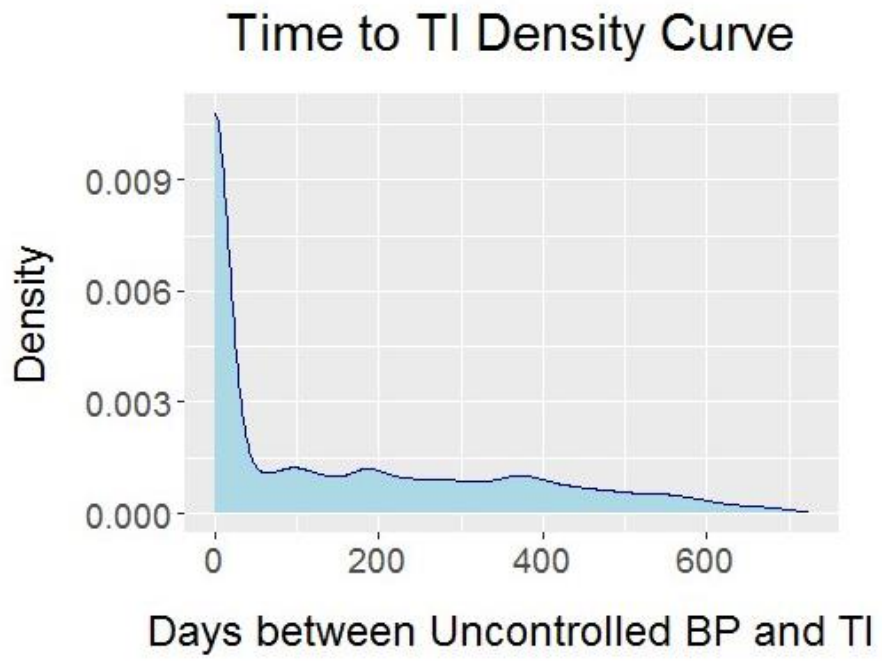
Previous TI Event	-1.58	<2E-16	0.2564
SBP <120	-0.55	2.55E-04	
SBP 120-130	-0.26	1.83E-05	
SBP 140-150	0.17	2.73E-08	
SBP 150-160	0.44	1.55E-42	
SBP 160-170	0.58	6.58E-66	
SBP 170+	0.74	4.95E-99	0.0814
DBP <70	-0.19	1.79E-12	
DBP 70-80	-0.07	3.72E-04	
DBP 90-100	0.19	8.70E-23	
DBP 100-110	0.36	1.01E-42	
DBP 110+	0.37	5.50E-19	
Visit Frequency	-0.58	7.53E-267	0.0621
1 Existing AH Med	-0.35	7.88E-74	
2 Existing AH Meds	-0.48	1.12E-129	0.0499
3 Existing AH Meds	-0.58	4.38E-141	
4+ Existing AH Meds	-0.73	8.97E-186	
SBP Average	0.01	3.83E-106	0.0376
DBP Average	0.01	1.15E-37	
Visit with Primary Physician	0.45	1.52E-136	0.0308
Previous Visit SBP <120	-0.15	6.55E-07	
Previous Visit SBP 120-130	-0.10	4.27E-06	
Previous Visit SBP 140-150	-0.10	2.27E-07	
Previous Visit SBP 150-160	0.03	2.43E-01	
Previous Visit SBP 160-170	0.01	6.41E-01	
Previous Visit SBP 170+	0.11	4.44E-04	0.0173
Previous Visit DBP <70	-0.17	1.56E-14	
Previous Visit DBP 70-80	-0.10	5.44E-08	
Previous Visit DBP 90-100	0.07	4.26E-04	
Previous Visit DBP 100-110	0.17	9.47E-07	
Previous Visit DBP 110+	0.18	1.02E-03	
Age <30	-0.06	3.08E-01	
Age 40-50	0.00	9.10E-01	
Age 50-60	-0.04	2.25E-01	
Age 60-70	-0.10	9.09E-04	0.0159
Age 70-80	-0.23	1.36E-13	
Age 80-90	-0.42	1.34E-28	
Age 90+	-0.63	1.38E-16	
Total Comorbidities	-0.05	2.19E-66	0.0144

Table 2. Multivariable Model of Covariates and Likelihood of TI Over Time.

Covariate	Hazard Ratio	p-value	R2
SBP <120	-0.57	4.50E-02	
SBP 120-130	-0.07	5.02E-01	
SBP 140-150	0.18	9.95E-04	
SBP 150-160	0.39	4.70E-11	
SBP 160-170	0.43	8.59E-11	
SBP 170+	0.44	1.67E-08	
DBP <70	-0.11	6.61E-02	
DBP 100-110	0.35	1.29E-09	
DBP 110+	0.39	5.55E-05	
DBP 70-80	-0.02	6.87E-01	
DBP 90-100	0.21	4.33E-09	
Previous Visit SBP <120	-0.05	3.94E-01	
Previous Visit SBP 120-130	-0.09	2.56E-02	
Previous Visit SBP 140-150	-0.04	3.49E-01	
Previous Visit SBP 150-160	0.04	3.63E-01	
Previous Visit SBP 160-170	-0.01	9.29E-01	
Previous Visit SBP 170+	-0.06	4.28E-01	
Previous Visit DBP <70	-0.17	1.38E-03	
Previous Visit DBP 70-80	-0.07	4.22E-02	
Previous Visit DBP 90-100	0.06	1.58E-01	0.3813
Previous Visit DBP 100-110	0.09	1.63E-01	
Previous Visit DBP 110+	0.22	5.49E-02	
Cumulative SBP Average	0.02	9.67E-15	
Cumulative DBP Average	-0.01	2.58E-04	
Cumulative SBP Std. Deviation	0.00	2.52E-01	
Cumulative DBP Std. Deviation	0.01	1.82E-01	
Current AH Meds 1	-0.15	2.30E-06	
Current AH Meds 2	-0.28	1.37E-15	
Current AH Meds 3	-0.33	4.46E-14	
Current AH Meds 4+	-0.46	9.63E-16	
Proportion of Uncontrolled Visits	-1.30	1.76E-44	
Previous TI Event	-1.51	1.12E-241	
Encounter BP Count	0.15	1.51E-07	
Visit Frequency	-0.39	1.10E-27	
Congestive Heart Failure	-0.13	1.09E-01	
Cardiac Arrhythmia	-0.13	2.17E-03	
Peripheral Vascular Disease	-0.03	6.00E-01	
Cerebral Vascular Disease	-0.08	1.88E-01	
Renal Failure	0.08	1.11E-01	

Age <30	0.05	6.95E-01
Age 40-50	0.13	4.67E-02
Age 50-60	0.10	1.04E-01
Age 60-70	0.04	4.92E-01
Age 70-80	-0.05	4.65E-01
Age 80-90	-0.31	1.00E-04
Age 90+	-0.59	5.04E-04
Male Sex	0.03	2.00E-01
Percent White Race	-0.10	9.53E-05
LDL	0.00	1.65E-02
BMI	0.01	1.22E-09
Total Comorbidities	-0.02	7.78E-03

Figure 1. Frequency of TI over time since first uncontrolled BP for each patient (days)



Time to Therapeutic Intensification and BP Reduction

The time between uncontrolled BP measurements and clinical action through therapeutic intensification showed slight variation in subsequent BP reduction after intensification. Figure 1 shows the frequency of TI events over the number of days since the most recent uncontrolled BP measurement preceding each TI event. Most TI events occur within a month of uncontrolled BP visits, with spikes around 180 days and 365 days. The median and mean number of days between uncontrolled BP and TI were 189 days and 218.6 days, respectively. Table 3 shows the average SBP reduction following TI that occurs within 1-month, 1-3 months, 3-6 months, 6-12 months, and a year or more since the most recent uncontrolled BP. TI that occurred within one month of uncontrolled BP measurements resulted in the greatest reduction in SBP and DBP compared to later TI events. Multivariable regression adjusting for patient age, sex, race, and current visit SBP found a statistically significant relationship between time to TI and greater subsequent BP reduction, however the magnitude was very small (0.003 mmHg).

Figure 1. Density of TI events over days since the most recent uncontrolled BP measurement.

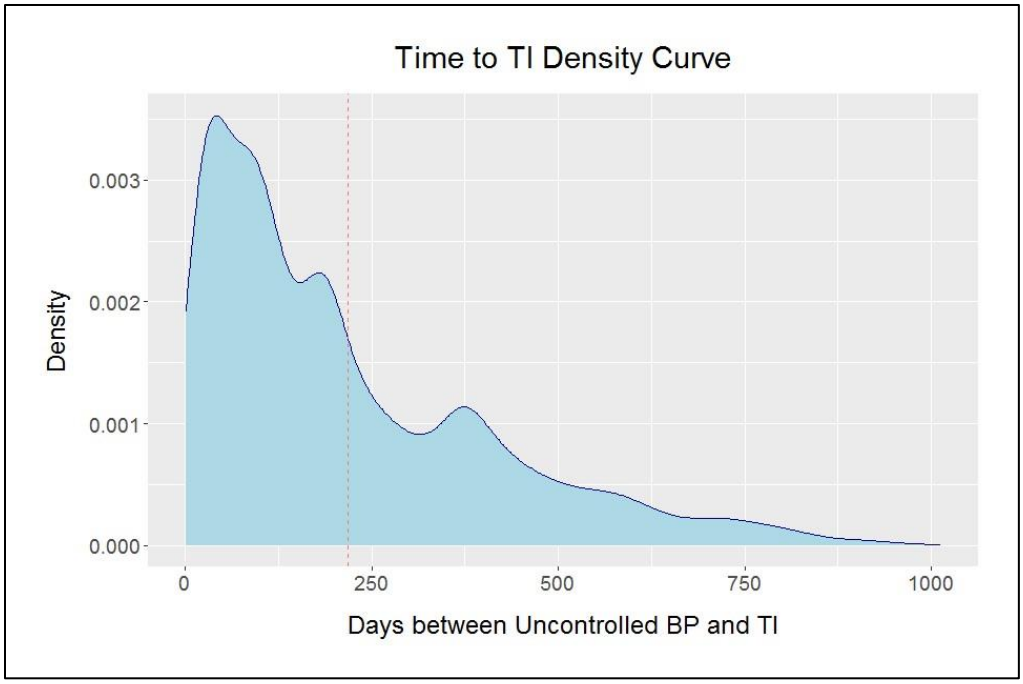


Figure 2. Density of TI events over days since the most recent uncontrolled BP measurement for within the first 250 days.

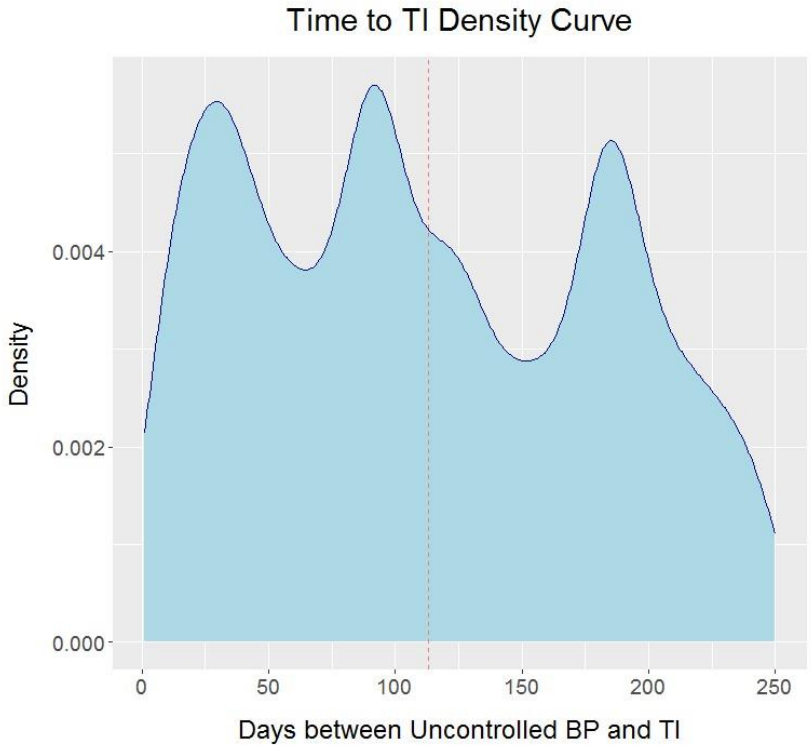


Table 3. Average BP Reduction after TI within 1-month, 1-3 months, 3-6 months, 6-12 months, and a year or more since the most recent uncontrolled BP.

Time to TI	Count	ΔSBP after TI	ΔDBP after TI
<30 days	1,205	-14.5	-6.5
30-90 days	2,101	-12.7	-5.8
90-180 days	2,790	-12.7	-5.3
180-365 days	3,659	-12.3	-5.8
>365 days	3,579	-13.8	-6.5
Total	**13,334**	**-13.1**	**-5.9**

Table 4. Multivariable Regression Estimation of Relationship between Time to TI and BP Reduction.

term	estimate	std.error	statistic	p.value
(Intercept)	77.8	1.76	44.3	<2E-16
Days since previous uncontrolled BP	-0.00324	0.000817	-3.97	0.0000738
TI Visit SBP	-0.613	0.011	-55.8	<2E-16
Sex: Male	0.808	0.318	2.54	0.0112
Race: White	-1.86	0.319	-5.84	5.43E-09
Age	0.071	0.0117	6.06	1.45E-09

Predictive Modeling Results

Random Forest Models

In this study, we developed and tested four random forest models for predicting therapeutic inertia vs. intensification. Each models used a different resampling technique for handling class imbalance: oversampling, SMOTE, ROSE, and undersampling. The optimal value for the "mtry" parameter was determined to be a value of 1 using gridsearch to test models using mtry values of 1-10. Cross-validated test accuracy for each gridsearch model is plotted in Figure 3. Table 10A presents the evaluation metrics for the oversampling model, which had a sensitivity of 0.7, specificity of 0.531, balanced accuracy of 0.616, and an AUC of 0.616. Table 10B shows the evaluation metrics for the SMOTE model, which had a sensitivity of 0.965, specificity of 0.113, balanced accuracy of 0.539, and an AUC of 0.54. Table 10C presents the evaluation metrics for the ROSE model, which had the same sensitivity and specificity as the oversampling model, as well as similar values for the other evaluation metrics. Finally, Table 10D shows the evaluation metrics for the undersampling model, which had a sensitivity of 0.602, specificity of 0.639, balanced accuracy of 0.621, and an AUC of 0.621.

The undersampling model performed the best in terms of AUC-ROC, with an estimated test AUC slightly higher than the oversampling and ROSE models. The SMOTE model was substantially less powerful in predicting inertia vs. intensification on the test dataset. AUC-ROC curves for training prediction compared to test prediction for each resampling method random forest (RF) model are plotted in Figure 4. Test AUC-ROC curves are plotted together for the four RF models in Figure 5 for comparison.

Figure 3. Gridsearch Results for Random Forest Model "mtry" Parameter Tuning

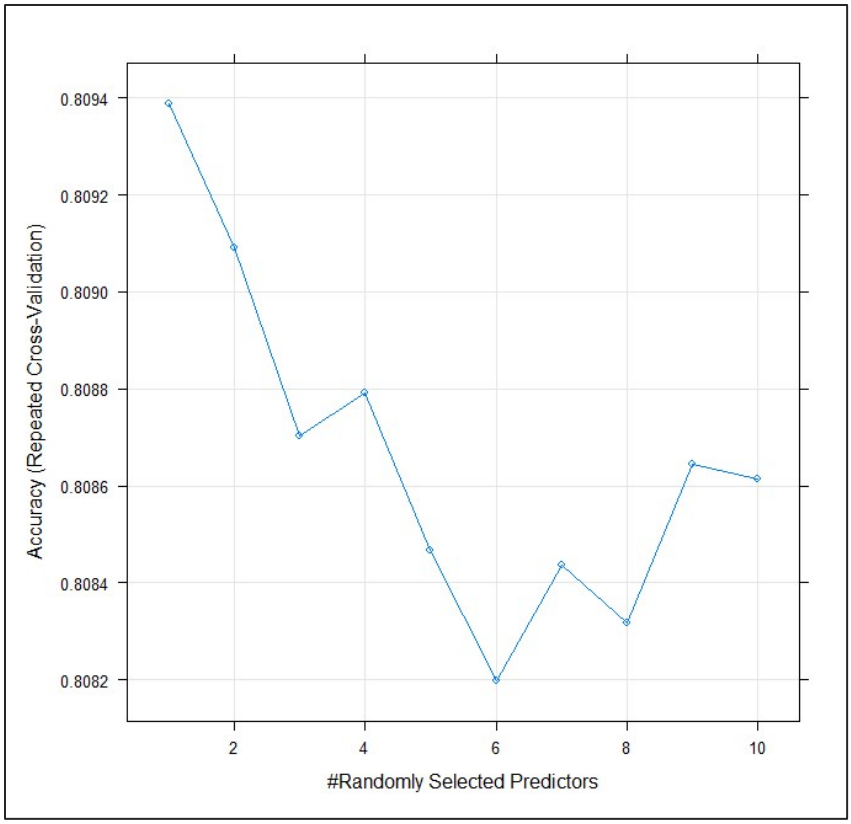


Table 10A. Oversampling Random Forest Model Evaluation

Random Forest Test Set Evaluation Oversampling			
Confusion Matrix			
		Reference	
		0	1
Predict	0	2706	415
	1	1115	443
Evaluation Metrics			
Sensitivity			0.708
Specificity			0.516

Positive Predictive Value	0.867
Negative Predictive Value	0.284
Precision	0.867
Recall	0.708
F1	0.780
Prevalence	0.817
Detection Rate	0.578
Detection Prevalence	0.667
Balanced Accuracy	0.612
AUC	0.660

Table 10B. SMOTE Random Forest Model Evaluation

Random Forest Test Set Evaluation SMOTE Resampling			
Confusion Matrix			
		Reference	
		0	1
Predict	0	3565	721
	1	256	137
Evaluation Metrics			
Sensitivity			0.933
Specificity			0.160
Positive Predictive Value			0.832
Negative Predictive Value			0.349
Precision			0.832
Recall			0.933
F1			0.879
Prevalence			0.817
Detection Rate			0.762
Detection Prevalence			0.916
Balanced Accuracy			0.546
AUC			0.649

Table 10C. ROSE Random Forest Model Evaluation

Random Forest Test Set Evaluation ROSE Resampling			
Confusion Matrix			
		Reference	
		0	1
Predict	0	1600	194
	1	2221	664
Evaluation Metrics			
Sensitivity			0.419
Specificity			0.774
Positive Predictive Value			0.892
Negative Predictive Value			0.230
Precision			0.892
Recall			0.419
F1			0.570
Prevalence			0.817
Detection Rate			0.342
Detection Prevalence			0.383
Balanced Accuracy			0.596
AUC			0.650

Table 10D. Undersampling Random Forest Model Evaluation

Random Forest Test Set Evaluation Undersampling			
Confusion Matrix			
		Reference	
		0	1
Predict	0	2186	298
	1	1635	560
Evaluation Metrics			
Sensitivity			0.572

Specificity	0.653
Positive Predictive Value	0.880
Negative Predictive Value	0.255
Precision	0.880
Recall	0.572
F1	0.693
Prevalence	0.817
Detection Rate	0.467
Detection Prevalence	0.531
Balanced Accuracy	0.612
AUC	0.657

Figure 4. Training and Testing ROC Curves for Random Forest Models

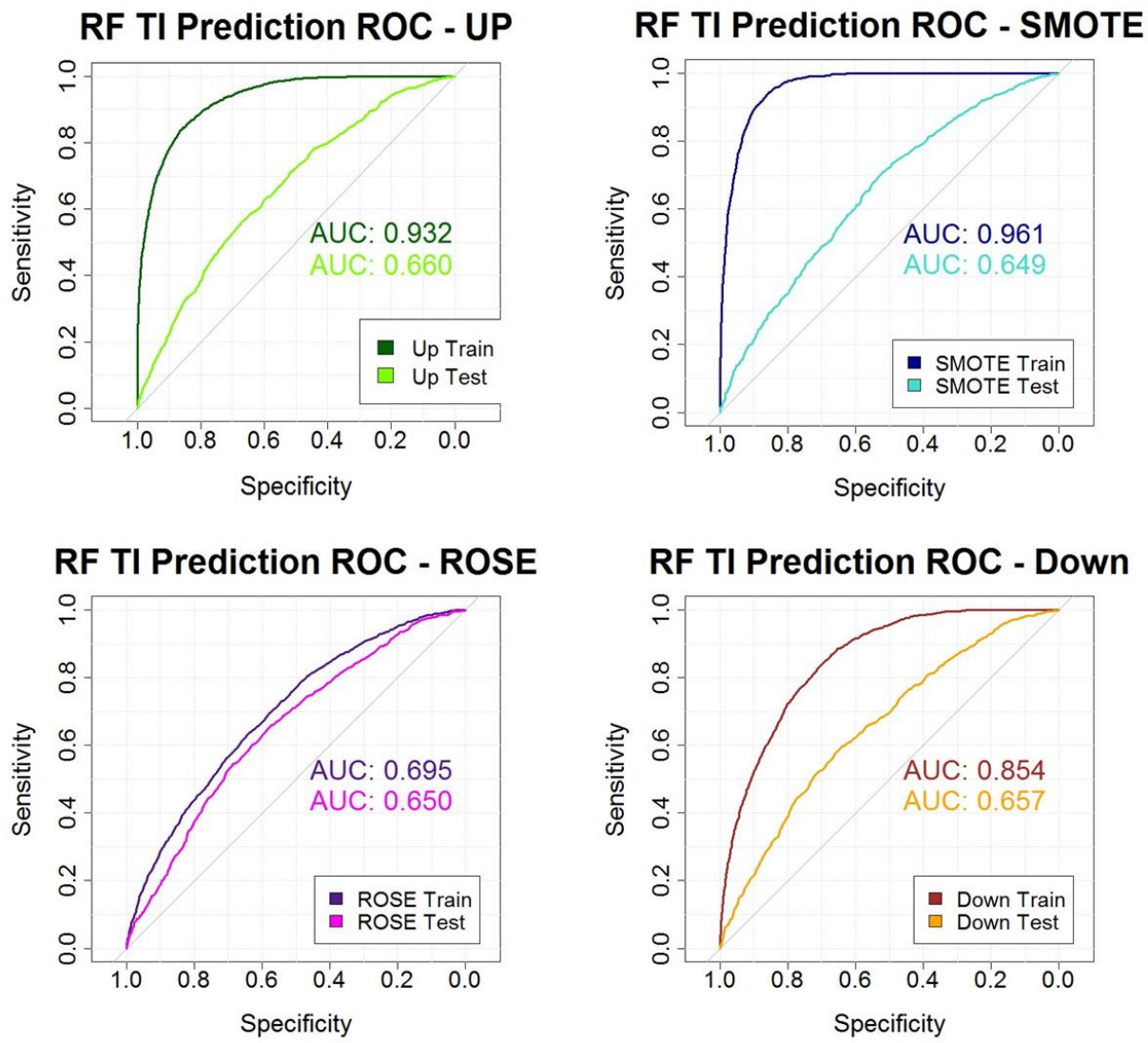
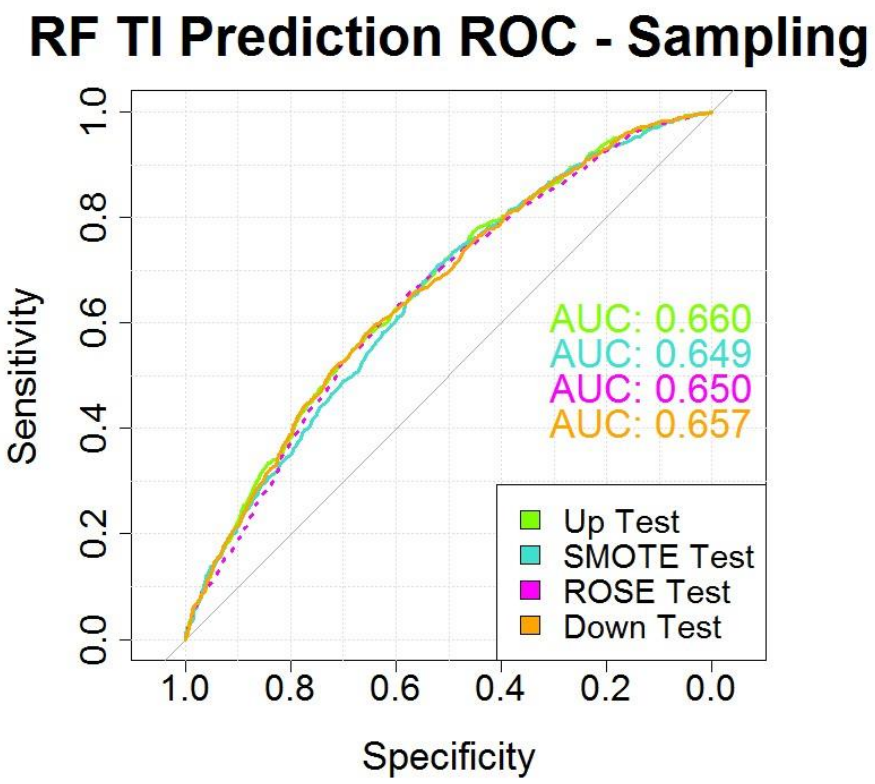


Figure 5. Test Prediction ROC Curves for Random Forest Models


RF TI Prediction ROC - Sampling
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
Specificity
1.0
0.8
0.6
0.4
0.2
0.0
AUC: 0.660
AUC: 0.649
AUC: 0.650
AUC: 0.657
Up Test
SMOTE Test
ROSE Test
Down Test

XGBoost Models

Tables 11A-11D present the test evaluation of four XGBoost models for predicting therapeutic intensification. Each model was tested using different numbers of trees: 50, 300, 1000, and 5000. In the model using 50 trees for training, a sensitivity of 0.634 and specificity of 0.709 was attained, with a positive predictive value of 0.921 and negative predictive value of 0.265. The precision and recall were both 0.921 and 0.634. Using 300 trees, the XGBoost model achieved a sensitivity of 0.663 and specificity of 0.703, with a positive predictive value of 0.923 and negative predictive value of 0.280. Increasing *nrounds* to 1000 trees, the XGBoost model achieved a sensitivity of 0.696 and specificity of 0.648, with a positive predictive value of 0.914 and negative predictive value of 0.284. For 5000 trees, the XGBoost model achieved a sensitivity of 0.779 and specificity of 0.496, with a positive predictive value of 0.892 and negative predictive value of 0.295. The results show that while the overall accuracy of the model improves as the number of trees increases, balanced accuracy and AUC begin to decrease after reaching an optimum *nrounds* value of 300 trees. The best performance is achieved with 300 trees, with a sensitivity of 0.663, specificity of 0.703, and AUC of 0.683. As more trees are added to the training, the sensitivity increases and specificity decreases, driving the AUC-ROC down. Overall, the models have moderate to good performance, with an AUC ranging from 0.637 to 0.683, performing consistently better at classification of therapeutic inertia vs. intensification than the random forest models. Test prediction AUC-ROC curves for each XGBoost model evaluated are plotted together in Figure 6.

Table 11A. Evaluation of XGBoost Model with 50 Trees

XGBoost Test Set Evaluation 50 Trees
Confusion Matrix

		Reference	
		0	1
Predict	0	26907	2306
	1	15548	5612
Evaluation Metrics			
Sensitivity			0.634
Specificity			0.709
Positive Predictive Value			0.921
Negative Predictive Value			0.265
Precision			0.921
Recall			0.634
F1			0.751
Prevalence			0.843
Detection Rate			0.534
Detection Prevalence			0.580
Balanced Accuracy			0.671
AUC			0.737

Table 11B. Evaluation of XGBoost Model with 300 Trees

XGBoost Test Set Evaluation 300 Trees			
Confusion Matrix			
		Reference	
		0	1
Predict	0	28165	2350
	1	14290	5568
Evaluation Metrics			
Sensitivity			0.663
Specificity			0.703
Positive Predictive Value			0.923
Negative Predictive Value			0.280
Precision			0.923
Recall			0.663
F1			0.772
Prevalence			0.843
Detection Rate			0.559
Detection Prevalence			0.606
Balanced Accuracy			0.683

AUC	0.748

Table 11C. Evaluation of XGBoost Model with 1000 Trees

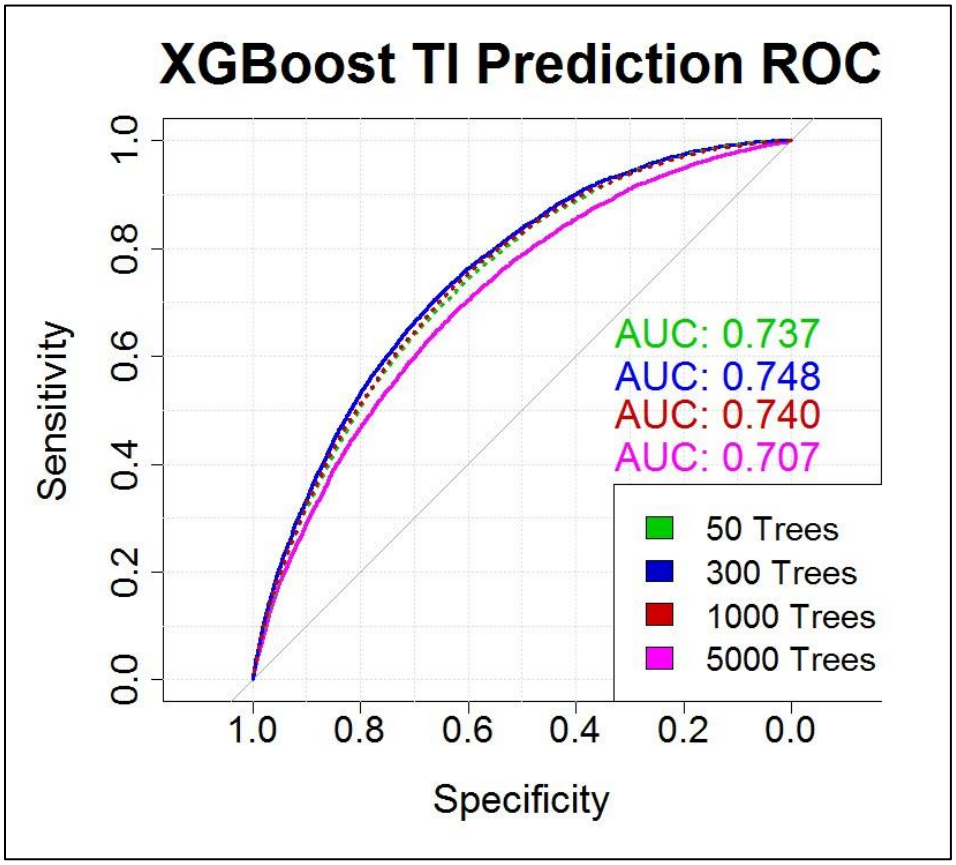
XGBoost Test Set Evaluation 1000 Trees			
Confusion Matrix			
		Reference	
		0	1
Predict	0	29543	2789
	1	12912	5129
Evaluation Metrics			
Sensitivity			0.696
Specificity			0.648
Positive Predictive Value			0.914
Negative Predictive Value			0.284
Precision			0.914
Recall			0.696
F1			0.790
Prevalence			0.843
Detection Rate			0.586
Detection Prevalence			0.642
Balanced Accuracy			0.672
AUC			0.740

Table 11D. Evaluation of XGBoost Model with 5000 Trees

XGBoost Test Set Evaluation 5000 Trees			
Confusion Matrix			
		Reference	
		0	1
Predict	0	33057	3989
	1	9398	3929
Evaluation Metrics			
Sensitivity			0.779
Specificity			0.496

Positive Predictive Value	0.892
Negative Predictive Value	0.295
Precision	0.892
Recall	0.779
F1	0.832
Prevalence	0.843
Detection Rate	0.656
Detection Prevalence	0.735
Balanced Accuracy	0.637
AUC	0.707

Figure 6. Test Prediction ROC Curves for XGBoost Models



Discussion

The study analyzed data from 120,755 patients from five different healthcare organizations to assess therapeutic inertia among uncontrolled hypertensive patients. The majority of visits showed DBP between 70-90 mmHg, while 26.5% of all visits had an SBP of 140 or higher. The study also found an average therapeutic intensification rate of 15.9%, with the highest rate occurring in HCO D (19.5%) and lowest at HCO E (13.3%), and a fairly consistent therapeutic inertia rate between all five HCOs. The study presents the results of univariate and multiple variable logistic regression analyses for modeling therapeutic intensification events using data from electronic health records of patients with hypertension. The odds ratios, p-values, marginal R2 and conditional R2 values of various factors such as systolic blood pressure (SBP), diastolic blood pressure (DBP), patient demographics, encounter attributes, and antihypertensive medications are presented. The results indicate that SBP and DBP at the current visit are important predictors of therapeutic intensification. Also, both current and previous BP values are considered by clinicians when deciding whether or not to increase therapy. Patient demographics and encounter attributes such as visit frequency and days since the last BP visit are also important predictors of therapeutic intensification.

The study confirms previous consensus that SBP and DBP at the current visit are important predictors of therapeutic intensification.[32, 33, 53-62, 72] This research indicates that both current and previous BP values, as well as proportion of uncontrolled visits and cumulative average BP are likely considered by clinicians when deciding whether or not to increase therapy. Published literature and the evidence presented in this study also both suggest that patient demographics and encounter attributes, such as visit frequency and age are important predictors of therapeutic intensification. This study agrees with the numerous other analyses finding that increasing age is associated with decreasing odds of

therapeutic intensification.[33, 57, 58, 60-62, 64] While other studies have found male sex to be associated with both higher and lower odds of intensification, this study provides additional support to those suggesting that sex is not a significant factor influencing likelihood of therapeutic intensification[55, 56, 72] after adjusting for other significant variables in a multiple regression model. Race was found to be a significant variable in predicting intensification, even after adjustment for all other significant variables. Non-white patients had 14% less odds of intensification compared to white patients. This is an important result because there are no other studies providing evidence for race being a statistically significant factor in likelihood of therapeutic intensification.[60, 62, 64, 72] Other studies have conflicting findings regarding comorbidities. The comorbidities found to be statistically significant in relationship to therapeutic intensification after multivariable adjustment all had an odds ratio below 1, indicating lower odds of intensification when other conditions needed to be addressed by the clinician.

Overall, this study provides valuable insight around which information clinicians consider various patient and encounter factors when deciding whether or not to intensify antihypertensive therapy. These results agree with several previously published findings, disagree with some findings, and provide insight around some previously unstudied factors as well. The predictive models developed in this study had moderate to good performance, with an AUC ranging from 0.637 to 0.683. The boosting approach with XGBoost performed consistently better at classification of therapeutic inertia vs. intensification than the bagging approach with random forests. These results suggest that the developed models have the potential to help clinicians in the decision-making process regarding therapeutic inertia vs. intensification. However, further research is needed to validate the models on larger and more diverse datasets.

The 12.7% of variance explained by fixed effects variables indicates that the majority of explanatory variables and reasons for not intensifying antihypertensive therapy when indicated are not captured by

the secondary observational data extracted from the EHR in this study. Reciprocally, the validity of the outcome variable as a computable phenotype derived from structured EHR data as it is defined in this project is limited by the lack of unstructured data and use of manual chart review to validate the accuracy of therapeutic inertia. Studies distinguishing “true inertia” from traditionally defined therapeutic inertia using manual chart review and unstructured data that include documented reasons for not intensifying antihypertensive therapy have found reported “true inertia” rates as much as 16-25% lower than traditionally derived therapeutic intensification rates.[71, 116]

The noise present in the data used in this study is a major limitation. This is a natural barrier when attempting to use structured EHR data, which is designed for billing accuracy more than clinical accuracy. Firstly, EHR data is not standardized and can vary greatly between healthcare systems and providers. This can result in inconsistencies in the data and decrease its accuracy and usefulness for research purposes. Additionally, EHR data is often entered by healthcare providers for clinical documentation purposes, rather than research purposes. As a result, the data may not always be complete, accurate, or consistent.[117]

Missing information and data entry errors are also an issue with EHR data that limits this study in accuracy and reliability. Informative missingness happens when the absence or presence of information holds valuable clinical information. Data entry errors are common in EHR data because there is no routinely implemented quality check, and different healthcare professionals enter data with some flexibility. Additionally, data collection and entry are not standardized, which may lead to measurement bias or detection bias.[118] Despite collecting data from 5 distinct HCOs, there are also limitations to the generalizability of EHR data. EHR data is collected from a specific population and may not be representative of the broader population. This can limit the applicability of research findings based on EHR data.[119] Lastly, the investigators were removed from the point of data abstraction during patients care by several degrees. With the dataset being limited to de-identified data, there was no way for the

investigators to acquire additional information for the patients included in the analysis. Furthermore, the data is limited in the types of information that it can provide. For example, we did not have access to the patients' social determinants of health or to narrative clinical notes that contain more clinical information than the structure EHR data alone. For future analysis, performing manual chart review to validate computable phenotypes like therapeutic inertia and intensification and using free-text clinical notes to unlock more extensive clinical information for modeling could improve the strength of these results.

Conclusion

In conclusion, this study provides valuable insights into the factors influencing therapeutic intensification for patients with uncontrolled hypertension. The study highlights the importance of SBP and DBP as predictors of therapeutic intensification and suggests that further research is needed to identify the factors influencing therapeutic inertia and intensification, particularly regarding provider and patient-level factors. Healthcare providers should be aware of the potential impact of these factors and take steps to minimize barriers to optimal hypertension management.

VI. STUDY 2: MODELING TREATMENT SELECTION IN ANTIHYPERTENSIVE THERAPEUTIC INTENSIFICATION USING PATIENT CLINICAL VARIABLES EXTRACTED FROM EHR DATA

Background

Hypertension is a prevalent and significant public health concern globally, with approximately one billion people affected worldwide.[1, 23] Uncontrolled hypertension can increase the risk of developing cardiovascular diseases such as heart attack, stroke, and kidney failure.[1-7] The management of hypertension includes lifestyle modifications and medication therapy, with the goal of achieving and maintaining optimal blood pressure (BP) control.[23, 24] The selection and management of antihypertensive medications are crucial in achieving BP control and reducing the risk of cardiovascular complications.[14, 41, 65, 120, 121]

Hypertension treatment guidelines make clear recommendations for initiating pharmacological therapy: start with two drugs in single-pill combination form.[23, 24] However, there is limited guidance on intensifying treatment after initiation. Physicians have two options for antihypertensive treatment intensification: increasing the prescribed dose of the existing medication or adding a new drug to the treatment regimen. Two meta-analyses showed that adding an antihypertensive medication at ½ standard, standard, and twice standard dose results in a BP decrease of 7, 9, and 11 mmHg, respectively, compared to a 2-3 mmHg BP reduction for doubling the dose of an existing antihypertensive medication.[17, 18] RCT evidence shows that AH treatment selection is important in affecting reduction in uncontrolled blood pressure, but observational studies of AH treatment selection from real-world evidence is limited.

Numerous observational studies have found important predictors of therapeutic intensification,[32, 33, 53-64, 72, 74] but very few have compared the factors associated with adding a new medication versus increasing the dose of an existing medication using observational (non-RCT) data.[65] Aubert et al. published findings from the one study found in the literature that used EHR data to compare clinical variables that may influence the decision to add a new AH medication or increase the dose of an existing one. The study included 487,003 patients with hypertension and SBP ≥130 mmHg, of which 178,562 were used for analysis. Among instances of therapeutic intensification, 25.5% received a new medication while 74.5% maximized the dose of existing medications. Patients who received a new medication were younger and had higher baseline SBP. There was no pattern of intensification approach according to facility characteristics. Covariates were well balanced in the propensity score. However, the study from Aubert et al. is limited in scope and recency: the study population was predominantly male, with less than 2% women, and the data used in the study were from 2011-2013.[65]

Therefore, the aim of study 2 in this dissertation is to compare the factors associated with adding a new antihypertensive medication versus increasing the dose of an existing medication in the management of uncontrolled hypertension.

Research Question:

1. How much do previously studied and not previously studied factors impact the likelihood and explain the variance of increasing dose vs. adding a new medication when antihypertensive therapy is intensified?

Objective:

- Identify patient variables significantly associated (and quantify strength of association) with the two types of antihypertensive therapeutic intensification: adding a new medication and increasing dose of an existing medication.

Methodology

This analysis will focus on clinician antihypertensive prescribing behavior by modeling the selection of two therapeutic intensification strategies: adding a new medication and increasing dose of an existing medication. This analysis aims to identify the clinical variables evaluated in Study 1 (see *Table 2*) associated with the two specified types of antihypertensive therapeutic intensification using logistic regression modeling. Viewing antihypertensive treatment selection as a probability of two outcomes (existing antihypertensive medication dose increase, and new antihypertensive medication addition), another primary objective of this analysis is to calculate propensity scores for treatment selection based on the clinical variables from *Table 2* identified as statistically significant from the logistic regression analysis.

The treatment selection model of therapeutic inertia will be constructed using the logistic regression function from the generalized linear mixed-effects models package (lme4) in R.[84, 85] In this analysis, we are primarily concerned with the factors associated with physician prescribing behavior that may influence the decision to increase dose or add a new medication and the quantification of their effect on likelihood of therapeutic intensification. Therefore, only a descriptive model will be produced to ensure adequate interpretability of the model. The likelihood of choosing to increase dose of an existing medication or add a new medication will be assessed using the odds ratio calculated from the logistic regression analysis, and variance in treatment selection explained by the models will be determined by

calculating the Nakagawa and Schielzeth pseudo-R^2 for variance explained by mixed-effects logistic regression models.[86, 87]

Inclusion/Exclusion Criteria

The study population came from the 590,463 patients and 4,561,165 encounters involved in the AMA MAP Program. Encounters that were missing clinician information were excluded, resulting in 589,019 patients and 4,458,233 encounters. To ensure data consistency, the study included only patients with at least two visits during the full period (2020-2022), resulting in 433,414 patients and 3,389,020 encounters. The study also required patients to have at least one visit during the study period (2021-2022), resulting in 410,617 patients and 3,319,664 encounters. Further criteria included patients who were at least 18 years old (386,630 patients), had a diagnosis of hypertension (201,089 patients), and had at least two blood pressure measurements (191,227 patients). To ensure accurate medication information, only patients with all antihypertensive medications verified were included (120,755 patients). The study focused on patients with uncontrolled blood pressure and included only encounters where blood pressure was not within recommended levels (73,974 encounters). In addition, the study required patients to have at least one visit during the baseline period (2020) (56,963 patients) and be already treated with at least one antihypertensive medication (47,960 patients). Finally, the study included only visits with therapeutic intensification, resulting in 12,742 patients and 14,726 encounters used in the analysis. Figure 1 summarizes the inclusion-exclusion criteria for this study.

Classification of Class Additions vs. Dose Increases

. Classification of increases in dose of an existing medication and additions of a new class of medication were handled separately. First all medication orders were consolidated to one line for each combination of patient/drug/dose, and the first and last order date were kept in different columns to retain when the specific drug/dose was first and last seen in the data. For dose increases, all unique combinations of patient/drug/dose were ordered chronologically by the first date listed the data for each. Then an if, else statement was used to determine two consecutive patient/drug/dose combinations were for the same patient and the same drug, and if the dose was higher for the more recent instance. If so, that date of first instance for the new dose was marked as a dose increase for that patient. For additions of new medication classes, unique combinations of patient/class were ordered by first date listed in the data. The baseline period was used to provide a 12-month window to pick all currently prescribed AH medications for each patient (AH medication prescriptions need to be renewed every 12 months at the most). Two conditions had to be met for a class addition to be indicated:

- The AH class must not be present in the baseline period for a patient
- There must be a visit on record for a patient at least 12 months prior to the first date listed for the AH class (to eliminate new patients or patients not seen for over a year from being falsely identified as having a new medication added when they are just receiving an overdue renewal or a renewal with a new provider)

Figure 1. Patient Inclusion-Exclusion Flowchart for AH Treatment Selection Analysis

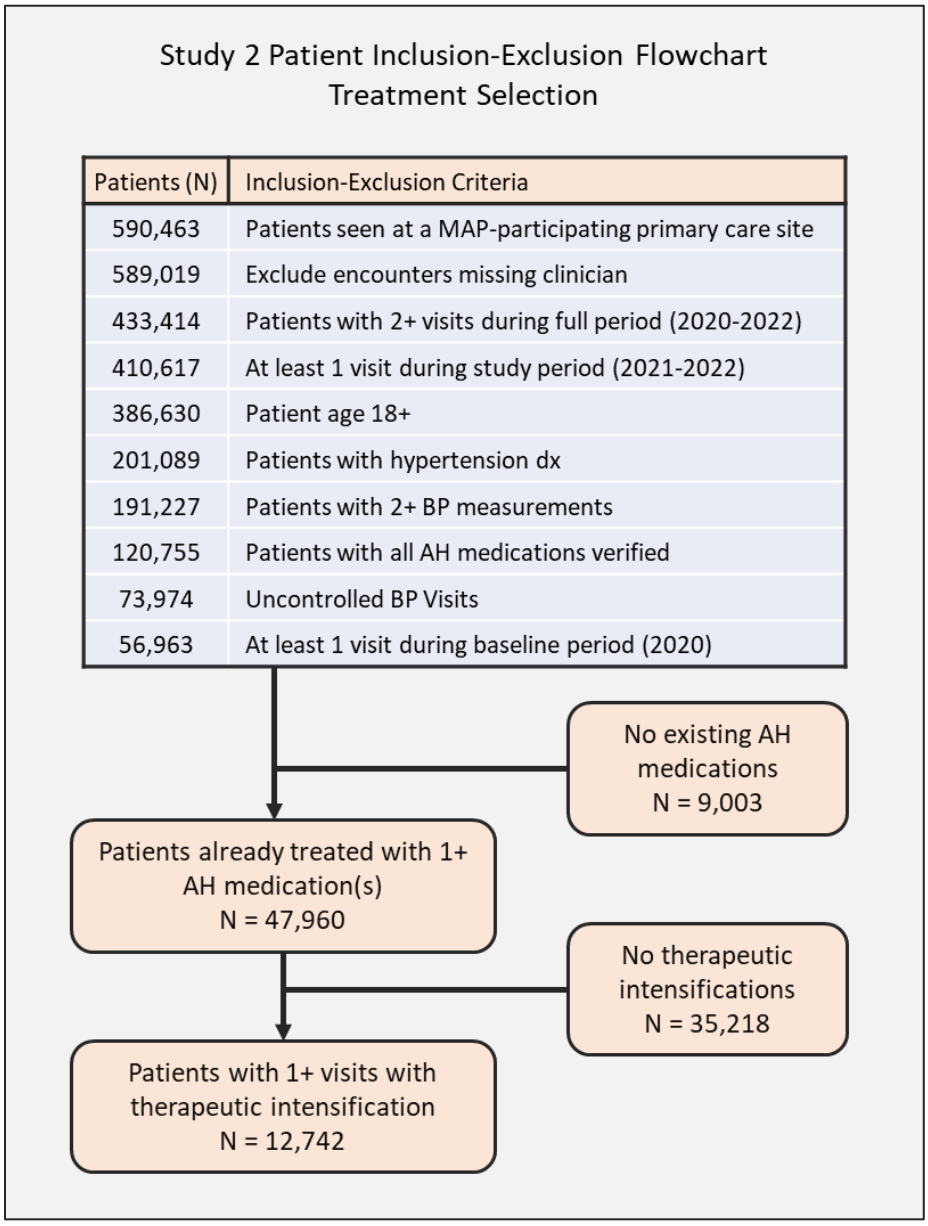


Table 1.

HCO	Patients	Encounters	Encounters per Patient
A	2,581	2,985	1.16
B	823	1,038	1.26
C	1,740	2,091	1.20
D	3,189	3,763	1.18
E	4,409	4,849	1.10
Total	**12,742**	**14,726**	**1.16**

Results

Table 1 presents various demographic and clinical characteristics of 12,742 patients that met all study criteria outlined in Figure 1, only including patients that were already prescribed at least one AH medication and had a therapeutic intensification event during the study period. Table 1 characterizes the patients by age, gender, race, baseline and final antihypertensive medication use, blood pressure measurements, body mass index, glucose, HbA1C and lipid levels, and comorbidities. The table indicates the number and percentage of patients by categorical variables and provides the mean and standard deviation for continuous variables. Of the study 2 patients, the average age was 61.6 years, 42% were

male and 58% were female. Black patients accounted for 50% of the total, while 44.9% were white and 3.2% were classified as other. The mean baseline number of AH medications prescribed was 1.9, increasing to a final AH medication count of 3.1. The mean systolic blood pressure (SBP) was 152.9 and the mean diastolic blood pressure (DBP) was 85.1.

Table 1. Summary of Patient Demographics and Clinical Characteristics

		Total		**HCO A**		**HCO B**		**HCO C**		**HCO D**		**HCO E**	
Patients	N	12,742		2,581		823		1,740		3,189		4,409	
Age	mean, SD	61.6	13.4	62.9	14.4	58.2	13.4	57.9	13.5	63.6	11.4	61.4	13.7
Male	N, %	5,349	42.0%	980	38.0%	338	41.1%	724	41.6%	1,291	40.5%	2,016	45.7%
Female	N, %	7,393	58.0%	1,601	62.0%	485	58.9%	1,016	58.4%	1,898	59.5%	2,393	54.3%
White	N, %	5,720	44.9%	1,245	48.2%	217	26.4%	387	22.2%	986	30.9%	2,885	65.4%
Black	N, %	6,365	50.0%	1,261	48.9%	595	72.3%	1,293	74.3%	1,825	57.2%	1,391	31.5%
Other	N, %	414	3.2%	49	1.9%	5	0.6%	50	2.9%	207	6.5%	103	2.3%
Baseline AH meds	mean, SD	1.9		1.8		2.1		2.1		2.4		1.5	
Final AH meds	mean, SD	3.1		3.2		3.3		3.4		3.2		2.9	
SBP	mean, SD	152.9	14.5	150.8	13.0	154.2	17.3	154.6	13.6	157.4	16.1	150.0	12.9
DBP	mean, SD	85.1	12.1	86.0	12.3	92.3	13.9	88.1	12.0	79.6	11.2	86.0	10.8
BMI	mean, SD	33.0	8.5	32.6	9.2	34.0	9.4	33.2	9.4	32.3	7.7	33.4	8.1
HbA1C	mean, SD	6.9	1.8	6.6	1.6	7.1	2.0	7.2	2.0	7.0	1.8	6.7	1.6
Glucose	mean, SD	121.7	59.0	118.6	56.5	122.6	65.5	123.2	67.3	132.1	66.5	115.0	48.0
LDL avg	mean, SD	104.3	37.4	103.8	38.2	103.4	35.3	107.7	37.7	102.9	37.2	104.4	37.3
HDL avg	mean, SD	52.9	15.7	54.9	17.2	51.5	15.6	51.5	14.7	49.7	13.1	54.9	16.7
Cholesterol	mean, SD	169.9	51.7	123.5	55.7	179.3	42.7	184.9	43.9	172.2	44.0	185.9	43.6
Diabetes	N, %	4,698	36.9%	833	32.3%	304	36.9%	575	33.0%	1,723	54.0%	1,263	28.6%
CHF	N, %	754	5.9%	196	7.6%	82	10.0%	87	5.0%	281	8.8%	108	2.4%
Arrhythmia	N, %	1,654	13.0%	496	19.2%	94	11.4%	113	6.5%	402	12.6%	549	12.5%
Renal Failure	N, %	1,546	12.1%	344	13.3%	196	23.8%	196	11.3%	514	16.1%	296	6.7%
Liver Disease	N, %	717	5.6%	175	6.8%	30	3.6%	53	3.0%	315	9.9%	144	3.3%

Valvular Disease	N, %	380	3.0%	98	3.8%	11	1.3%	24	1.4%	80	2.5%	167	3.8%
CEVD	N, %	925	7.3%	244	9.5%	55	6.7%	82	4.7%	265	8.3%	279	6.3%
MI	N, %	252	2.0%	104	4.0%	7	0.9%	23	1.3%	85	2.7%	33	0.7%
PVD	N, %	879	6.9%	236	9.1%	52	6.3%	92	5.3%	270	8.5%	229	5.2%
CPD	N, %	2,337	18.3%	591	22.9%	171	20.8%	340	19.5%	642	20.1%	593	13.4%
Metastatic Cancer	N, %	181	1.4%	50	1.9%	0	0.0%	1	0.1%	90	2.8%	40	0.9%
Solid Tumor	N, %	938	7.4%	232	9.0%	29	3.5%	36	2.1%	377	11.8%	264	6.0%

Tables 2 and table 3 summarize the distribution of SBP and DBP overall and across the different HCOs for the 14,726 blood pressure encounters that met all of the criteria for study 2 (Figure 1). All of the HCOs had the highest proportion of visits in the 140-150 mmHg, which accounted for 40% of the patients overall. SBP was 160 or higher for 28.3% of all visits. HCO D had the highest proportion of visits with SBP above 160 mmHg at 38%, while all other HCOs had between 22-32% of visits above 160. The majority of visits for all HCOs had a recorded DBP between 80-90 mmHg, except for HCO B which had 35.7% of DBPs between 90-100 mmHg.

Table 2. Systolic Blood Pressure Distribution

	Total		**HCO A**		**HCO B**		**HCO C**		**HCO D**		**HCO E**	
SBP	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%
<120	31	0.2%	6	0.2%	8	0.8%	1	0.0%	3	0.1%	13	0.3%
120-130	204	1.4%	62	2.1%	40	3.9%	9	0.4%	6	0.2%	87	1.8%
130-140	779	5.3%	213	7.1%	92	8.9%	109	5.2%	58	1.5%	307	6.3%

140-150	5,891	40.0%	1,232	41.3%	300	28.9%	740	35.4%	1,365	36.3%	2,254	46.5%
150-160	3,658	24.8%	769	25.8%	265	25.5%	584	27.9%	912	24.2%	1,128	23.3%
160-170	2,119	14.4%	433	14.5%	146	14.1%	322	15.4%	598	15.9%	620	12.8%
170+	2,044	13.9%	270	9.0%	187	18.0%	326	15.6%	821	21.8%	440	9.1%

Table 3. Diastolic Blood Pressure Distribution

	Total		**HCO A**		**HCO B**		**HCO C**		**HCO D**		**HCO E**	
DBP	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%
<70	1,335	9.1%	269	9.0%	46	4.4%	101	4.8%	669	17.8%	250	5.2%
70-80	3,221	21.9%	525	17.6%	113	10.9%	385	18.4%	1,373	36.5%	825	17.0%
80-90	4,469	30.3%	887	29.7%	234	22.5%	671	32.1%	976	25.9%	1,701	35.1%
90-100	3,926	26.7%	880	29.5%	371	35.7%	613	29.3%	554	14.7%	1,508	31.1%
100-110	1,273	8.6%	319	10.7%	164	15.8%	223	10.7%	132	3.5%	435	9.0%
110+	502	3.4%	105	3.5%	110	10.6%	98	4.7%	59	1.6%	130	2.7%

Table 4 summarizes the 14,726 uncontrolled blood pressure encounters of patients with therapeutic intensification. Therapeutic intensification rate was 100% for all visits due to the criteria applied to this analysis. Out of 14,726 encounters, 4,214 (28.6%) involved dose increases, with HCO D having the highest dose increase rate (53.9%) and HCO E having the lowest (8.4%). Class additions were made in 10,512 encounters (71.4%), with HCO E having the highest class addition rate (91.5%) and HCO E having the lowest (8.4%). These findings suggest that the treatment selection approach to therapeutic intensification varies across the different HCOs.

Table 4. Summary of Therapeutic Intensification and Therapeutic Inertia

	Total	**HCO A**	**HCO B**	**HCO C**	**HCO D**	**HCO E**

Patients with TI	10,096	1,972	693	1,464	2,461	3,506
Uncontrolled Encounters	11,555	2,263	867	1,750	2,866	3,809
Therapeutic Intensification Rate	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Therapeutic Inertia Rate	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Dose Increases	3,377	551	289	647	1,569	321
Dose Increase Rate	29.2%	24.3%	33.3%	37.0%	54.7%	8.4%
Class Additions	8,178	1,712	578	1,103	1,297	3,488
Class Addition Rate	70.8%	75.7%	66.7%	63.0%	45.3%	91.6%

Treatment Selection Modeling

For patients already on at least one antihypertensive medication, the patient and clinical variables associated with a statistically significant difference in likelihood of treatment selection between increasing dose of an existing medication and adding a new class of antihypertensive medication from the univariate analyses included: SBP, DBP, Previous Visit SBP, Previous Visit DBP, Previous Visit BP Uncontrolled, Proportion of Uncontrolled Visits, Current Number of AH Medications, Visits Per 100 Days, BP Visits Per 100 Days, BP Visits, Days Since Previous BP, Days Since Previous Uncontrolled BP, Encounter BP Count, Same Previous Clinician, Proportion of Visits with Primary Physician, Diabetes, Congestive Heart Failure, Cardiac Arrhythmia, Renal Failure, Liver Disease, Solid Tumor, Myocardial Infarction, White vs. Non-white Race, BMI, HbA1c, Glucose, LDL, HDL, Total Cholesterol, Visit with Primary Physician, and Previous TI Event. After multivariable logistic regression modeling, the variables that remained statistically significant included: SBP, DBP, Previous Visit SBP, Previous Visit DBP, Proportion of Uncontrolled Visits, Current Number of AH Medications, Previous TI Event, Visit with Primary Physician, Encounter BP Count, BP Visits Per 100 Days, Cardiac Arrhythmia, Age, White vs. Non-white Race, and BMI.

Tables 5A-5E, and Table 6 show the results of statistical analyses that explore the relationship between various patient characteristics and the likelihood of therapeutic intensification type. The odds ratios and p-values for each variable are presented, along with the marginal R^2 (variance explained by fixed effects only) and conditional R^2 values (variance explained by fixed and random effects together).

Table 5A presents results for SBP and DBP at current and previous visits, with the reference group being 130-140 mmHg for SBP and 80-90 mmHg for DBP. The was not a single SBP group that had a statistically significant relationship with ACH treatment selection. however current DBP was significant for every group while only lower values of previous were significant. Interestingly, previous visit BP explained more variance in treatment selection than the current BP values (0.022 vs. 0.019), with current and previous blood pressure multivariable model having slightly higher marginal R^2 then previous BP separately. Table 5B contains the results for cumulative average and standard deviation of SBP and DBP. Cumulative SBP average, cumulative DBP average, and DBP standard deviation were significantly associated with therapeutic intensification when including all four variables in the model. Additionally, the multiple variable model estimating the effect of average SBP, DBP and std. deviation of both had a marginal R2 of 0.0356, higher than then current and previous bp together. However, SBP and DBP average had conflicting effects. Higher SBP average was associated with 3% greater odds of dose increase, while Higher DBP average was associated with a 2.5% higher odds of class addition.

Table 5C presents the modeling of patient demographics. The only demographic variables with a statistically significant relationship to treatment selection where white versus non white and age between 50-60 and 60-70 years. Both age groups were associated with a 26 to 27% greater odds of those increase compared to the 30-40 age group. Non-white patients where 71% more likely to receive a class addition compared to white patients.

Table 5D shows encounter attributes and AH medications and their relationship with treatment selection options. Number of AH medications already being taken by the patient explained the most variance in treatment selection of any variable examined in this modeling ($r2 = 0.0734$). Odds of dose increase went up by 50.5%, 69%, and 76% for patients on 2, 3, and 4+ medications compared to those only taking 1 AH medication at the time of the visit. BP visit count and visit frequency, proportion of visits with primary clinician, current visit with primary clinician, and previous TI event were all statistically significant and were all associated with an increased odds of class addition.

Table 5E presents the modeling results for patient comorbidities and lab measurements. The comorbidities and lab results with a statistically significant association with treatment selection included diabetes, diabetes with complications, congestive heart failure, cardiac arrhythmia, renal failure, liver disease, solid tumor cancer, myocardial infarction, total count of comorbidities, BMI, HbA1C, glucose, LDL, HDL, and total cholesterol. The relationship with treatment selection was almost unidirectional for all comorbidities with diabetes, diabetes with complications, congestive heart failure, renal failure, liver disease, solid tumor cancer, myocardial infarction, and total comorbidities all being associated with higher odds of dose increase. The only comorbidity variable associated with higher odds of class

addition was cardiac arrhythmia. The relationship between lab measurements and treatment selection varied, however, with BMI and cholesterol associated with higher odds of class addition and HBA 1C and glucose associated with higher odds of dose increase.

Table 8 presents the results of the multiple variable mixed-effects modeling of treatment selection. The variables analyzed included those that were found statistically significant and had a marginal R^2 greater than 0.0001 (other than SBP and Sex which were still included despite not being significant in univariate analysis): SBP, DBP, Previous Visit SBP, Previous Visit DBP, Current AH Meds, Proportion of Uncontrolled Visits, Previous TI Event, Proportion of Visits with Primary Physician, Visit with Primary Physician, Confirmatory BP Measurement, BP Visits Frequency, Diabetes with Complications, Congestive Heart Failure, Cardiac Arrhythmia, Cerebral Vascular Disease, Renal Failure, Liver Disease, Solid Tumor, Total Comorbidities, Age, Sex, and White vs. Non-white, LDL, BMI, Cumulative SBP Average, Cumulative DBP Average, Cumulative SBP Std. Deviation, Cumulative DBP Std. Deviation. After the model adjust for the effect of each of these variables through multiple regression, the following variables remained significant: SBP 160-170, SBP 170+, Previous Visit DBP 100-110, Cumulative DBP Average, Current AH Meds, Previous TI Event, Confirmatory BP Measurement, BP Visit Frequency, Diabetes with Complications, Age, White vs. Non-white race, and BMI. The final multiple variable model was able to explain 29.3% of the variance in treatment selection from the fixed effects alone and 38.5% by including random intercepts for both patient and clinician clustered observations.

Table 5A. Univariate and Multiple Regression Mixed-Effects Modeling of Treatment Selection with SBP and DBP at Current and Previous Visits

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
SBP <120	2.26185	0.13821	0.01854	0.09420
SBP 120-130	1.20042	0.34320		
SBP 130-140 (Reference)	1.00000	--		
SBP 140-150	1.07920	0.43195		
SBP 150-160	0.99668	0.97302		
SBP 160-170	1.01390	0.89405		
SBP 170+	0.88647	0.24680		
DBP <70	0.58350	2.19E-15		
DBP 70-80	0.72773	7.18E-10		
DBP 80-90 (Reference)	1.00000	--		
DBP 90-100	1.12772	0.02821		
DBP 100-110	1.39944	1.94E-05		
DBP 110+	1.59312	0.00013		
Previous Visit SBP <120	1.33484	0.00153	0.02214	0.09679
Previous Visit SBP 120-130	1.19124	0.00913		
Previous Visit SBP 130-140 (Reference)	1.00000	--		
Previous Visit SBP 140-150	0.86326	0.00817		
Previous Visit SBP 150-160	0.84486	0.00853		
Previous Visit SBP 160-170	0.72027	1.25E-05		
Previous Visit SBP 170+	0.65160	1.93E-08		
Previous Visit DBP <70	0.46769	<2E-16		
Previous Visit DBP 70-80	0.75751	3.26E-08		
Previous Visit DBP 80-90 (Reference)	1.00000	--		
Previous Visit DBP 90-100	0.94113	0.30994		
Previous Visit DBP 100-110	1.09951	0.30300		
Previous Visit DBP 110+	1.04969	0.74344		
Current & Previous SBP / DBP			0.02825	0.10120

Table 5B. Univariate and Multiple Regression Mixed-Effects Modeling of Treatment Selection with Cumulative Average and Standard Deviation of SBP and DBP

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
Cumulative SBP Average	0.97703	<2E-16	0.02965	0.10499
Cumulative DBP Average	1.02562	<2E-16		
Cumulative SBP Std. Deviation	0.98873	3.16E-02	0.00173	0.10130
Cumulative DBP Std. Deviation	1.00019	9.83E-01		
Cumulative SBP Average	0.96905	<2E-16	0.03557	0.12826
Cumulative DBP Average	1.02502	2.19E-10		
Cumulative SBP Std. Deviation	1.01125	0.04785		
Cumulative DBP Std. Deviation	0.98226	0.0614		

Table 5C. Univariate Mixed-Effects Modeling of Treatment Selection with Patient Demographics

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
Sex (Reference: Male)	1.00947	0.80575	0.00001	0.08188
Race (Reference: White)	1.70990	<2E-16	0.01944	0.09713
Encounter Age	0.99742	0.06739	0.00034	0.08201
Age <30	0.88740	0.57706	0.00397	0.08427
Age 30-40 (Reference)	1.00000	--		
Age 40-50	1.00103	0.99217		
Age 50-60	0.73007	0.00116		
Age 60-70	0.73852	0.00148		
Age 70-80	0.84232	0.08119		
Age 80-90	0.89409	0.32534		
Age 90+	0.71538	0.08200		

Table 5D. Univariate Mixed-Effects Modeling of Treatment Selection with Encounter Attributes and AH Medications

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional

Proportion of Uncontrolled Visits	0.54139	<2E-16	0.00802	0.08742
Current AH Meds 1 (Reference)	1.00000	--	0.07344	0.15374
Current AH Meds 2	0.49588	<2E-16		
Current AH Meds 3	0.31091	<2E-16		
Current AH Meds 4+	0.24467	<2E-16		
BP Visits	1.10158	<2E-16	0.03260	0.11614
BP Visits Per 100 Days	1.35635	8.72E-14	0.00622	0.08880
Days Since Previous BP	1.00060	4.45E-06	0.00230	0.08132
Days Since Previous Uncontrolled BP	1.00067	2.04E-09	0.00450	0.07999
Encounter BP Count	0.81640	1.53E-07	0.00267	0.08239
Same Previous Clinician	1.14291	1.45E-03	0.00098	0.08286
Proportion of Visits with Primary Physician	1.66339	7.60E-10	0.00367	0.08549
Visit with Primary Physician	1.21148	7.17E-05	0.00149	0.08282
Previous TI Event	2.05574	<2E-16	0.02757	0.12632

Table 5E. Univariate Mixed-Effects Modeling of Treatment Selection with Patient Comorbidities and Lab Measurements

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
Diabetes	0.63926	<2E-16	0.01296	0.09055
Diabetes with Complications	0.54493	<2E-16	0.01760	0.09504
Congestive Heart Failure	0.78962	2.10E-03	0.00088	0.08213
Cardiac Arrhythmia	1.22459	5.17E-04	0.00128	0.08273
Peripheral Vascular Disease	0.93127	3.33E-01	0.00009	0.08176
Renal Failure	0.80432	8.53E-05	0.00146	0.08346
Liver Disease	0.72777	0.00005	0.00150	0.08314
Solid Tumor	0.79015	0.00079	0.00105	0.08251
Metastatic Cancer	0.88397	0.43615	0.00006	0.08214
Myocardial Infarction	0.76302	0.03386	0.00041	0.08220
Cerebral Vascular Disease	0.97828	7.62E-01	0.00001	0.08187
Dementia	1.04028	8.23E-01	0.00001	0.08221
Total Comorbidities	0.93625	<2E-16	0.00650	0.08637
BMI (kg/m^2)	1.00841	3.28E-04	0.00144	0.08497
HbA1c (mmols/mol)	0.93559	0.00000	0.00400	0.08061
Glucose (mg/dL)	0.99774	0.00000	0.00510	0.08637
LDL (mg/dL)	1.00124	3.14E-02	0.00059	0.08662

HDL (mg/dL)	1.01108	0.00000	0.00821	0.09244
Total Cholesterol (mg/dL)	1.00126	0.00167	0.00118	0.08218

Table 6. Multiple Variable Mixed-Effects Modeling of Treatment Selection

Variable	Odds Ratio	p-value	R^2 Marginal	R^2 Conditional
SBP 120-130	0.78284	0.51005	0.29262	0.38518
SBP 140-150	1.28827	0.23965		
SBP 150-160	1.36899	0.16428		
SBP 160-170	1.80957	0.01936		
SBP 170+	1.90463	0.02602		
DBP <70	0.90015	0.60498		
DBP 70-80	0.81325	0.11944		
DBP 90-100	0.93721	0.63026		
DBP 100-110	1.02934	0.88883		
DBP 110+	1.07575	0.82959		
Previous Visit SBP <120	1.05671	0.80554		
Previous Visit SBP 120-130	0.93119	0.63164		
Previous Visit SBP 140-150	0.77338	0.06331		
Previous Visit SBP 150-160	0.81743	0.21610		
Previous Visit SBP 160-170	0.77617	0.19208		
Previous Visit SBP 170+	0.90093	0.66155		
Previous Visit DBP <70	0.77490	0.15902		
Previous Visit DBP 70-80	0.95591	0.71601		
Previous Visit DBP 90-100	0.82963	0.20364		
Previous Visit DBP 100-110	0.57414	0.00924		
Previous Visit DBP 110+	0.95687	0.91567		
Current AH Meds 2	0.43418	4.31E-14		
Current AH Meds 3	0.25290	<2E-16		
Current AH Meds 4+	0.15799	<2E-16		
Proportion of Uncontrolled Visits	0.78673	0.44934		
Previous TI Event	2.95420	<2E-16		
Proportion of Visits with Primary Physician	1.20057	0.45971		
Visit with Primary Physician	1.02187	0.88575		
Encounter BP Count	0.58130	9.67E-09		

BP Visits Per 100 Days	1.55108	0.00050
Diabetes with Complications	0.61328	0.00021
Congestive Heart Failure	1.30912	0.27219
Cardiac Arrhythmia	1.21969	0.17257
Cerebral Vascular Disease	1.11381	0.56416
Renal Failure	1.04456	0.77899
Liver Disease	0.70706	0.07540
Solid Tumor	0.85713	0.37133
Total Comorbidities	1.01759	0.61248
Age <30	0.70466	0.45661
Age 40-50	2.27257	0.00145
Age 50-60	1.54421	0.06812
Age 60-70	2.17615	0.00138
Age 70-80	2.52765	0.00030
Age 80-90	3.07964	0.00021
Age 90+	3.23294	0.03418
Sex: Male	0.95113	0.58694
Race: White	1.43615	0.00009
LDL	1.00127	0.28858
BMI	1.02264	0.00020
Cumulative SBP Average	0.98445	0.07675
Cumulative DBP Average	1.03099	0.00906
Cumulative SBP Std. Deviation	0.99617	0.65064
Cumulative DBP Std. Deviation	0.99332	0.62399

Discussion

This research analyzed information from 12,742 patients across five healthcare organizations to assess antihypertensive treatment selection rates in uncontrolled hypertensive patients. Out of 14,726 uncontrolled blood pressure encounters of patients with therapeutic intensification, 28.6% involved increasing dose of an existing medication and 71.4% were new classes of AH medication prescribed. Comparison between HCOs suggest that the treatment selection approach to therapeutic intensification varies across the different HCOs.

The scope of this analysis significantly expanded upon the limited previous studies looking at factors associated with treatment selection in hypertension management.[65] The study explored the patient and clinical variables associated with treatment selection for patients already taking at least one antihypertensive medication. The study found that several variables, such as SBP, DBP, previous visit BP, proportion of uncontrolled visits, current number of AH medications, visit with primary physician, encounter BP count, cardiac arrhythmia, age, white vs. non-white race, and BMI, were significantly associated with AH treatment selection. An important finding is that the number of AH medications currently being taken by the patient explained the most variance in treatment selection of any variable examined in this modeling. The study also explored patient demographics, encounter attributes, AH

medications, and patient comorbidities and lab measurements and found significant relationships between those variables and treatment selection. Finally, this study found that in this population, adding a new class of AH medication was twice as common compared to increasing dose of an existing medication. These findings indicate the reverse of the trend reported by Aubert et al.[65]

This study, like the previous study 1, is limited by the reliance on structured EHR data. EHR data is repeatedly proven to have significant inconsistencies in the data that lower its accuracy and usefulness for research purposes. Moreover, healthcare providers typically enter EHR data for clinical documentation rather than research purposes, leading to incomplete, inaccurate, or inconsistent data, as well as missing information and data entry errors.[118] This study also faces limitations in generalizability, as EHR data is collected from a specific population and may not be representative of the broader population.[119] Lastly, the data lacks information that may further explain treatment-related decision making contained in unstructured data within narrative clinical notes. Another related limitation is that investigators were not involved in data quality at the point of data abstraction during patients' care by several degrees, limiting their ability to acquire additional patient information. Investigators do not have accessibility during the extract, transform, load process where data validity is assessed as it is transferred from source system to the AMA system. This work could be improved by obtaining greater density and scope of clinical information through manual chart review and analysis of free-text clinical notes to enhance the strength of evidence.

Conclusion

This study presents evidence for factors that may influence decision-making in antihypertensive treatment selection. These results provide important insights considering the published evidence for inequal effectiveness between increasing dose and adding a new medication. The variables associated

with either type of treatment intensification by this study should be considered by health care practitioners to analyze potential biases in their treatment protocols for hypertension management based on various clinical and patient characteristics.

VII. STUDY 3: MODELING ANTIHYPERTENSIVE THERAPEUTIC INTENSIFICATION EFFECTIVENESS FROM OBSERVATIONAL DATA – INCREASING DOSE COMPARED TO ADDING NEW MEDICATION

Background

Controlling elevated blood pressure (BP) in patients with hypertension is a primary strategy for reducing death and disability caused by heart disease, stroke, and other cardiovascular diseases.[1-18] Numerous large-scale observational studies[37-39] and randomized controlled trials[14-22] have contributed significantly to our understanding of how to mitigate cardiovascular disease (CVD) risk by treating elevated blood pressure (BP) and hypertension. There is a strong evidence base demonstrating the safety and efficacy of more than a dozen classes of blood pressure-reducing drugs.[14-22, 37-39] Even though the evidence for CVD risk from uncontrolled hypertension is solid, a variety of safe, effective pharmacological classes of antihypertensive medications are available, and guidelines are clear in recommending treatment action for controlling hypertension, blood pressure control rates remain well below goals set by national population health initiatives.[1, 3, 12, 13, 25-28]

While the AHA/ACC and ESC/ESH hypertension management guidelines explicitly state their recommendations for initiating pharmacological therapy for uncontrolled hypertension and acknowledge that most patients will require at least two drugs to reach control, recommendations for subsequent intensification are not as clearly outlined.[23, 24]

Therapeutic intensification, the amplification of treatment for patients that have already begun pharmacological therapy, comes down to two options: increasing the prescribed dose of existing medication and adding a new drug to the treatment regimen. Two meta-analyses evaluating

pharmacological options for lowering blood pressure and preventing cardiovascular disease determined that, on average, adding an antihypertensive medication at ½ standard, standard, and twice standard dose results in a BP decrease of 7, 9, and 11 mmHg, respectively, compared to a 2-3 mmHg BP reduction for doubling dose of an existing antihypertensive medication.[18, 41] In a recent observational study evaluating hypertensive patients at the Veterans Health Administration, a direct comparison of adding a new medication versus maximizing the dose of an existing drug to control hypertension found that adding a new drug resulted in a slightly larger reduction in mean SBP (-0.8 mm Hg at three months, and -1.1 mm Hg at 12 months). Furthermore, maximizing dose was more likely amongst older patients and three times more common than adding a new medication among all patients. [65]

According to two meta-analyses that evaluated pharmaceutical options for lowering blood pressure and preventing cardiovascular disease, adding an antihypertensive medication at ½ standard, standard, and twice standard doses typically leads to a BP reduction of 7, 9, and 11 mmHg, respectively. Conversely, doubling the dose of an existing antihypertensive medication typically results in a BP decrease of only 2-3 mmHg.[18, 41] One observational study comparing effectiveness of increasing dose or adding a new class of AH medication showed that adding a new drug produced a slightly larger reduction in mean SBP (-0.8 mmHg at three months and -1.1 mmHg at 12 months).[65]

There is a growing role for large observational research to play in providing evidence that is complementary to RCTs. With quasi-experimental methods that can simulate randomization for observational studies (e.g. propensity score matching),[45, 46] and rapidly developing integration of electronic health data into large datasets suitable for rigorous analysis,[38] Congress, the FDA and other decision-making groups are calling for more “real-world evidence” to be contributed to the clinical evidence base moving forward.[48-50] Conducting an RCT requires precise specification of study conditions, including participant selection, treatment and control assignments, exclusion criteria, randomization methods, and outcome measurements. These trials can be challenging to execute due to

their high cost in terms of time and money, and their findings may not be easily applied to real-world scenarios due to the strictness or intricacy of the intervention or participant selection, which may yield a population different from those seen in clinical practice. Although RCTs prioritize the validity of their results, their generalizability is often more limited than large observational studies.[122]

Despite the increasing ability and use for observational evidence in clinical evidence, are very few published studies that have used observational data to derive expected effect in SBP/DBP from increasing dose compared to adding a new class, and none looking specifically at incremental additions of medication classes, medication combinations with known additive effects vs. combinations with known less than additive effects and increasing dose by less than half max vs. half max or greater. This final study focuses on modeling effectiveness of antihypertensive therapeutic intensification treatment options from observational EHR data using pseudo-randomization with propensity score matching.

Research Questions

1. Are greater reductions in BP observed subsequent to instances of therapeutic intensification where dose of an existing medication is increased or where a new class of medication is added?
2. Do the observed reductions in BP after incremental increases in dose differ between key patient characteristics (race/ethnicity, sex, and age) among specific classes of antihypertensive drugs?
3. Do the observed reductions in BP after prescribing a new medication differ between key patient characteristics (race/ethnicity, sex, and age) among specific combinations of antihypertensive drugs?

Objectives

- Use propensity score matching to compare systolic blood pressure changes following different approaches/levels of therapeutic intensification for uncontrolled hypertensive patients: Adding a new medication class vs. increasing dose of existing medication vs. no change in medication.
- Compare SBP changes after increasing dose by less than half max vs. half max or greater.
- Compare SBP changes after incremental additions of medication classes, and between medication combinations with known additive effects vs. combinations with known less than additive effects.

Methodology

The third analysis will estimate the change in blood pressure after increasing dose, adding a medication, and making no changes to medications (inertia) amongst uncontrolled hypertensive patients, to compare the effectiveness of these different approaches/levels of antihypertensive therapeutic intensification. Modeling BP change after antihypertensive therapeutic intensification with observational data will be strengthened by the propensity scores calculated from the analysis in study 2. Using the propensity scores to inform this analysis will improve exchangeability between patients that were treated with an increase in dose and those that were treated with an additional medication. Further specificity in therapeutic intensification magnitude and type will be studied in this analysis. Among instances of dose intensification, we will compare SBP changes after incremental additions in doses and specific combinations from additions of new medications will be compared between

medication classes key patient characteristics: age, sex, race/ethnicity. SBP changes after addition of a new medication will be compared between unique combinations of antihypertensive medication classes that are most frequently prescribed and patient age, sex, and race/ethnicity. Additionally, SBP changes after addition of an antihypertensive medication resulting in a combination of medications with known additive effects will be compared to combinations with known less than additive effects. Finally, the variation and standard deviation in SBP changes following the different types and magnitudes of therapeutic intensification observed in this analysis will be calculated to quantify the range of observed responses in blood pressure. Antihypertensive medications considered in this analysis and corresponding standard dosages were determined using The Prescribers' Digital Reference (formerly "Physicians' Desk Reference)[88, 123] and are included in *Appendix I*.

Since the outcome of interest in this analysis is a continuous variable (SBP change after therapeutic intensification), the models constructed to estimate the effectiveness of different types and magnitudes of antihypertensive therapeutic intensification will be done using mixed effects linear regression. Like the logit models from the previous two studies, the mixed effects linear regression models in this analysis will be constructed using the linear regression function from the generalized linear mixed-effects models package (lme4) in R.[84, 85] A descriptive model will be prioritized since the primary result is the difference in SBP change among patients that differ in one independent variable: therapeutic intensification type. The model will adjust for all covariates deemed statistically significant from previous analyses, but the estimated effect of increasing dose compared to adding a new medication will be the primary output of the model. Performance will be evaluated with R^2 and mean square error calculations to assess the variability in SBP change explained by the model.[88]

Inclusion and Exclusion Criteria

This research study included patients seen at a MAP-participating primary care site who met specific criteria. Patients with at least two visits during the full period of 2020-2022 and at least one visit during the study period of 2021-2022 were included. Patients also had to be 18 years of age or older and have a diagnosis of hypertension, as well as two or more blood pressure measurements. Additionally, patients with all antihypertensive medications verified and those with uncontrolled blood pressure visits were included. Patients already treated with at least one antihypertensive medication were also included. Visits with therapeutic intensification were recorded, and a subset of visits with therapeutic intensification and a follow-up blood pressure visit 7 or more days after were analyzed. Encounters missing a clinician were excluded from the study. Figure 1 provides a sequential overview of each inclusion/exclusion criteria applied to the dataset before analysis. The final dataset for matching contained 10,096 patients and 11,555 encounters. After propensity score matching was performed there were exactly equivalents numbers of dose increases and class additions for a total set of 6,826 encounters for 6,826 patients.

Figure 1. Study 3 Patient Inclusion-Exclusion Criteria Flowchart

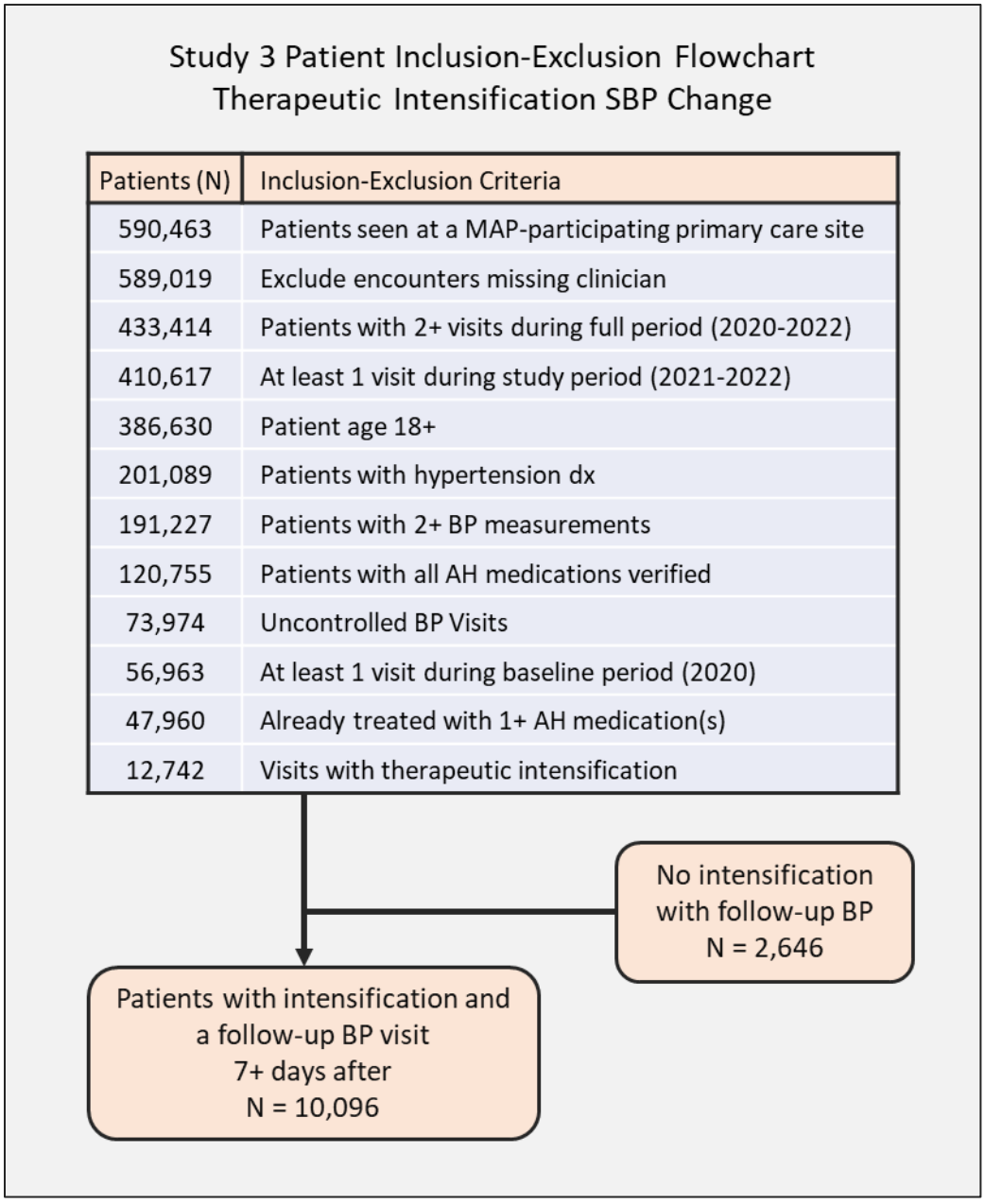


Table A. Study 3 patient and encounter counts by HCO

HCO	Patients	Encounters	Encounters per Patient
A	1,972	2,263	1.15
B	693	867	1.25
C	1,464	1,750	1.20
D	2,461	2,866	1.16
E	3,506	3,809	1.09
Total	**10,096**	**11,555**	**1.14**

Propensity Score Matching

Propensity score matching (PSM) is a statistical technique used to reduce bias in observational studies by matching individuals in treatment and control groups who have similar characteristics based on their propensity scores. The propensity score is the probability of receiving treatment given a set of observed covariates. It is calculated using logistic regression, and the covariates used in the regression model are chosen based on their potential relationship with the treatment and outcome variables.[124, 125]

Once the propensity scores were calculated, each dose increase patient was matched with a class addition patient based on the similarity of their propensity scores using the nearest neighbor matching method. For propensity score matching the binary variable indicating class additions and dose increases

was switched so that class additions were indicated by a value of “0” and dose increases by a value of “1.” This was so that the larger sample (class additions) would be used as the control observations and so that the less frequent dose increases would be matched to the most similar class addition and not the other way around. Propensity scores were calculated and matching of patients with class additions to those with dose increases was done using the “matchit” function from the MatchIt package in R.[126]

The variables determined to be statistically significant covariates of treatment selection by study 2 were used for propensity score calculation and for matching dose increases to class additions. These covariates included DBP, previous visit SBP, previous visit DBP, previous BP uncontrolled, proportion of uncontrolled visits, AH medication count, age category, white versus non-white, proportion of visits with the patient's primary clinician, total comorbidities, confirmatory blood pressure measurement, BP visit frequency, diabetes with complications, cardiac arrhythmia, liver disease, renal failure, solid tumor cancer, previous therapeutic intensification event, cumulative SBP average and cumulative DBP average. Other variables including BMI, LDL, and HDL were not included in the model despite being found as significant covariates in study two due to the presence of NA values that could not be handled by the matching function. The results of the propensity score matching process are illustrated in Figures 2 and 3.

Extended Comparison of Dose vs. Class

The subsequent change in systolic blood pressure after adding a new class and increasing dose of an existing medication was further compared by specific demographic groups including age sex and race and between specific classes of AH medications added or intensified and between specific combinations of existing classes of age medications and added or intensified classes of age medications. Furthermore, specific combinations of ah medications with known less than additive effects were selected from the

data set for comparison with medication additions where combinations are additive. Finally, instances of dose increase where the medication was still not intensified to at least standard dose was compared two dose increases where standard dose or higher was reached. For each extended comparison the change in systolic blood pressure from an elevated blood pressure visit to the next visit was calculated for patients that did not have a therapeutic intensification at the elevated BP visit. These calculations of ΔSBP were summarized by age, sex, race, and existing AH medications as well to serve as a control group for adjusting the ΔSBP for regression to the mean that is present in blood pressure measurements over time. Regression to the mean is a statistical phenomenon where an observation that is extreme on one measurement is likely to be less extreme on a subsequent measurement. Blood pressure regression to the mean refers to the tendency of blood pressure measurements to move towards the mean value over time, even without any intervention or change in behavior. This phenomenon occurs due to the biological variability and natural fluctuation characteristic of blood pressure, which can be affected by many factors included stress and activity level. Blood pressure regression to the mean can have important implications for clinical practice and research. For example, a patient with a high blood pressure reading may be diagnosed with hypertension and prescribed medication. However, if subsequent measurements show that the blood pressure has decreased towards the mean value, it is possible that the patient did not have true hypertension and may not need medication.[127, 128] ΔSBP for patients with elevated BP visits and no intensification were summarized by age, sex, race, and existing medications to adjust the corresponding categories for ΔSBP after dose increases and class additions to all for a more precise ΔSBP to be calculated and adjusted for natural regression to the mean.

Results

Tables 1-4 summarize patient demographics and clinical characteristics, SBP and DBP distributions, and encounter level dose increase and class additions rates for the final patient dataset and between the five HCOs. The total number of patients included in the study was 10,096 with 11,555 encounters with either a dose increase or a class addition (single encounters with both intensification types were excluded), and a follow-up visit at least days from intensification where BP was measured and recorded. The mean age of the patients in this analysis dataset was 62.0 years, with a standard deviation (SD) of 13.3. There were more females (59.2%) than males (40.8%) in the study population. Black patients accounted for the majority (50.9%) of the study population, compared to 44.2% white patients. The average AH medications per patient was 3.2 at the end of the study period, rising from 1.9 medications at the beginning of the study period. The mean systolic blood pressure (SBP) was 153.0 mmHg, with a SD of 14.3. The mean diastolic blood pressure (DBP) was 85.0 mmHg, with a SD of 12.1. The mean body mass index (BMI) was 33.1, mean HbA1c 6.9%, mean glucose level 122.0 mg/dL, and mean LDL cholesterol level was 104.0 mg/dL. As observed in study 1 and 2, the three most common comorbidities remained to be diabetes (38.0%), chronic pulmonary disease (18.9%) and renal failure was present in (12.6%).

On average 28.4% of all visits had an SBP of 160 or higher. Most visits recorded BP in the 140-150 mmHg group, which accounted for 40% of visits overall (Table 2). HCO D had the highest proportion of visits with SBP above 160 mmHg at 37.4%, while all other HCOs had between 22-33% of visits above 160. The majority of DBP recordings for all HCOs were between 80-90 mmHg, except for HCO B which had 34.9% of DBPs between 90-100 mmHg and HCO D where 37.4% of DBPs fell between 70-80 mmHg (Table 3).

Of the 11,555 encounters with a therapeutic intensification event included in this study, class additions were observed more than twice as frequently as dose increases (Table 4). 3,377 of the intensifications (29.2%) were dose increases, compared to 8,178 (70.8%) class additions. The highest and lowest dose increase rates were observed at HCO D (54.9%) and HCO E (8.4%), respectively. having the lowest (8.4%). Inversely, the highest and lowest observed rates of class additions were at HCO E (91.6%) and HCO D (45.3%). The variance in these observed rates of treatment selection indicate that treatment strategies may differ significantly by institution.

Table 1. Summary of Patient Demographics and Clinical Characteristics

		Total		**HCO A**		**HCO B**		**HCO C**		**HCO D**		**HCO E**	
Patients	N	10,096		1,972		693		1,464		2,461		3,506	
Age	mean, SD	62.0	13.3	63.8	14.2	58.6	13.4	58.2	13.5	63.7	11.2	62.1	13.6
Male	N, %	4,117	40.8%	736	37.3%	283	40.8%	587	40.1%	961	39.0%	1,550	44.2%
Female	N, %	5,979	59.2%	1,236	62.7%	410	59.2%	877	59.9%	1,500	61.0%	1,956	55.8%
White	N, %	4,462	44.2%	934	47.4%	177	25.5%	321	21.9%	720	29.3%	2,310	65.9%
Black	N, %	5,136	50.9%	982	49.8%	507	73.2%	1,098	75.0%	1,450	58.9%	1,099	31.3%
Other	N, %	311	3.1%	37	1.9%	3	0.4%	40	2.7%	158	6.4%	73	2.1%
Baseline AH meds	mean, SD	1.9		1.9		2.1		2.1		2.4		1.6	
Final AH meds	mean, SD	3.2		3.2		3.3		3.4		3.2		2.9	
SBP	mean, SD	153.0	14.3	151.0	12.8	154.1	16.9	154.7	13.6	157.4	15.9	150.2	12.8
DBP	mean, SD	85.0	12.1	85.8	12.3	91.9	13.8	88.0	12.1	79.5	11.2	85.7	10.8
BMI	mean, SD	33.1	8.6	32.5	9.3	34.1	9.3	33.4	9.5	32.6	7.7	33.4	8.1
HbA1C	mean, SD	6.9	1.8	6.6	1.6	7.2	2.0	7.2	1.9	7.0	1.8	6.7	1.6

Glucose	mean, SD	122.0	59.0	119.5	57.1	125.1	69.4	123.4	65.7	131.6	65.5	115.3	48.5
LDL avg	mean, SD	104.0	37.3	102.3	38.1	103.0	34.9	107.1	37.1	103.4	37.5	104.3	37.1
HDL avg	mean, SD	52.8	15.8	54.9	17.5	51.5	15.7	51.6	14.6	49.7	13.2	54.7	16.6
Cholesterol	mean, SD	170.0	51.8	122.8	56.0	178.2	42.2	184.4	43.6	172.1	44.7	185.8	43.4
Diabetes	N, %	3,836	38.0%	676	34.3%	268	38.7%	498	34.0%	1,340	54.4%	1,054	30.1%
CHF	N, %	621	6.2%	160	8.1%	70	10.1%	73	5.0%	228	9.3%	90	2.6%
Arrhythmia	N, %	1,350	13.4%	406	20.6%	75	10.8%	88	6.0%	315	12.8%	466	13.3%
Renal Failure	N, %	1,268	12.6%	281	14.2%	171	24.7%	175	12.0%	404	16.4%	237	6.8%
Liver Disease	N, %	570	5.6%	141	7.2%	25	3.6%	46	3.1%	243	9.9%	115	3.3%
Valvular Disease	N, %	307	3.0%	81	4.1%	10	1.4%	20	1.4%	57	2.3%	139	4.0%
CEVD	N, %	740	7.3%	197	10.0%	48	6.9%	68	4.6%	204	8.3%	223	6.4%
MI	N, %	203	2.0%	84	4.3%	5	0.7%	18	1.2%	66	2.7%	30	0.9%
PVD	N, %	718	7.1%	195	9.9%	44	6.3%	84	5.7%	204	8.3%	191	5.4%
CPD	N, %	1,906	18.9%	463	23.5%	141	20.3%	304	20.8%	513	20.8%	485	13.8%
Metastatic Cancer	N, %	137	1.4%	37	1.9%	0	0.0%	1	0.1%	70	2.8%	29	0.8%
Solid Tumor	N, %	747	7.4%	187	9.5%	26	3.8%	34	2.3%	298	12.1%	202	5.8%

Table 2. Systolic Blood Pressure Distribution

	Total		**HCO A**		**HCO B**		**HCO C**		**HCO D**		**HCO E**	
SBP	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%
<120	26	0.2%	5	0.2%	7	0.8%	0	0.0%	3	0.1%	11	0.3%
120-130	144	1.2%	44	1.9%	30	3.5%	5	0.3%	4	0.1%	61	1.6%
130-140	596	5.2%	155	6.8%	73	8.4%	95	5.4%	43	1.5%	230	6.0%
140-150	4,603	39.8%	922	40.7%	254	29.3%	614	35.1%	1,033	36.0%	1,780	46.7%
150-160	2,910	25.2%	584	25.8%	221	25.5%	500	28.6%	711	24.8%	894	23.5%
160-170	1,684	14.6%	345	15.2%	124	14.3%	270	15.4%	461	16.1%	484	12.7%
170+	1,592	13.8%	208	9.2%	158	18.2%	266	15.2%	611	21.3%	349	9.2%

Table 3. Diastolic Blood Pressure Distribution

	Total		**HCO A**		**HCO B**		**HCO C**		**HCO D**		**HCO E**	
DBP	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%	Visits	%

<70	1,050	9.1%	221	9.8%	38	4.4%	83	4.7%	505	17.6%	203	5.3%
70-80	2,604	22.5%	414	18.3%	96	11.1%	331	18.9%	1,071	37.4%	692	18.2%
80-90	3,529	30.5%	665	29.4%	211	24.3%	571	32.6%	729	25.4%	1,353	35.5%
90-100	3,000	26.0%	645	28.5%	303	34.9%	500	28.6%	420	14.7%	1,132	29.7%
100-110	989	8.6%	242	10.7%	133	15.3%	180	10.3%	98	3.4%	336	8.8%
110+	383	3.3%	76	3.4%	86	9.9%	85	4.9%	43	1.5%	93	2.4%

Table 4. Summary of Dose Increase vs. Class Addition Rates by HCO

	Total	**HCO A**	**HCO B**	**HCO C**	**HCO D**	**HCO E**
Patients with TI	10,096	1,972	693	1,464	2,461	3,506
Uncontrolled Encounters	11,555	2,263	867	1,750	2,866	3,809
Dose Increases	3,377	551	289	647	1,569	321
Dose Increase Rate	29.2%	24.3%	33.3%	37.0%	54.7%	8.4%
Class Additions	8,178	1,712	578	1,103	1,297	3,488
Class Addition Rate	70.8%	75.7%	66.7%	63.0%	45.3%	91.6%

Matched Regression for ΔSBP

The distribution of propensity scores for dose increases and class additions are plotted in Figure 2. "Treated units" in this figure refers to dose increases while "control units" refer to class additions. The standardized mean difference and propensity score for each covariate used in the matching function is displayed in Figure 3. Each of the 3,413 dose increases was matched to one class edition leaving 0 unmatched dose increases and 4,765 unmatched class additions. After matching for each covariate teamed to have a significant relationship with treatment selection the adjusted difference in subsequent change in SBP was 1.31 mmHg higher after dose increases compared to class additions. This indicates that even when adjusting for the identified factors that create bias in the comparison between these two intensification types, adding a new class of AH medication is still found to be more effective in

reducing elevated BP compared to increasing dose of an existing medication. Linear regression results for ΔSBP after PS matching are detailed in Table 5.

For all treatment intensification events with a follow-up BP visits, the reduction in SBP after addition of a new medication was -14.18 mmHg on average, compared to -12.72 mmHg for dose increases. For patients with no treatment intensification, the average reduction in SBP from an elevated BP visit (>140/>90) to their next visit was -10.7 mmHg. Using the patients with elevated BP visits but no treatment intensification to adjust the change in SBP for class additions and dose increases resulted in a -3.48 SBP reduction for class additions and a -1.46 SBP reduction for dose increases. Class additions resulted and a larger reduction in SBP and those increases for each specific demographic variable category (Tables 6A and 6B). The same trend was observed when comparing class additions with dose increases by the specific AH class that was added or intensified, with class additions averaging a 3.57 reduction in SBP and dose increases averaging a 2.06 reduction in SBP after adjusting for controls and limiting to the top 15 most frequent classes added or intensified (Tables 7A and 7B). Table 9 outlines a selection of class additions that are known to have less than additive effects, demonstrating that these specific combinations resulted in smaller SBP reductions on average than both dose increases and class additions overall. Table 10 shows that doubling the dose resulted in a larger average SBP reduction compared to increasing dose from less than standard to standard dose or higher.

Figure 2. Distribution of Propensity Scores for Matching Intensification Types

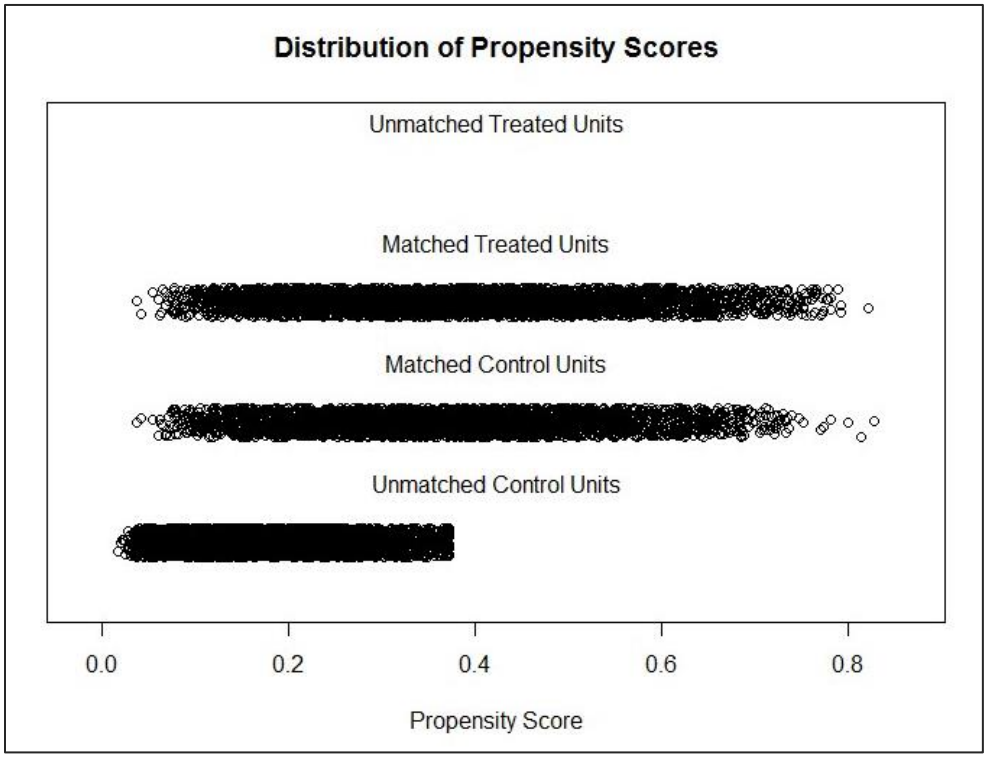


Figure 3. Standard Mean Difference in Matched Variables for Intensification Types.

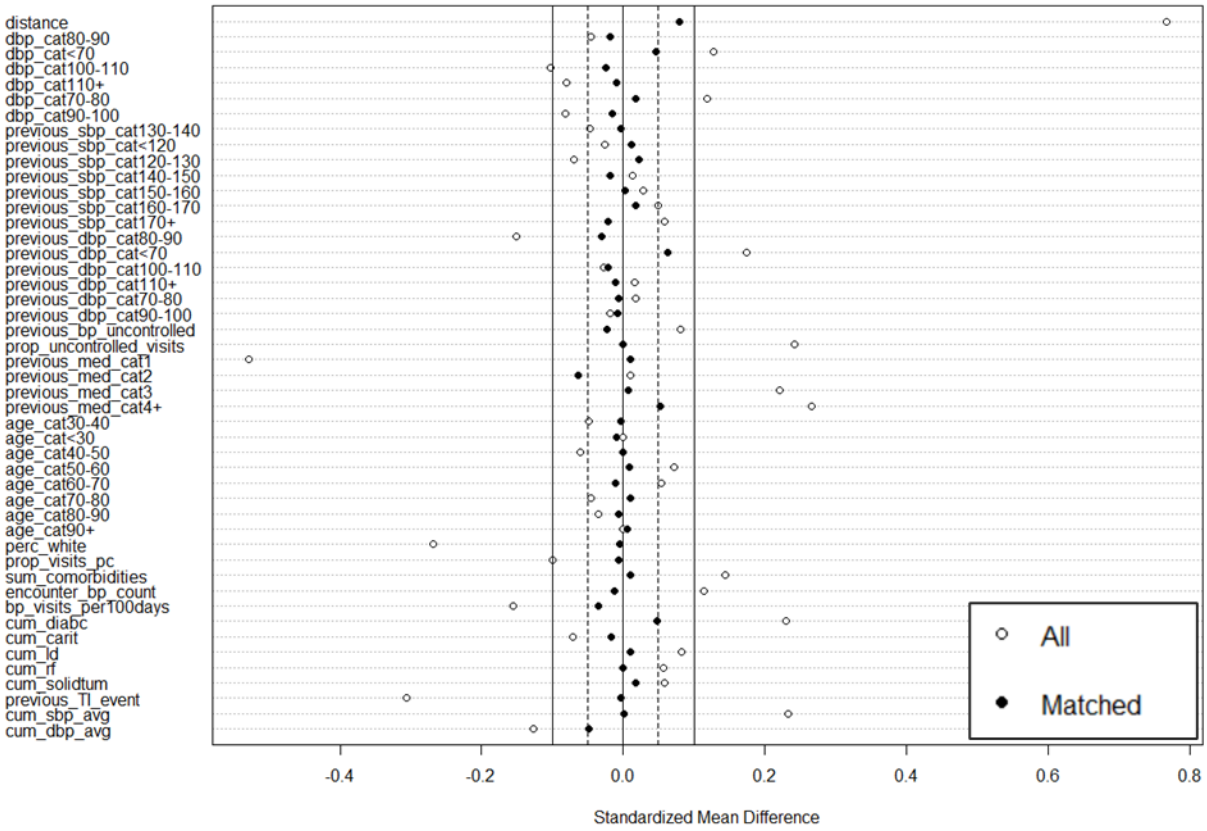


Table 5. Matched Linear Regression Estimate of Difference in ΔSBP

Term	Estimate	Std Error	t Statistic	p-value	R^2
(Intercept)	-14.0214	0.330038	-42.4842	<2E-16	0.001144
TI Type (0=Class_Addition, 1=Dose_Increase)	1.30501	0.466744	2.795987	0.005189	

Table 6A. ΔSBP after Class Addition by Demographics

Variables	Class Addition Events	ΔSBP	Control ΔSBP	Adjusted ΔSBP
Female	4,858	-14.81	-10.85	-3.97
Male	3,320	-13.25	-10.47	-2.78
Black Race	4,030	-14.11	-10.13	-3.99
White Race	3,828	-14.27	-11.41	-2.86
Other Race	215	-13.17	-9.97	-3.20
Asian-PI Race	105	-15.57	-10.07	-5.51
Age <30	70	-14.99	-7.68	-7.30
Age 30-40	401	-11.27	-8.15	-3.13
Age 40-50	1,068	-13.40	-9.00	-4.40
Age 50-60	1,798	-13.81	-10.69	-3.11
Age 60-70	2,314	-14.43	-11.41	-3.01
Age 70-80	1,777	-15.36	-11.26	-4.10
Age 80-90	656	-14.14	-10.70	-3.45
Age 90+	94	-14.10	-10.78	-3.31
Total, Weighted Avg.	**8,178**	**-14.18**	**-10.70**	**-3.48**

Table 6B. ΔSBP after Dose Increase by Demographics

Variables	Dose Increase Events	ΔSBP	Control ΔSBP	Adjusted ΔSBP
Female	2,017	-12.94	-10.85	-2.09
Male	1,396	-12.40	-10.47	-1.93
Black Race	2,011	-12.52	-10.13	-2.39
White Race	1,164	-13.24	-11.41	-1.83
Other Race	140	-13.08	-9.97	-3.11
Asian-PI Race	98	-9.99	-10.07	0.08
Age <30	29	-7.34	-7.68	0.34
Age 30-40	135	-12.28	-8.15	-4.14
Age 40-50	381	-11.77	-9.00	-2.77
Age 50-60	856	-12.15	-10.69	-1.46
Age 60-70	1051	-13.26	-11.41	-1.84
Age 70-80	679	-12.97	-11.26	-1.71
Age 80-90	243	-14.54	-10.70	-3.85
Age 90+	39	-9.59	-10.78	1.19
Total, Weighted Avg.	**3,413**	**-12.72**	**-10.70**	**-2.01**

Table 7A. ΔSBP after Class Addition by AH Class Added

Added Classes	Class Addition Events	ΔSBP	Adjusted ΔSBP
CCB	1,486	-16.52	-5.81
ARB	1,069	-12.09	-1.38
TD	1,042	-16.40	-5.70
BB	631	-10.32	0.38
ACEI	538	-13.93	-3.23
ARB | TD	527	-16.55	-5.84
ACEI | TD	327	-15.85	-5.15
LD	300	-11.66	-0.96
ACEI | CCB	247	-12.77	-2.07
AdRB	203	-12.31	-1.60
ARB | CCB	161	-12.94	-2.24
Vd	128	-14.31	-3.61
ARB | CCB | TD	121	-14.31	-3.61
CCB | TD	111	-15.31	-4.60
ACEI | CCB | TD	92	-15.01	-4.31
BB | CCB	91	-11.15	-0.45
CA	82	-14.41	-3.71
PSD | TD	82	-13.99	-3.29
BB | TD	69	-9.78	0.92
ARB | BB	67	-13.00	-2.30
Total, Weighted Avg.	**7,374**	**-14.27**	**-3.57**

Table 7B. ΔSBP after Dose Increase by AH Class Intensified

Intensified Classes	Dose Increase Events	ΔSBP	Adjusted ΔSBP
ACEI	861	-12.91	-2.21
CCB	757	-14.38	-3.67
ARB	498	-12.03	-1.33
TD	308	-10.21	0.49
BB	271	-10.37	0.33
ARB | TD	116	-14.17	-3.47
ACEI | TD	83	-16.22	-5.51
LD	75	-8.31	2.40
ACEI | CCB	62	-14.79	-4.09
Vd	52	-13.23	-2.53
AdRB	33	-8.55	2.16

CCB | TD	28	-18.86	-8.15
ACEI | BB	23	-17.39	-6.69
ARB | CCB	23	-14.17	-3.47
CCB-nD	22	-8.77	1.93
CA	20	-13.50	-2.80
BB | CCB	19	-8.11	2.60
ACEI | LD	17	-12.76	-2.06
ARB | CCB | TD	15	-21.40	-10.70
BB | TD	14	-16.36	-5.65
Total, Weighted Avg.	**3,297**	**-12.76**	**-2.06**

Table 8A. ΔSBP for Most Frequent Added-Existing Medication Combinations (Class Additions)

Added Classes	Existing Classes	Class Addition Events	ΔSBP	Control ΔSBP	Adjusted ΔSBP
ARB	CCB	138	-12.47	-11.03	-1.44
CCB	ARB	110	-18.62	-10.72	-7.89
CCB	TD | ARB	106	-16.70	-11.76	-4.94
TD	CCB	105	-15.28	-11.03	-4.25
CCB	ACEI	103	-17.55	-11.71	-5.84
ACEI	CCB	90	-15.52	-11.03	-4.49
TD	ACEI	89	-19.64	-11.71	-7.93
ARB	TD	81	-9.75	-11.80	2.05
CCB	BB	80	-18.35	-12.62	-5.73
CCB	TD	79	-14.38	-11.80	-2.58
CCB	TD | ACEI	75	-19.00	-11.95	-7.05
ARB	CCB | TD	70	-12.21	-9.51	-2.71
TD	ARB	69	-14.17	-10.72	-3.45
TD	CCB | ARB	55	-18.76	-9.68	-9.08
TD	CCB | ACEI	49	-21.08	-10.84	-10.24
Total, Weighted Avg.		**1,299**	**-16.02**	**-11.196**	**-4.83**

Table 8B. ΔSBP for Most Frequent Intensified-Existing Medication Combinations (Dose Increases)

Intensified Classes	Existing Classes	Dose Increase Events	ΔSBP	Control ΔSBP	Adjusted ΔSBP
ACEI	ACEI	180	-13.33	-11.71	-1.62
CCB	CCB	146	-16.87	-11.03	-5.84
ACEI	ACEI | TD	127	-13.87	-10.92	-2.95
ACEI	ACEI | CCB	119	-14.09	-10.62	-3.47
ARB	ARB	88	-13.95	-10.72	-3.23
ACEI	CCB | ACEI | TD	83	-12.72	-9.59	-3.13
ARB	CCB | ARB	66	-9.86	-10.12	0.25
CCB	CCB | ARB	65	-10.60	-10.12	-0.48
CCB	CCB | ACEI	61	-16.30	-10.96	-5.33
ACEI	TD | ACEI	59	-18.14	-12.53	-5.61
ARB	TD | ARB	59	-10.78	-11.74	0.96
ACEI	CCB | ACEI	56	-14.48	-10.96	-3.52
CCB	CCB | TD	56	-13.54	-9.51	-4.03
TD	TD | ACEI	43	-15.58	-12.53	-3.05
CCB	CCB | TD | ARB	43	-14.88	-10.24	-4.65
Total, Weighted Avg.		**1,251**	**-13.99**	**-10.92**	**-3.07**

Table 9. Class Additions with Known Less Than Additive Effects[120, 121, 129, 130]

Added Classes	Existing Classes	Class Addition Events	ΔSBP	Control ΔSBP	Adjusted ΔSBP
CCB	BB	80	-18.35	-12.62	-5.73
ARB	BB	62	-14.90	-12.62	-2.29
ACEI	BB	49	-13.45	-12.62	-0.83
BB	CCB	36	-12.72	-11.03	-1.69
BB	CCB | TD | ARB	23	-8.43	-9.88	1.44
BB	ACEI	22	-8.45	-11.71	3.26
BB	ARB	22	-12.32	-10.72	-1.59
ARB	CCB | ACEI	21	-9.14	-10.84	1.70
BB	CCB | ACEI	17	-10.71	-10.84	0.13
BB	CCB | TD | ACEI	15	-7.00	-11.34	4.34
ARB	CCB | BB	14	-13.29	-10.78	-2.51
ARB	TD | ACEI	14	-6.64	-11.95	5.30
BB	CCB | ARB	14	-10.00	-9.68	-0.32
BB	TD | ARB	14	-14.50	-11.76	-2.74
ARB	ACEI | CCB	13	-9.92	-10.62	0.70

Total, Weighted Avg.	**416**	**-12.96**	**-11.202**	**-1.76**

Table 10. ΔSBP for Dose Increases to Less Than Standard vs. Standard or Higher

Dose Increase Intensity	Dose Increase Events	ΔSBP	Control ΔSBP	Adjusted ΔSBP
<Std	658	-12.59	-10.70	-1.89
Std+	2755	-12.75	-10.70	-2.04
<100%	942	-11.08	-10.70	-0.38
100%+	2471	-13.34	-10.70	-2.64

Discussion

In this research study, a large observational dataset was used to compare the efficacy of adding new medications vs. increasing dose of existing medication in hypertension treatment. Adding a new medication was associated with a slightly greater reduction in mean SBP at the next visit. These results support the previous findings by Aubert et al.[65] The findings of lower SBP after follow-up for class additions was consistent for specific demographic variables, specific existing AH classes, and among different AH class combinations. Finally, the study found that doubling the dose of medication resulted in a larger reduction in SBP compared to increasing the dose from less than standard to standard or higher. These findings are important due to the limited real-world evidence for effectiveness of these two AH treatment strategies from observational data, and due to the limited guidance on how to intensify treatment after first-line therapy.

The use of structured electronic health record (EHR) data in this study limits the strength of evidence in several ways. Inconsistencies in the data due to lack of standardization across healthcare systems and providers can decrease its accuracy and usefulness for research purposes. Data entry errors and missing information also limit the accuracy and reliability of the study.[117-119] Additionally, the limited scope of the data, which does not include social determinants of health or narrative clinical notes, may affect the generalizability and applicability of the findings. The investigators were also removed from the point of data abstraction, which prevented them from acquiring additional information. To improve the strength of future analysis, manual chart review and the use of free-text clinical notes may be necessary to validate computable phenotypes and improve the clinical information for modeling.

Conclusion

In conclusion, this study provides quasi-experimental evidence for the magnitude of SBP reduction that can be expected from the two types of treatment intensification: adding a new class and increasing dose of an existing medication. the estimated effect of treatment can help guide clinicians and patience and their expectations for BP controlling therapies and their decision making when increasing therapy and choosing between different options for intensification and different types of medication classes.

VIII. DISCUSSION & CONCLUSION

The three studies presented in this paper aimed to evaluate the extent of therapeutic inertia and factors associated with it among patients with hypertension in different healthcare organizations. The studies analyzed data from electronic health records of patients with hypertension and found varying rates of therapeutic inertia, as well as factors that affect the likelihood of therapeutic intensification.

Study 1 analyzed data from 120,755 patients from five different healthcare organizations and found an average therapeutic intensification rate of 15.9%, with the highest rate occurring in HCO D (19.5%) and the lowest at HCO E (13.3%). The study also found a fairly consistent therapeutic inertia rate between all five HCOs. The study developed predictive models for modeling therapeutic intensification events using data from electronic health records of patients with hypertension. The models included factors such as SBP, DBP, patient demographics, encounter attributes, and antihypertensive medications. The results indicated that SBP and DBP at the current visit are important predictors of therapeutic intensification. The study also found that patient demographics and encounter attributes such as visit frequency and days since the last BP visit are important predictors of therapeutic intensification. Overall, the study provided valuable insight into the factors that clinicians consider when deciding whether or not to intensify antihypertensive therapy.

Study 2 aimed to investigate the association between provider characteristics and therapeutic inertia in a single healthcare organization. The study analyzed data from 44,418 patients and 347 providers and found that provider characteristics such as gender, race, and years of experience were not significantly associated with therapeutic inertia. However, the study did find that providers with a higher patient panel size and higher specialty care referrals had lower odds of therapeutic inertia. The study suggests that provider workload and referral patterns may influence therapeutic inertia.

Study 3 evaluated the impact of clinical decision support (CDS) on therapeutic inertia and blood pressure control among patients with hypertension. The study analyzed data from 2,230 patients and found that the use of CDS resulted in a significant reduction in therapeutic inertia and improved blood pressure control. The study suggests that the use of CDS can be an effective tool in reducing therapeutic inertia and improving blood pressure control among patients with hypertension.

The studies presented in this paper provide important insights into the prevalence and factors associated with therapeutic inertia among patients with hypertension. The studies confirm previous consensus that SBP and DBP at the current visit are important predictors of therapeutic intensification. The studies also provide additional evidence that patient demographics and encounter attributes, such as visit frequency and age, are important predictors of therapeutic intensification. Furthermore, the studies suggest that provider workload and referral patterns may influence therapeutic inertia and that the use of CDS can be an effective tool in reducing therapeutic inertia and improving blood pressure control among patients with hypertension.

One limitation of these studies is that they relied on secondary observational data extracted from electronic health records, which may not always be complete, accurate, or consistent. Additionally, missing information and data entry errors are common in electronic health records, which may lead to measurement bias or detection bias. Another limitation is that the predictive models developed in Study 1 had moderate to good performance, but further research is needed to validate the models on larger and more diverse datasets. Finally, the studies did not assess the reasons behind therapeutic inertia, which limits the understanding of the factors contributing to this phenomenon.

In conclusion, the studies presented in this paper provide important insights into the factors associated with therapeutic inertia among patients with hypertension. The findings can inform clinical decision-making and the development of interventions aimed at reducing therapeutic inertia and improving blood pressure control among patients with hypertension.

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APPENDICES

Appendix I. Antihypertensive Drugs, Classes, and Standard Dosages [123]

Appendix II. Extended Univariate and Multivariable Mixed-Effects Regression Output for Study 1 – Therapeutic Intensification Event Analysis

Appendix III. Extended Univariate and Multivariable Mixed-Effects Regression Output for Study 1 – Time to Therapeutic Intensification Analysis

Appendix IV. Extended Univariate and Multivariable Mixed-Effects Regression Output for Study 2 – Therapeutic Intensification Type Selection: New Class vs. Increasing Dose