Outcomes of Treatment Modifications of Antihypertensive Regimens

by

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Abstract

Antihypertensive treatment modifications (TMs)—addition, uptitration, switching, and downtitration–often are necessary to address issues such as unattained blood pressure (BP) goals, adverse drug events, drug cost, or patient dissatisfaction with first-line treatment. Despite a high prevalence, our understanding of TMs is limited. The objectives of this dissertation were: (a) to assess the patterns of TMs, (b) to compare adherence across the TM strategies and assess the factors associated with adherence, and (c) to compare the healthcare costs across TM strategies and understand its association with adherence.

A retrospective cohort study of the BlueCross-BlueShield of Texas claims database (2008-2012) was conducted. A total of 21,642 newly treated patients were followed for 12 months to determine if and when they received a TM. Adherence (measured as proportion of days covered (PDC)) and costs were compared over a 12-month duration. Cox regression models were used to determine the likelihood of TM and discontinuation, while generalized linear models were used to compare adherence and costs. About 48.5% of patients received TMs within one year of initiating treatment. Rates of TM were significantly different across drug classes ($P<0.05$). Patients adding medications were about 25% (vs. uptitration) and 50% (vs. switching) less likely to discontinue treatment. Adherence was lowest in the addition group (mean=0.68 ± 0.27). The odds of adherence was lower for the free-pill combination (FPC) group but higher

for the fixed-dose combination (FDC) group compared to other TM strategies (P<0.05). The total all-cause annual healthcare costs were higher for addition and downtitration compared to other competing strategies (P<0.001). Drug costs were higher for addition compared to alternative strategies (P<0.0001). However, the costs of hypertension and cardiovascular-related inpatient visits were lower for the FDC group compared to the uptitration ($11,348.8 lower; P=0.004) and switching ($2,655.41 lower; P=0.19) groups. Overall, the use of FDCs appear to be an advantageous intensification strategy while switching of medication may be a preferred approach over downtitration. Further research is required to understand the long-term cost-effectiveness of alternative TM strategies and the actual relationship of these findings with BP control and long-term outcomes.

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List of Abbreviations

US United States

TM Treatment modification

BP Blood Pressure

RCT Randomized controlled trial

ADE Adverse drug event

CV Cardiovascular

CHAPTER ONE: INTRODUCTION

1.1 Overview

Hypertension is one of the most common chronic conditions, affecting one out of every three adults in the US.[1] Pharmacotherapy is effective for the treatment of hypertension,[2] and approximately 70% of diagnosed patients use antihypertensive drugs to treat the condition.[1] Most patients initiating antihypertensive therapy are treated with monotherapy. Data from observational studies show that about 50-75% of hypertensive patients undergo modifications in their antihypertensive regimen within the first year of treatment initiation.[3-6]

Patients undergo treatment modifications (TMs) due to various reasons including inadequate blood pressure (BP) control, adverse drug events, poor adherence, costs, and patient dissatisfaction.[7] Inadequate BP control is one of the most common reasons for TM. Data from randomized controlled trials (RCTs) suggest that only about 50% of the patients treated with monotherapy will achieve BP goal.[8-11] Studies have shown that even with high adherence to first-line monotherapy, less than half of the patients manage to attain recommended BP level.[12,13] TM is critical for intensifying treatment of patients who fail to attain BP goal after first-line treatment.[14-16] Intensification of treatment regimens are prevalent among newly treated hypertensive patients.[7,17] Another common reason for TM is adverse events. Antihypertensive drugs have dose dependent ADEs; therefore, patients may be prescribed a lower dose of the current drug. Alternatively, the healthcare provider may switch the drug. Similarly, concerns regarding costs, patient dissatisfaction, contraindications, and poor adherence are often addressed by modifying the patient's treatment regimen. Such modifications can be

broadly classified into – titration (both increase and decrease) of the dose, addition of another drug or using combination therapy, and switching of the drug. Modifications of antihypertensive regimens are crucial for the management of hypertension. Although TMs are highly prevalent, their implications on patients' adherence and the healthcare costs are not well understood.

One of the key aspects of pharmacotherapy of any disease is adherence. Adherence to the treatment regimen has been shown to be associated with BP control,[13,18,19] decreased hospitalizations,[20-22] and lower medical care costs.[20,23,24] Persistent use of antihypertensive drugs has been shown to increase the odds of BP goal attainment by 40%.[25] Adherence is also associated with long-term reduction of the risk of cardiovascular (CV) and cerebrovascular events.[20,23,26] The risk of a CV event is reduced by more than 50% in patients who are adherent to antihypertensive drugs, compared to their low-adherent counterparts.[27] Non-adherence to the modified regimen has been shown to significantly reduce the likelihood of BP control after TM.[28] Currently there are no preferred strategies for TM. For example, to intensify treatment, the provider may increase drug dose or add another drug to the regimen. Also, both switching of drug or reduction of drug dose are reasonable alternatives for managing poor tolerance. These alternative strategies have not been compared in terms of adherence. A strategy with a better adherence profile will lead to better short-term (i.e., BP control) and long-term (i.e., CV risk) outcomes. Hence, it is important to compare patients' adherence to the TM strategies.

Patients' healthcare costs are expected to change if and when TM is required.[29] Changes in the cost of medications are most obvious with TMs such as up-titration of

dose, addition of drugs, or switching that are likely to increase the medication costs. Clinical practice guidelines recommend monthly follow-up for newly treated patients undergoing TMs; thus, utilization of ambulatory visits and outpatient visits may also contribute to increase in health care expenditures.[2] Previous studies suggest that TMs are associated with increases in the total healthcare expenditure.[30-32] However, the differences in healthcare costs across the TM strategies, if any, have not been studied before. Because adherence is required for attaining BP goals and it is strongly associated with reduction in healthcare costs,[20,23,24] it is important that we understand its role in determining the healthcare costs after TM.

The objectives of the proposed study are: (a) to assess the patterns of TMs among patients previously treated with first-line antihypertensive drugs, (b) to compare adherence across the TM strategies, and assess the factors associated with adherence, and (c) to estimate and compare the total healthcare costs across TM strategies and understand the impact of adherence on costs. Understanding the differences between TM strategies will be helpful to the patients and healthcare provider for choosing a TM strategy with the most beneficial outcomes.

1.2 Specific Aims

We identified three specific aims to examine the outcomes of TM. The aims of this study were as follows-

<u>Aim 1</u>: To determine the rates of TM among patients treated with first-line antihypertensive drugs, and to compare the rates of discontinuation across TM strategies.

We determined the rates of TM across first-line monotherapy drugs including – diuretics, beta-blockers, calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). Patients starting treatment with first-line antihypertensive drugs were followed for 12-months duration from their index prescription fill date to identify TMs. We used descriptive statistics to summarize the type of TM at follow-up according to the first-line monotherapy drug class. Cox proportional hazards models were used to determine the likelihood of TM across drug classes, and the discontinuation rates across TM strategies for each monotherapy drug class.

<u>Aim 2</u>: To determine the adherence rates and characterize factors associated with adherence after TM among patients previously treated with first-line antihypertensive drugs.

Adherence to the modified regimen was calculated using the proportion of days covered (PDC) for the four groups (switching, addition, downtitration, and uptitration). Adherence was measured as both continuous and categorical outcome. Factors that were

assessed include health services utilization, use of concomitant antidiabetic or antihyperlipidemic drugs, and existing CV conditions.

<u>Aim 3</u>: To determine healthcare utilization costs, and examine the association of adherence with healthcare utilization costs after TM among patients previously treated with first-line antihypertensive drugs.

Total healthcare costs including inpatient, outpatient, and drug costs were compared after TM. Costs of individual components — inpatient, outpatient, and drug costs – were also compared across TM strategies. We also examined the association between adherence and costs after TM.

1.3 Importance of proposed research

Antihypertensive drugs have been shown to be effective and safe in the treatment of hypertension. Several antihypertensive drugs are available, and these drugs are prescribed as monotherapy or in combination. More than one-third of hypertensive patients in the US have Stage I hypertension[33], and the recommended first-line treatment for these patients is monotherapy.[2] A large number of patients who start with monotherapy undergo TMs due to poor efficacy, adverse events, costs, or other reasons. The treatment regimens of these patients are modified by one of the following strategies: A. titration of the initial monotherapy, B. addition of a second drug, or C. switching to another drug. Currently there is no strategy that is recommended as a preferred strategy by clinical guidelines. Literature suggests that about 50%-75% of patients receive TM within 12 months of initiating hypertension treatment.[3-6] However, the prescribing patterns TM strategies are not well understood. Knowledge of prescribing patterns of these strategies will be useful to understand the current preferences for a TM strategy when the initial pharmacotherapy regimen cannot be continued. In addition, it will also help us understand the issues underlying with antihypertensive drugs currently used as first-line monotherapy such as poor efficacy and ADEs which are addressed through TMs by intensification, switching, or deintensification.

Only a few published studies have assessed the outcomes of TM strategies (summarized in section 2.5.1). However, outcomes of alternative strategies have not been compared previously. A comparative assessment of these strategies is important because outcomes of these strategies have been shown to vary considerably. Notable

differences in adherence and costs have been documented in studies that evaluated these parameters after titration of drugs, addition, and switching of antihypertensive medications. For example, clinical guidelines for hypertension recommend increase of dose or addition of drugs as TM strategies for patients requiring aggressive treatment.[34] Similarly, for those patients who require TMs due to adverse events the provider can choose between decreasing drug dose vs. switching to a different drug. Most patients receive TMs based on their provider's preference as there is no preferred approach recommended by guidelines. A comparative assessment of these strategies will be informative for physicians and patients for decision-making when a TM is required.

In this study we proposed to: 1. Determine the patterns of TMs and rates of discontinuation, 2. Compare the adherence profile and associated factors across TM strategies, and 3. Estimate healthcare costs associated with these strategies and the impact of adherence on these costs. Several empirical studies have assessed the patterns of persistence among patients treated with first-line drugs. Data from these studies show that TMs are common.[3-6] Therefore, in the first Aim of our study we assessed the patterns of TMs across antihypertensive drug classes. We also determined the likelihood of TM across these drug classes. This information will be useful to understand the underlying issues of first-line drugs and the current trends in approaches physicians take to resolve them. Also, the time-to-TM will help us understand time-line for TMs in the real-world and recognize area of needed improvements, if any. Finally, comparing discontinuation rates across strategies will be useful to determine differences in patients' persistence to their regimen.

Adherence to the modified regimen is essential for BP goal attainment.[28] Therefore, in Aim 2 of our study we determined and compared adherence across the TM strategies. Additionally, factors associated with adherence will be examined. Knowledge of adherence to the TM strategies will inform the providers regarding the adherence rates expected from TM strategies. It will help to inform healthcare providers of factors associated with adherence among patients who receive TMs. Finally, in Aim 3 we compare the healthcare costs between TM strategies and the association of adherence with these costs. Data from the previous studies suggests that TMs are associated with changes in the healthcare costs.[30-32] TMs have a direct impact on the costs of medications. Frequency of ambulatory and outpatient visits for follow-up with the healthcare provider after TMs also contribute to increase in the burden of costs. There is limited knowledge about the implication of TMs on inpatient costs.[32] In addition, the effects of patients' adherence on healthcare costs are not well understood. One study that estimated health care costs after uptitration showed that higher adherence was associated with lower health care expenditure after uptitration (R=-0.97 ; P≤0.05).[35] Another study reported that switching and discontinuation of drugs constitute nearly 20.8% and 31.1% of total costs of hypertension, respectively.[36] Knowledge of the costs of TM and the impact of adherence on these costs will be a useful resource for providers and patients to understand the costs of TMs. For public and private insurers, and managed care organizations, information on excess cost burden associated with TMs will be useful for designing cost containment strategies for these patients. We have summarized the current evidence, gaps in literature, and the importance of this study in Table 1.

Table 1: Current evidence, gap in literature, and importance of the study on treatment modifications of antihypertensive regimens.

Evidence	Gap	Importance of study
1. Stage I hypertensive patients initiate monotherapy treatment. 2. 50-75% of these patients undergo treatment modifications (TMs) within 12-months of treatment. 3. Reasons for TM include uncontrolled BP, adverse events, drug cost, and patient dissatisfaction.	1. What are the current rates of TM after treatment with first-line monotherapy drugs? 2. How much is the time-to-TM from initiation of first-line treatment? 3. How long do patients continue to stay on treatment and is there a difference across TM strategies?	1. Assessed current patterns of TMs after first-line treatment 2. Determined the real-world time-to-TM after first-line treatment 3. Identified differences in the persistence patterns between TM strategies. **Aim 1**
1. Clinical outcomes (blood pressure control and adverse events) may vary by type of TM. 2. Adherence is significantly associated with outcomes after TM.	1. Does adherence vary between two competing TM strategies? 2. What factors are associated with adherence after a TM?	1. Determined and compared adherence across TM strategies. 2. Identified factors associated with adherence after TM. **Aim 2**
1. Costs of health services utilization are higher for patients who undergo TMs compared to those who do not.	1. Do healthcare costs vary across TM strategies? 2. Is there an association between adherence and costs after TM?	1. Determined and compared costs across TM strategies. 2. Examined the association between adherence and costs. **Aim 3**

CHAPTER TWO: BACKGROUND AND LITERATURE REVIEW

2.1 Hypertension

2.1.1 Prevalence

Hypertension is one of the most common chronic diseases in the US. It is defined as a systolic BP greater than or equal to 140 mm Hg, or diastolic BP greater than or equal to 90 mm Hg.[2] In 2013, approximately 77.9 million individuals in the US were estimated to have hypertension; thus, one out of every three adults in the US suffers from hypertension.[37] It is estimated that by 2030, the prevalence of hypertension will rise by 7%.[37]

The prevalence of hypertension varies by its stages. The current guidelines for hypertension classify hypertension into two stages according to the BP level. Patients with systolic BP in the range of 140-150 mm Hg and/or diastolic BP of 90-99 mm Hg are classified as stage 1, while those with systolic BP ≥160 mm Hg and/or diastolic BP ≥100 mm Hg are classified as stage 2. According to a study of the National Health and Nutrition Examination Survey (NHANES), about 36% of the population has stage 1 hypertension, while about 11% of the population has stage 2 hypertension.[33] The stage-wise prevalence of hypertension was stable during the past decade. The prevalence of Stage 1 hypertension (systolic/diastolic BP 140-159/90-99 mm Hg), prehypertension (systolic/diastolic BP, 120-139/80-89 mm Hg), and normal BP (<120/<80 mm Hg) did not change significantly from 1998-2008.[33]

Significant demographic disparities exist in the prevalence of hypertension. Age-wise, the prevalence of hypertension is highest among adults aged 60 years and over (about

65%).[38] However, in recent years, a significant increase among adults between the age groups of 18-39 years and 40-59 years has been reported.[39] Sex disparities in the prevalence of hypertension have also been reported. A higher number of men were diagnosed with hypertension compared to women from 1988 to 2008.[33] The prevalence of hypertension is high among men until age 45, and from ages 45-64 the prevalence is the same for men and women; however, the prevalence among women increases for ages 64 years and greater.[37] The burden of hypertension varies by race and a higher number of cases are reported among non-Hispanic Blacks (about 41%), followed by non-Hispanic Whites (28%) , and Mexican-Americans (22%).[40]

2.1.2 Awareness

According to a study of the NHANES, from 2007 to 2010, about 82% of the adults with hypertension were aware of their condition.[37] Awareness was higher among women compared to men, and was significantly higher among patients aged 40-50 years compared to other ages.[38] Highest awareness of hypertension has been reported among non-Hispanic Blacks, followed by non-Hispanic Whites, and Mexican-Americans.[40]

2.1.3 Treatment

From 1988 to 2000 the proportion of hypertensive patients who received treatment for their condition has increased by about 6%.[39] According to the most recent estimates, about 75% of hypertensive patients receive treatment for the condition.[37] Nearly 93% of patients are prescribed lifestyle modifications or pharmacotherapy; of these, patients who take a prescription medication account for almost 85% of the treated patients.[38] Hypertension treatment rates vary demographically. Among hypertensive patients aged

18-59 years, men have a lower odds of being treated compared to women; however for patients aged 60 and above, the odds do not differ by sex.[40] Treatment of hypertension is low among Hispanic-Americans compared to non-Hispanic Blacks and non-Hispanic Whites.[38,40]

2.1.4 Control

Attainment of the recommended BP goal is important for CV risk reduction. Therefore, only reducing patients' BP level may not be significant for management of hypertension, and attainment of target BP goal is crucial. The recommended BP goal by Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC)-8 for patients aged 18-59 years is <140/90 mm Hg while for elderly patients it is <150/90 mm Hg.[41] Moreover, patients with certain clinical conditions such as diabetes and chronic kidney diseases have a recommended a goal of <130/80 mm Hg by the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative.[42] According to a recent study of the NHANES, only about 48% of treated patients have their BP under control.[37] Out of the total patients treated with pharmacotherapy, only 64% attain the recommended BP goal.[40] Rates of hypertension control is reportedly lower among women, Mexican Americans, and those aged 60 years or older compared with men, younger individuals, and non-Hispanic whites.[39]

2.1.5 Burden of disease

Hypertension is a major risk factor for CVD and diseases of the kidney. Statistics suggest that of the 69% of people who have a first heart attack, 77% of the people who have a first stroke, and 74% of the people with chronic heart failure had a history of hypertension.[43] The annual direct medical expenses for hypertension are about $47.5

billion, while the loss of productivity due to the condition accounts for $3.5 billion annually.[44] These consequences may be attenuable if patients receive timely treatment for hypertension and attain BP goal.[43]

2.2 Treatment

2.2.1 Treatment strategies

One or more of the following strategies are currently used for the treatment of hypertension –

a) Lifestyle modification

Dietary modification is an effective strategy to treat hypertension. This includes healthy eating habits, maintaining a healthy weight, physical activity, reducing of salt intake, reducing alcohol consumption, and avoiding tobacco smoke. The effectiveness of lifestyle modification in reducing BP ranges from 2 to 20 mm of Hg.[2] Unfortunately, not many patients adhere to a healthy lifestyle or may not attain BP goals with lifestyle modifications alone; hence, pharmacotherapy is required to treat most patients. The recommended lifestyle modifications and their effectiveness in BP reduction are summarized in Table 2.

Table 2: Lifestyle modifications to prevent and manage hypertension.[2*]

Modification	**Recommendation**	**Approximate SBP reduction (Range)†**
Weight reduction	Maintain normal body weight (body mass index 18.5-24.9 kg/m^2).	5-20 mmHg/10kg
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low fat dairy products with a	8-14 mmHg

	reduced content of saturated and total fats.	
Dietary sodium reduction	Reduced dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2-8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).	4-9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men, and no more than 1 drink per day in women and lighter weight person.	2-4 mm Hg

DASH, Dietary Approaches to stop hypertension; SBP, systolic blood pressure
*for overall cardiovascular risk reduction, stop smoking
†The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.

b) Pharmacotherapy

Seven out of every ten US adults with high BP use pharmacotherapy to treat the condition.[43] Choice of antihypertensive medication for treating a patient is generally made according to the stage of hypertension and presence of comorbid conditions, if any.[2] The different classes of antihypertensive drugs currently available are listed in Table 3. These drugs are used as monotherapy, or in combination.

Table 3: Antihypertensive drugs for pharmacotherapy.

Monotherapy

Class	Drug (Trade Name)	Usual dose range (mg/day)	Usual daily frequency*

Thiazide diuretics	Chlorothiazide (Diuril)	125-500	1-2
	Chlorthalidone (generic)	12.5-25	1
	Hydrochlorothiazide (Microzide, HydroDIURIL†)	12.5-50	1
	Polythiazide (Renese)	2-4	1
	Indapamide (Lozol)	1.25	1
	Metolazone (Mykrox)	0.5-1.0	1
	Metolazone (Zaroxolyn)	2.5-5	1
Loop diuretics	Bumetanide (Bumex)	0.5-2	2
	Furosemide (Lasix)	20-80	2
	Torsemide (Demadex)	2.5-10	1
Potassium-sparing diuretics	Amiloride(Midamor)	5-10	1-2
	Triamterene (Dyrenium)	50-100	1-2
Aldosterone receptor blockers	Eplerenone(Inspra)	50-100	1
	Spironolactone (Aldactone)	25-50	1
BBs	Atenolol (Tenormin)	25-200	1
	Betaxolol(Kerlone)	5-20	1
	Bisoprolol(Zebta)	2.5-10	1
	Metoprolol(Lopressor)	50-100	1-2
	Metoprolol extended release (Toprol XL)	50-100	1
	Nadolol(Corgard)	40-120	1
	Propanolol(Indreal)	40-160	1
	Propanolol long-acting ((Inderal LA)	60-180	1
	Timolol (Blocarden)	20-40	1
BBs with intrinsic sympathomimetic activity	Acebutolol(Sectral)	200-800	2
	Penbutolol (Levatol)	10-40	1
	Pindolol (generic)	10-40	1
Combined alpha- and beta-blockers	Carvedilol (Coreg)	12.5-50	2
	Labetalol (Normodyne,Trandate)	200-800	2
ACEIs	Benazepril (Lotensin)	10-40	1
	Captopril (Capoten)	25-100	2
	Enalapril (Vasotec)	5-40	1-2
	Fosinopril(Monopril)	10-40	1
	Lisinopril (Prinivil, Zestril)	10-40	1
	Moexipril(univasc)	7.5-30	1
	Perindopril(Aceon)	4-8	1
	Quinapril (Accupril)	10-80	1
	Ramipril (Altace)	2.5-20	1
	Trandolapril (Mavik)	1-4	1

Antiotensin II antagonists	Candesartan (Atacand)	8-32	1
	Eprosartan (Teventen)	400-800	1-2
	Irbesartan (Avapro)	150-300	1
	Losartan (Cozaar)	25-100	1-2
	Olmesartan(Benicar)	20-40	1
	Telmisartan (Micardis)	20-80	1
	Valsartan (Diovan)	80-320	1-2
CCBs-nondihydropyridines	Diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac)	180-420	1
	Diltiazem extended release (Cardizem LA)	120-540	1
	Verapamil immediate release (Calan, Isoptin)	80-320	2
	Verapamil long acting (calan SR, Isopotin SR)	120-480	1-2
	Verapamil (Coer, Covera HS, Verelan PM)	120-360	1
CCBs-dihydropyridines	Amlodipine (Norvasc)	2.5-10	1
	Felodipine(Plendil)	2.5-20	1
	Isradipine(Dynacirc CR)	2.5-10	2
	Nicardipine sustained release (Cardene SR)	60-120	2
	Nifedipine long-acting (Adalat CC, Procardia XL)	30-60	1
	Nisoldipine (Sular)	10-40	1
Alpha-1 blockers	Doxazosin (Cardura)	1-16	1
	Prazosin (Minipress)	2-20	2-3
	Terazosin (Hytrin)	1-20	1-2
Central alpha-2 agonists and other centrally acting drugs	Clonidine (Catapres)	0.1-0.8	2
	Clonidine patch (catapress-TTS)	0.1-0.3	1 wkly
	Methyldopa (Aldomet)	250-1,0000	2
	Reserpine (generic)	0.1-0.25	1
	Guanfacine (Tenex)	0.5-2	1
Direct vasodilator	Hydralazine (Apresoline)	25-100	2
	Minoxidil (Loniten)	2.5-80	1-2

ACEIs, angiotensin converting enzyme inhibitors; BBs, beta blockers; CCBs, calcium channel blockers

* In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval (trough effect).

BP should be measured just prior to dosing to determine if satisfactory BP control is obtained. Accordingly, an increase in dosage or frequency may need to be considered. These dosages may vary from those listed in the Physician's Desk Reference (57th ed.).

† Available now or becoming available soon in generic preparations.

Source: Physician's Desk Reference. 57th ed. Montvale, NJ: Thompson PDR, 2003.

Combination drugs

Combination Type*	Fixed-dose combination, mg†	Trade Name
ACEI and CCBs	Amlodipine-benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20)	Lotrel Lexxel
	Enalapril-felodipine (5/5)	Tarka
	Trandolapril-verapamil (2/180, 1/240, 2/240, 4/240)	
ACEIs and diuretics	Benazepril-hydrochlorothiazide (5/6.25, 10/12.25, 20/12.5, 20/25)	Lotensin HCT
	Captopril-hydrochlorothiazide (25/15, 25/25, 50/15, 50/25)	Capozide
	Enalapril-hydrochlorthiazide (5/12.25,10/25)	Vaseretic
	Fosinopril-hydrochlorothiazide (10/12.5, 20/12.5)	Monopril/HCT
	Lisinopril-hydrochlorothiazide (10/12.5, 15/25)	Prinzide,Zestoretic
	Moexipril-hydrochlorothiazide (7.5/12.5, 15/25)	Uniretic
	Quinapril-hydrochlorothiazide (10/12.25, 20/12.5, 20/25)	Accuretic
ARBs and diuretics	Candesartan-hydrochlorothiazide (16/12.5, 32/12.5)	Atacand HCT
	Eprosartan-hydrochlorothiazide (600/12.5, 600/25)	Teventen-HCT
	Irbesartan-hydrochlorothiazide (150/12.5, 100/12.5)	Avalide
	Losartan-hydrochlorothiazide (50/12.5, 32/25)	Hyzaar
	Olmesartan-medoxomil-hydrochlorothiazide (20/12.5, 40/12.5,40/25)	Benicar HCT
	Telmisartan-hydrochlorothiazide (40/12.5, 80/12.5)	Micardis HCT
	Valsartan-hydrochlorothiazide (80/12.5, 160/12.5,160/25)	Diovan HCT
BBs and diuretics	Atenolol-chlorthalidone (50/25,100/25)	Tenoretic Ziac
	Bisoprolol-hydrochlorothiazide (80/12.5,160/12.5, 160/25)	Lopressor HCT
	Metoprolol-hydrochlorothiazide (50/25, 100/25)	Corzide
	Nadolol-bendroflumethiazide (40/5, 80/5)	Inderide LA

	Propranolol LA-hydrochlorothiazide (40/25, 80/25) Timolol-hydrochlorothiazide (10/25)	Timolide
Centrally acting drug and diuretic	Methyldopa-hydrochlorothiazide (250/15, 250/25, 500/300, 500/50)	Aldoril
	Reserpine-chlorthalidone (0.125/25, 0.25/50)	Demi-Regroton, Regroton
	Reserpine-chlorothiazide (0.125/250, 0.25/505)	Diupres
	Reserpine-hydrochlorothiazide (0.125/25, 0.125/50)	Hydropres
Diuretic and diuretic	Amiloride-hydrochlorothiazide (5/50)	Moduretic
	Spironolactone-hydrochlorothiazide (25/25, 50/50)	Aldactazide
	Triamterene-hydrochlorothiazide (37.55/25, 75/50)	Dyazide, Maxzide

* ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BBs, beta blockers; CCBs, calcium channel blockers
† Some drug combinations are available in multiple fixed doses. Each drug dose is reported in milligrams.

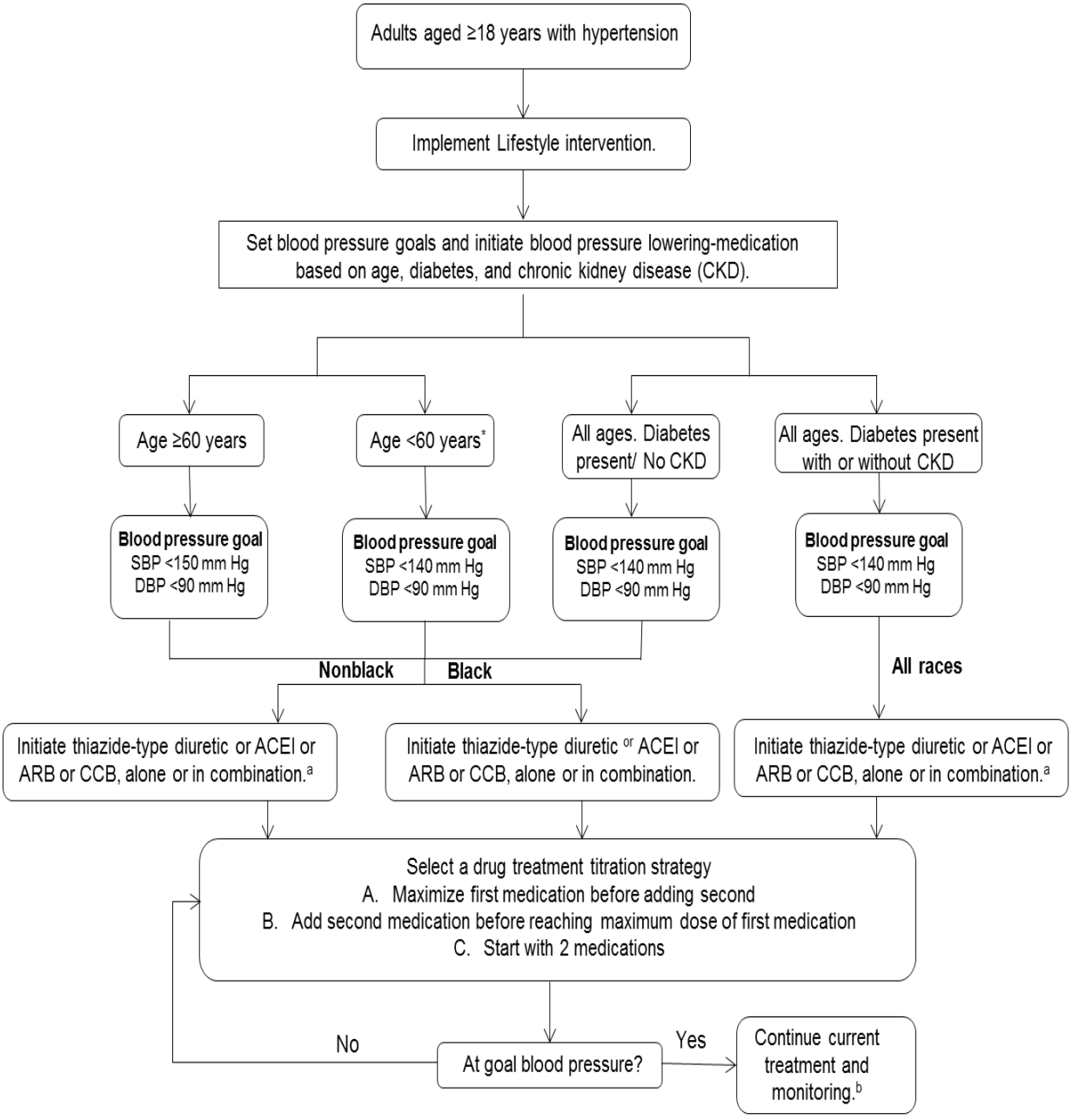
2.2.2 Guidelines

Several agencies have developed clinical guidelines for the treatment of hypertension including the International Society of Hypertension (ISH) and World Health Organization (WHO), the International Society on Hypertension in Blacks (ISHIB), the American Diabetes Association (ADA), the National Kidney foundation (NKF), and the National Heart, Lung and Blood Institute (NHLBI). The JNC-8 guidelines developed by the NHLBI is one of the most widely used resources for hypertension treatment among clinicians in the US.[34] The JNC-8 guidelines for treatment of hypertension are summarized in Figure 1.

Lifestyle modifications are indispensable for the management of hypertension, and the adoption of healthy lifestyle is recommended to all persons with hypertension. Details on lifestyle modifications have been discussed in section 2.2.1.a. Patients who fail to

attain goal BP after lifestyle modifications are treated with pharmacotherapy. Drugs are primarily prescribed based on age, race, and existing health conditions.

Figure 1: Hypertension Treatment algorithm.



SBP indicates systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker.[a] ACEIs and ARBs should not be used in combination.[b] If blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan.

About 38% of the patient population with elevated blood pressure have stage 1 hypertension.[33] Treatment for most of these patients is initiated using thiazide-type diuretics or any other approved first-line monotherapy including beta-blockers, CCBs, ACEIs, or ARBs. The JNC-8 guidelines[34] recommend initiation of thiazide-type diuretics for most patients (except those with chronic kidney disease (CKD) who are recommended ACEI or ARB). For non-Black patients, alternative first-line drugs include ACEIs, ARBs, and CCBs. For Black patients CCB are an alternative to diuretics. Unlike stage 1 hypertensive patients, combination therapy is recommended if patients' systolic BP >160 mm Hg and/or diastolic BP >100 mm Hg, or if the systolic BP is >20 mm Hg above goal and/or diastolic BP is >10 mm Hg above goal (i.e., stage 2 hypertension).

The JNC-8 guidelines[34] for the treatment of hypertension recommended a strategic plan to dose antihypertensive drugs (Figure 1). If the patients fail to attain BP goal after initial treatment one of the following three strategies may be used –

a. Maximizing first medication before adding second or
b. Adding second medication before reaching the maximum dose of first-line medication or
c. Starting with two medication classes separately or as fixed-dose combination

If goal BP is not attained, subsequent intensification strategies are recommended to bring patient to goal BP as described in the figure 1.

2.3 Adherence

2.3.1 Importance of adherence in pharmacotherapy

Non-adherence to medications is known as the “silent epidemic” in the US. Adherence to the medication regimen is important for BP goal attainment[13,18,19] and overall reduction of CV risk.[20,21,26] However, reportedly half of the patients treated with antihypertensive drugs discontinue treatment within 12 months of the treatment initiation, and those who are still engaged in the dosing regimen omit approximately 10% of the scheduled doses.[45]

Non-adherence leads to poor clinical and economic outcomes. Sub-optimal BP control in hypertensive patients is largely attributed to patient’s non-adherence to the antihypertensive regimen. Adherence has been shown to be positively associated with BP control.[18] In a retrospective study, 43% of patients with high-adherence attained BP goals, compared to 34% and 33% of patients with medium- and low- adherence, respectively.[12] The long-term outcomes of antihypertensive treatment are also affected by patients’ adherence to the regimen. The risk of acute CV events was reported to be significantly lower (hazards ratio (HR) = 0.62, 95% CI: 0.40-0.96) in patients highly adherent to their antihypertensive regimens compared to their counterparts with low-adherence.[27] The likelihood of coronary artery disease, cerebrovascular disease, and chronic heart failure is higher among patients with poor adherence to antihypertensive agents.[20] Moreover, all-cause mortality and hospitalization rates for CVD has been shown to be significantly higher among non-adherent patients.[21]

Non-adherence has economic consequences and the burden of medical costs has been shown to be positively correlated with patients' adherence to the antihypertensive regimen. For instance, an increase in costs of approximately $3,574 per person was reported for patients with low adherence to their antihypertensive regimen.[20] The healthcare costs of non-adherence to antihypertensive therapy are primarily attributed to poor BP control and adverse CV outcomes. The odds of CV-related hospitalization and ER visits were significantly higher (P<0.001) in a sub-group of patients with moderate and low adherence. The mean total healthcare costs for these patients were $7,560 and $7,995, respectively; however, for those with high adherence the mean cost was $7,182.[46] Patients with adherence rates of 80% up to 100% had lower all-cause hospitalization costs; in addition, the hypertension-related costs were lowest for patients with high adherence to their medication regimen.[24]

2.3.2 Factors related to adherence

Several factors may affect a patient's adherence to the medication regimen. These factors can be broadly categorized as follows –

a) Patient-related factors

The demographic and clinical factors associated with patients' adherence to the medication regimen have been studied extensively. Demographic factors such as age, sex, and race have been shown to be significantly associated with patients' adherence to their medication regimen. Odds of adherence to the antihypertensive regimen are higher for older patients,[47-49] and a positive linear trend exists between age and medication adherence.[50] Females have been shown to have poorer adherence than

males; however, the differences were not statistically significant.[47,48,50,51] Lower adherence rates have been reported in African- American hypertensive patients.[47,52,53] Patients marital status is also associated with the likelihood of adherence, and higher adherence rates have been reported among married patients.[47] In addition to demographics, patient's clinical status (co-morbid conditions and smoking) may also affect adherence to the medication regimen. The comorbidity score of patients is positively associated with the likelihood of non-adherence.[54] Adherence to antihypertensive drugs may also vary according to specific disease conditions. The likelihood of adherence to antihypertensive drugs is higher for patients with comorbid CV diseases.[55,56] Depression has been strongly associated with the increased likelihood of non-adherence to antihypertensive regimens.[47,52,56] Similarly, asthma, gastrointestinal disorders, and arthritis are also associated with poor adherence to antihypertensive drugs.[56] No significant association was reported between antihypertensive medication adherence and smoking.[47]

b) Provider-related factors

Effective patient-provider communication is of vital importance for patients' adherence to antihypertensive regimens.[57] Higher frequency of patient-provider interaction and higher frequency of physician visits has been shown to be positively associated with adherence.[50,56,58] Multiple provider visits have been shown to increase the odds of adherence (odds ratio (OR) = 2.2; 95% CI: 1.8-2.5).[55] Also, patients are less likely to be adherent to antihypertensive drugs if their healthcare provider is a physician (P<0.05) compared to other healthcare providers.[59]

c) Psychological and behavioral characteristics

Several studies have assessed the impact of psychological and behavioral characteristics on adherence. Depressive symptoms (similar to the earlier discussion in section 2.3.2 b as a co-morbid condition) and anxiety have been shown to be significantly associated with non-adherence to antihypertensive medications.[60-65] High self-efficacy is a strong predictor of patients' adherence to antihypertensive regimens.[65,66] Patients knowledge about hypertension and antihypertensive medications [67-69] and perceived control [67] have been shown to significantly improve patients adherence.

d) Initial drug choice

Several studies have examined the association between antihypertensive drug and patients' adherence to the antihypertensive regimen. Evidence suggests that patients initiating their antihypertensive regimen with ACEIs are more adherent compared to those who initiate with other drug classes.[50-52] More patients using ACEIs and ARBs were adherent to the regimen compared to the percentage of adherent patients using CCBs, beta-blockers, and diuretics (P<0.0001).[70] High adherence has been reported with CCBs compared to diuretics plus CCBs; however, the adherence is not higher than ACEIs and ARBs.[55,70] Overall, lower adherence rates have been reported among patients using beta-blockers and diuretics compared to CCBs, ACEIs, and ARBs.

e) Medication regimen

The complexity of the antihypertensive regimen and the burden of concomitant medications have been shown to be associated with adherence. Frequency of dosing is

positively associated with adherence.[50,71] Simplification of the dosing regimen has shown to improve patients' adherence between 8% to 20%.[71] Use of once-daily dosing vs. twice-daily dosing significantly affects patients' adherence to their antihypertensive regimen.[72,73] Patients who take fewer concomitant medications have a higher likelihood of being adherent to their antihypertensive therapy.[49,56] The likelihood of adherence decreases with increase in the number of medications (OR=0.8; 95% CI: 0.7-0.9).[55]

f) Adverse drug events (ADEs)

ADEs are associated with non-adherence to antihypertensive regimens (*P*=0.0051).[74] Patients experiencing ADE are twice as likely to discontinue treatment compared to those who do not experience an ADE.[75] The perceived side effects of drugs by patients vary across the different classes of antihypertensive drugs ranging from 52.5% to 69.6%, which may contribute to lower adherence.[76] ADE is a common reason for cessation of treatment, and about 15% of patients initiating antihypertensive drugs discontinue treatment due to ADEs.[51]

g) Drug costs

A positive association between drug cost and adherence has been reported in the literature (*P*=0.014).[74] In the HealthStyles survey (a consumer survey conducted in collaboration with the Centers of Disease Control and Prevention), drug cost was the second most common reason for non-adherence to antihypertensive medications reported by participants (about 22.6%).[64] In a retrospective study using an administrative claims database, drug co-pay was found to be significantly associated with first-fill rates of antihypertensive drugs (*P*<0.05).[54] In a German multicenter study,

drug costs were attributed to be a common cause for changes in antihypertensive therapy (about 5%).[7]

2.4 Healthcare costs of hypertension

In 2009, hypertension was the seventh leading cause of direct health expenditures related to diseases in the US with estimated total medical costs of $51 billion.[37] Of these, about $47.5 billion were spent on direct medical expenses while $3.5 billion were indirect costs.[77] It was estimated that by 2013, total cost of hypertension will rise up to $343 billion.[37] The burden of costs of hypertension treatment on patients, providers, and the society is substantial. The components of healthcare costs for hypertension are summarized below.

Drug costs: Drug costs constitute the largest portion of direct medical care costs of hypertension. Approximately 80% of the direct medical care costs are attributed to antihypertensive medications.[78] The cost of medications for hypertension increases with increase in BP (P<0.001).[79] In the CHOICE study, the total estimated costs of medications for patients newly treated for hypertension during the 4-month follow-up were $170 per patient.[80]

Ambulatory visit costs: Poor control of hypertension is associated with more office visits and therefore higher office visit costs (P<0.001).[79] Office visits are main drivers of short term costs of hypertension management. The total costs for office-visits during the 4-month follow-up in the CHOICE study were $283 per patient.[80]

Inpatient visit costs: An estimated $113 billion in the US are spent on hypertension-related hospitalizations.[81] The costs of hypertension-related CV conditions are also

high. Among patients with a secondary hypertension diagnosis, hypertension alone contributes to about 13% ($2,734 per patient/ year) of the average annual costs of hospitalization (*P*<0.01).[82] The estimated average annual hospitalization cost per patient attributable to hypertension as secondary diagnosis were reported to be $3,540, $1,133, and $2,254 for ischemic heart disease (IHD), cerebrovascular disease, and other non-IHD or non-cerebrovascular diseases, respectively.[82]

Adherence/Persistence and healthcare costs of hypertensive patients

Adherence (the extent to which a patient acts in accordance with the prescribed interval of a dosing regimen) and persistence (a measure of patients' medication taking behavior over an extended period of their hypertension treatment) both significantly impact the healthcare costs of hypertension. Non-adherence has been shown to be significantly associated with higher medical care costs for hypertension.[83] Reductions of up to 12% in total costs of medical care can be achieved by improving patients' compliance to the antihypertensive regimen (*P*<0.003).[84] Non-persistent patients spend $873 extra annually on healthcare compared to those patients who are persistent (*P*<0.0001).[30] A large portion of these costs are comprised of hospital expenditures (about $637) as a result of poor BP control due to non-persistence.[85] In another study, patients who were adherent to their medication regimen had almost 50% lower healthcare costs ($341) compared to those who were non-adherent ($694) or non-persistent ($735).[83] Overall, a clear association exists between adherence and healthcare costs of hypertension.

2.5 Treatment modifications

TMs are common among hypertensive patients, especially those patients who are newly treated with antihypertensive medications. TMs have several implications for patients, including implications on adherence and costs. This is because TMs involve changes in the drug dose, drug class, or addition of drugs. Adherence and costs are important aspects of hypertension treatment, and it is important to understand the effect of TMs on these outcomes.

2.5.1 Rates of TMs

Only one study in the literature has compared the rates of all types of TM strategies (i.e., addition, titration, and switching).[32] However, several studies have investigated the discontinuation rate of first-line monotherapy drugs among newly treated hypertensive patients and some of these studies have reported rates of a specific TM strategy, mainly switching of drugs.[6,31,32,86,87] A few studies have reported TMs that can be classified as increase of drug dose, and addition of drugs.[30,32,88] The result of these studies suggests that TMs are common, especially, among newly treated hypertensive patients.

The most commonly studied TM type is switching of medications. Conlin *et al* studied the four year persistence patterns of patients initiating antihypertensive therapy.[6] During the 48 months of follow-up approximately 20% of patients switched therapy from their initially prescribed antihypertensive drug class. Switch rates were higher for diuretics (33%) compared to other drug classes (13% -19%). Rates of switching varied by sex, and females were found to be switching drugs more frequently compared to their male counterparts (21% vs. 19%). A retrospective cohort study conducted using Netherlands PHARMO database found that patients who initiate ACEIs switch more frequently (16.5%; $P<0.001$) compared to ARBs (10%) and diuretics users (8%).[86] Another

retrospective study conducted by Bloom reported a switching rate of 6-9% among newly treated hypertensive patients at the end of a 12-month follow-up period.[87] The percent of switchers in each drug class were–diuretics (6%), beta-blockers (7%), CCBs (9%), ACEIs (9%) and ARBs (7%). A retrospective study of Italian patients had a switch rate of 9% during a 12-month follow-up among a cohort of newly treated hypertensive patients.[31] The switch rate was highest among users of ARBs (13%), followed by ACEIs (11%), CCBs (9%), beta-blockers (7%) and diuretics (7%). A recent study conducted by Saleh and colleagues had a total switch rate of 4%, and the drug class-wise switch rate was as follows—CCBs (5.4%), diuretics (5%), ACEIs (4%), ARBs (4%), and beta-blockers (3%).[32]

Only a few studies are available in the literature regarding addition of drugs or increase of dose. McCombs and colleagues conducted a study of the California Medicaid program to study the association of a change in regimen and healthcare costs.[30] More than 30% patients in this study who had a hypertension related diagnosis added drugs to their regimens. In a nested case-control study of the Eastern Massachusetts health insurance plan, about 935 (18%) patients out of 5,089 newly treated patients had drugs added to their initially prescribed antihypertensive regimen.[88] Similarly, in the study conducted by Saleh *et al*, about 15% and 8% hypertensive patients had titrations of initial regimen and added drugs to initial regimen, respectively.[32]

2.5.2 Outcomes of TMs

Only four studies in the current literature have looked at the outcomes of TMs. Of these studies, three evaluated economic consequences of TM (1 of switching, 1 of addition, and 1 all types of TMs), and evaluated adherence after addition. In the study conducted

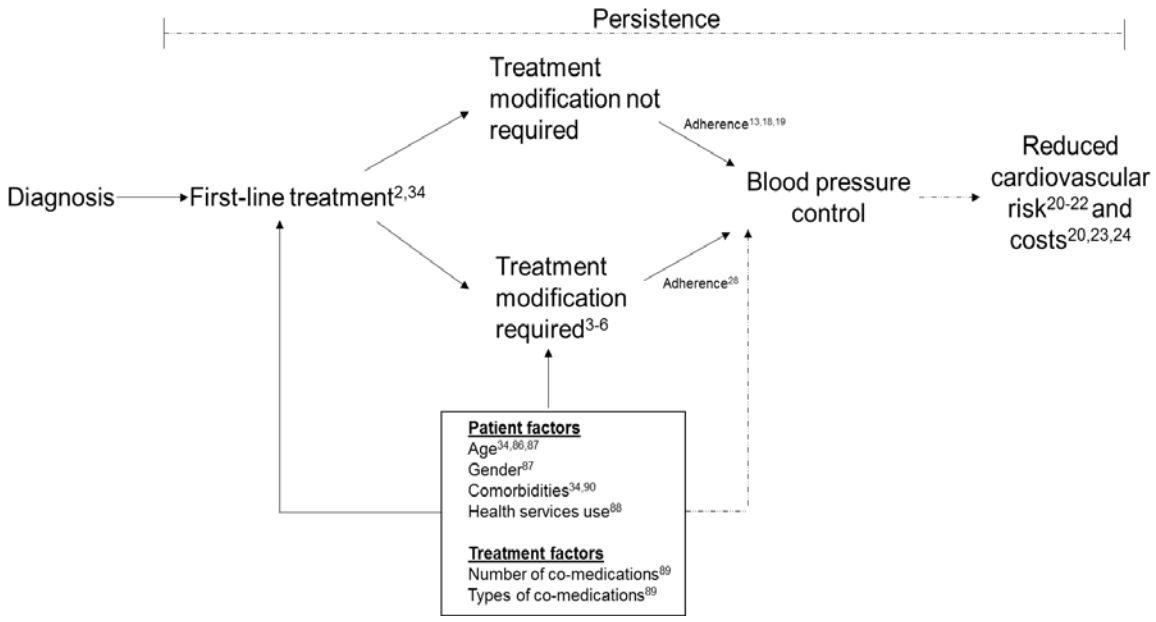
by Grant et al, patients who received an increase in antihypertensive regimen had a higher cumulative medication adherence (CMA) compared to those who remained on initial regimen (93% vs. 81%, respectively; *P*<0.001).[88] To date, no studies have evaluated the effect of titration of dose and switching of antihypertensive drugs on adherence. Moreover, a comparative assessment of adherence among these strategies is unavailable.

The impact of addition of drug to antihypertensive regimen on costs was determined in the California Medicaid study. Addition of drugs resulted in the increase in total healthcare costs by $543 for one drug, $1,326.83 for two drugs and $2,237.30 for three drugs.[30] In the Italian prospective study conducted by Esposti *et al*, the costs of patients switching their antihypertensive drugs from the initially prescribed regimen had the highest costs ($229.09) compared to patients who stayed on the same regimen ($191.82) and those who discontinued their regimen ($31.59) (*P*<0.001).[31] The annual average cost by drug class for switchers were – diuretics ($171.01), beta-blockers ($177.30), CCBs ($222.97), ACEIs ($265.32) and ARBs ($299.43). Saleh *et al* reported the costs of health services after modifications (comprehensive of all modifications including addition, deletion, titration, switching and discontinuation) by drug class and found significant increase in health services costs for all classes (*P*<0.05). A comparative assessment of the burden of costs associated with the TM strategies is not available in the current literature.

2.6 Conceptual framework

Figure 2 illustrates the conceptual framework of this study. The framework depicts the course of treatment for a newly diagnosed hypertensive patient. Lifestyle modification is recommended to all patients diagnosed with hypertension. However, lifestyle modification alone is effective in BP goal attainment in very few patients, and about 93% of the patients are prescribed antihypertensive pharmacotherapy.[38]

Figure 2: *Conceptual model.*



For those patients detected with stage I hypertension, monotherapy is the recommended first-line treatment. Traditionally, diuretics have been the initial drug of choice for the treatment of newly diagnosed hypertensive patients. However, with growing evidence regarding the efficacy and safety of other antihypertensive drug classes, the JNC-8 guidelines now recommends thiazide-type diuretics, CCBs, ACEIs and ARBs as optional drug classes for first-line treatment. More recent studies have reported different trends in the utilization patterns of all first-line monotherapy drug

classes. The use of ACEIs, CCBs, and diuretics among newly treated patients is more or less similar, while the use of beta-blockers and ARBs is comparatively lower.[6,31,89] Overall, most patients are prescribed drugs from one of these five drug classes as starting agent, but patients may be prescribed combination therapy if BP is ≥160/90 mm Hg. Among those patients receiving monotherapy as starting treatment, a need for TM may occur if issues such as unattained BP goal, ADEs, costs, and patient dissatisfaction arise. In the absence of these issues a patient is expected to attain BP goal. Moreover, persistence with treatment will ultimately lead to long-term CV benefit. The two scenarios—1. Patient who does not need a TM, and 2. Patient who needs a TM—will determine the short-term and long-term outcome of the treatment. A detailed discussion on the outcomes of these two scenarios is explained below.

Scenario 1 represents patients who achieve desired adherence and desired short-term clinical outcome (i.e., BP goal) and economic outcome (i.e., health services use and drug costs) after first-line treatment. Adherence to antihypertensive medications is crucial for BP goal attainment.[13,18,19] Patients who have optimum adherence have a higher likelihood of BP goal attainment compared to their counterparts. For these patients, attainment of BP goal as the short-term clinical outcomes will help them attain long term CV risk benefits. There is strong evidence of the CV benefits of BP control in hypertensive patients.[20,23,26,27] The rates of CV events are lower in patients who are adherent and attain BP goals compared to their counterparts. Because these patients attains the desired short-term and long-term clinical outcomes, the costs of health services use for hypertension and related conditions, and costs of antihypertensive drugs are relatively lower compared to patients in Scenario 2.[32]

Scenario 2 represents patients who do not continue the initial treatment and have to undergo a modification in their treatment regimen due to issues such as unattained BP goal, ADEs, costs, or dissatisfaction with the treatment. Healthcare provider of such a patient will prescribe a TM strategy such as titration of drug dose, addition of drug, or switching to address the concerns with initial treatment. Because TMs involve changes in drug dose, drug frequency, addition of drugs, or using a different drug class, these changes are likely to affect adherence and costs. Adherence to the modified regimen is essential for BP goal attainment.[28] If the patient is not adherent to the modified regimen, the short-term benefit (i.e., BP control) will not be attained which will ultimately lead to poor long-term clinical outcomes (i.e., increase in the CV risk). The poor clinical outcomes in patients receiving TMs will result in increased health services utilization and costs. A previous study using claims database that estimated the 12-month total health services costs of patients who received TMs reported significantly higher costs compared to their counterparts.[32]

Several factors may be involved in the selection of first-line monotherapy or treatment modification strategy for a patient. These factors can be broadly classified into-1.patient-related factors, and 2. Drug-related factors. Patient related factors that affect the selection of treatment include demographic and clinical factors of the patients. For instance, specific recommendations have been made by the JNC-8 for the treatment of patients depending on the age, and presence of comorbid conditions as shown in Figure 1. Use of antihypertensive drugs has also been shown to vary by sex. More women use antihypertensive drugs to treat their condition compared to men.[90] Hypertensive women have been shown to have a higher likelihood of being treated with

diuretics (32% vs. 22%) and angiotensin receptor blockers (11% vs. 9%) compared to males.[91] Also, the odds of using >1 antihypertensive drugs is lower among women compared to men.[91] The use of health services has been shown to be associated with monotherapy dosing regimen.[92] Similarly, the choice of drug class and dosing regimen of antihypertensive drugs may vary by the type of and number of concomitant drugs taken by the patient.[41] The patient- and drug-related factors also affect the likelihood of BP control after treatment. For example, only 45% of women treated for hypertension achieve BP goal compared to 51% men.[91] The likelihood of BP control is lower among patients aged 18-39 years compared to patients aged 40-59 years (P<0.001).[33] Patients with comorbidities are more likely to have uncontrolled BP (OR=1.6; 95% CI: 1.1-2.4).[93] The BP status of patient determines his/her long-term CV health. Poor control of this factor will lead to increased costs and utilization of health services by the patient.[94,95]

The short- term and long-term clinical outcomes of TM strategies have not been compared previously. Our understanding of TM is limited due to several gaps in the literature. First, the current patterns of TM are not well understood. The odds of receiving TM and the time-to-TM are not known. Discontinuation is prevalent among hypertensive patients, and changes in treatment increase patient's risk of treatment discontinuation. Differences in rates of discontinuation between TM strategies, if any, have not been assessed. Several studies have highlighted the importance of TMs. A population based study in Switzerland has shown that changes in antihypertensive regimens leads to favorable changes in the BP status.[11] Another study of US managed care enrollees concluded that most patients required TM for BP goal attainment.[96] Adherence to antihypertensive regimen after TM is positively associated with BP goal

attainment;[28] however, its association with long-term outcomes is not well understood. Given the critical role adherence plays in short- and long- term clinical outcomes in hypertension, it is important to understand how different strategies might affect adherence. Finally, the burden of costs on patients who undergo TMs is high;[32] whether the costs differ across TM strategies is not known. Understanding adherence profiles and cost burden associated with these strategies will be useful for treatment decision-making, especially in scenarios when alternative competing strategies are available. For example, a provider may choose to either increase the dose or add a second drug when the initial drug was ineffective in controlling BP. Since the treatment guidelines do not have a preferred strategy, the choice of TM will be based on provider's preference. Similarly, a patient who had an adverse event may be switched to a different drug class or prescribed a lower dose of the same drug. The patterns of TMs have not been well documented in the literature. Moreover, adherence rates, clinical outcomes, and economic outcomes related to these strategies have not been compared.

CHAPTER THREE: METHODS

3.1 Data source and Aims

This study was conducted using the Blue Cross Blue Shield of Texas (BCBSTX) claims database. Data from the year 2008 to 2012 were used for analyses. BCBSTX is a limited data source and consists of enrollment and provider information, medical claims, and pharmacy claims for about 3.4 million lives. The dataset was used to address the following specific aims.

Aim 1: To determine the rates of TM among patients treated with first-line antihypertensive drugs, and to compare the rates of discontinuation across TM strategies.

A new-user design was used to identify naïve users of first-line antihypertensive monotherapy. Cox proportional hazards models were used to determine the rates of TM and the likelihood of treatment discontinuation.

Aim 2: To determine the adherence rates and characterize factors associated with adherence after TM among patients previously treated with first-line antihypertensive drugs.

We determined 12-month adherence rates of each TM strategy using the Proportion of days covered (PDC). Propensity score weighted Generalized linear models (GLMs) were used to compare difference in adherence rates between TM strategies and to examine the factors associated with adherence.

<u>Aim 3</u>: To determine healthcare utilization costs, and examine the association of adherence with healthcare utilization costs after TM among patients previously treated with first-line antihypertensive drugs.

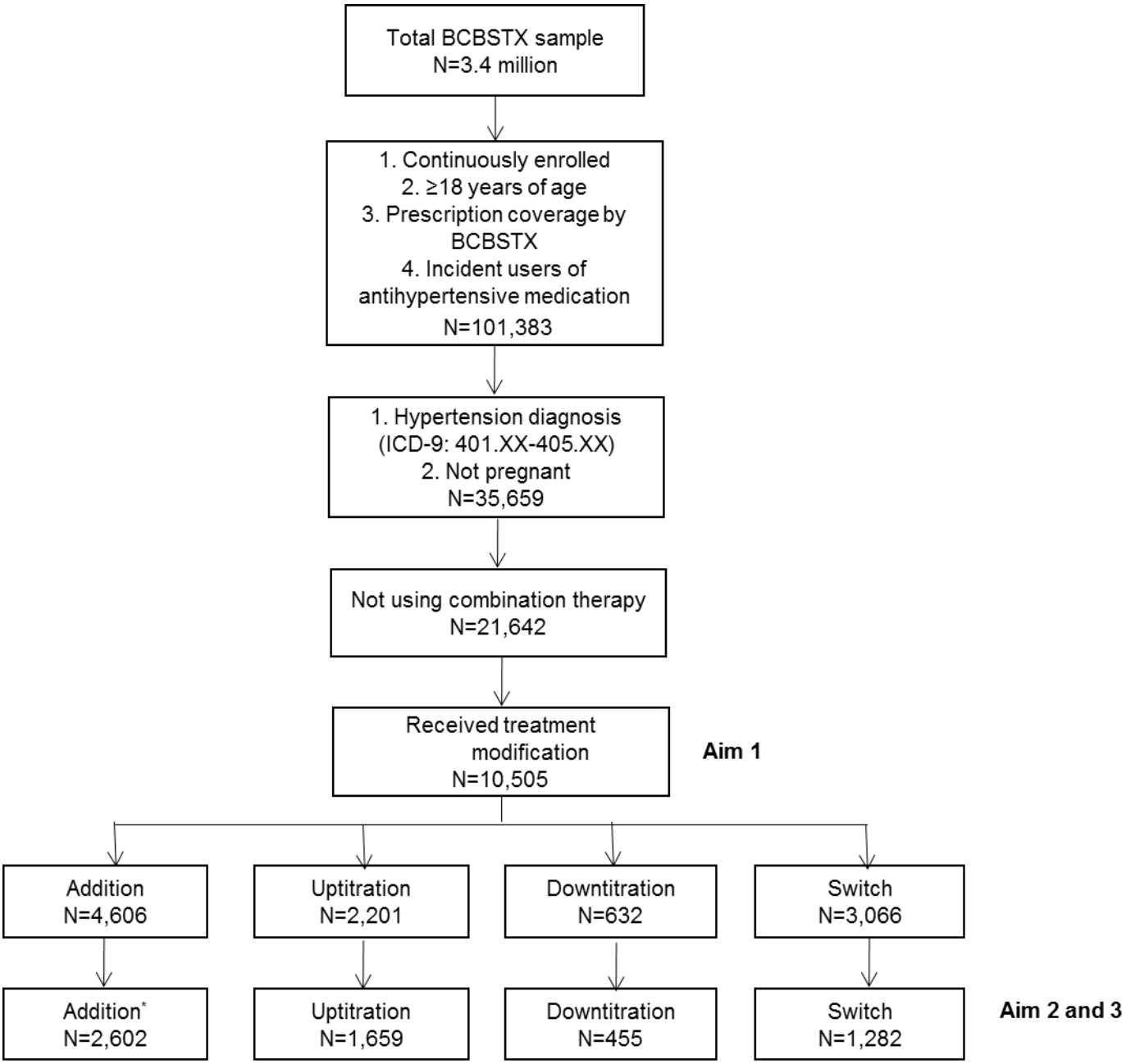
Propensity score adjusted GLMs were used to compare healthcare costs over a 12-month duration between the TM strategies. In addition, the association between adherence and costs after TM was also determined.

We will first discuss the sample selection and variables of interest in our study, and aim-wise specific methods will be discussed in details later in this section.

3.2 Study Sample

In order to accomplish our proposed aims, we applied several inclusion and exclusion criteria to identify our analytical cohorts. Figure 3 illustrates the sample flow of our study. For the purpose of Aim1a, we identified patients who were newly treated with the five classes of first-line monotherapy antihypertensive drugs (i.e., diuretics, beta-blockers, CCBs, ACEIs, and ARBs). A total sample of 21,642 patients was identified after restricting to patients who were continuously enrolled during the observation period, ≥18 years, not pregnant, not using combination therapy, and had an eligible diagnosis of hypertension. These patients were then followed to identify the cohort of patients who received a TM within 12 months from initiation of first-line monotherapy (Aim1b). These included about 10,505 newly treated patients who received a TM.

Figure 3: Sample flow diagram.



BCBSTX= Blue Cross Blue Shield of Texas.

*addition group constitutes of free-pill combination (N=1,395) and fixed-dose combination users (N=1,659).

These patients were classified into four groups—uptitration, downtitration, addition, and switching—based on the TM strategy that was used. Patients who did not receive multiple TMs during the 12 months were included in our analysis for Aim 2 and Aim 3 (N=5,998). The patient selection criteria for each aim are discussed in the sections below.

We started with a total sample of 3.4 million enrollees in BCBSTX database in our 5-years of data (2008-2012). Because the BCBSTX database does not include prescription claims of enrollees not covered under prescription plans by BCBSTX, we excluded these patients. About 50% of the patients have prescription drug covered by BCBSTX. Next, we identified patients' age using date of birth available in the enrollment file. Only those patients who were 18 years and older on or before their index date of monotherapy prescription were included. The enrollment file was also used to determine continuous enrollment of the patients over the 12-month follow-up period. Patients who were not enrolled continuously during the 12-month period were excluded from our study. Further, we identified naïve patients with a prescription claim for an antihypertensive using a new-user design (discussed later in section 3.4). A total 101,383 patients were identified after this process.

Aim 1: New-user cohort (New users of first-line monotherapy)

In Aim 1, we assessed the patterns of TM strategies prescribed by healthcare providers. For this purpose we identified a cohort of new-users of first-line monotherapy drugs. A wash-out period of 6 months prior to the index date of the first claim for antihypertensive drug was used to identify prior exposure to antihypertensive drugs. Only those patients

who did not have a claim for antihypertensive drug during the wash-out period were included in the cohort. To ensure that the antihypertensive drugs were being used for the purpose of treatment of hypertension, we included only those patients who had an eligible diagnosis of hypertension during the 6-month period prior to their first claim of antihypertensive drug. A primary diagnosis for hypertension was identified using International classification of diseases (ICD)-9 diagnostic codes for hypertension (Table 4) on at least one outpatient visit or inpatient visit from the medical claims file. This hypertension identification criterion was based on previous studies that have explored the validity of these case definitions for identifying cases of hypertension in large administrative claims databases.[11,97-99]

Table 4: ICD-9* diagnostic codes for identifying cases of hypertension.

ICD-9 Code	Description
401.XX	Essential hypertension
402.XX	Hypertensive heart disease
403.XX	Hypertensive chronic kidney disease
404.XX	Hypertensive heart and chronic kidney disease
405.XX	Benign secondary hypertension

*ICD-9: International classification of diseases, version 9.

After the identification of hypertension diagnosis, we excluded pregnant patients from the identified sample. Pregnant patients were identified using the ICD-9 codes 630.XX-

690.XX. A sample of 35,659 patients was identified after applying these inclusion and exclusion criteria.

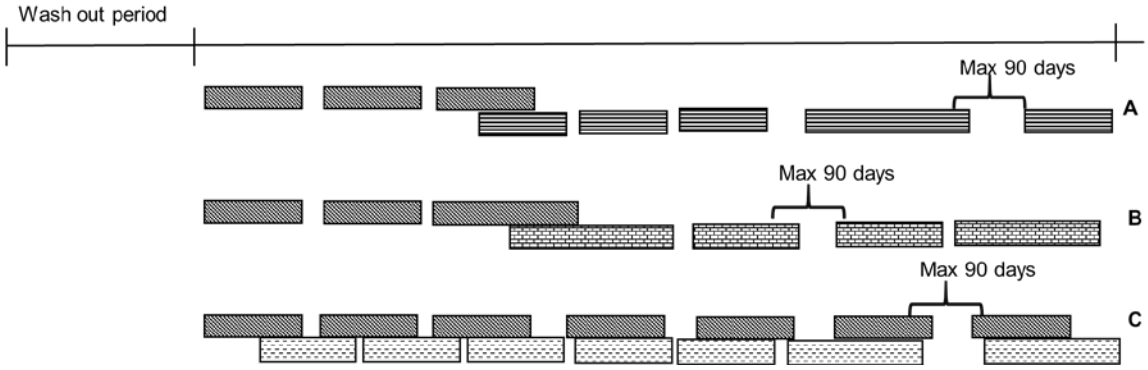
Next, we restricted our sample to include only those patients who were treated with first-line monotherapy. This was done to minimize selection bias. Patients treated with combination therapy as their first-line treatment are most likely to be stage 2 hypertensive patients. Therefore, we excluded these patients. The final analytical cohort for Aim1a of our study consisted of 21,642 patients.

Aim 1a: TM cohort

In Aim 1a, we followed the patients who were prescribed first-line monotherapy from Aim 1a and identified those who received a TM. The purpose of aim 1a was to: a. determine the likelihood of receiving any type of TM strategy, b. determine the likelihood of receiving a specific type of TM strategy, and c. compare the time-to-TM after first-line treatment. We followed the cohort of 21,642 eligible patients for a duration of 12 months from their index date of first-line monotherapy prescription. Patients with a treatment gap of >90 days over the 12-month period were excluded from our cohort due to non-persistent use of first-line monotherapy. The criteria was based on previous studies that have defined non-persistence as a >90-day gap in treatment.[32,89] The overall median time-to-TM modification was determined. In addition, the likelihood of any TM and likelihood of specific TM was determined according to the four types of TM. Figure 4 illustrates the different types of TM. Strategies were defined as follows –

a. Addition: Patients who added a drug to their existing regimen without the deletion of initial monotherapy (or free-pill combination (FPC)), or those patients who started a fixed dose combination (FDC) regimen.
b. Uptitration: Patients who had an increase in the dose or increase in the frequency of dose of the initial monotherapy.
c. Switch: Patients who stopped their initial antihypertensive regimen and changed drug within the same class or to a different drug class.
d. Downtitration: Patients who had a decrease in the dose or decrease in the frequency of dose of the initial monotherapy

Figure 4: Criteria for defining treatment modification groups.



A illustrates patients who uptitrated or downtitrated drug dose; **B** illustrated who switched to a new drug, also illustrates patients who added drugs by starting a fixed-dose combination regimen; **C** illustrates patients who added drugs by starting a free-pill combination regimen.

Aim 1b: Treatment discontinuation cohort

The purpose of Aim1b was to compare the discontinuation rates across the TM strategies. For this purpose, we applied additional 12-month enrollment criteria (total of up to 24 months from the date of TM) for those who continued to stay on therapy until the end of follow-up. For those who discontinued treatment, continuous enrollment was

required until their date of discontinuation of treatment. A complete discontinuation of treatment was identified as a >90-day[32] period between the last day patient had an antihypertensive drug in hand until the end of the observation period for that patient. The final analytical sample for Aim1c after applying the follow-up criteria was 9,516 (not presented in figure 3).

Aim 2 and 3: Cohort study

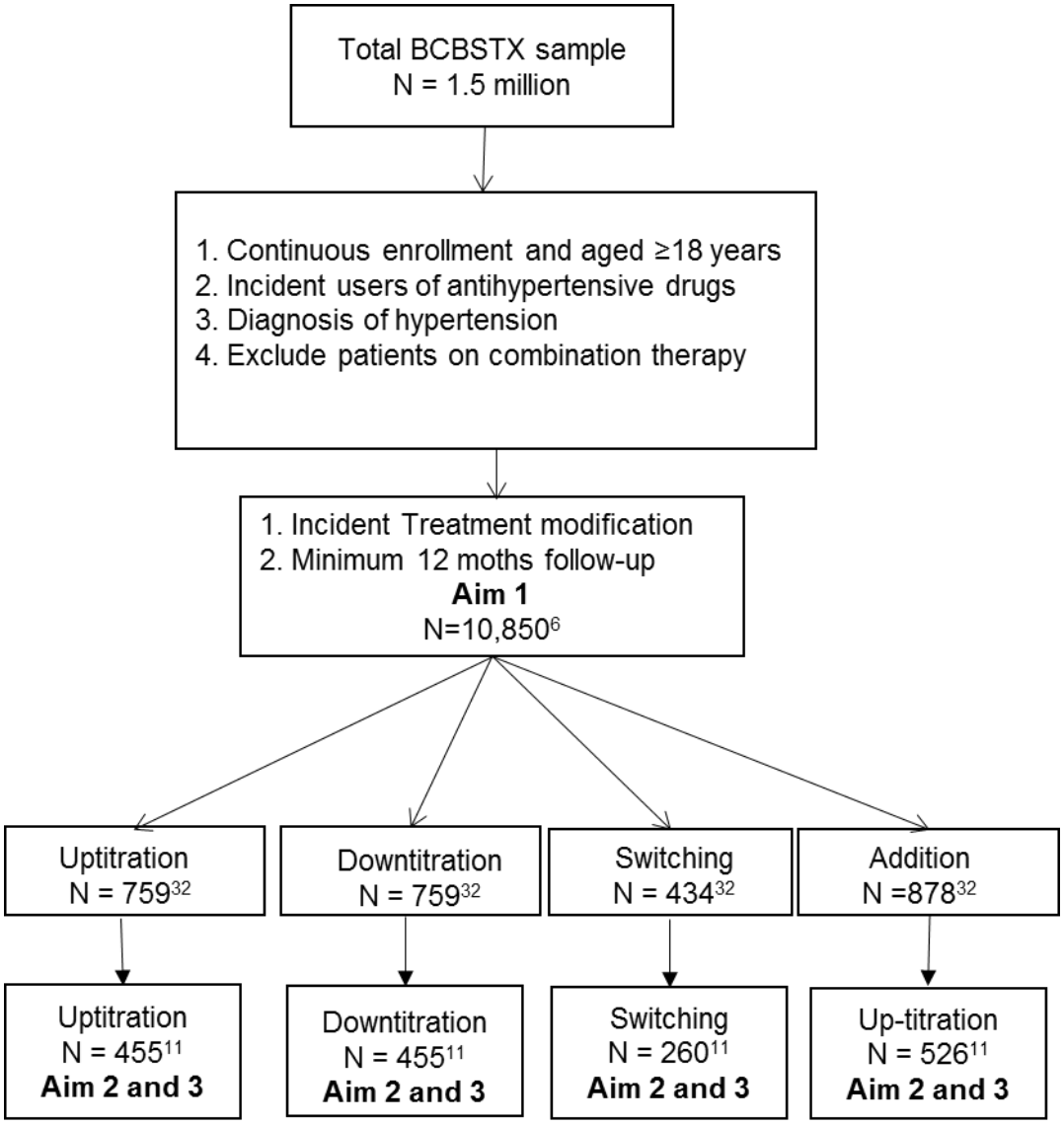
The sample of patients with incident TM identified in Aim 1b and who were continuously enrolled for 12 months starting from the index date of their first TM were included in the cohort. For the purpose of Aim 2 and 3 we only included those patients who did not have multiple TMs. Patients with multiple TMs were excluded to minimize measurement bias in calculation of adherence and estimation of costs. The sample is fairly representative of the total TM cohort (N=10,505) and represents an approximate 60% (N=5,998) patients from the total cohort. The sample proportion is similar to a published study which validated TMs using medical records and reported a single event of TM in about 60-75% of the total cohort.[11]

3.3 Sample size feasibility

Observational studies using large claims databases for studying high prevalence chronic diseases such as hypertension generally yield large sample sizes. Due to the large sample sizes, the analyses conducted using such databases have sufficient power. An estimation of sample size feasibility was performed prior to data access authorization to the BCBSTX database based on previous studies.[6,11,32] We used the percent of population included from initial cohort in these previous studies (after

applying the selection criteria, e.g., continuous enrollment, hypertension diagnosis, etc.) and applied it to a starting sample of approximately 1.5 million participants to estimate the final sample sizes of TM groups. The final sample sizes of TM groups from the BCBSTX database were greater than our estimated sample size and previously published studies.

Figure 5: Sample size feasibility for BlueCross BlueShield of Texas data



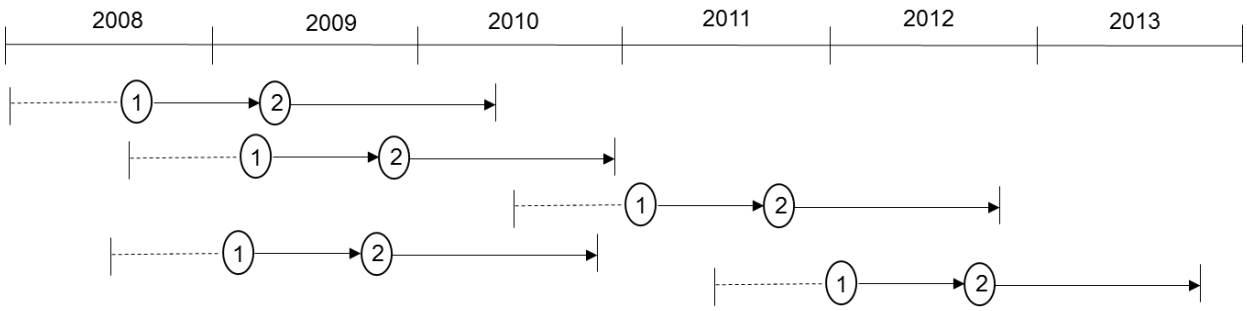
BCBSTX: Blue Cross Blue Shield of Texas.

3.4 Study Design

This is a retrospective cohort study. A 'new-user'[100,101] design (illustrated in Figure 6) was used to identify patients who started their treatment with first-line monotherapy on or after July 1, 2008. This included patients who began treatment with diuretics, beta-blockers, CCBs, ACEIs, or ARBs. The period from January 1, 2008 until June 31, 2008 (total 6 months) was the minimum wash-out period that was used to identify prior-exposure to antihypertensive drugs, and a formal diagnosis of hypertension. Patients were followed for a 12-month duration following the index date of their first prescription of antihypertensive drug. Additional inclusion and exclusion criteria discussed in section 3.2 were applied to identify the final cohort for Aim 1a. This sample was followed for 12 months and patients receiving TMs were identified (Aim 1b cohort). We reported the patterns of TM strategies in this cohort, the time-to-TM was determined, and the likelihood of receiving a TM. An additional 12-month follow-up criterion was applied after TM to assess the likelihood of discontinuation.

For the subsequent aims, we followed patients who received TMs (identified in Aim 1b); therefore, aims 2 and 3 also follow a retrospective cohort design. Only those patients with a minimum 12-month follow-up from the index date of TM were included in these analyses. Additional exclusion criteria were applied as mentioned in section 3.2. In Aim 2, we determined and compared the adherence across the four TM groups (Aim 2a), and characterized the factors associated with adherence after TM (Aim 2b). In aim 3, we compared the healthcare costs across TM strategies (Aim 3a), and assessed the association of adherence with healthcare costs (Aim 3b).

Figure 6: The new-user design.



Dotted line indicate minimum 6-month wash-out period.
① indicates incidence date of first-line drug. Incidence of treatment modification occurs during the 12-month follow-up period.
② indicates incidence of treatment modification. Patients were followed for 12 months after treatment modification to determine adherence and healthcare costs.

3.5 Measures

Based on the aims of our study we identified the independent and dependent variables. In addition to these variables, we identified several other covariates based on the conceptual model and evidence in the literature. We broadly classify the covariates into patient-related and drug-related factors.

1. **Patient-related factors:** The demographic and clinical characteristics of the patients were obtained from the enrollment files and medical claims data, respectively. Details of each variable are discussed below–
    a. Age: Date of birth (DOB_DT) of the enrollees available in the enrollment file was used to calculate the age of the patient. Age was calculated for each enrollee as a continuous variable. For the purposes of descriptive presentation of the cohort, patients were categorized into age groups of 18-24, 25-35, 36-59, and ≥60 years.

b. Sex: The enrollee sex (GNDR_CD) was available in the enrollment file. Males were coded as ‘1’, while females were coded as ‘2’.

c. Comorbidity: The comorbidity score of each patient was calculated using the Charlson comorbidity index (CCI).[102] We used Quan’s[103] algorithm for calculating the CCI. The algorithm, which is available as a SAS® macro, uses ICD-9 diagnostic codes (ICD_CD1, ICD_CD2, and ICD_CD3 in BCBSTX) available in administrative claims databases to calculate the comorbidity index. CCI was calculated as a continuous variable. For the purpose of a descriptive presentation of the cohort, we classified patients into four categories (0, 1, 2, and ≥3).

d. Frequency of outpatient visits: The total number of outpatient visits (INPAT_OUTPAT_CD= 2 OR 3) during the observation period of each patient in the cohort was determined from medical claims. Number of visits were calculated as the sum of unique claims for outpatient visits for each patient. Multiple claims on the same date were counted as a single encounter. For the purposes of descriptive presentation of the cohort, we classified patients into three categories (0-3, 4-7, and >7 visits).

e. Frequency of inpatient visits: The total number of inpatient visits (INPAT_OUTPAT_CD= 1) during the observation period of each patient in the cohort was determined from medical claims. The number of visits was calculated as the sum of unique claims for inpatient visits for each patient. Multiple claims on the same date were counted as a single encounter. For the

purposes of descriptive presentation of the cohort, we classified patients into three categories (0, 1-3, and >3 visits).

f. Pre-existing conditions: We identified pre-existing CV conditions of the patients including cerebrovascular diseases (CRVD), ischemic heart diseases (IHD), congestive heart failure (CHF), and peripheral vascular diseases (PVD).[103-105] A primary diagnosis (ICD_CD1) in the medical claims before the index date of the first claim for an antihypertensive drug was used to identify the diagnosis for these conditions. The ICD-9 codes are presented in Table 5.

Table 5: ICD-9* diagnostic code for identifying cardiovascular conditions.

ICD-9 Code	Description
410.XX, 411.XX, 412.XX, 413.XX, 414.XX	Ischemic heart disease
362.34, 430.XX, 431.XX, 432.XX, 433.XX, 434.XX, 435.XX, 436.XX, 437.XX, 438.XX	Cerebrovascular disease
437.30, 440.XX, 441.XX, 443.10, 443.20, 443.80, 443.90, 447.10, 557.10, 557.90, V434	Peripheral vascular disease
398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.40, 425.50, 425.70, 425.80, 425.90, 428.XX	Congestive Heart Failure

*ICD-9: International classification of diseases, version 9.

2. **Drug-related factors:** The drug related factors were obtained from prescription claims data. Details of each variable are discussed below–

a. Drug class: The monotherapy drug class that was prescribed as first-line treatment was identified from the prescription claims file. We used the Medispan's Therapeutic Classification System Generic Product Identifier

(GPI) (GPI_CD), which is a 14-character hierarchical drug classification system that can be used to identify and classify antihypertensive drugs. The antihypertensive drug classes recommended by the JNC-8[34] are presented in Table 2 in the Section 2.2.1.b. Except for beta-blockers, all monotherapy drugs (numbered 0-4) have been recommended by JNC-8[34] as first-line treatment. However, we included beta-blockers because the JNC-7[2] guidelines—the latest guideline available during the years of data in our analyses (i.e., 2008-2012)—recommended beta-blockers. Therefore, five first-line monotherapy drug classes were identified including diuretics, beta-blockers, CCBs, ACEIs, and ARBs.

b. Number of co-medications: Prescription claims for medications other than antihypertensive drugs were identified using GPI codes (GPI_CD). Number of unique non-antihypertensive medications taken by each patient during the observation period were counted.

c. Type of co-medication: We used GPI codes (GPI_CD) to identify and classify antihyperlipidemic and antidiabetic medications. Patients who had a prescription claim for these drugs were identified. Categorical variables were created to identify use of these drugs. Users of these drugs were coded ‘1’ and ‘0’ otherwise.

Independent and dependent variables

a. TM strategy: Patterns of medication use inherent in the prescription claims of the patients were used to identify the TM strategies. These four TM strategies have been defined previously in section 3.2. Multiple variables were used to identify the

TM strategies including those available in the prescription claims and user-created. Details of these variables and identification criteria are given below—

A) Variables

1. Days' supply: The days' supply of each prescription that was dispensed was available in the prescription claims file (DAY_SPLY_CNT).
2. Drug: Individual drugs used by the patient were identified and classified using GPI codes (GPI_CD).
3. Drug dose: The drug dose of each drug that was dispensed were available in the prescription claims file (INGRD_STNGTH_UOM_CD).
4. Dosing frequency: The per day dosing frequency (DF) was calculated using days' supply (DAY_SPLY_CNT) and total packaged quantity (TOT_PKG_QTY_CNT) using the following formula-

   Dosing frequency = packaged quantity ÷ days' supply

5. Drug count: The number of unique drugs (GPI_CNT) used by the patients during the observation period were determined as occurrence of unique GPI codes (GPI_CD).
6. Fill pattern: A character string (DRUG_PAT_CD) characterizing the drug fill pattern was created for each patient using GPI codes (GPI_CD). The GPI codes were pre-sorted by fill date (FST_SVC_DT) and transposed to generate arrays. Patterns of X's and O's were created, where O represented a GPI code match with the following claim and X represented consecutive non-matching code. For example, a claim of GPI code 0000001

if followed by 0000001 will be indicated by ‘O’. On the other hand GPI code 0000001 if followed by 0000002 will be indicated by ‘X’.

B) Identification process

We used criteria based on combination of multiple variables described above. The criteria are presented in Table 6.

Table 6: Treatment modification strategy identification criteria.

Strategy	Required criteria			
	Fill pattern	**Type of drug**	**Drug count**	**Dosing**
Switch	Single occurrence of ‘X’	Type of drug initiated during TM was not of FDC.	=2	NA
FDC*	Single occurrence of ‘X’	Type of drug initiated during TM was a FDC.	=2	NA
FPC*	Multiple occurrences of ‘X’	Type of drug initiated during TM was not of FDC.	=2	NA
Uptitration	No occurrence of ‘X’	N.A.	=1	Drug dose or frequency increase.
Downtitration	No occurrence of ‘X’	N.A.	=1	Drug dose or frequency increase.

FDC=Fixed-dose combination; FPC= Free-pill combination; NA= Not applicable.

*Addition group constituted of the FDC and FPC group.

b. Time-to-TM: Time-to-TM (DUR) was calculated as the number of days between the index date of first fill of antihypertensive drug (FIRST_DT) and the starting date of TM (MOD_DT). The maximum follow-up of our study was 12 months, therefore, observations exceeding this period were censored at 365 days.

c. Adherence: We determined patients' adherence before and after TM. We used Proportion of days covered (PDC) to calculate adherence. Adherence measured as PDC is a continuous variable. A categorical adherence variable was created to identify adherent and non-adherent patients. Details on adherence are discussed later in section 3.6.

d. Costs

    1. Drug cost: Drug costs for the total 12-month duration of treatment post-TM were estimated from the prescription claims file (PD_AMT).
    2. Inpatient and outpatient cost: Health services costs for the 12-month duration after TM were estimated from the medical claims file (PAID_AMT). Costs of inpatient (INPAT_OUTPAT_CD= 1) and outpatient visits (INPAT_OUTPAT_CD= 2 OR 3) were estimated individually.
    3. Total costs: Total costs were calculated as the sum of drug, inpatient, and outpatient costs.

    Further details on cost estimation are discussed in section 3.6.

Data across the enrollment, medical and prescription claims file were merged using the unique patient identifier (DW_ALT_INDIVL_KEY) provided by BCBSTX.

The variables used in the analyses, their definition and coding are summarized in the Table 7.

Table 7: Variable definition and coding.

Variable	Coding	Attribute	Definition
Age	1-99 years	Continuous	Age of the patient during the study period.
	18-24 years 25-35 years 36-59 years 60 years and over	Categorical	
Sex	"1"- Male "2"- Female	Categorical	Sex of the patient as reported in the enrollment file.
Charlson Comorbidity Score	0-37	Continuous	Risk of mortality of patient due to co-morbid conditions.
	0 1 2 ≥3	Categorical	
Type of modification	"UP"- Up-titration "DN"- Down-titration "ADD"- Addition "SWI"- Switching "FDC"- Fixed-dose combination "FPC"- Free-pill combination	Categorical	The type of treatment regimen that was initiated by the patients.
Frequency of outpatient visits	1-unknown	Continuous	Number of outpatient visits during the observation period.
	0-3 4-7 >7	Categorical	
Frequency of inpatient visits	1-unknown	Continuous	Number of inpatient during the observation period.
	0 1-3 >3	Categorical	

Burden of concomitant medications	0-100	Continuous	Indicates the number of medications other than antihypertensive drugs taken by patient during the study period.
Type of concomitant medication	“1” Yes “2” No	Categorical	Indicated whether patient was using antihyperlipidemic or antidiabetic drug.
Pre-existing CV condition	“1” Yes “2” No	Categorical	Indicated presence of CV conditions including IHD, CHF, PVD, and CRVD.
Drug class	Diuretics Beta-blockers CCBs ACEIs ARBs	Categorical	The antihypertensive drug class of the first-line agent that was used by the patient.
Time-to-TM	0-365 days	Continuous	The difference between first fill date of first-line antihypertensive drug and the initiation of modified regimen.
Type of TM	Addition Uptitration Downtitration Switch FPC FDC	Categorical	The type of TM that occurred.
Adherence	1-100%	Continuous	a. Patients’ adherence to first-line treatment.
	“1”-Adherent “0”-Non-adherent	Categorical	b. Patients’ adherence after TM.
Drug cost	0-unknown	Continuous	Drug cost in dollars for antihypertensive

			drug 12-month after TM.
Inpatient/outpatient cost	0-unknown	Continuous	Inpatient/outpatient cost in dollars for 12-month after TM.
Total costs	0-unknown	Continuous	The sum of drug, inpatient, and outpatient costs 12-month after TM.

3.6 Data analysis by aims

Aim 1: To determine the rates of TM among patients treated with first-line antihypertensive drugs, and to compare the rates of discontinuation across TM strategies.

In Aim 1, we assessed the patterns of TM across the five monotherapy drug classes recommended as first-line treatment (Aim1a), and compare the time-to-TM and rate of discontinuation across TM strategies (Aim1b). To assess the patterns of TMs after initiation of first-line monotherapy, we identified patients without prior exposure to antihypertensive drugs using a "new-user" design.[101] The "new-user" design minimizes selection bias when using secondary data sources to conduct research. We started by identifying patients with a claim for an antihypertensive drug. Several inclusion and exclusion criteria were applied to the 6-month time period preceding this first claim to identify our final analytical cohort. Patients who filled a prescription of first-line antihypertensive drug (i.e., diuretic, beta-blocker, CCB, ACEI, or ARB monotherapy) during the observation period (starting July 1, 2008) were identified. Because combination therapy (use of more than one drug) is a recommended first-line treatment

for patients with stage 2 hypertension, we excluded these patients to minimize selection bias. To ensure that the patient was a new-user of an antihypertensive, we reviewed into the patient's medication history for a period of 6-months prior to their index antihypertensive fill-date (i.e., wash-out period). The index date for the minimum 6-month wash-out period for this study started on Jan 1, 2008. Only those patients who did not have a claim of antihypertensive drug the wash-out period were included in the cohort. A diagnosis of hypertension for at least one inpatient or outpatient visit was required prior to the index date of the claim for the first-line antihypertensive drug. The new-user design used for cohort identification has been illustrated in Figure 6.

After we identified the cohort of new-users, we grouped the cohort according to first-line recommended drug classes including diuretics, beta-blockers, CCBs, ACEIs, and ARBs as per the clinical guideline recommendation (presented in Table 2 section 2.2.1.b). Next, we determined the baseline demographic and clinical characteristics of the five groups. Age, sex, and comorbidities were determined from the enrollment and medical files. We also determined the concomitant medications (including number of co-medications, and use of antihyperlipidemic and antidiabetic medications during the observation period), CV conditions prior to the index date of first-line monotherapy, and health services utilization of the patients. Demographic and clinical characteristics were reported as frequencies and means.

Patients were then followed for 12 months to identify if they received a TM. TMs were identified from the patterns of prescription claims of the patients as described in the section 3.5. We identified four TM strategies including addition, uptitration, downtitration, and switching. The addition group consists of patients who started using either FDCs or

FPCs. Uptitration and downtitration consisted of those who either had an increase in dose or frequency of dose of the monotherapy drug. Based on previous studies, patients with a >90-day gap between refills of their first-line monotherapy, or between the end of first-line treatment and start of the TM regimen were identified as non-persistent and excluded from our analyses.[32,89] Non-persistent patients were excluded from the analyses. TMs were summarized as a percentage within each first-line monotherapy. The likelihood of receiving any type of TM was determined using Cox's proportional hazards model. The likelihood of receiving a specific TM strategy was also compared using a competing risk model. The time-to-TM was calculated as the number of days between the start of monotherapy until the start date of the TM regimen. Mean time-to-TM was compared using Analysis of Variance (ANOVA) techniques. Patients who did not receive TM during the follow-up were censored at 365 days. The model for determining likelihood of any TM and specific TM were as follows-

Model for likelihood any TM:

$$\text{Likelihood of any TM} = \beta_0 + \beta_1 (\text{Drug class of first-line treatment}) + \beta_2 (\text{Inverse probability treatment weights})$$

Where,

TM= 1 (received a TM) and 0 (no TM).

Drug class= Diuretics, beta-blockers, CCBs, ACEIs, and ARBs.

Models for likelihood of a specific TM strategy:

Likelihood of Addition= $\beta_0 + \beta_1$ (Drug class of first-line treatment) + β_2 (Inverse probability treatment weight)

Likelihood of Uptitration= $\beta_0 + \beta_1$ (Drug class of first-line treatment) + β_2 (Inverse probability treatment weight)

Likelihood of Downtitration= $\beta_0 + \beta_1$ (Drug class of first-line treatment) + β_2 (Inverse probability treatment weight)

Likelihood of Switch= $\beta_0 + \beta_1$ (Drug class of first-line treatment) + β_2 (Inverse probability treatment weight)

Where,

Addition/ Uptitration/Downtitration/Switch= Specific outcome of interest competing versus other strategies. For example likelihood of addition was modeled as a competing outcome versus switching, downtitration, uptitration, and no event.

Drug class= Diuretics, beta-blockers, CCBs, ACEIs, and ARBs.

For Aim1b we followed the patients who received a TM for a total of 2 years. Only those patients who were continuously enrolled during the follow-up period or until the event of discontinuation were included in our analysis of treatment discontinuation rates. Patients who did not have a medication in hand for >90 days and did not begin a new treatment were classified as treatment discontinuers.[32] Those who did not discontinue treatment until the end of follow-up period were censored at 730 days. An extended Cox regression model was used to compare the likelihood of discontinuation across TM strategies.

We used propensity score technique to minimize the selection bias in our study. Propensity score techniques are used for causal analysis in observational studies.[106] A propensity score is the probability of treatment assignment conditional on observed baseline characteristics.[107] The technique minimizes selection bias when random allocation of treatment is not possible. We used the inverse probability treatment weighting technique which estimates the inverse probability of receiving the treatment which a subject actually received.[108] Weights are calculated as- $w_i = \frac{Z_i}{e_i} + \frac{(1-Z_i)}{1-e_i}$, where Z indicates whether or not the ith subject received was treated and e denotes the propensity score for the ith subject. Treatment weights were calculated for the likelihood of receiving first-line monotherapy drug class using logistic regression (PROC LOGISTIC). Based on the conceptual model, baseline covariates including- age, sex, Charlson comorbidity index, drug class of first-line monotherapy, number of co-medications, type of co-medications, and health services utilization were used for calculating propensity scores. The model was also adjusted to account for the 'healthy-adherer' effect and for this purpose we used patients' adherence to their first-line treatment (details discussed in Aim 2). 'Healthy-adherer' refers to the phenomenon where patients with healthy habits (e.g., healthy eating habits, physical activity, good adherence, etc.) have likelihood of better outcomes compared to their counterparts because of an overall healthy attitude. In the absence of data on other health behaviors, adherence to medications has been shown to be a surrogate marker for a healthy-adherer effect.[109] Inverse probability treatment weights were calculated for each patient and adjusted in the final model to minimize selection bias.[110]

Model for likelihood of discontinuation:

$$\text{Likelihood of discontinuation} = \beta_0 + \beta_1 (\text{Type of TM strategy}) + \beta_2 (\text{Inverse probability treatment weight})$$

Where,

Discontinuation= 1(Yes) and 0 (No)

Type of TM strategy= Addition, uptitration, downtitraion, and switch.

Because patients who add drugs to a regimen may do so by either using FDCs or two separate pills (i.e., FPCs), we conducted a sensitivity analysis to determine if the type of addition strategy used affected the likelihood of our outcome of interest (i.e., discontinuation). Propensity scores were recalculated to determine weights for the FDC and FPC group.

Model for sensitivity analysis for likelihood of discontinuation:

$$\text{Likelihood of discontinuation} = \beta_0 + \beta_1 (\text{Type of TM strategy}) + \beta_2 (\text{Inverse probability treatment weight})$$

Where,

Discontinuation= 1(Yes) and 0 (No)

Type of TM strategy= FDC, FPC, uptitration, downtitraion, and switch.

All analyses were conducted using SAS® 9.3, Cary, NC. PHREG procedure was used to construct likelihood of TM and likelihood of discontinuation models. Significance were tested at $P<0.05$.

Aim 2: To determine the adherence rates and characterize factors associated with adherence after TM among patients previously treated with first-line antihypertensive drugs.

Adherence after TM is necessary for BP goal attainment.[28] While patients are highly likely to have a TM after being treated with a first-line drug (about 50-75%), patients' requiring more than one TM is not as common. In a previous study looking at TMs among first-line antihypertensive drug users, only about 25% of patients required subsequent TMs.[11] Therefore, it is reasonable to compare the adherence across the different TM strategies after the first TM. In aim 2, we determined patients' adherence after their first TM and compared it across the TM strategies (Aim 2a). In Aim2b we characterized the factors associated with adherence. To accomplish this, we followed the TM cohort identified in Aim 1b from their index date of TM up to 12 months. Only those patients who continued to stay on the same regimen during the 12 month follow-up period were included in our final cohort for Aim 2. The cohort was divided into four groups according to the type of TM which includes up-titration, addition, down-titration and switching, similar to Aim1b. Adherence of patients during the 12 months was determined using proportion of days covered (PDC) as follows –

$$PDC = \frac{Total\ days\ supply}{(Last\ date\ of\ fill - First\ date\ of\ fill) + Days\ supply\ of\ last\ fill}$$

The PDC provides a more conservative estimate of medication adherence (compared to other measures, e.g., medication possession ratio (MPR)) when multiple medications are intended to be used concomitantly.[111] Patients in the 'addition' group were users of fixed dose combination (FDC), or more than one drug administered as separate pills (i.e., FPC). For the latter group, we determined adherence as the mean of the PDC for the two drugs that the patient was using.[112] We calculated the mean PDC for each individual drug. The sum of PDC of the two drugs was then divided it by 2 to obtain patient's adherence to the FPC regimen. The PDC may underestimate adherence if the patient had an inpatient visit during the observation period. This is because the patient's drugs during his/her inpatient stay are covered under inpatient charges and not included in the prescription claims. Therefore, we adjusted for the inpatient days by subtracting the number of days spent in hospital from our total duration of observation (i.e., 365 days).[113] The PDC is a continuous measure of adherence, but we dichotomized the variable to identify adherent and non-adherent patients. Patients were categorized into "adherent" and "non-adherent" using an 80% cut-off. Patients with PDC >0.80 were categorized as adherent which has been validated in a previous study as a reasonable cut-point for identifying adherent patients suffering from chronic conditions such as hypertension.[114]

We compared adherence as a continuous and categorical variable; therefore, we used two types of GLMs. Differences in adherence as a continuous variables were compared using a GLM with identity link. For comparison of TM strategies measuring adherence as a categorical variable, GLM with log link was used. The TM groups were adjusted using inverse probability treatment weights for baseline characteristics including age,

sex, comorbidities, drug class of previous monotherapy, and time-to-TM based on the conceptual. Treatment weights were calculated for the likelihood of receiving a TM strategy using logistic regression (PROC LOGISTIC). The GLMs used for comparing adherence were as follows-

Model for comparing adherence as a continuous variable:

Adherence = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weight)

Where,

Adherence= PDC

Type of modification= addition, uptitration, downtitration, and switch.

Model for comparing likelihood of adherence:

Likelihood of adherence = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weight)

Where,

Adherence= 1 (adherent) and 0 (not adherent)

Type of modification= addition, uptitration, downtitration, and switch.

Additional analysis was conducted to compare adherence for the FDC and FPC groups. Propensity scores were recalculated for the groups for model adjustment.

Model for comparing adherence as a continuous variable for FPC and FDC group:

Adherence = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weight)

Where,

Adherence= PDC

Type of modification= FPC, FDC, uptitration, downtitration, and switch.

Model for comparing likelihood of adherence for FPC and FDC group:

Likelihood of adherence = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weight)

Where,

Adherence= 1 (adherent) and 0 (not adherent)

Type of modification= FPC, FDC, uptitration, downtitration, and switch.

To determine the factors associated with adherence after TM, we used GLMs. Two estimating equations were constructed modelling adherence as a continuous and categorical variable. The factors that were assessed include age, sex, drug class of first-line monotherapy, comorbidities, time-to-TM, frequency of inpatient visits, frequency of outpatient visits, number of co-medications, type of co-medications, and prior CV diagnosis.

Model for Aim 2b was as follows-

Adherence = $\beta_0 + \beta_{2a}$ (type of modification) β_{2b} (age) + β_{2c} (sex) + β_{2d} (first-line drug class) + β_{2e} (comorbidities) + β_{2e} (time to treatment modification) + β_{2f} (number of inpatient visits) + β_{2g} (number of outpatient visits) + β_{2h} (number of

concomitant medications) + β_{2i} (type of concomitant medications) + β_{2j} (prior CV diagnosis)

In addition to our main analysis, a subgroup analysis was conducted for patients who were not adherent to their first-line drug. A previous study has shown that adherence to the modified regimen is critical for BP goal attainment.[28] Moreover, TMs increase the risk of non-adherence in patients.[5] Therefore, differences in TM strategies in terms of adherence will be more valuable for patients needing TM but having a history of non-adherence to first-line monotherapy. We used the GLM and model adherence as a dichotomous variable to compare TM strategies in our subgroup analysis.

All analyses were conducted using SAS® 9.3, Cary, NC. GLM procedure were used to construct adherence models. Significance were tested at $P<0.05$.

<u>Aim 3:</u> To determine healthcare utilization costs and examine the association of adherence with healthcare utilization costs after TM among patients previously treated with first-line antihypertensive drugs.

A comparative assessment of costs according to the TM strategies is currently unavailable. In Aim 3a, we estimated the healthcare costs after TM and compared them across the TM strategies. Costs were compared between four TM subgroups – uptitration, addition, downtitration, and switching. Patients who received TM and were continuously enrolled for 12 months after TM were included in our analyses for Aim 3.In our preliminary analyses, we estimated the all-cause healthcare costs. Costs were computed as all-cause total healthcare costs, and also within each component of the

total cost which included inpatient, outpatient, and drug costs. All costs were computed for 12-months from the index date of TM. We estimated the costs from the payer's perspective (i.e., BCBSTX), and for this purpose we used the amount paid by the insurance company (i.e., BCBSTX) from the medical and prescription claims files. Because hypertension is a major risk factor for CV diseases, we performed a secondary analysis by estimated costs restricting to claims incurred for hypertension and CV-related visits. For identifying hypertension (Table 4) and CV-related (Table 5) claims, we used ICD-9 diagnostic codes validated in previous studies. We included all claims with primary diagnosis for these codes for estimating costs. Analysis was also performed on the addition group to compare costs of FDC and FPC users with other TM strategy users.

Cost estimation

Costs were computed using the index date of TM as the starting point and then following for up to 12-months after TM. Costs of prescription drug use for each patient were estimated from pharmacy claims. Antihypertensive medications were identified using GPI codes. Costs were adjusted to reflect the dollar amount for the year 2012. Consumer price indices (CPI) for prescription drugs were used for adjusting the costs (Table 8).

Table 8: Consumer price indices for prescription drugs.

Year	Consumer price index
2008	379.943
2009	396.526
2010	412.786
2011	429.817
2012(reference year)	437.905

*Available from Bureau of labor statistics (http://www.bls.gov/cpi/cpid1412.pdf).

All-cause costs for inpatient and outpatient visits were inclusive of visits related to any reason. As mentioned earlier, hypertension and CV-related costs were identified based on ICD-9 codes. All costs were adjusted using CPI for healthcare services (Table 9).

Table 9: Consumer price indices for health services.

Year	Consumer price index
2008	367.133
2009	379.516
2010	391.946
2011	405.629
2012 (reference year)	418.654

*Available from Bureau of labor statistics (http://www.bls.gov/cpi/cpid1412.pdf).

The total healthcare costs will be computed by adding the prescription drug costs and the health services use costs.

Total health services costs= Inpatient costs + outpatient costs + prescription drug costs

Bias

To minimize selection bias, we adjusted the analysis using the propensity score technique. Based on the conceptual model, propensity scores were calculated using baseline characteristics including– age, sex, comorbidities, drug class of previous monotherapy, and time-to-TM. Inverse probability treatment weights were calculated and adjusted in the GLMs. Treatment weights were calculated for the likelihood of receiving a TM strategy using logistic regression (PROC LOGISTIC).

Modeling framework

GLMs with gamma distribution and *log* link function were used to compare the TM strategies. GLMs are commonly used in econometrics for analysis of costs because these models account for skewed cost distribution. We constructed several models for comparing costs in our preliminary analysis, analysis for hypertension and CV-related costs, and examining the association between adherence and costs.

<u>Models for comparison of all-cause total costs and component costs were as follows</u>:

$$\text{Total all-cause costs} = \beta_0 + \beta_1 (\text{type of modification}) + \beta_2 (\text{inverse probability treatment weights})$$

All-cause inpatient costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

All-cause outpatient costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

Drug costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

Where,

Costs= costs in $ over the 12-month duration for any visit

Type of modification= addition, uptitration, downtitration, and switch

Models for comparison of hypertension and CV-related total costs and component costs were as follows:

Total hypertension and CV-related costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

Hypertension and CV-related inpatient costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

Hypertension and CV-related outpatient costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

Drug costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

Where,

Costs= costs in $ over the 12-month duration for any hypertension and CV-related visits

Type of modification= addition, uptitration, downtitration, and switch

Analysis was conducted for FDC and FPC groups. Propensity weights were recalculated for these groups for adjusting the cost models.

Models for comparison of all-cause total costs and component costs for FPC and FDC:

$$\text{Total all-cause costs} = \beta_0 + \beta_1 (\text{type of modification}) + \beta_2 (\text{inverse probability treatment weights})$$

$$\text{All-cause inpatient costs} = \beta_0 + \beta_1 (\text{type of modification}) + \beta_2 (\text{inverse probability treatment weights})$$

$$\text{All-cause outpatient costs} = \beta_0 + \beta_1 (\text{type of modification}) + \beta_2 (\text{inverse probability treatment weights})$$

$$\text{Drug costs} = \beta_0 + \beta_1 (\text{type of modification}) + \beta_2 (\text{inverse probability treatment weights})$$

Where,

Costs= costs in $ over the 12-month duration for any visit

Type of modification= FDC, FPC, uptitration, downtitration, and switch

Models for comparison of hypertension and CV-related total costs and component costs were as follows:

Total hypertension and CV-related costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

Hypertension and CV-related inpatient costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

Hypertension and CV-related outpatient costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

Drug costs = $\beta_0 + \beta_1$ (type of modification) + β_2 (inverse probability treatment weights)

Where,

Costs= costs in $ over the 12-month duration for any hypertension and CV-related visits

Type of modification= FDC, FPC, uptitration, downtitration, and switch

Association between adherence and costs

Adherence has been shown to be positively associated with reduction in healthcare costs. For Aim 2b, we examined the association between adherence after TM and the costs after TM over the 12-month follow-up duration.

Model for examining the association between adherence and costs was as follows-

Costs = $\beta_0 + \beta_{3a}$ (type of modification) + β_{3b} (adherence) + β_{3c} (inverse probability treatment weights)

Where,

Costs= costs in $ over the 12-month duration for any hypertension and CV-related visits.

Type of modification= FDC, FPC, uptitration, downtitration, and switch.

Adherence= 0 (not adherent), 1 (adherent)

All analyses were conducted using SAS® 9.3, Cary, NC. GENMOD procedure were used to construct cost models. Significance were tested at $P<0.05$.

CHAPTER FOUR: RESULTS

4.1 Patterns of TM and likelihood of discontinuation across TM strategies

Approximately 1.5 million patients in the BCBSTX database had at least one prescription claim for an antihypertensive drug during 2008-2012. After applying the inclusion and exclusion criteria, 21,642 users who newly started their antihypertensive treatment with a diuretic, beta-blocker, CCB, ACEI, or ARBs were included in the cohort for Aim 1a. The demographic and clinical characteristics of patients are presented in Table 10. As seen in the table 10, we ended up with very large sample sizes; even after classifying into groups by the prescribed first-line drug class, the smallest group (i.e., diuretics) had >2,000 patients with up to 9,700 patients in the ACEIs group. Because of such large sample sizes, the tests for statistical differences (for ANOVA and chi-square) were significant across all comparisons on baseline characteristics (P<0.0001).

Typically, observational studies with large sample sizes such as our study use standardized scores to report statistical differences between groups. Standardized scores have limited application and can be used only to compare differences between two groups. Because the number of groups in our study is >2, we were unable to use standardized score to detect statistical differences in our study.

Table 10: Baseline characteristics of patients starting monotherapy (N=21,642).

Characteristic	Drug Class*				
	Diuretics (N=2,008)	**BBs (N=3,915)**	**CCBs (N=2,664)**	**ACEIs (N=9,684)**	**ARBs (N=3,371)**
Age N (%)					
18-24 years	24 (1.20)	54 (1.38)	30 (1.13)	128 (1.32)	20 (0.59)
25-35 years	213 (10.61)	437 (11.16)	252 (9.46)	997 (10.30)	253 (7.51)
36-59 years	1426 (71.02)	2779 (70.98)	1879 (70.53)	6999 (72.27)	2478 (73.51)
60 years and over	345 (17.18)	645 (16.48)	503 (18.88)	1560 (16.11)	620 (18.39)
Sex N (%)					
Male	721 (35.91)	2023 (51.67)	1503 (56.42)	6045 (62.42)	1974 (58.56)
Comorbidity index N (%)					
0	1529 (76.15)	2987 (76.30)	1998 (75.00)	7339 (76.40)	2535 (75.20)
1	328 (16.33)	609 (15.56)	444 (16.67)	1685 (17.40)	566 (16.79)
2	92 (4.58)	202 (5.16)	128 (4.80)	357 (3.69)	165 (4.89)
≥3	59 (2.94)	117 (2.99)	94 (3.53)	243 (2.51)	105 (3.11)
Number of co-medications mean (± SD)**	4.92 (2.23)	4.26 (2.22)	4.18 (2.23)	4.04 (2.08)	4.22 (2.26)
Co-medications N (%)**	368 (18.33)	854 (21.81)	552 (20.72)	2148 (22.18)	724 (21.48)
Antihyperlipidemic	104 (5.18)	169 (4.32)	147 (5.52)	842 (8.69)	214 (6.35)
Antidiabetic					
Cardiovascular diseases N (%)*†					
IHD	77 (3.83)	361 (9.22)	134 (5.03)	310 (3.20)	127 (3.77)
CHF	50 (2.49)	70 (1.79)	45 (1.69)	93 (0.96)	30 (0.89)
PVD	29 (1.44)	83 (2.12)	59 (2.21)	119 (1.23)	54 (1.60)
CRVD	37 (1.84)	166 (4.24)	71 (2.67)	194 (2.00)	90 (2.67)
Healthcare utilization N (%)†**					
Inpatient visits					
0	1882 (93.73)	3593 (91.78)	2453 (92.08)	9281 (95.84)	3234 (95.94)
1-15	11 (0.55)	91 (2.32)	78 (2.93)	159 (1.64)	46 (1.36)
>15	115 (5.73)	231 (5.90)	133 (4.99)	244 (2.52)	91 (2.70)
Outpatient visits					
0-3	510 (25.40)	1025 (26.18)	850 (31.91)	3426 (35.38)	843 (25.01)
4-7	613 (30.53)	1203 (30.73)	792 (29.73)	3128 (32.30)	1134 (33.64)
>7	885 (44.07)	1687 (43.09)	1022 (38.36)	3130 (32.32)	1394 (41.35)

*CCBs= Calcium Channel Blockers; ACEIs= Angiotensin-converting enzyme inhibitors; ARBs= Angiotensin receptor blockers.

** Comedications used by patients during the follow-up period were identified from prescription claims file.

*** IHD: Ischemic heart diseases; CHF: Congestive heart failure; PVD: Peripheral vascular diseases; CRVD: Cerebrovascular diseases.

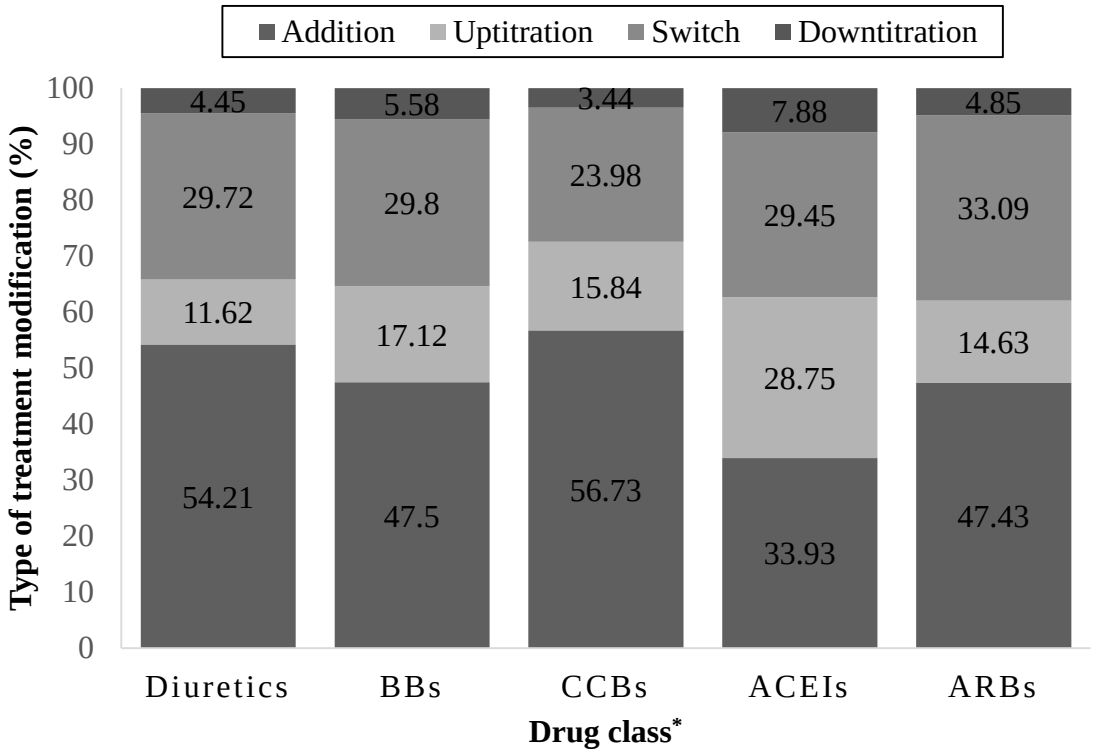
† Cardiovascular conditions at baseline were identified from medical claims file.

†† Health services utilization during the baseline period was determined from medical claims file.

Rates of TM

The cohort of 21,642 patients was followed to identify TMs. Over the follow-up period of 12-months 10,505 patients received at least one TM. The incidence of TMs was high in our study; almost half of the patients (48.53%) had changes in their first-line treatment. ACEIs (N=4,418) accounted for the highest number of patients who underwent TMs followed by BBs (N=2,907), CCBs (N=1,597), ARBs (N=1,360), and diuretics (N=1,033). Overall, intensification of treatment regimens were more common and constituted more than half of the TMs. Addition of drugs to an existing regimen accounted for the highest proportion of TMs (43.85%) followed by switching (29.19%), uptitration (20.95%), and downtitrations (6.02%).

Figure 7: Types of treatment modification according to the starting drug class (N=10,505)



*BBs= Beta-blockers; CCBs= Calcium Channel Blockers; ACEIs= Angiotensin-converting enzyme inhibitors; ARBs= Angiotensin receptor blockers.

The types of TMs occurring within a drug class are presented in Figure 7. The highest percentage of drug additions occurred in patients who started their antihypertensive treatment with CCBs (56.73%), while ACEIs had the lowest number of additions (33.93%). On the contrary, uptitrations were more common in ACEIs (28.75%) and least common in diuretics (11.62%). Deintensification strategies constituted fewer TMs compared to intensification strategies. Switching of drugs occurred more frequently among patients starting treatment with an ARB, accounting for about one-third of TMs in this drug class. Downtitrations were the least common type of TMs across all five drug classes and constituted less than 8% of all TMs.

A Cox proportional hazards model was used to compare the overall likelihood of TM across the five antihypertensive drug classes. The model was adjusted using propensity score weighting. Because inverse probability treatment weight estimates the average effect of treatment in the sample, we examined observations with extremely low propensity scores (i.e., score less than 0.05). Less than 0.02% of the sample had propensity score less than 0.05, the unadjusted and propensity score weighted group differences are presented in Appendix. The hazards ratios are presented in Table 11. The likelihood of receiving a TM was significantly different across the five drug classes. The probability of receiving a TM was lower for drugs acting on the renin-angiotensin system (i.e., ACEIs and ARBs) when compared with BBs, CCBs, and diuretics. When comparing between ACEIs and ARBs, the probability of TM was higher for those starting treatment on ACEIs (HR=1.21, 95% CI: 1.14-1.28). Patients starting treatment with BBs or CCBs had significantly higher likelihood of TM (HR=1.09; 95% CI: 1.00-1.17) and (HR=1.33; 95% CI: 1.23-1.44), respectively, compared with diuretics.

Between CCBs and BBs, the probability of TMs was lower for BBs (HR = 0.82; 95% CI: 0.77-0.87).

Table 11: Likelihood of receiving any treatment modification by starting drug class.*

Drug Class comparison	**Hazards Ratio (95% Confidence interval)**
ACEIs vs ARBs	1.21 (1.14-1.28) †
ACEIs vs BBs	0.79 (0.75-0.83) †
ACEIs vs CCBs	0.64 (0.61-0.68) †
ACEIs vs Diuretics	0.86 (0.80-0.92) †
ARBs vs BBs	0.65 (0.61-0.70) †
ARBs vs CCBs	0.53 (0.50-0.57) †
ARBs vs Diuretics	0.71 (0.65-0.77) †
BBs vs CCBs	0.82 (0.77-0.87) †
BBs vs Diuretics	1.09 (1.01-1.17) †
CCBs vs Diuretics	1.33 (1.23-1.44) †

*BBs= Beta-blockers; CCBs= Calcium Channel Blockers; ACEIs= Angiotensin-converting enzyme inhibitors; ARBs= Angiotensin receptor blockers.
† significant at $P<0.05$.

Similar to the overall likelihood of TMs, we compared the likelihood of receiving each type of TM – addition, uptitration, switch, and downtitration – across the five drug classes using proportional hazards models. The likelihood of receiving a specific TM strategy for the five drug classes is presented in Table 12.

Table 12: Likelihood of treatment modification by antihypertensive drug class.

Drug class comparison*	Hazards Ratio (95% Confidence interval)			
	Addition	**Uptitration**	**Switch**	**Downtitration**
ACEIs vs ARBs	0.86 (0.79-0.95) †	2.35 (2.02-2.73) †	1.08 (0.97-1.20)	1.95 (1.50-2.54) †
ACEIs vs BBs	0.56 (0.52-0.61) †	1.34 (1.19-1.51) †	0.77 (0.70-0.85) †	1.11 (0.90-1.37) †
ACEIs vs CCBs	0.39 (0.36-0.42) †	1.20 (1.05-1.38) †	0.77 (0.69-0.87) †	1.47 (1.19-1.96) †
ACEIs vs Diuretics	0.53 (0.49-0.59) †	2.135 (1.77-2.58) †	0.84 (0.74-0.95) †	1.51 (1.11-2.05) †
ARBs vs BBs	0.65 (0.59-0.72) †	0.57 (0.48-0.68) †	0.71 (0.63-0.81) †	0.57 (0.42-0.77)
ARBs vs CCBs	0.45 (0.40-0.49) †	0.51 (0.43-0.62) †	0.72 (0.63-0.82) †	0.75 (0.53-1.08) †
ARBs vs Diuretics	0.62 (0.56-0.70) †	0.91 (0.73-1.14)	0.78 (0.67-0.90) †	0.77 (0.53-1.13)
BBs vs CCBs	0.68 (0.65-0.75) †	0.90 (0.76-1.05)	1.00 (0.88-1.14)	1.33 (0.96-1.83)
BBs vs Diuretics	0.95 (0.86-1.06)	1.59 (1.29-1.96) †	1.09 (0.95-1.25)	1.36 (0.97-1.91)
CCBs vs Diuretics	1.39 (1.25-1.55) †	1.77 (1.43-2.20) †	1.09 (0.94-1.26)	1.02 (0.69-1.52)

*BBs= Beta-blockers; CCBs= Calcium Channel Blockers; ACEIs= Angiotensin-converting enzyme inhibitors; ARBs= Angiotensin receptor blockers.
† significant at $P<0.05$.

Addition: With the exception of BBs vs. diuretics, the likelihood of addition was significantly different across all drug classes. Patients using ACEIs or ARBs had a lower likelihood of adding a drug compared to those using diuretics, BBs, and CCBs. The likelihood of adding a drug was lower for BBs compared with CCBs (HR=0.68; 95% CI: 0.65-0.75) and for ACEIs compared with ARBs (HR= 0.86; 95% CI: 0.79-0.95), while the likelihood was higher for patients using CCBs when compared with those starting diuretics (HR=1.39; 95% CI: 1.25-1.55).

Uptitration: With the exception of BBs vs. CCBs and ARBs vs. diuretics, the likelihood of uptitration was significantly different across all drug classes. Patients on ACEIs were

significantly more likely to increase their drug dose compared to those on ARBs, BBs, CCBs, and diuretics. Patients on BBs and CCBs had a higher likelihood of uptitration compared to those on ARBs or diuretics.

Switch: Patients on ACEIs and ARBS were less likely to switch medications compared to BBs, CCBs, and diuretics. There was no statistically significant difference between the likelihood of switching drugs between CCBs, BBs, and diuretics.

Downtitration: The likelihood of downtitration did not differ significantly between ARBs, CCBs, BBs and diuretics. The only drug class with a significantly higher likelihood of downtitration was ACEI. Patients on ACEIs were more likely to decrease drug dose compared to ARBs, CCBs, and diuretics.

Time-to-TM

We determined the mean time-to-TM by TM strategy for the five antihypertensive drug classes. Results are presented in Table 13. The mean time for a patient to receive TM from initiation of treatment varied according to the type of TM. Mean time to addition (133.34 days) and uptitration (102.00 days) was lower than switching (162.18 days) and downtitration (145.58 days). Thus, intensification of regimens occurred earlier over the course of treatment compared to deintensification. The time-to-TM did not vary significantly across the five drug classes for uptitration, switching, and downtitration. The mean time for addition of drugs was statistically significantly different for ARBs, CCBs, and BBs compared to diuretics ($P<0.05$); however, there was no significant difference between ACEIs and diuretics.

Table 13: Time-to-treatment modification by type of strategy by starting drug class.

Drug Class*	Time-to-TM Mean (±Standard deviation)			
	Addition	**Uptitration**	**Switch**	**Downtitration**
ACEIs	145.82 (95.29)	119.57 (102.63)	159.43 (95.65)	142.19 (105.98)
ARBs	153.15 (92.32)	146.69 (108.21)	171.04 (99.19)	153.34 (96.13)
BBs	119.61 (89.36)	121.76 (104.75)	161.30 (99.12)	150.00 (109.45)
CCBs	111.52 (86.36)	99.12 (98.12)	158.20 (101.12)	144.18 (108.76)
Diuretics	136.81 (91.51)	118.93 (102.69)	167.59 (98.32)	150.52 (98.41)

*BBs= Beta-blockers; CCBs= Calcium Channel Blockers; ACEIs= Angiotensin-converting enzyme inhibitors; ARBs= Angiotensin receptor blockers.

Likelihood of treatment discontinuation

The cohort of 10,505 patients who received a TM were followed until complete discontinuation of treatment, or up to a maximum of 12-months from the index date of TM. The likelihood of treatment discontinuation for TM strategies is presented in Table 14. Results of the propensity score adjusted model suggest that patients who add a drug to intensify treatment are significantly less likely to discontinue hypertension

treatment. The likelihood of treatment discontinuation is about 25% less if patients add a drug to the regimen vs. increasing the dose of the initial drug to intensify the treatment. Similarly, the likelihood of discontinuation is lower for patients who add medications compared to those who switch drugs (HR=0.53; 95% CI: 0.47-0.59). When comparing uptitration to switching, the likelihood of discontinuation is lower for patients who uptitrate drug dose (HR=0.69; CI: 0.63-0.75).

Table 14: Likelihood of discontinuation by treatment modification strategy.

Strategies	**Hazards Ratio*** **(95% Confidence interval)**
Addition vs. Uptitration	0.77 (0.70-0.83) †
Addition vs. Switch	0.53 (0.47-0.59) †
Addition vs. Downtitration	0.43 (0.36-0.52) †
Uptitration vs. Switch	0.69 (0.63-0.75) †
Uptitration vs. Downtitration	0.56 (0.49-0.65) †
Switch vs. Downtitration	0.82 (0.73-0.92) †

*Hazards ratio adjusted for age, sex, Charlson comorbidity index, number of co-medications, type of co-medications, adherence to first-line drug, existing cardiovascular diseases, and health services utilization.

TM strategies for ADE may include deintensification of drug dose, or switching. The results of our adjusted model show that the likelihood of discontinuation was significantly lower for those who switch medications compared to those downtitrating drug dose (HR=0.82; 95% CI: 0.73-0.92).

Subgroup analysis

We performed a subgroup analysis to determine if the rates of discontinuation differed in the addition group according to type of addition, defined as FDCs or FPCs. Results were consistent with our main analyses (Table 15). Patients were less likely to discontinue treatment if they received addition as TM strategy, irrespective of whether FDCs or FPCs was used. The likelihood of discontinuation was up to 55% lower for FDC or FPC users compared to those uptitrating or switching medication. Between FPC and FDC, there were no significant differences in the likelihood of treatment discontinuation.

Table 15: Likelihood of discontinuation for fixed-dose combination and free-pill combination group.

Strategies	**Hazards Ratio (95% Confidence interval)***
FDC vs FPC	0.99 (0.91-1.09)
FDC vs. Uptitration	0.76 (0.68-0.85) †
FDC vs. Switch	0.55 (0.48-0.64) †
FDC vs. Downtitration	0.48 (0.39-0.58) †
FPC vs. Uptitration	0.76 (0.70-0.84) †
FPC vs. Switch	0.56 (0.50-0.62) †
FPC vs. Downtitration	0.48 (0.41-0.56) †

FDCs= Fixed-dose combinations; FPCs= Free-pill combinations.
*Hazards ratio adjusted for age, sex, Charlson comorbidity index, number of co-medications, type of co-medications, adherence to first-line drug, existing cardiovascular diseases, and health services utilization.

4.2 Adherence and factors associated with adherence after TM

The 12-month adherence of patients who received a TM was determined. After applying additional inclusion criteria, a final cohort of 5,998 patients was used for calculating the adherence using the PDC ratio. The cohort is comprised of patients who added (N=2,602), uptitrated (N=1,659), switched (N=1,282), and downtitrated (N=455) their medications. We conducted several analyses to assess differences in adherence across TM strategies.

Table 16: Baseline characteristics of the treatment modification cohort

Characteristics	Treatment modification strategy			
	Addition (N=2,602)	**Uptitration (N=1,659)**	**Switch (N=1,282)**	**Downtitration (N=455)**
Age N (%)				
18-24 years	23 (0.88)	28 (1.69)	20 (1.56)	7 (1.54)
25-35 years	182 (6.99)	201 (12.12)	161 (12.56)	53 (11.65)
36-59 years	1,912 (73.48)	1,191 (71.79)	911 (71.06)	324 (71.21)
60 years and over	485 (18.64)	239 (14.41)	190 (14.32)	71 (15.60)
Gender N (%)				
Male	1473 (56.61)	995 (59.98)	670 (52.26)	259 (56.92)
Comorbidity index N (%)				
0	1542 (59.26)	1074 (64.74)	812 (63.34)	300 (65.93)
1	636 (24.44)	381 (22.97)	298 (23.24)	93 (20.44)
2	215 (8.26)	109 (6.57)	90 (7.02)	39 (8.57)
≥3	209 (8.03)	95 (5.73)	82 (6.40)	23 (6.40)
First-line drug[*]				
Diuretics	300 (11.53)	88 (5.30)	141 (11.00)	25 (5.49)
Beta-blockers	551 (13.76)	260 (15.67)	234 (18.25)	78 (17.14)
CCBs	546 (20.98)	196 (11.81)	134 (10.45)	39 (8.57)
ACEIs	847 (32.55)	976 (58.83)	582 (45.40)	270 (59.34)
ARBs	358 (32.55)	139 (8.38)	191(14.90)	43 (9.45)
Number of co-medications mean (± SD)[**]	4.40 (2.22)	4.01 (2.11)	4.46 (2.17)	4.25 (2.17)
Co-medications N (%)[**]				
Antihyperlipidemic	618 (23.75)	359 (21.64)	258 (20.12)	101 (22.20)
Antidiabetic	201 (7.72)	93 (5.61)	59 (4.60)	33 (7.25)
Cardiovascular diseases N (%)[***†]				
IHD	156 (6.00)	66 (3.98)	55 (4.29)	21 (4.62)
CHF	44 (1.69)	26 (1.57)	19 (1.48)	6 (1.32)
PVD	42 (1.61)	21 (1.27)	21 (1.64)	5 (1.10)
CRVD	76 (2.92)	38 (2.29)	30 (2.34)	16 (3.52)
Healthcare utilization N (%)[††]				
Inpatient visits				
0	2458 (94.47)	1576 (95.00)	1215 (94.77)	430 (94.51)
1-15	51 (1.96)	36 (2.17)	19 (1.48)	9 (1.98)
>15	93 (3.57)	47 (2.83)	48 (3.74)	16 (3.52)
Outpatient visits				
0-3	177 (6.80)	169 (10.19)	109 (8.50)	42 (9.23)
4-7	174 (6.69)	132 (7.96)	94 (7.33)	38 (8.35)
>7	2251 (86.51)	1358 (81.86)	1079 (84.17)	375 (82.42)

[*]CCBs= Calcium Channel Blockers; ACEIs= Angiotensin-converting enzyme inhibitors; ARBs= Angiotensin receptor blockers.
[**]Comedications used by patients during the follow-up period were identified from prescription claims file.
[***] IHD: Ischemic heart diseases; CHF: Congestive heart failure; PVD: Peripheral vascular diseases; CRVD: Cerebrovascular diseases.
[†] Cardiovascular conditions at baseline were identified from medical claims file.
[††] Health services utilization during the baseline period was determined from medical claims file.

Mean adherence

Table 17: Adherence and mean difference in adherence between treatment modification strategies.

Adherence	Addition=0.68 ± 0.27	Downtitration=0.68 ± 0.30
Mean(±SD)	Uptitration=0.70 ± 0.29	Switch=0.64 ± 0.32
Strategy Comparison	**Difference between mean**	**95% Confidence interval**
Uptitration-Downtitration	0.019	-0.019 -0.058
Uptitration-Addition	0.024	0.0007-0.047†
Uptitration-Switch	0.064	0.037-0.092†
Downtitration-Addition	0.004	-0.033-0.042
Downtitration-Switch	0.045	0.0004-0.084†
Addition-Switch	0.041	0.016-0.066†

† significant at $P<0.05$.

First, we determined the mean differences in adherence across the TM strategies using a propensity score weighted GLM (with identity link function). Less than 1% of the sample had propensity score less than 0.05, the propensity score weighted data is presented in Appendix. Adherence was highest for uptitration (mean PDC= 0.70 ± 0.29) followed by addition (mean PDC=0.68 ± 0.27), downtitration (mean PDC=0.68 ± 0.30), and switch (mean PDC=0.64 ± 0.32). Differences in PDC are presented in Table 16. The mean PDC for uptitration was significantly different compared to addition (mean difference = 0.024; 95% CI= 0.0007-0.047) and switch (mean difference = 0.064; 95% CI= 0.037-0.092); patients who received an uptitration had a higher adherence. Mean

adherence was higher for downtitration (4%) and addition (0.4%) compared to switching.

Next, we classified the addition group into- 1. FPCs (N=1,395), and 2. FDCs (N=1,207). The adherence for FPCs and FDCs was 0.67 ± 0.25 and 0.69 ± 0.29, respectively. Result of the GLM shows that the mean differences between adherence for uptitration group and FPCs (mean difference=0.035; 95% CI: 0.009-0.068), and FDCs and switch (mean difference=-0.054; 95% CI: -0.085--0.022) were significant (Table 17). Overall, differences in adherence were statistically significant across the TM strategies.

Table 18: Mean adherence for fixed-dose combination and free-pill combination group.

Adherence Mean(±SD)	FPC=0.67 ± 0.25	FDC=0.69 ± 0.29
Strategy comparison*	**Difference between means**	**95% Confidence interval**
Uptitration-FDCs	0.011	-0.022-0.040
Uptitration-FPCs	0.035	0.009-0.068†
Downtitration-FDCs	-0.008	-0.052-0.035
Downtitration-FPCs	0.016	-0.027-0.059
Switch-FDCs	-0.054	-0.085- -0.022†
Switch-FPCs	-0.030	-0.060-0.001

* FDCs= Fixed-dose combinations; FPCs= Free-pill combinations.
† significant at *P*<0.05.

We also examined factors that are associated with adherence including demographic and clinical factors of the patient, and treatment-related factors (Table 18). Age (*P*<0.0001), presence of comorbid conditions (*P*=0.01), drug class of first-line treatment (*P*<0.05), time-to-TM (*P*=0.01), number of concomitant drugs (*P*=0.04), use of a concomitant antihyperlipidemic drug (*P*=0.07), frequency of outpatient visits (*P*=0.009), and frequency of inpatient visits (*P*=0.01) were significantly associated with adherence (measured as continuous variable) to the TM strategies.

Table 19: Factors associated with adherence (continuous) after treatment modification.

Factor*	**Estimate**	**t value**	**P**
Drug class of first-line treatment			
ACEI vs ARB	0.01	0.87	0.38
ACEI vs BB	-0.00	-0.10	0.92
ACEI vs CCB	0.002	0.25	0.80
ACEI vs Diuretics	0.041	2.99	0.002†
ARB vs BB	-0.01	-0.83	0.40
ARB vs CCB	-0.007	-0.53	0.59
ARB vs Diuretics	0.03	1.90	0.05
BB vs CCB	0.003	0.30	0.76
BB vs Diuretics	0.042	2.78	0.005†
CCB vs Diuretics	0.038	2.43	0.015†
Sex (Female)	-0.014	-1.84	0.06

Age	0.005	13.14	<0.0001†
Number of concomitant drugs	0.004	1.99	0.04
Comorbidities	-0.009	-2.41	0.01†
Time to treatment modification	-0.0001	-2.51	0.01†
Inpatient visits	-0.004	-2.38	0.01†
Outpatient visits	0.0009	2.61	0.009†
Use of antidiabetic medications	-0.0004	-0.03	0.97
Use of antihyperlipidemic medication	0.024	2.67	0.007†
CRVD	0.003	0.14	0.89
IHD	0.012	0.62	0.53
CHF	0.032	1.21	0.30
PVD	0.021	0.68	0.50

*CRVD: Cerebrovascular diseases; IHD: Ischemic heart diseases; CHF: Congestive heart failure; PVD: Peripheral vascular diseases.

Likelihood of being adherent

Table 20: Likelihood of adherence by treatment modification strategy.

Strategies	**Odds Ratio (95% Confidence interval)**
Addition vs. Downtitration	0.91 (0.75-1.13)
Addition vs. Switch	0.97 (0.84-1.11)
Addition vs. Uptitration	0.80 (0.71-0.90) †
Downtitration vs. Switch	1.06 (0.86-1.31)
Downtitration vs. Uptitration	0.87 (0.71-1.08)
Switch vs. Uptitration	0.83 (0.71-0.96) †

† significant at $P<0.05$.

The likelihood of being adherent to each TM strategy was determined using a propensity score weighted GLM (with log link function, i.e., a logistic regression) (Table 19). Patients with PDC>0.8 were classified as adherent to the TM strategy. Results of the logistic regression indicates that patients who added drug (OR=0.80; 95% CI: 0.71-0.90) and those who switched drugs (OR=0.82; 95% CI: 0.71-0.95) were less likely to be adherent compared to those who uptitrated drug dose. There were no significant differences in the likelihood of TM between other comparisons of strategies.

The differences in our main analyses were consistent and more prominent after classification of addition group (Table 20). Patients using FPCs were less likely to be

adherent than those who uptitrated or switched drugs. In addition, the likelihood was also significantly lower for those who downtitrated drug dose. Comparing between FPCs and FDCs, the likelihood of adherence was lower for FPCs (OR=0.62; 95% CI: 0.53-0.73). On the contrary, the likelihood for patients who used FDCs did not vary significantly except versus switching. The likelihood of adherence was higher for FDCs compared to switching (OR=1.22; 95% CI: 1.04-1.44).

Table 21: Likelihood of adherence by treatment modification strategy for free-pill combination and fixed-dose combination groups.

Strategy comparison*	**Odds Ratio (95% Confidence interval)**
FPCs vs Downtitration	0.72 (0.58-0.90) †
FPCs vs FDCs	0.62 (0.53-0.73) †
FPCs vs Switch	0.76 (0.65-0.89) †
FPCs vs Uptitration	0.64 (0.55-0.74) †
Downtitration vs FDCs	0.86 (0.69-1.07)
FDCs vs Switch	1.22 (1.04-1.44) †
FDCs vs Uptitration	1.03 (0.88-1.20)

* FDCs= Fixed-dose combinations; FPCs= Free-pill combinations.
† significant at $P<0.05$.

Similar to our previous analyses for mean adherence, we examined the factors associated with the likelihood of being adherent (Table 21). It was found that the likelihood of being adherent was higher for patients treated with ACEIs or CCBs as first-line monotherapy drug compared to those treated with diuretics. Moreover, age of

patient (OR=1.03; 95% CI: 1.02-1.03), number of concomitant medications (OR=1.03; 95% CI: 1.00-1.06), frequency of outpatient visits (OR=1.01; 95% CI: 1.00-1.01), and frequency of inpatient visits (OR=0.95; 95% CI: 0.92-0.98).

Table 22: Factors associated with the likelihood of being adherent after treatment modification.

Factor	**Odds Ratio (95% Confidence interval)**
Drug	
ACEIs vs ARBs	1.06 (0.89-1.26)
ACEIs vs BBs	1.00 (0.86-1.17)
ACEIs vs CCBs	0.91 (0.77-1.07)
ACEIs vs Diuretics	1.23 (1.01-1.49) †
ARBs vs BBs	0.95 (0.79-1.15)
ARBs vs CCBs	0.85 (0.70-1.05)
ARBs vs Diuretics	1.15 (0.92-1.46)
BBs vs CCBs	0.91 (0.75-1.09)
BBs vs Diuretics	1.22 (0.98-1.52)
CCBs vs Diuretics	1.35 (1.08-1.69) †
Sex	
Female vs Male	0.94 (0.84-1.05)
Age	1.03 (1.02-1.03) †

Number of concomitant medications	1.03 (1.00-1.06) †
Comorbidity	0.95 (0.90-1.00)
Time to treatment modification	1.00 (0.99-1.00)
Inpatient visits	0.95 (0.92-0.98) †
Outpatient visits	1.01 (1.00-1.01) †
Antidiabetic medications	
Yes vs No	1.05 (0.83-1.31)
Antihyperlipidemic medication	
Yes vs No	1.09 (0.96-1.24)
CRVD	
Absent vs Present	0.93 (0.67-1.30)
IHD	
Absent vs Present	0.95 (0.74-1.22)
CHF	
Absent vs Present	0.98 (0.64-1.52)
PVD	
Absent vs Present	1.21 (0.78-1.89)

*CRVD: Cerebrovascular diseases; IHD: Ischemic heart diseases; CHF: Congestive heart failure; PVD: Peripheral vascular diseases.
† significant at $P<0.001$.
† †significant at $P<0.05$.

Subgroup analysis

A subgroup analysis was performed for 2,271 patients who were not adherent to their first-line treatment. Because there were significant differences between FPCs and FDCs in our previous analyses, we conducted out subgroup analyses by classifying addition group. The results of the subgroup analysis varied significantly from the overall analyses and highlighted important differences between adherences across the TM strategies.

Table 23: Likelihood of adherence by treatment modification strategies in patient subgroup who were non-adherent to first-line treatment.

Strategy comparison*	**Odds ratio (95% Confidence interval)**
FPCs vs Downtitration	0.42 (0.28-0.62)†
FPCs vs FDCs	0.32 (0.24-0.44)†
FPCs vs Switch	0.41 (0.30-0.56)†
FPCs vs Uptitration	0.56 (0.39-0.80)†
Downtitration vs FDCs	0.78 (0.56-1.08)
Downtitration vs Switch	0.98 (0.71-1.36)
Downtitration vs Uptitration	1.35 (0.93-1.95)
FDCs vs Switch	1.26 (1.00-1.57)†
FDCs vs Uptitration	1.73 (1.30-2.30)†
Switch vs Uptitration	1.37 (1.03-1.83)†

* FDCs= Fixed-dose combinations; FPCs= Free-pill combinations.
†significant at $P<0.05$.

Patients who were non-adherent to their first-line treatment and used FDC were more likely to be adherent compared to those who uptitrated drug dose or switched drugs. Also, patients who used FPCs were less adherent (OR=0.32; 95% CI: 0.24-0.44) than those using FDCs. Overall, the likelihood of patients being adherent to FPCs was about 50% lower compared to other strategies. On the other hand, patients using FDCs had higher likelihood of being adherent. The likelihood of being adherent for FDCs was higher compared to switching (OR=1.26; 95% CI: 1.00-1.57) and uptitration of drug dose (OR=1.73; 95% CI: 1.30-2.30).

The factors associated with the likelihood of discontinuation are presented in the Appendix. A detailed discussion of these results is beyond the scope of this study. Briefly, factors that were found to be associated with likelihood of discontinuation on our study were age, burden of comorbidities, type of first-line drug class, adherence to first-line drug, and the use of concomitant antihyperlipidemic drugs.

4.3 Costs and the association between adherence and costs after TM

The costs of patients who received a TM (N=5,998) were compared according to the TM strategies they received. The baseline characteristics of the cohort is presented in Table 16. In the main analysis, we compared the all-cause healthcare across the TM strategies. In addition, we also compared costs for hypertension and CV-related visits. Finally, we examined the association between patients' adherence and healthcare costs after TM. All models were propensity weighted to minimize selection bias. Less than 1% of the sample had propensity score less than 0.05, the unadjusted and propensity score weighted group differences are presented in Appendix.

All-cause healthcare costs

In our main analysis, we compared all-cause total healthcare costs (which includes the inpatient, outpatient, and drug costs) across the four TM types— addition, uptitration, switch, and downtitration (Table 23). The all-cause total healthcare costs were higher for the addition strategy compared to uptitration (*P*<0.0001) and switching (*P*=0.0002), respectively. Annual total costs were $755.06 lower for patients who downtitrated drug dose compared to those who switched their medications, but the difference was not statistically significant. There was no significant difference in the all-cause total costs between the uptitration and switch group.

Table 24: All-cause total healthcare costs by treatment modification strategies.

All-cause total costs Mean (±SE)	Addition= 7,830.02 (295.23)	Uptitration=5,900.56 (297.99)
	Switch=5,697.20 (297.88)	Downtitration=4,942.14 (453.52)
Strategies	**Mean difference in annual cost($)**	**P**
Addition vs. Downtitration	2,887.88	<0.0001
Addition vs. Switch	2,132.82	<0.0001
Addition vs. Uptitration	1,929.46	<0.0001

Downtitration vs. Switch	-755.06	0.17
Uptitration vs. Downtitration	958.42	0.08
Uptitration vs. Switch	203.36	0.61

†significant at P<0.05.
SE= Standard error.

The all-cause costs were also compared across TM strategies within each cost component (Table 24). There were no significant differences in annual all-cause inpatient visits for patients who added, switched, or uptitrated medications. Patients who downtitrated medications spent $18,405 (*P*=0.02) more on all-cause inpatient costs compared to those who switched medications. However, the all-cause outpatient costs were not significantly different between downtitration and switch group. The difference between all-cause outpatient costs were $823.5 (*P*=0.0002) and $929.63 (*P*<0.001) higher for addition group compared to switching and uptitration, respectively.

Table 25: All-cause healthcare costs by treatment modification strategies (by cost components).

Strategy	**Cost component** Mean(± SE)		
	Inpatient	Outpatient	Drug
Addition	17,208 (2062.82)	4,484 (143.51)	1,688.21 (72.39)
Uptitration	13,479 (2234.47)	3,554.46 (143.57)	1,154.62 (62.24)
Switch	15,910 (2807.04)	3,660.00 (164.65)	1,222.66 (72.67)
Downtitration	34,315 (9993.51)	3700.59 (278.85)	958.53 (100.33)

Strategies	**Mean difference in annual cost ($)**	**P**
Inpatient cost		
Addition vs. Downtitration	-17,208	0.03
Addition vs. Switch	1,298	0.71
Addition vs. Uptitration	3,729	0.24
Downtitration vs. Switch	18,405	0.02†
Uptitration vs. Downtitration	-20,836	0.005†
Uptitration vs. Switch	-2,431	0.49
Outpatient cost		
Addition vs. Downtitration	783.5	0.02†
Addition vs. Switch	823.5	0.0002†
Addition vs. Uptitration	929.63	<0.0001
Downtitration vs. Switch	40.59	0.90
Uptitration vs. Downtitration	-146.13	0.64
Uptitration vs. Switch	-105.54	0.63
Drug cost		
Addition vs. Downtitration	729.68	<0.0001
Addition vs. Switch	465.55	<0.0001
Addition vs. Uptitration	533.59	<0.0001
Downtitration vs. Switch	-264.13	0.04†
Uptitration vs. Downtitration	196.09	0.11
Uptitration vs. Switch	-68.04	0.48

SE: standard error
†significant at *P*<0.05.

Results of the analysis of the drug cost component indicates a very high burden of cost on patients who add medication to regimen. People who added drug to their regimen had higher drug costs compared to those who uptitrated, or switched medications (*P*<0.0001). Similarly, patients switching medications spent $68.04 (*P*=0.48) and $264.13 (*P*<0.0001) more annually on drug costs compared to those who uptitrated or downtitrated drug dose.

Analysis of all-cause healthcare costs for FPC and FDC group

In addition to our main analysis, we classified the addition group into those who used FDCs and FPCs. Results classifying the addition group were consistent with our main analysis for all-cause healthcare costs (Table 25). FPC group had higher all-cause total healthcare costs compared to switching and uptitration (*P*<0.001); moreover, costs for FPC group were $1,315.39 (*P*=0.02) higher compared to the FDC group. The costs for FDC group were $1,216.36 (*P*=0.01) higher compared to uptitration and $1,440.82 (*P*=0.002) higher compared to switching.

Table 26: All-cause total healthcare costs by treatment modification strategy (free-pill and fixed-dose combination group).

All-cause total costs	FDC=7,105.36	FPC=8,420.75
Mean (±SE)	(392.81)	(427.25)

	Uptitration=5,889.00 (278.53)	Switch=5,664.54 (295.87)
	Downtitration= 4,953.61 (453.84)	
Strategies	**Mean difference in annual cost ($)**	**P**
FPC vs. Downtitration	3,467.14	0.0008†
FPC vs. FDC	1,315.39	0.02†
FPC vs. Switch	2,756.21	<0.0001
FPC vs. Uptitration	2,531.79	<0.0001
FDC vs. Switch	1,440.82	0.002†
FDC vs. Uptitration	1,216.36	0.01†

SE: standard error
†significant at *P*<0.05.

Costs by component after classification of addition group are presented in Table 26. There were no significant differences in all-cause inpatient costs for FPC or FDC when compared to other TM strategies. However, there were significant differences in the annual all-cause outpatient visit costs for FPC compared to other TM strategies. Patients using FPC spent $1,400 (*P*<0.0001) more on inpatient visits compared to those who uptitrated, switched, or used FDCs. There were no significant differences for FDC users compared to those who switched or uptitrated drug dose.

Table 27: All-cause healthcare costs by treatment modification strategies (by cost components).

Strategy	**Cost component** Mean(± SE)		
	Inpatient	Outpatient	Drug
FPC	15,465 (2,308.60)	5,164 (223.85)	1,775.76 (102.48)
FDC	19,166 (3,729.15)	3,715 (172.66)	1,592.05 (99.57)

Strategies	**Mean difference in annual cost ($)**	**P**
Inpatient cost		
FPC vs. Downtitration	-20,297	0.01†
FPC vs. FDC	-3,701	0.38
FPC vs. Switch	-550	0.88
FPC vs. Uptitration	1,359	0.67
FDC vs. Switch	3,151	0.49
FDC vs. Uptitration	5,060	0.23
Outpatient cost		
FPC vs. Downtitration	1,479.29	0.0001†
FPC vs. FDC	1,448.38	<0.0001
FPC vs. Switch	1,527.27	<0.0001
FPC vs. Uptitration	1,631.18	<0.0001
FDC vs. Switch	78.99	0.74
FDC vs. Uptitration	183.43	0.41

Drug cost		
FPC vs. Downtitration	825.35	<0.0001
FPC vs. FDC	183.71	0.20
FPC vs. Switch	556.47	<0.0001
FPC vs. Uptitration	630.17	<0.0001
FDC vs. Switch	372.76	0.002†
FDC vs. Uptitration	446.46	<0.0001

SE: standard error
†significant at *P*<0.05.

Results of the drug cost component were consistent with our main analysis. Drug costs were higher for patients using FPCs compared to those who switched or uptitrated drug dose (*P*<0.0001). Similarly, costs were higher for FDC users compared to switch and uptitration group. Between FDCs and FPCs, annual drug costs were $183.71 more for the FPC group, but the difference was not statistically significant.

Hypertension and CV-related costs

We performed a secondary analysis restricted to hypertension and CV-related costs (Table 27). The total annual healthcare costs (including hypertension and CV-related inpatient and outpatient visits, and drug costs) were significantly higher for patients on FPCs compared to those who switched or uptitrated drug doses (*P*<0.0001); but costs did not differ compared to FDC users (P=0.50). The FDC group also had higher total healthcare costs compared to those who switched and uptitrated drug dose, and spent $119.24 (*P*=0.0002) and $76.94 (*P*=0.02) more, respectively. The difference in total

annual hypertension and CV-related costs did not differ between switch and uptitration group. Patients who downtitrated drugs spent $130.91 (*P*<0.0001) less on total costs related to hypertension and CV diseases compared to those who switched their medication.

Table 28: Hypertension and cardiovascular-related total costs and costs by component by treatment modification strategies.

Strategy	**Cost component** Mean(± SE)			
	Total	Inpatient	Outpatient	Drug
FPC	1,014.60 (46.48)	6,492.62 (2,127.44)	734.48 (32.82)	279.64 (18.51)
FDC	533.24 (26.25)	1,696.20 (918.78)	259.99 (12.78)	328.52 (23.31)
Uptitration	456.30 (19.42)	13,045 (6,134.67)	304.10 (12.93)	58.00 (3.74)
Switch	414.00 (19.61)	4,351.61 (2,015.40)	305.77 (15.14)	138.15 (9.17)
Downtitration††	283.09 (22.52)	6,687.63 (7166.21))	233.61 (18.94)	61.52 (7.18)

Strategies	**Mean difference in total cost ($)**	**P**
Total cost		
FPC vs. FDC	481.36	0.50

FPC vs. Switch	600.60	<0.0001
FPC vs. Uptitration	558.30	<0.0001
FDC vs. Switch	119.24	0.0002
FDC vs. Uptitration	76.94	0.02†
Inpatient cost		
FPC vs. FDC	4,796.42	0.03†
FPC vs. Switch	2,141.01	0.48
FPC vs. Uptitration	-6,552.38	0.23
FDC vs. Switch	-2,655.41	0.19
FDC vs. Uptitration	-11,348.8	0.004†
Outpatient cost		
FPC vs. FDC	474.47	<0.0001
FPC vs. Switch	428.71	<0.0001
FPC vs. Uptitration	430.38	<0.0001
FDC vs. Switch	-45.78	0.02†
FDC vs. Uptitration	-44.11	0.01†
Drug cost		
FPC vs. FDC	-48.88	0.08
FPC vs. Switch	141.49	<0.001
FPC vs. Uptitration	221.64	<0.001
FDC vs. Switch	190.37	<0.001
FDC vs. Uptitration	270.52	<0.001

SE: standard error
†significant at *P*<0.05.
††statistical validity is questionable due to high standard error

We also compared the hypertension and CV-related costs within the inpatient and outpatient cost components. The differences in inpatient costs were not significantly different between FPC users compared to those who uptitrated or switched their medication. However, FDC users spent $4,796 less on hypertension and CV-related inpatient visits compared to FPC users. For the FDC group the inpatient costs were $11,348.80 (*P*=0.004) lower compared to those who uptitrated drug dose. Inpatient costs were not different for switch group compared to those who uptitrated drug dose or those who downtitrated drug dose, however, the statistically validity of the result of this comparison is questionable due to the large differences in confidence interval of the cost estimates. Results of analysis of the outpatient component showed significantly higher hypertension and CV-related outpatient costs for patients using FPCs or FDCs. While the costs for FPC users were higher compared to those who switched or uptitrated drug dose (*P*<0.001); costs were lower for FDC users compared to uptitration and switch group by $44.11 and $45.78, respectively. Annual hypertension and CV-related outpatient costs for downtitration group were $72.16 lower compared to those who switched medications (*P*=0.005).

Drug costs were higher for patients using FPCs compared to those who switched or uptitrated drug dose (*P*<0.0001). Similarly, costs were higher for FDC users compared to switch and uptitration group. Between FDCs and FPCs, annual drug costs were $48.88 more for the FDC group but the difference was statistically insignificant.

Association of adherence with costs after TM

We examined the association of hypertension and CV-related total costs with patients' adherence to the TM regimen. Results of the adjusted GLM shows that hypertension and CV-related healthcare visit costs were $73.22 (*P*=0.004) higher for non-adherent patients compared to those who were adherent to their modified regimen.

CHAPTER FIVE: DISCUSSIONS

In this study, we determined the rate of TM and time-to-TM among the most commonly prescribed antihypertensive drug classes, and determined the rate of discontinuation across the TM strategies - addition, uptitration, switching, and downtitration. We also compared the adherence across these strategies and assessed factors associated with the likelihood of being adherent. Finally, we estimated the costs between the four types of TM strategies and examined the association between costs and adherence. Several empirical studies have reported high rates of discontinuation among patients using antihypertensive drugs, especially, among naïve patients starting hypertension treatment. Data reported in these studies shows that roughly 30% to 50% of patients completely discontinue their medications within a year after starting their hypertension treatment.[4,115-117] Among those who stay persistent, a high proportion undergo TMs by titrating, adding, or switching medications. Despite the high discontinuation and TM rates among the newly treated patients, our understanding of the course of changes following the initially prescribed treatment regimen is limited. Our study addresses the current gaps in evidence regarding the patterns of TM, and adherence and costs associated with TM strategies.

Patterns of treatment modification and discontinuation rates

In our study 49% of patients received a TM within one year from the initiation of hypertension treatment. In comparison, a retrospective study of discontinuation and changes among hypertensive patients was conducted by Jones and colleagues.[4] By six months 40% to 50% of patients changed or discontinued their medication. Two other

studies reported specific addition and switching rates. In the first study, 18% of patients added and 17% switched medications[3], while in the second study 22% added and 15% switched medications.[118] Only one prior study has reported rates of changes of all of the types of TMs that we considered. In this study, 15% patients had received drug titrations, 8% received combination, and 4% switched drugs within the first year of initiating treatment.[32] In our study, the proportion of patients adding medications appears to be highest among all patients receiving TMs. Additions or combinations constituted roughly 44% of TMs followed by switching (29%) and titrations (27%).

Ours is the first study to compare the probabilities of receiving TMs across the five antihypertensive drug classes. The overall probabilities of any type of TM across all the five drug classes varied significantly. Results of our analyses suggest that patients who initiate their hypertension treatment with drugs acting on the renin-angiotensin system (i.e., ACEIs and ARBs) are less likely to receive TMs compared to those starting treatment on diuretics, BBs, or CCBs. Traditionally, thiazide-type diuretics have been the choice of first-line treatment for hypertension. However, due to the growing evidence in favor of ACEIs and ARBs, the recent JNC-8 guidelines[41] recommend these two drug classes as a reasonable first-line treatment option. The low TM rates among patients treated with ACEIs and ARBs provide additional indirect support for use of these agents as first-line treatment.

In addition to the overall likelihood of receiving any type of TMs, the likelihood of receiving a particular TM strategy was compared across the five drug classes. Patients initiating ACEIs and ARBs had a lower likelihood of adding drugs, while those on CCBs had higher likelihood when compared with diuretics. With the exception of ARBs, the

likelihood of uptitration was significantly higher for ACEIs, CCBs, and BBs compared with diuretics. The likelihood of switching drugs was also low for ACEIs and ARBs compared with diuretics. It is not clear whether these differences exist because of the inherent properties of the drug class, or if these differences reflect the TM practice by healthcare providers.

Time-to-TM is critical for management of hypertension. Delays in BP goal attainment has been shown to significantly affect long-term CV benefits.[119] Clinical guidelines recommend TMs at monthly intervals if BP goal is not attained within 30 days from the initiation of treatment.[2] Results of our study indicate that in the real-world TMs occur much later than the recommended guideline. It is possible that the patient's frequency of follow-up with the provider may play a role determining the time-to-TM. We conducted additional analysis to explore this factor and found that frequency of outpatient visit were significantly associated with reduction in time-to-TM (P=0.03). The time-to-TM reduces by approximately 25% for each additional interaction between the patient and provider. Thus, it is important to emphasize the need for follow-up visit with healthcare provider among newly treated hypertensive patients. A less aggressive approach by the healthcare provider may be another reason for delayed TM. A previous study found that in a cohort of hypertensive patients that had ≥4 visits and ≥1 instance of elevated BP, TMs occurred only among 13.1% of total patients with uncontrolled BP.[15] One of the common reasons cited by healthcare providers for not prescribing TM in the Reasons for not Intensifying Antihypertensive Treatment (RIAT) trial was the assumption that the time after starting the new drug is too short to attain full effect.[120] The average time for addition or uptitration of hypertension treatment in our study was >100 days. Moreover,

the mean time for switching drug and downtitration of dose was >140 days which may be unfavorable for patients dealing with ADEs. Delays in TMs compromise patients' adherence to antihypertensive drugs,[7] and may lead to long-term treatment discontinuation.[121] Our study could not determine the relationship of BP control with TM, but the inconsistencies of these patterns with guidelines identifies an area for practice improvement.

Poor efficacy and ADEs are the most common reasons for TMs.[7,11,122] The most recent JNC-8 guidelines recommend uptitration of the current drug dose or addition of another drug class when patients do not attain BP goal.[41] In our study almost 50% of the patients intensified their regimen by adding a drug and another 21% uptitrated drug dose. The odds of treatment discontinuation are higher for patients who receive TM in comparison to those who receive none (RR=1.25; 95% CI: 1.12-1.37), and the trend of non-persistence among patients receiving TMs was shown to be consistent up to 3 years.[5] Our results are similar to a previous study that reported lower discontinuation rates among patients initiating combination treatment compared to monotherapy.[123] The odds of discontinuation were significantly lower by 57% and 50% for patients starting FDC and FPC, respectively, compared to those starting diuretic monotherapy.[123] Knowledge about the differences in the persistence is valuable for the appraisal of the TM strategies. A comparison of the discontinuation rates between these two TM strategies in our analyses shows that patients who add a drug, irrespective of whether it was a FDC or FPC, to their regimen are less likely to discontinue treatment. Also, the likelihood of discontinuation is almost half for patients adding drugs compared to those

who switch drugs. Thus, an addition strategy may be preferred for TM of patients who are at high risk for discontinuation of treatment.

Adherence after TM and factors associated with adherence

Continuity of treatment is a measure of patients' medication taking behavior over an extended period of their hypertension treatment. We also determined 'adherence' after TM in our study which measures the extent to which a patient acts in accordance with the prescribed interval of a dosing regimen. Short-term outcomes of a therapeutic regimen cannot be achieved without adherence. Patients who undergo TMs are at a higher risk of non-adherence to treatment compared to those who do not receive TMs.[5] Adherence to antihypertensive medications is important for achieving short-term outcome (i.e., BP goal)[13,18,19] that will essentially have long-term CV benefits.[20,23,26] Several studies have shown that there is strong association between adherence and BP control.[13,18,19] Adherence was also shown to be strongly associated with decrease in hospitalizations[20-22], and lower medication costs.[20,23,24] Non-adherent patients are at a 50% higher risk of CV events compared to those who adhere to their medications.[27] A large number of patients receive TM,[3-6] and a high risk of non-adherence in these patients will be an impediment in attaining short-term and long-term benefits of the treatment. Therefore, it is important to understand patients' adherence after TM and whether adherence varies across the TM strategies.

The mean adherence between TM strategies was statistically significant in our study. However, the differences were <6% which may be clinically insignificant. A comparison of adherence or the likelihood of being adherent across all TM strategies within a single

study is unavailable in the current literature. One study reported differences in adherence between monotherapy vs. FDCs. It was found that patients using FDC of a diuretic had higher medication possession ratio (MPR) with a mean difference of >12% (*P*<0.0001) compared to diuretic monotherapy.[124] The difference in PDC between these two groups (FDC vs. uptitration) were not significant in our study. To the best of our knowledge, a comparative assessment of adherence rates among those using FPCs vs. uptitrating dose, uptitrating vs. switching, or switching vs. downtitration have not been published. The only two strategies that have been more frequently compared and extensively published on in the literature are FPCs vs. FDCs. Sherrill and collegues published a meta-analysis of these studies which includes data on adherence from 22 studies.[125] Patients on FDCs had a significantly higher MPR compared to those on FPCs (mean difference=13.31; 95% CI: 8.26-18.35).[125]

A comparison of the odds of adherence across the TM strategies had more distinct differences than adherence measured as a continuous outcome, and provided a better understanding of the adherence profiles. Results of our main analysis shows that patients who switch drugs have lower odds of being adherent compared to those who uptitrate drug dose. Moreover, patients who add drugs to intensify their regimens were significantly less likely to be adherent when compared to those who uptitrate drug dose. In addition to these differences, differences in the likelihood of adherence can be seen between those who intensified regimens by using FDCs and those who used FPCs within the addition group compared to other strategies. Patients who uptitrated drug dose were significantly more likely to adhere to treatment compared to those on FPCs, but the differences were not statistically significant when compared to those on FDCs.

A further distinction in the likelihood of adherence was observed in our subgroup analysis. Patients who intensified treatment using FDCs had the highest odds of being adherent to their regimen compared to any other TM strategy. Patients using FDCs were 26% more likely to be adherent compared to those switching drugs, while the odds were 73% higher compared to those uptitrating drug dose. The results of the FDCs vs. uptitration comparison were similar to a previous study which reported 50% lower odds of adherence among patients using monotherapy compared to those on FDCs.[124] On the other hand, patients on FPCs showed lowest adherence compared to any other TM strategy in our subgroup analysis. The likelihood of being adherent was less than 60% for FPC users compared to any strategy. Results of the meta-analysis conducted by Sherrill shows that patients on FDCs are more likely to be adherent compared to FPCs (RR=2.13; 95% CI: 1.11-4.09) which is consistent with our study.[125]

A positive association between TMs and non-adherence has been shown in a previous study.[126] Patients not adherent to medications have 39% higher odds of receiving TMs when compared with adherent patients. It is notable that the differences in the odds were more profound across TM strategies in the subgroup of patients with poor adherence to their first-line treatment. Non-adherence after TM has been shown to be associated with an increased likelihood of uncontrolled BP (OR=1.73; 95% CI: 1.34-2.24).[28] TMs increase the odds of non-adherence and this risk is elevated further if the patient has a history of non-adherence. Given the favorable adherence profile of FDCs, they should be prioritized for TM in patients with a history of poor adherence.

We assessed the association between adherence and several factors including age, sex, burden of comorbidities, drug class of first-line monotherapy, number of co-

medications, type of co-medication (antidiabetic and antihyperlipidemic), time to treatment modification, frequency of health services use, and existing cardiovascular conditions. Age of patient, number of co-medications, presence of comorbid conditions, frequency of inpatient visits, and frequency of outpatient visits were significant in both continuous and categorical models of adherence. In addition, time to treatment modification and use of antihyperlipidemic drugs were associated with higher adherence in the continuous model, and drug class associated effect was seen in the categorical model. Previous studies have shown that demographic factors of the patients such as age,[47-50] sex, [47,48,50,51], and race [47,52,53] are associated with adherence to antihypertensive drugs. Clinical factors such as presence of comorbidities have been shown to reduce patient's adherence to their medication regimen.[47,52,60]

Drug-related factors also have been shown to be associated with patient's adherence to their regimen. Higher burden of co-medications has been shown to increase patients' non-adherence to antihypertensive drugs.[49,55,56] A strong correlation between adherence to antihyperlipidemic and antihypertensive drugs was shown in a previous study.[127] There is a growing evidence suggesting that starting antihypertension and antihyperlipidemic treatment closer in time increases the odds of adherence.[49] Even the long term persistence has been shown to be higher for antihypertensive drugs among patients who were using lipid lowering drugs (OR=2.4 95% CI: 1.8-3.2).[86] The use of ACEI or CCB was associated with higher adherence after TM compared to those who were treated with diuretics as first-line monotherapy. The choice of first-line monotherapy drug class has been shown to be vary across first-line drug class which is

attributed to the efficacy and adverse events that varies among these drug classes.[12,70,128]

Next, a strong association between frequency of physician visits and adherence has been shown in previous studies.[50,56,58] Follow-up visits with healthcare providers was positively associated with higher adherence rates (OR=3.21; 95% CI: 3.06-3.36).[129] Another study reported an increased odds of adherence among patients who had multiple provider visits (OR=2.2; 95% CI: 1.8-2.5).[55] On the contrary, inpatient visits have been shown to decrease the likelihood of persistence with antihypertensive medications (OR=0.80; 95% CI: 0.74-0.87).[130] Results of our analysis resonate with a previous study; higher inpatient visits in our study decreased the likelihood of adherence after a TM. Patients who undergo TMs are at a higher risk of non-adherence to treatment compared to those who do not receive TMs.[5] It is important to understand differences across TM strategies and the factors that affect adherence to the modified regimen because adherence is a factor that moderates both the short-term and long-term outcome of hypertension treatment.

Costs and its association with adherence after treatment modification

Healthcare cost is one of the important outcomes of hypertension treatment. Every year $51 billion dollars are spent as direct and indirect costs for treatment of hypertension in the US.[36] Of the total direct cost spent for hypertension, drug costs account for almost 50% up to 70% of the expenditure, while the remaining constitutes of health care services utilization costs.[131,132] Studies have shown that patients who receive TMs have significantly higher healthcare costs compared to those patients who do not receive

TMs,[31,32,118] and the costs are high irrespective of the starting drug class.[32] For instance, a cohort study of Italy's National health system (NHS) shows that patients who continue to use first-line treatment spend an average $191.15 on healthcare over a 12 month period, while those who switched medications spent an average $229.09.[31] Another study of the NHS reported high drug costs for patients combining ($321.66) and switching ($203.57) compared to those continuing initial treatment ($135.72).[36] Similarly, higher drug acquisition costs were shown to be associated with TMs that were required to address ADEs.[133] The main reasons that drive increase in healthcare costs for these patients is attributable to the changes in drug costs;[36] moreover, constant follow-ups with the healthcare provider result in increased utilization of outpatient visits.[29,133] Because the burden of costs is high on patients who undergo TMs, it is important to understand if differences exist in the costs between alternative TM strategies.

Our initial analysis of all-cause healthcare costs showed that burden of healthcare expenditure is highest for patients who add drugs to their regimen. Patients adding drugs spent >$1,900 more annually on healthcare compared to those who uptitrate drug dose and switch to another drug to intensify their treatment. Results were consistent even after classification of addition group into those who used FPCs or FDCs, costs were $1,200 up to $2,750 higher compared to other strategies. Differences between all-cause total healthcare costs were not significant for switching and downtitration. No studies in the current literature were found that have compared all-cause healthcare costs across TM strategies.

Differences in all-cause healthcare costs within the outpatient cost component varied significantly across TM strategies. All-cause outpatient costs were higher for patients adding drugs compared to those uptitrating or switching medications ($P<0.05$). The differences were consistent in FPC subgroup ($P<0.0001$). However, costs for FDC users were not different compared to uptitration or switching. In the inpatient component, most differences between competing strategies appeared to be statistically insignificant. Addition or FDC or FPC did not differ significantly in terms of annual all-cause inpatient costs. Overall, the differences in all-cause inpatient costs were insignificant for identifying a preferential TM strategy for intensification. However, for addressing ADE-related issues, switching drugs may be preferred over downtitration as the all-cause inpatient costs appear to be $18,405 ($P=0.02$) lower for switchers. The large difference in inpatient costs may be a result of lowering drug efficacy due to downtitration.

The JNC-7 recommends monthly follow-up with physicians to patients who undergo TMs.[2] Costs of outpatient visits of up to $283 per patient for physician follow-up have been reported.[80] Outpatient costs are significantly higher for patients who receive TMs.[29,133] When compared across TM strategies in our main analysis, costs of all-cause outpatient visits in our study were significantly higher for addition compared to switching and uptitration. The differences in outpatient visit costs were significantly higher for FPC within the addition group and the costs saving in inpatient visits were not greater than or equal to the annual all-cause outpatient visit expenditures. Thus, the all-cause health service costs are higher for patients on FPCs and are attributed to high outpatient visits

costs. Healthcare providers should take into consideration these costs associated when prescribing FPC for TM.

As mentioned earlier, the drug costs constitute a large portion of high TM costs. Previous studies have shown that drug costs are major drivers of high healthcare costs of hypertension among patients receiving TMs.[118,120,121] In a study of the US department of defense outpatient uniformed services prescription database, the mean overall cost of drugs was higher by $60 among patients receiving TM compared to those who did not change therapy.[134] Another retrospective claims study reported that the average prescription cost of TM can be up to $391 for one modification, and it may be $880 for six TMs.[135] In our study costs were compared across the TM strategies. Patients who added drug to their regimen had higher drug costs compared to those who uptitrated or switched drugs (P<0.0001). This was consistent with a previous study that reported highest drug costs for patients adding drugs—$167 (34%)—more than those who received with no change, and those receiving titration, or switch.[134] Another study reported average cost per patient to be $321.66 for patients adding drugs compared to those switching $213.41 drugs.[36] Results after classifying the addition group indicates that costs remains high for the addition group irrespective of whether they used FPC and FDC (P<0.05). The costs for the addition group are anticipated to be higher because use of FPC and FDC is expensive compared to use of a single drug. Drug costs were also considerably higher for patients switching medications in our study when compared to those downtitrating medications (P<0.05). The costs of patients switching medication has been shown to be higher compared to those who continue to use initial drugs;[136] however, a comparison with titration strategies is unavailable.

The costs of direct medical expenditure attributable to hypertension and CV complications among hypertensive patients are about $22.8 billion and $29.7 billion, respectively.[104] We estimated the costs of hypertension and CV-related visits and compared them across TM strategies. The total hypertension and CV-related costs were higher for patients on FPC compared to those who switched or uptitrated drug dose. Also, significantly higher total hypertension and CV-related costs were found for FDC users compared to those uptitrating drug dose or switching drugs. The total costs could be high for these groups due to disproportionally higher drug costs, therefore, we compared the costs within the inpatient and outpatient component. It was found that annual the hypertension and CV-related inpatient costs were not significantly different for patients using FPCs when compared to those uptitrating or switching medications. Moreover, the inpatient costs for FDC users were significantly lower compared to those who uptitrated drug doses (P=0.004). In the hypertension and CV-related outpatient cost analysis, the costs were significantly higher for FPC users compared to those who switched or uptitrated drug dose. Compared to uptitration and switching, the costs were $430.30 and $428.71 higher more for those using FPC (P<0.0001). However, for the FDC group, costs were approximately $45 lower compared to switch and uptitration group (P<0.05). It is possible that the high drug cost of addition may be off-set by better long-term outcomes as indicated in our analysis of the hypertension and CV-related inpatient cost component. Further investigation with a longer follow-up duration is required to validate the long-term benefits of the addition strategy.

There is a strong positive correlation between adherence and healthcare costs. Patients who are adherent with their antihypertensive regimen have a higher healthcare cost

compared to non-adherent patients ($6,570 vs. $7,658-10,286; *P*<0.05).[137] Non-adherence to antihypertensive drugs is associated with poor hypertension and CV health. Patients with low adherence to antihypertensive drugs have a higher risk of CHD (OR=1.07; 95% CI: 1.00-1.13), CRVD (OR=1.13; 95% CI: 1.03-1.25), and CHF (OR=1.42; 95% CI: 1.27-1.58) compared to their adherent counterparts.[20] Poor adherence to antihypertensive medications was shown to increase the costs by approximately $3,574 per person within a 3-year period.[20] In our study non-adherent patients spent $77.53 (*P*=0.004) more annually on hypertension and CV-related health services compared to those who were adherent to their modified regimen. Our results further emphasize the importance of adherence after TM and highlight the value of evidence-based selection of TM strategy that will result in better patient adherence.

Current clinical guidelines for hypertension management do not recommend a preferred strategy for treatment intensification. Results of our analyses indicate that addition of drug may be advantageous because of the low likelihood of discontinuation. Moreover, FDCs in our study had better medication adherence, and spent less on hypertension and CV-related health services compared to uptitration or switching. In addition to this evidence from our study, a previous study has shown that FDCs have better clinical efficacy than titrating drug to a higher dose.[138] Therefore, addition of drugs may be preferred when TM is required to address efficacy related issues. Similarly, switching drug, although has higher drug costs, may be a preferred approach over downtitration of drug dose for patients with poor tolerance because patients' downtitrating drugs are more likely to discontinue treatment, and downtitration can present compromises in drug efficacy associated with lower drug dose.

Limitations

This study has several limitations. This is a claims data study and the information is limited to utilization behaviors captured through claims. Clinical parameters such as BP value and poor drug tolerance were not available in the claims database. Therefore, the underlying causes of TMs were not known. Patients were assigned to TM groups based on the patterns inherent in their medication use. Therefore, the study may be prone to selection bias. We took several measures to minimize selection bias. First, we eliminated patients who started treatment with combination therapy because guidelines recommend combination therapy as first-line treatment for stage 2 hypertension patients.[34] Next, factors that may have led to changes in regimen such as age, sex, and comorbidities could not be assessed from the claims data. To account for selection bias due to these factors, we used propensity score techniques. We adjusted the analysis for drug class of first-line treatment to account for selection bias due to the inherent properties of drug including efficacy, costs, and ADEs. As described earlier, a healthy adherer effect may introduce bias and overestimate the short- and long-term benefits. We used patients' adherence to their first-line treatment as a proxy to control for this effect. Inverse probability treatment weights were calculated to adjust our adherence and cost models.

Finally, differences within a single treatment group could have underestimated the differences in outcomes across the TM strategies. Therefore, we conducted several subgroup analyses. The addition group was classified into those using FPC and FDC for all adherence and cost models. A subgroup analysis was conducted for patients not adherent to their first-line monotherapy to determine if the differences in adherence to

TM strategies differed from our main analysis that consisted of all patients. In addition, we constructed separate models for our cost components—inpatient, outpatient, and drug cost—to compare the costs of each component across the TM strategies. We found significant differences in our subgroup analyses which helped us to identify advantages and disadvantages of the competing strategies.

Similar to other studies that use secondary databases, patients' refill history was used as a proxy for persistence with treatment. The sample sizes of our component analyses for inpatient costs were small, therefore, the validity of our likelihood estimates for downtitration strategy compared to other TM strategies is questionable. Finally, we used a commercial claims database and excluded patients enrolled in managed care organizations. Therefore, results of our study may not be generalizable to the US population, including those covered by managed care organizations or non-commercial sources.

CONCLUSIONS

TMs are common among newly treated hypertensive patients. More than half of the patients treated with first-line antihypertensive drugs undergo TMs within the first 12 months of starting treatment. Intensification of regimens occur more commonly than switching and deintensification. The rates of TMs vary across the drug classes used for first-line treatment of hypertension; however, it is not understood whether these differences exist because of the inherent properties of the drug class, or if these differences reflect the TM practice by healthcare providers. The rates of discontinuation vary according to TM strategies. The addition strategy appears to be beneficial by reducing the odds of complete discontinuation of medication by the patient in future. Similarly, the switching strategy had lower discontinuation rates in our study. These strategies may be preferred for TM in patients who are at high risk of discontinuation of treatment.

Adherence rates vary significantly across TM strategies. Although the rate of adherence were lower for the addition strategy in our main analysis, when analyzed according to those using FPCs and FDCs, a clear distinction in adherence profile of the two strategies compared to other strategies was evident. The use of FDC was associated with higher likelihood of adherence compared to uptitration, switching, or the use of FPC. Thus, in addition to long-term persistence, FDCs may be advantageous due to better adherence in the short-term. Benefits may be especially greater for treating patients with a history of poor adherence to first-line treatment. Adherence after TM is significantly associated with outpatient visits, which emphasizes the importance of follow-up with the healthcare provider recommended by the treatment guidelines.

Although the total healthcare costs appear to be highest for the addition group, when sub-grouped according to use of FDC and FPC the results help to identify considerable differences within the addition group. Similarly, analyzing the costs by components indicates that the costs are prone to characterization by the type of component. The differences increase further when costs are restricted to hypertension and CV-related costs. While the hypertension and CV-related total healthcare costs were higher for FDC and FPC users in our study (due to high burden of drug costs), the differences in inpatient costs were insignificant for FPC and even lower for FDC compared to alternative strategies (i.e., uptitration or switching). Results of our study indicate that the cost of adding drugs is high, but the long-term benefits (i.e., lower hypertension and CV related hospitalization costs) of addition strategy may off-set these costs.

Overall, use of FDCs appear to have an advantage as an intensification strategy over uptitration, switching and FPCs due to lower discontinuation rates, better adherence profile, and lower hypertension and CV-related inpatient costs. These advantages add-on to the higher BP reducing efficacy of FDCs (compared to uptitration of drug dose) reported in clinical studies. Similarly, switching of medication may be a preferred approach over downtitration of drug dose despite higher drug costs because downtitration increases the odds of discontinuation and can present compromises in drug efficacy associated with lower drug dose. We believe the findings of this study have important implications in the management of hypertension and the impact of TMs related to adherence and costs. Further research is required to understand the long-term cost-effectiveness of alternative TM strategies and the actual relationship of these findings with BP control and long-term outcomes.

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APPENDIX: Institutional review board approval

AUBURN UNIVERSITY INSTITUTIONAL REVIEW BOARD for RESEARCH INVOLVING HUMAN SUBJECTS
RESEARCH PROTOCOL REVIEW FORM
FULL BOARD or EXPEDITED

For Information or help contact **THE OFFICE OF RESEARCH COMPLIANCE (ORC)**, 115 Ramsay Hall, Auburn University
Phone: 334-844-5966 **e-mail:** IRBAdmin@auburn.edu **Web Address:** http://www.auburn.edu/research/vpr/ohs/index.htm

Revised 2.1.2014 **Submit completed form to IRBsubmit@auburn.edu or 115 Ramsay Hall, Auburn University 36849.**

Form must be populated using Adobe Acrobat Pro 9 or greater standalone program (do not fill out in browser) Hand written forms will not be accepted

1. PROPOSED START DATE of STUDY: 01 August 2014

PROPOSED REVIEW CATEGORY (Check one): ☐ FULL BOARD ☑ EXPEDITED

SUBMISSION STATUS (Check one): ☑ NEW ☐ REVISIONS (to address IRB Review Comments)

2. PROJECT TITLE: Outcomes of Treatment Modifications of Antihypertensive Regimen in Hypertensive Patients

3. Kalyani Sonawane	Graduate Student	Health Outcomes Resear	kbs0009@tigermail.auburn.edu
PRINCIPAL INVESTIGATOR	TITLE	DEPT	AU E-MAIL
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MAILING ADDRESS		PHONE	ALTERNATE E-MAIL

4. FUNDING SUPPORT: ☑ N/A ☐ Internal ☐ External Agency: _____ ☐ Pending ☐ Received

For federal funding, list agency and grant number (if available). _____

5a. List any contractors, sub-contractors, other entities associated with this project:
University of Texas Health Science Center at Houston

b. List any other IRBs associated with this project (including Reviewed, Deferred, Determination, etc.):
NA

The Auburn University Institutional Review Board has approved this document for use from 5/8/14 to 5/7/15
Protocol # 14-182 EP 1405

PROTOCOL PACKET CHECKLIST

All protocols must include the following items:

☑ **Research Protocol Review Form** (All signatures included and all sections completed)
(Examples of appended documents are found on the OHSR website: http://www.auburn.edu/research/vpr/ohs/sample.htm)

☑ **CITI Training Certificates** for all Key Personnel.

☐ **Consent Form or Information Letter** and any Releases (audio, video or photo) that the participant will sign.

☑ **Appendix A, "Reference List"**

☑ **Appendix B** if e-mails, flyers, advertisements, generalized announcements or scripts, etc., are used to recruit participants.

☐ **Appendix C** if data collection sheets, surveys, tests, other recording instruments, interview scripts, etc. will be used for data collection. Be sure to attach them in the order in which they are listed in # 13c.

☐ **Appendix D** if you will be using a debriefing form or include emergency plans/procedures and medical referral lists (A referral list may be attached to the consent document).

☑ **Appendix E** if research is being conducted at sites other than Auburn University or in cooperation with other entities. A permission letter from the site / program director must be included indicating their cooperation or involvement in the project. NOTE: If the proposed research is a multi-site project, involving investigators or participants at other academic institutions, hospitals or private research organizations, a letter of **IRB approval** from each entity is required prior to initiating the project.

☐ **Appendix F** - Written evidence of acceptance by the host country if research is conducted outside the United States.

FOR ORC OFFICE USE ONLY

DATE RECEIVED IN ORC: _____ **by** _____ **PROTOCOL #** _____
DATE OF IRB REVIEW: _____ **by** _____ **APPROVAL CATEGORY:** _____
DATE OF IRB APPROVAL: _____ **by** _____ **INTERVAL FOR CONTINUING REVIEW:** _____
COMMENTS:

APPENDIX: Propensity weight adjustment for cohort characteristics for likelihood of discontinuation after treatment modification.

Characteristics	**Unadjusted**		**Propensity weight adjusted**‡	
	Test statistic*	*P*	Test statistic*	*P*
Age	37.12	<0.0001	0.01	0.99
Sex	30.05	<0.0001	0.06	0.99
Comorbidities	7.72	<0.0001	0.40	0.76
Number of co-medications	39.11	<0.0001	0.06	0.98
Co-medications				
Antihyperlipidemic	11.95	<0.0001	1.89	0.59
Antidiabetic	15.37	<0.0001	0.14	0.98
Existing CV conditions				
IHD	15.05	0.0018	2.95	0.39
CHF	0.24	0.97	3.92	0.26
PVD	2.67	0.44	0.89	0.82
CRVD	5.31	0.15	2.25	0.04
Health services utilization				
Inpatient visits	183.92	<0.0001	0.07	0.97
Outpatient visits	299.29	<0.0001	0.42	0.74

Drug class of first-line monotherapy	450.50	<0.0001	3.57	0.98
Adherence to first-line drugs	188.79	<0.0001	0.43	0.73

‡Inverse probability treatment weights were estimated form age, sex, comorbidities, number and type of co-medications, drug class of first-line monotherapy, adherence to first-line drug, and health services utilization.*F-value for continuous variables and chi-square for categorical. Propensity scores were calculated for the likelihood of receiving addition, uptitration, switch, or downtitration strategy.

APPENDIX: Propensity score adjustment for cohort characteristics for adherence and cost models (Main analysis for addition, uptitration, downtitration, and switch).

Characteristics	**Unadjusted**		**Propensity score adjusted‡**	
	Test statistic*	*P*	Test statistic*	*P*
Age	28.03	<0.0001	0.38	0.77
Sex	17.53	0.0005	0.12	0.98
Comorbidities	6.26	0.0003	0.50	0.73
Number of co-medications	13.97	<0.0001	0.08	0.97
Co-medications				
Antihyperlipidemic	7.08	0.06	0.78	0.85
Antidiabetic	16.74	0.0008	18.07	0.004
Existing CV conditions				
IHD	8.05	0.04	2.23	0.52
CHF	1.01	0.79	0.10	0.99
PVD	0.54	0.90	1.96	0.57
CRVD	3.11	0.37	6.63	0.08
Health services utilization				
Inpatient visits	4.41	0.65	5.03	0.001
Outpatient visits	10.26	0.002	2.27	0.08

Drug class of first-line monotherapy	390.64	<0.0001	1.43	0.99
Time to treatment modification	73.28	<0.0001	2.92	0.04

‡Inverse probability treatment weights were estimated form age, sex, comorbidities, number of co-medications, drug class of first-line monotherapy, and health services utilization.*F-value for continuous variables and chi-square for categorical.

APPENDIX: Propensity score adjustment for cohort characteristics for adherence and cost models (Analysis for free-pill combination, fixed-dose comabintion, uptitration, downtitration, and switch).

Characteristics	**Unadjusted**		**Propensity score adjusted**	
	Test statistic*	*P*	Test statistic*	*P*
Age	8.24	<0.0001	0.21	0.93
Sex	20.66	0.0004	0.55	0.97
Comorbidities	11.52	<0.0001	0.58	0.67
Number of co-medications	11.79	<0.0001	0.21	0.93
Co-medications				
Antihyperlipidemic	27.37	<0.0001	5.15	0.27
Antidiabetic	18.48	0.0010	15.99	0.003
Existing CV conditions				
IHD	30.05		3.37	0.49
CHF	2.59	0.63	5.93	0.20
PVD	13.12	0.01	7.28	0.12
CRVD	9.60	0.04	8.16	0.08
Health services utilization				
Inpatient visits	0.83	0.50	0.59	0.26
Outpatient visits	8.20	<0.0001	3.4	0.008

Drug class of first-line monotherapy	867.26	<0.0001	1.25	0.99
Time to treatment modification	61.57	<0.0001	1.70	1.00

‡Inverse probability treatment weights were estimated form age, sex, comorbidities, number of co-medications, drug class of first-line monotherapy, and health services utilization.*F-value for continuous variables and chi-square for categorical.

APPENDIX: Factors associated with the likelihood of discontinuation after treatment modification.

Factor	**Hazards Ratio**	**95% Confidence Interval**
Age (in years)		
18-24 vs 25-35	1.36	1.09-1.69†
18-24 vs 36-59	1.84	1.49-2.26†
18-24 vs 60 and above	1.73	1.40-2.14†
25-35 vs 36-59	1.35	1.25-1.47†
25-35 vs 60 and above	1.27	1.15-1.40†
36-59 vs 60 and above	0.94	0.88-1.00
Gender		
Female vs Male	0.99	0.93-1.04
Comorbidity	1.04	1.02-1.07†
Existing cardiovascular* conditions (Yes vs No)		
CRVD	0.88	0.76-1.02
CHF	0.95	0.78-1.14
IHD	0.96	0.84-1.08
PVD	1.15	0.93-1.42
First-line drug class**		
ACEIs vs ARBs	1.01	0.93-1.09
ACEIs vs BBs	1.07	1.00-1.14†

ACEIs vs CCBs	1.11	1.03-1.20†
ACEIs vs Diuretics	0.98	0.90-1.07
ARBs vs BBs	1.07	0.97-1.16
ARBs vs CCBs	1.11	1.00-1.21†
ARBs vs Diuretics	0.98	0.88-1.08
BBs vs CCBs	1.04	0.95-1.14
BBs vs Diuretics	0.92	0.84-1.01
CCBs vs Diuretics	0.88	0.80-0.98†
Adherence to first-line drug	0.55	0.50-0.60†
Number of co-medications	0.98	0.97-0.99†
Type of co-medications		
Antidiabetic	1.01	0.91-1.12
Antihyperlipidemic	0.89	0.83-0.95†
Health services utilization		
Outpatient visits		
0-3 vs 4-7	1.04	0.97-1.11
0-3 vs >7	0.99	0.92-1.06
4-6 vs >7	0.95	0.89-1.01
Inpatient visits		
0 vs 1-3	0.83	0.70-0.99†

0 vs >3	0.93	0.83-1.06
1-3 vs >3	1.27	0.91-1.39

*IHD: Ischemic heart diseases; CHF: Congestive heart failure; PVD: Peripheral vascular diseases; CRVD: Cerebrovascular diseases.
**CCBs= Calcium Channel Blockers; ACEIs= Angiotensin-converting enzyme inhibitors; ARBs= Angiotensin receptor blockers.
†significant at $P<0.05$ compared to diuretics as reference group.