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2022

The Economic Value of Pharmacist-Physician Collaborative Care Models in Hypertension Management

Jessica S. Jay
Virginia Commonwealth University

The Economic Value of Pharmacist-Physician Collaborative Care Models in Hypertension Management

A Thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Pharmaceutical Sciences with a concentration in pharmacoeconomics and health outcomes at Virginia Commonwealth University

By

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Virginia Commonwealth University
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LIST OF ABBREVIATIONS

PPCCM	Pharmacist-physician collaborative care model
BP	Blood pressure
TTR	Time in target range
CV	Cardiovascular
MI	Myocardial infarction
HF	Heart failure
CVD	Cardiovascular disease
US	United States
SPRINT	Systolic Blood Pressure Intervention Trial
MACE	Major adverse cardiovascular event
CARDIA	Coronary Artery risk Development in Young Adults
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
DIMM	Diabetes Intense Medical Management
PCP	Primary care physician
A1c	Hemoglobin A1c
QALY	Quality-adjusted life years
CAPTION	Collaboration Among Pharmacist and Physicians to Improve Blood Pressure Now
CPT	Current Procedural Terminology
USD	United States Dollar
CPA	Collaborative practice agreement
QA	Quality assurance

ABSTRACT

The Economic Value of Pharmacist-Physician Collaborative Care Models in Hypertension Management

By Jessica S. Jay, PharmD

A Thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Pharmaceutical Sciences with a concentration in pharmacoeconomics and health outcomes at Virginia Commonwealth University

Virginia Commonwealth University, 2022

Advisor: Julie A. Patterson, PharmD, PhD
Assistant Professor, Department of Pharmacotherapy and Outcomes Science

Background: Hypertension is highly prevalent in the United States, affecting nearly half of all adults (43%). Studies have shown that pharmacy-physician collaborative care models (PPCCM) for hypertension management significantly improve blood pressure (BP) control rates and provide consistent control of BP. Time in target range (TTR) for systolic BP is a novel measure of BP control consistency that is independently associated with decreased cardiovascular (CV) risk. There is no evidence observed improvement in TTR for systolic BP with PPCCM is cost effective.

Objective: This study aimed to compare the cost-effectiveness of PPCCM with usual care for the management of hypertension from the payer perspective with a decision analysis model and a Markov model.

Methods: Both the decision analysis model and the Markov model utilized a three-year time horizon based on published literature and publicly available data. The population consisted of adult patients who had a previous diagnosis of high BP (defined as office-based BP ≥ 140/90 mmHg) or were receiving antihypertensive medication(s). Effectiveness data were drawn from two published studies evaluating the effect of PPCCM (vs. usual care) on TTR for systolic BP and the impact of TTR for systolic BP on four CV outcomes (nonfatal myocardial infarction (MI), stroke, heart

failure (HF), and cardiovascular disease (CVD) death). Both models incorporated direct medical costs, including both programmatic costs (i.e., direct costs for provider time) and downstream healthcare utilization associated with the acute CV events; the Markov model also included the incremental post-CV event costs and recurrences of the same acute CV event. One-way sensitivity and threshold analyses examined model robustness.

Results: In base case analyses for the decision analysis model and Markov model, PPCCM hypertension management was associated with lower downstream medical expenditures (difference: -$162.86 and -$173.05, respectively) and lower total program costs (difference: $-108.00) per person treated when compared to usual care. PPCCM was associated with lower downstream medical expenditures across all parameter ranges tested in the deterministic sensitivity analysis. For every 10,000 hypertension patients managed with PPCCM vs. usual care over a three-year time horizon, the decision analysis and Markov models suggested that approximately 27 and 16 CVD deaths, 29 and 51 strokes, 21 and 42 non-fatal MIs, and 12 and 48 incident HF diagnoses, respectively, are expected to be averted.

Conclusion: This is the first study to model the cost-effectiveness of PPCCM compared to usual care on TTR for systolic BP in adults with hypertension. For both the decision analysis and Markov models, PPCCM was less costly to administer and resulted in downstream healthcare savings and fewer acute CV events relative to usual care. Although further research is needed to evaluate the long-term costs and outcomes of PPCCM, payer coverage of PPCCM services may prevent future healthcare costs and improve patient CV outcomes.

CHAPTER 1: INTRODUCTION

Section 1.1: Background

Hypertension is highly prevalent in the United States (US), affecting nearly half of all adults (47%).[1] Hypertension is defined as having a systolic blood pressure (BP) ≥ 130 or diastolic BP ≥ 80 mmHg and is a major risk factor for ischemic heart disease, heart failure (HF), stroke, chronic kidney disease, and death.[1,2] Only about a quarter (24%) of adults with hypertension have it under control. From 2003-2014, it was estimated that hypertension accounts for $131 billion per year in US healthcare costs.[3]

It has been shown that high BP variability is associated with increased risks of all-cause mortality, coronary heart disease, stroke, and end-stage renal disease.[4–6] The concept of time in target range (TTR) for systolic BP is a novel measure of BP variability.[7] A longitudinal study from 15 Veterans Administration Medical Centers categorized TTR for systolic BP into 4 quartiles (0-25%, 26-50%, 51-75%, and 76-100%) and found an inverse and gradual association between time in therapeutic range and all-cause mortality.[7] To determine if TTR for systolic BP had an effect on cardiovascular (CV) outcomes, Fatani et al. conducted a post hoc analysis of the SPRINT data.[8,9] In the fully adjusted models, the authors found that for every one standard deviation increase in TTR for systolic BP, the risk of first major adverse cardiovascular event (MACE) was significantly decreased.[8] This study is consistent with other studies suggesting greater variability in BP is associated with coronary heart disease, stroke, CV mortality, and all-cause mortality.[4–6]

Studies have shown that pharmacists play a key role within primary care settings in managing chronic diseases, such as hypertension, and clinical pharmacy services decrease overall healthcare costs.[10–12] A pharmacy-physician collaborative care model (PPCCM) is a practice model where pharmacists provide medication management for common primary care conditions

often under a collaborative practice agreement (CPA) with a physician to adjust medications, as well as order necessary laboratory tests to monitor drug therapy.[13] Pharmacy-physician collaborative care model has been shown to not only be successful within an office-based setting,[13] but even within barbershops and churches.[14,15] A study by Matzke et al. found significant improvements ($p < 0.01$) in hemoglobin, BP, and cholesterol in patients with multiple chronic conditions that were in the PPCCM group compared to those seen by usual care. Additionally, hospitalizations declined within the PPCCM group, which led to an estimated cost savings of $2,619 per patient.[16] Carter et al. have conducted multiple randomized clinical trials to assess the effectiveness of PPCCM for hypertension management and found that patients treated under the PPCCM model achieve significantly better mean BP and overall BP control rates.[17,18] Recently, a study conducted by Dixon et al. investigated the impact of PPCCM on TTR for systolic BP, as defined by the proportion of clinical encounters with systolic BP between 120-140 mmHg during a 12-month follow-up period.[13] The mean TTR for systolic BP was significantly higher among PPCCM patients (46.2% ± 24.3%) than patients who received usual care (24.8% ± 27.4%) ($p < 0.0001$).[13] Additionally, a majority of patients in the usual care group had a TTR for systolic BP in the lowest quartile (0-25%), while PPCCM patients were more likely to have TTR for systolic BP in the highest quartile (76-100%).[13]

Section 1.2: Objective and Specific Aims

Despite the available evidence supporting PPCCM as an effective model at improving TTR for systolic BP compared to usual care[13] and that patients with higher TTR for systolic BP have decreased risk of adverse CV events, [7–9] no pharmacoeconomic analysis has combined these findings to model the cost-effectiveness of PPCCM. Therefore, the objective of this study was to compare the cost-effectiveness of PPCCM with usual care on TTR for systolic BP in patients with

hypertension utilizing two commonly utilized modeling approaches: a BP-based decision analysis model and a BP-based Markov model. This study was conducted from the payer perspective to quantify the value added to a payer of covering PPCCM services.

Specific Aim 1:

To assess the cost-benefit and cost-effectiveness of PPCCM relative to usual care in patients with hypertension with a TTR for systolic BP-based decision analysis model.

Specific Aim 2:

2a. To assess the cost-benefit and cost-effectiveness of PPCCM relative to usual care in patients with hypertension with a TTR for systolic BP-based Markov model.

2b. To compare the cost-benefit and cost-effectiveness of PPCCM relative to usual care in patients with hypertension as assessed by the decision analysis and Markov models.

CHAPTER 2: LITERATURE REVIEW

Section 2.1: Hypertension

Hypertension occurs when the force exerted by circulating blood against the walls of the body's arteries is too high.[19] It is a serious medical condition that increases the risk ischemic heart disease, HF, stroke, chronic kidney disease, and death.[1,2] The US Centers for Disease Control and Prevention reports that approximately 116 million Americans – nearly one out of two adults - have hypertension. Further, over half a million Americans die annually from high BP or an event for which high BP contributed.[1]

Blood pressure consists of two numbers, systolic and diastolic BP. The systolic number represents the pressure in blood vessels when the heart contracts or beats, and the diastolic number represents the pressure in the vessels when the heart rests between beats.[19] Hypertension is diagnosed if the patient's systolic BP reading is ≥140 mmHg and/or their diastolic BP reading is ≥90 mmHg on two separate days (Table 1).[1,19] Both modifiable and non-modifiable risk factors contribute to hypertension. Modifiable risk factors include physical inactivity, consumption of tobacco and alcohol, and being overweight. Diets high in salt, saturated fat, trans fat, and low in fruits and vegetables also contribute to hypertension risk.[2,19] Non-modifiable risk factors include coexisting diseases, family history of hypertension, and age over 65 years.[2,19] Although hypertension is known as the "silent killer", some patients experience symptoms such as early morning headaches, nosebleeds, irregular heart rhythms, vision changes, and buzzing in the ears. Patients with severe hypertension can have symptoms that include fatigue, nausea, vomiting, confusion, anxiety, chest pain, and muscle tremors.[19]

Table 1: Blood Pressure Categories

Blood Pressure Category	Systolic mmHg (upper number)		Diastolic mmHg (lower number)
Normal	Less than 120	And	Less than 80
Elevated	120 – 129	And	Less than 80
High Blood Pressure (Hypertension) Stage 1	130 – 139	Or	80 – 89
High Blood Pressure (Hypertension) Stage 2	140 or higher	Or	90 or higher
Hypertensive Crisis (consult doctor immediately)	Higher than 180	And / Or	Higher than 120

Blood pressure control, through lifestyle modifications with or without medications, is critically important to the treatment of hypertension and the reduction of its humanistic and economic burden.[20] In the US, controlled BP is defined as systolic BP <130 mmHg and diastolic BP <80 mmHg.[21,22] Uncontrolled BP, even among patients treated with antihypertensives, is associated with higher risk of all-cause, cardiovascular disease (CVD)-specific, heart-disease specific, and cerebrovascular disease-specific mortality. Conversely, hypertension patients whose BP is adequately controlled are not at increased risk of mortality later in life compared to patients who are either untreated for their hypertension or have uncontrolled hypertension.[20] Despite the well-documented consequences of uncontrolled hypertension, fewer than 1 in 4 Americans (24%) with hypertension have it under control.[1]

Section 2.2: Time in Target Range for Systolic Blood Pressure

As previously discussed, despite clear evidence of the positive health outcomes associated with hypertension control, control rates have remained suboptimal and even worsened over the years.[21] Blood pressure control has historically been defined by BP(s) taken at a single clinical visit, with the last recorded BP of a calendar year determining BP control for performance

measurement purposes.[8] However, BP is a dynamic measure that fluctuates over time. Even without any change in a patient's drug regimen, BP can vary throughout the day and over time, including from physician visit to physician visit.[7] Therefore, the last recorded BP measurement may not adequately reflect hypertension control. Studies have shown that high BP variability is associated with increased risks of all-cause mortality, coronary heart disease, stroke, and end-stage renal disease.[4–6] Therefore, appropriate performance measure and clinical management of systolic BP should account for the variation both within and out of target range. By expressing the percentage of BP measurements in a patient's therapeutic range (e.g., TTR for systolic BP range 120-140mmHg), TTR incorporates both the patient's average BP value prevailing during long-term follow up and their degree of BP variability.[7] This concept of TTR for systolic BP is a novel measure of BP variability and control[7] and has the potential to become a favored performance measure for hypertension.

The following studies are a summarization of literature that discuss how variability of BP is associated with myocardial structure, MACE, CVD, and all-cause mortality. These studies were selected for additional discussion based on their inclusion of systolic BP variability and its cardiovascular health consequences. A cohort study by Nwabuo et al. utilized data from the Coronary Artery risk Development in Young Adults (CARDIA) study to evaluate associations between visit-to-visit BP variability in early adulthood and myocardial structure and function in middle age.[23] Patients within the CARDIA study were aged 18 to 30 years at baseline and were followed for 30 years, including 8 visits over 25 years and an echocardiogram at year 5. The study results suggested that every 1-standard deviation increase in visit-to-visit systolic BP variability was associated with higher left-ventricular mass ($p < 0.001$), worse diastolic function ($p < 0.001$), higher left-ventricular filling pressures ($p < 0.001$), and worse global longitudinal strain ($p =$

0.002). Additionally, greater visit-to-visit diastolic BP variability was associated with higher left-ventricular mass ($p < 0.001$), worse diastolic function ($p < 0.001$), and worse global longitudinal strain ($p = 0.02$). They concluded that greater visit-to-visit systolic and diastolic BP variability was associated with adverse alterations in cardiac structure that were independent of mean BP levels.[23]

A systematic review and meta-analysis by Wang et al. examined the association between visit-to-visit variability of BP, CVD and all-cause mortality. This study searched PubMed and EMBASE up until May 18, 2014 with the following terms: visit-to-visit variability, blood pressure, cardiovascular disease, coronary heart disease, myocardial ischemia, stroke, and mortality. In their primary analyses of 23 included studies (Table 2), Wang et al. found that increased BP variability was significantly associated with outcomes of all-cause mortality (RR = 1.14; 95% CI: 1.05, 1.09), CVD mortality (RR = 1.18; 95% CI: 1.09, 1.28), coronary heart disease (RR = 1.12; 95% CI: 1.06, 1.19), and stroke incidence (RR = 1.34; 95% CI: 1.11, 1.61). This meta-analysis incorporated studies in heterogenic and high-risk populations, suggesting that standardized approaches of monitoring visit-to-visit variability of BP are necessary for diverse patients.[5]

Table 2: Baseline Characteristics of Studies Included in Wang et al. Meta-Analysis on the Association Between Visit-to-Visit Variability of BP, CVD and All-Cause Mortality[5]

Study	Publish year	Country	Cohort	Sample size	Men/ women	Mean age or age range (years)	Follow-up duration (years)	Outcomes measured
Grove *et al.*	1997	US	The Honolulu Heart Program	1433	1433/0	45–65	11.6	Incident CHD
Pringle *et al.*	2003	UK	The multicenter Syst-Eur trial	744	290/454	60–92	4.4	CVD mortality, incident stroke, and cardiac events
Kikuya *et al.*	2008	Japan	The Ohasama Study	2455	1021/1483	35–96	11.9	All-cause mortality and CVD mortality
Rothwell *et al.*	2010	UK	The UK-TIA aspirin trial, ESPS-1, Dutch TIA trial, and ASCOT-BPLA trial	–	–	–	–	Incident stroke
Muntner *et al.*	2011	US	NHANES III, 1988–1994	956	464/492	≥20	14	All-cause mortality
Eguchi *et al.*	2012	US	Karatsu–Nishiarita study	457	172/285	33–88	5.58	Incident CVD
Poortvliet *et al.*	2012	Scotland, Ireland, and the Netherlands	PROSPER study	1808	876/932	70–82	7.1	Incident CHD, incident stroke, and all-cause mortality
Schutte *et al.*	2012	Belgium	The Flemish Study	2944	1450/1494	≥20	12	All-cause mortality, CVD mortality, incident CVD, incident CHD, and incident stroke
Shimbo *et al.*	2012	US	WHI study	58 228	0/58 228	50–79	5.4	Incident stroke
Johansson *et al.*	2012	Finland	The Finn-Home Study	1866	815/629	45–74	7.8	Incident CVD and all-cause mortality
Rossignol *et al.*	2012	France	FOSIDIAL	397	208/189	66.8	2	Incident CVD
Di Iorio *et al.*	2012	Italy	Multicenter study in three tertiary care nephrology outpatient clinics in Italy	374	232/142	≥18	2.75	All-cause mortality
Hsieh *et al.*	2012	Taiwan	A longitudinal cohort study	2161	936/1225	63.5 ± 11.9	5.56	All-cause mortality and CVD mortality
Suchy-Diecy *et al.*	2013	US	CHS	3852	1578/2274	≥65	10	All-cause mortality, incident MI, and incident stroke
Lau *et al.*	2014	China	Patients with lacunar infarct from the Tung Wah Hospital Stroke Unit, Hong Kong	281	147/134	70 ± 10	6.5	All-cause mortality, CVD, incident stroke, and acute coronary syndrome
Kawai *et al.*	2013	Japan	A part of the NOAH study	485	258/227	61.7 ± 11.5	7.59	Incident CVD
Hastie *et al.*	2013	UK	Hospital-based cohort in the west of Scotland	14 522	6952/7570	50.5	29.32	All-cause mortality, CVD mortality, IHD mortality, and stroke mortality
Hata *et al.*	2013	UK	ADVANCE trial	8811	6405/4735	≥55	2	All-cause mortality, incident MI, incident stroke, and CVD mortality
Mallamci *et al.*	2013	Italy	Multicenter, nonoverlapping cohort studies based on Italian Nephrology Units	1618	950/668	64 ± 12	3.08	Incident CVD
McMullan *et al.*	2013	US	AASK trial	908	562/346	55	4.3	All-cause mortality, CVD mortality, and incident CVD
Chang *et al.*	2014	US	The HEMO study	1846	782/1064	18–80	2.5	All-cause mortality and CVD mortality
Lau *et al.*	2014	China	Hospital-based cohort in Hong Kong	656	446/210	66 ± 10	6.75	Incident CVD
Lau *et al.*	2014	China	Hospital-based cohort from Tung Wah Hospital, Hong Kong	632	337/295	71 ± 11	6.33	CVD mortality

Abbreviations Used: ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm; CHD, coronary heart disease; CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; TIA, transient ischemic attack; UK-TIA, United Kingdom TIA.

A post-hoc analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) also aimed to examine the association of visit-to-visit variability of systolic BP with CVD and mortality outcomes. In their analysis, Muntner et al. defined visit-to-visit variability of systolic BP as the standard deviation across systolic BP measurements from 7 visits that occurred between 6 and 28 months after randomization and the outcomes included were fatal coronary heart disease or nonfatal myocardial infarction (MI), all-cause mortality, stroke, and HF. The patients were then followed until they had an occurrence of an outcome event or the end of the ALLHAT follow-up. During this follow-up period with a mean of 2.7 to 2.9 years and after multivariable adjustment including mean systolic BP, patients with the most variability in systolic BP, as indicated by being in the highest versus lowest quintile of standard deviation of systolic BP (≥14.4 mmHg vs. <6.5 mmHg), had a statistically significant higher risk for fatal coronary heart disease or nonfatal MI (HR = 1.30; 95% CI: 1.06, 1.61), mortality (HR = 1.58; 95% CI: 0.97, 1.61), stroke (HR = 1.46; 95% CI: 1.06, 2.01), and HF (HR = 1.25; 95% CI: 0.97, 1.61). In conclusion, this study determined that higher visit-to-visit variability of systolic BP was associated with an increased risk for CVD and mortality.[24]

In 2017, Doumas et al. became the first study to specifically analyze patient outcomes based on time in therapeutic range for systolic BP. They performed a retrospective analysis from 15 Veterans Administration Medical Centers over a 10-year period to determine if consistent control of TTR for systolic BP was a strong determinant of all-cause mortality among US veterans. TTR for systolic BP was categorized into 4 quartiles, 0-25%, 26-50%, 51-75%, and 76-100%. The population for this study consisted of a total of 689,051 Veterans with 54% as hypertensive (≥3 elevated BPs during the follow-up period), 19.9% as intermediate (MID-hypertension, had 1 or 2 elevated BPs), and 26.1% as normotensive (no elevated BPs). The mortality rates for these

corresponding 3 groups were 11.5%, 8%, and 1.9%, respectively ($p < 0.0001$). Among patients with hypertension, all-cause mortality rates were lowest among patients with high TTR, increasing gradually from 6.54% in the most controlled group (76-100%), to 8.87%, 15.62%, and 23.52% in the less controlled groups (51-75%, 26-50%, 0-25%, respectively, $p < 0.0001$). Cox regression estimates for survival based on TTR for systolic BP and found that mortality risk with less consistency in BP control, but the difference between 51-75% and 76-100% were very minimal. Collectively, these findings suggest that consistency of BP control over time plays a vital role in all-cause mortality, with TTR $\geq$51% to realize long-term survival benefits from BP control.[7]

In a post hoc analysis of SPRINT, Fatani et al. sought to estimate the independent association between TTR in systolic BP and major adverse CV events among adults with hypertension. The TTR was estimated over the first 3 months of follow-up by using linear interpolation. Fatani et al. categorized TTR for systolic BP into the same 4 quartiles as Doumas et al., 0-25%, 26-50%, 51-75%, and 76-100%. CV outcomes were then analyzed across TTR groups over the SPRINT trial time horizon, an average of 3.3 years. Specifically, associations between TTR and MACE (CVD death, MI, nonmyocardial infarction acute coronary syndrome, stroke, or acute decompensated HF), individual MACE components, and treatment-related serious adverse events were analyzed using adjusted Cox proportional hazards regression models. Patients with TTR for systolic BP of 75-100% were younger and had a lower 10-year CV risk. Additionally, patients with a greater TTR for systolic BP also had a lower mean systolic BP. For every 1-standard deviation increase in TTR for systolic BP, there was a significantly decreased risk of first MACE in the unadjusted model (HR = 0.78; 95% CI: 0.70, 0.77; $p < 0.001$). In the fully adjusted models, TTR for systolic BP was significantly associated with first nonfatal MI (HR = 0.75; 95% CI: 0.72, 0.90; $p = 0.002$) and first HF hospitalization (HR = 0.79; 95% CI: 0.65, 0.97; $p = 0.023$). However,

Fatani et al. found no associations between TTR for systolic BP and nonmyocardial infarction acute coronary syndrome, CVD death, or all-cause death. Overall, TTR for systolic BP was found to independently predict MACE risk,[8] suggesting that TTR monitoring for BP control may be a useful tool for long-term treatment decision-making.

Section 2.3: Economic Evaluation of Pharmacist Physician Collaborative Care Models

For over a decade, PPCCMs have gained significant traction as a way to implement team-based-care and improve patient outcomes in the primary care setting.[25] Within a PPCCM, pharmacists practice under a collaborative agreement with physicians allowing them to provide direct patient care for one or more chronic conditions, generally including comprehensive medication management. For example, pharmacists are often permitted to initiate, titrate, and discontinue medications as well as order and interpret laboratory tests to help patients manage their common primary care conditions.[26] Although a well-established body of literature has demonstrated that pharmacists in collaborative primary care settings both effectively improve patient outcomes for chronic diseases, such as hypertension, and decrease overall healthcare costs,[10–12] economic evaluations of PPCCM are needed to promote implementation of and reimbursement for these models.

Several past studies have evaluated the cost-effectiveness of PPCCM services for different chronic disease states in the US.[27–31] A study by Hirsch et al. estimated the cost-effectiveness and cost-benefit of a collaborative endocrinologist-pharmacist Diabetes Intense Medical Management (DIMM) "Tune Up" clinic for complex diabetes patients versus primary care physician (PCP) care from 3 separate perspectives: clinic, health system, and payer. They conducted a retrospective analysis of a cohort of adult patients with type 2 diabetes mellitus and glycosylated hemoglobin A1c (A1c) ≥8% who were referred to the DIMM clinic at the Veterans Affairs San Diego Health

System or were managed by a PCP alone. In general, patients participating in the DIMM clinic spent more time with clinicians, including medication therapy management, personalized care, and diabetes education, than those managed by a PCP alone. In base case analyses from the clinic perspective, DIMM clinics were associated with higher costs but improved patient outcomes. Specifically, the study authors reported that DIMM clinics, compared to PCP care, cost an additional $21 per additional percentage point of A1c improvement and $115-164 per additional patient at target A1c goal level. In contrast, from the health system perspective, DIMM clinicals were associated with both lower costs and improved patient outcomes. Medical cost avoidance due to improved A1c associated with each model of care was, on average, $8,793 per DIMM patient versus $3,506 per PCP patient ($p = 0.009$). Finally, from the payer perspective, DIMM group had lower estimated medical costs and greater quality-adjusted life years (QALYs) gained versus the PCP group over 2-, 5-, and 10-year time frames. For example, at the 5-year time frame, the DIMM group incurred $2,137,659 medical costs and gained 222 QALYs, while the PCP group incurred $2,272,572 medical costs and gained 218 QALYs. DIMM was therefore dominant at each time frame from the payer perspective since it was both more effective and had a lower total cost.[27]

Overwyk et al. aimed to assess the potential health and budgetary impacts of implementing a pharmacist-involved team-based hypertension management model in the US. They conducted a microsimulation model where they evaluated a pharmacist-involved team-based care intervention among 3 different groups to help estimate CV event incidence and associated healthcare spending in a cross-section of individuals that were representative of the US population. These 3 groups included: (1) newly diagnosed hypertension, (2) persistently (≥1 year) uncontrolled BP, or (3) treated, yet persistently uncontrolled BP. They reported outcomes over 5 and 20 years and provided spending thresholds for the intervention to achieve budget neutrality in 5 years from three

payer perspectives: Medicare, Medicaid, and private payers. The cost of the intervention was assumed to be $525 per enrollee based on an average of a 1-hour long initial visit and 11 15-minute visits annually, including three in-person and eight phone visits. Their results showed that a pharmacist-involved team-based hypertension management model could substantially improve patient outcomes, preventing 22.9-36.8 million person-years of uncontrolled BP and 77,200-230,900 heart attacks and strokes in 5 years. The intervention generated the most favorable health and economic impact among the groups with persistent uncontrolled BP (i.e., groups 2 and 3). Assuming an intervention cost $525 per enrollee, the intervention was cost-saving over a five-year time horizon for Medicare among groups 2 and 3. The intervention was not cost-savings for Medicaid or private payers but would be budget neutral at an intervention cost of $35 and $180 for Medicaid or private payers, respectively. Overwyk et al. concluded that a physician-pharmacist collaborative model for hypertension management could significantly improve patient outcomes, generate cost savings for many Medicare patients, and likely also has acceptable budget impact for private insurers. [28]

Although the studies discussed above depict PPCCM as being less costly compared to usual care, studies by Polgreen et al. and Kulchaitanaroaj et al. reported PPCCM to be more costly – but also more effective - than usual care for hypertension management.[29–31] Polgreen et al. conducted a cost-effectiveness analysis of physician-pharmacist collaborations to improve hypertension control from the societal perspective with data from the Collaboration Among Pharmacist and Physicians to Improve Blood Pressure Now (CAPTION) trial. Costs were assigned to medications as well as pharmacist and physician time, and cost-effectiveness ratios were calculated based on changes in BP and hypertension control rates. Specifically, provider costs were generated by multiplying patient-specific pharmacist or provider time by the average compensation rates for

pharmacists ($56.01/hr) or physicians ($88.43/hr). Patients spent 15 to 1,044 minutes with the pharmacist, with an average of 155 minutes, and they had more visits compared to that of the physician group.[29] After 9 months, patients in the pharmacist group had lower average systolic (6.1 mmHg) and diastolic BP (2.9 mmHg) and were more likely to be controlled (43% vs. 34%) than patients managed by physicians alone.. Total costs, which were the sum of drug costs, physician time, and pharmacist costs, were higher among the collaboratively managed patients ($1,462.87 vs. $1,259.94). Polgreen et al. reported three cost-effectiveness ratios: the incremental cost to lower systolic ($33.27) and diastolic BP by 1 mmHg ($69.98) and the cost to increase the population-level rate of BP control by 1 percentage point ($22.55).The findings from Polgreen et al. showed that although pharmacists spent a substantially longer time with patients during visits, the additional pharmacist care resulted in statistically and clinically significant reductions in BP compared to physicians alone that were highly cost-effective.[29]

Kulchaitanaroaj et al. performed two separate economic studies to determine the economic impact of PPCCM. The first study, published in2012, compared the costs associated with usual physician-based care vs. a physician-pharmacist collaborative intervention for the management of hypertension. The cost calculation, which included costs of provider time, laboratory tests, and antihypertensive medications for a six-month period, was determined by using healthcare utilization and outcomes from prospective, cluster randomized controlled clinical trials. Like the study by Polgreen et al., provider costs were generated by using the average compensation rate of the physician ($77.64 per hour for family and general practitioners, $79.33 per hour for other physicians and surgeons, and $50.14 per hour for pharmacists). However, this 2012 study by Kulchaitanaroaj et al. also included the time physician and pharmacists collaborated into the total costs. Although physicians spent similar among of time on direct-patient care in both groups, the

total time spent by primary care physicians in the intervention group was higher than the control group due to the added time spent on collaboration with pharmacist. This resulted in higher adjusted total costs in the collaborative intervention group ($774.90) than the control group ($445.75; difference: $329.16, p <0.001).The results of the cost-effectiveness analysis suggested that the incremental cost of pharmacist-physician collaborative care, over physician care alone, was $1,338.05 for each additional patient who attains BP control over a 6-month time horizon.[30]

The second study by Kulchaitanaroaj et al., published in 2017 and it was a cost-utility analysis that estimated long-term costs and outcomes of a physician-pharmacist collaborative intervention compared with physician management along for treating essential hypertension. This study utilized a Markov model cohort simulation with a 6-month cycle to predict acute coronary syndrome, stroke, and HF throughout a patient's lifetime. Direct medical costs were based on the payer perspective; treatment costs of the physician-pharmacist intervention included time primary care physicians and pharmacists spent providing direct patient care and collaborating, specialist time for direct patient care during acute care visits, laboratory tests, antihypertensive medications, and overheads. In their base case analysis, they found that the average discounted costs of hypertension treatment and vascular diseases in the physician-pharmacist collaborative intervention were greater than the costs of usual care by $3,817.54 per person over a lifetime horizon. The intervention increased QALYs by 0.14 per person compared with that of usual care, resulting in a lifetime incremental cost for collaborative pharmacist-physician management of hypertension of $26,807.83 per QALY gained.[31] Compared to the other studies mentioned above, Polgreen et al. and Kulchaitanaroaj et al. found PPCCM to be more costly due to their utilization of time-based costing and pharmacists spend more time with their patients compared to usual care.[29–31] Nonetheless, the three studies reported incremental cost-effectiveness and cost-utility

ratios generally recognized to indicate that PPCCMs are cost-effective in the management of hypertension.

CHAPTER 3: SPECIFIC AIM 1

Specific Aim 1:

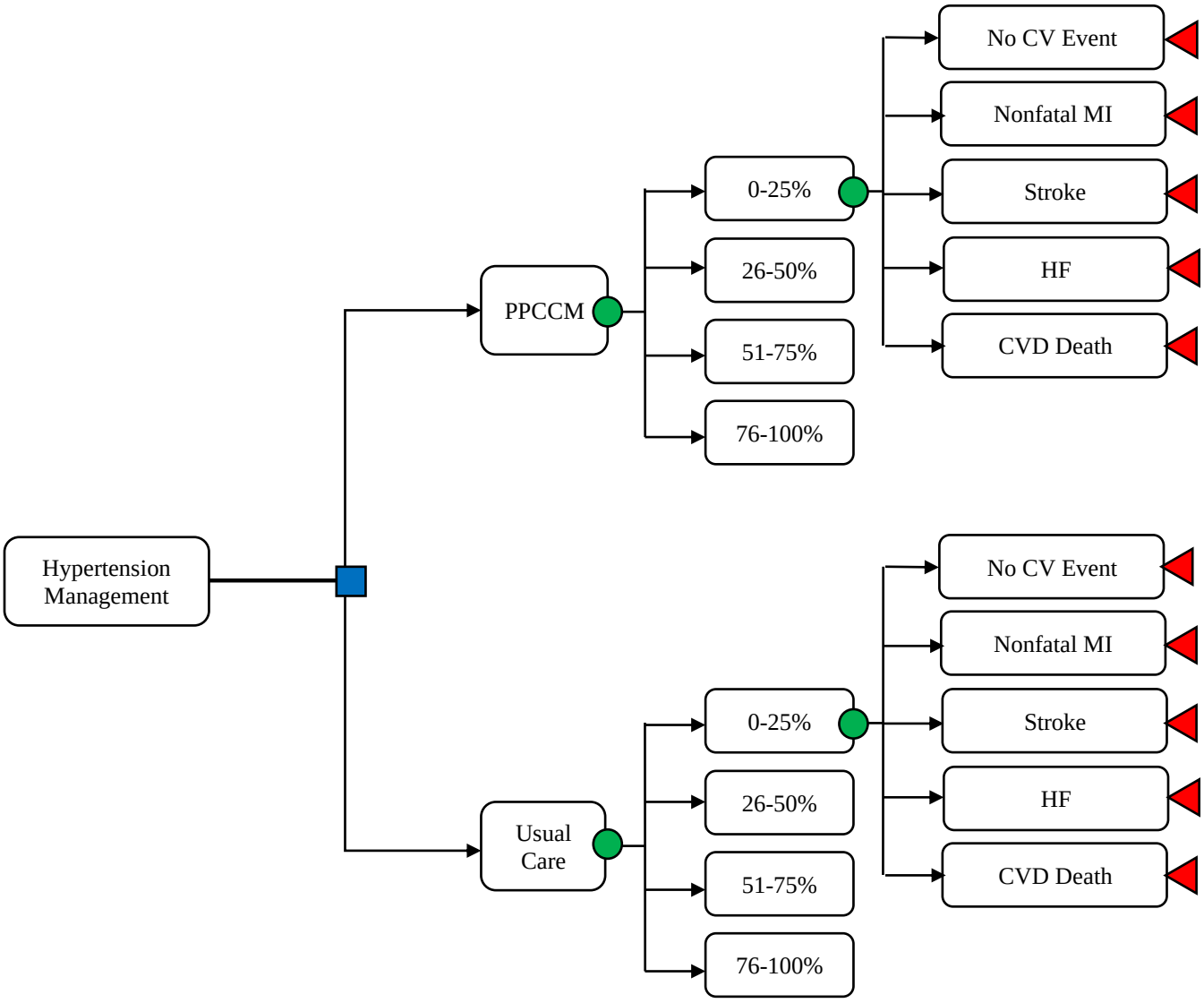
To assess the cost-benefit and cost-effectiveness of PPCCM relative to usual care in patients with hypertension with a TTR for systolic BP-based decision analysis model.

Section 3.1: Methods

Model Overview:

For specific aim 1, we used a decision analysis model (Figure 1) to evaluate the cost-effectiveness of two hypertension management practices, PPCCM and usual care. The PPCCM model was based on that reported by Dixon et al., consisting of an urban safety-net free clinic in Richmond, Virginia that primarily serves uninsured patients. In this model, volunteer physicians and nurse practitioners establish diagnoses and provide yearly wellness visits while pharmacists manage all aspects of drug therapy to achieve therapeutic goals for chronic diseases such as hypertension, diabetes, and heart failure.[13] The population studied in this analysis consisted of adult patients who were previously diagnosed with hypertension (defined as office-based BP ≥ 140/90 mmHg) or were receiving antihypertensive medication(s).[13] A three-year time horizon was chosen, reflecting the time frame of available data linking TTR for systolic BP (0-25%, 26-50%, 51-75%, and 76-100%) to CV outcome measures (nonfatal MI, stroke, HF, and CVD death).[8,9] The time horizon is consistent with the follow-up duration from the SPRINT trial, which was terminated early given the clinical benefit of intensive BP control within three years of treatment.[9,32] Further, the time horizon aligns with the shorter time frame utilized in cost-effectiveness models from the payer perspective.[33] The decision analysis model was developed in TreeAge Pro (TreeAge Software Inc, Williamstown MA). Institutional Review Board approval was not required as this research did not qualify as human subjects research.

Figure 1: Decision Tree Analysis for the Cost-Benefit of PPCCM Compared with Standard Usual Care on Time in Target Range for Systolic Blood Pressure in Hypertension Management



Abbreviations Used: PPCCM, pharmacist-physician collaborative care model; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; HF, heart failure

Effectiveness: Time in Target Systolic Blood Pressure Range and CV Event Outcomes

Base case parameters for the decision analysis model are listed in Table 3. The probabilities that patients managed with PPCCM and usual care would achieve levels of BP control within each of the 4 TTR for systolic BP quartiles were based on previously published data.[13] Although the published data on the effectiveness of PPCCM had a one-year study duration,[13] subjects in the model were assumed to stay in the same quartile of target BP range over the 3-year time horizon to facilitate linking the PPCCM effectiveness data to the clinical data on the association between TTR for systolic BP and CV events. Four CV events (nonfatal MI, stroke, HF, and CVD death) were selected for model inclusion based on available probabilities and hazard ratios from published data on CV outcomes associated with TTR for systolic BP quartiles.[8,9] Specifically, data on TTR for systolic BP quartiles and CV outcomes were derived from a post-hoc analysis of the SPRINT trial, a randomized, controlled, open-label trial of intensive versus standard BP control.[9] Patients within the SPRINT trial were censored after their first CV event, precluding analysis of subsequent events. Accordingly, CV events in this study were assumed to be mutually exclusive. Patients who did not incur one of these four events were assumed to have had no major CV event.

Hypertension Management and CV Event Costs

The decision analysis model incorporated direct medical costs, including both programmatic costs (i.e., direct costs for provider time) and downstream healthcare utilization associated with CV events (Table 3). Cost data were obtained from publicly available data and recently published cost-effectiveness analysis.[32,34,35] Provider visit utilization data were obtained from a real world analysis of PPCCM vs. usual care for the management of hypertension.[13] Specifically, for the cost of the PPCCM program, patients were assumed to have been seen for hypertension management six times per year by a pharmacist[13] and once per year by a physician.

Subjects in the usual care group were assumed to be seen three times per year by a physician.[13] The cost per pharmacist visit reflected the Current Procedural Terminology (CPT) code 99211 (level 1), an "incident-to" billing code used by pharmacists given a lack of provider status and eligibility to bill at a higher level. [34] For usual care visits, the CPT code 99213 was used for evaluation and management/outpatient visits.[35] One-time costs of treating each CV event were obtained from the cost-effectiveness analysis of the SPRINT trial.[32] Costs of hypertensive medications were assumed to be the same for both PPCCM and usual care given a lack of comparative medication use data and hence excluded from the model. Additionally, since the most commonly utilized hypertensive medications are generic and typically inexpensive,[36] they were unlikely to have a major impact on costs of care. All costs were inflated to 2020 United States Dollar (USD) using the medical care component of the Consumer Price Index.

Table 3: Effectiveness and Cost Inputs for Decision Analysis Model

Variables	Base-case value	Range	Reference
Probability of TTR for Systolic BP by Hypertension Management Approach			
PPCCM			
0-25%	0.210	0.170-0.260	Dixon et al, 2020[13]
26-50%	0.360	0.290-0.430	Dixon et al, 2020[13]
51-75%	0.310	0.240-0.370	Dixon et al, 2020[13]
76-100%	0.120	0.098-0.150	Dixon et al, 2020[13]
Usual Care			
0-25%	0.550	0.400-0.600	Dixon et al, 2020[13]
26-50%	0.340	0.270-0.400	Dixon et al, 2020[13]
51-75%	0.050	0.042-0.064	Dixon et al, 2020[13]
76-100%	0.060	0.044-0.066	Dixon et al, 2020[13]
Probability of CV Events by TTR for Systolic BP			
Outcome event rates of patients in TTR for Systolic BP 0-25%			
Nonfatal MI	0.035	0.027-0.045	Wright et al, 2015[9]
Stroke	0.020	0.014-0.028	Wright et al, 2015[9]
Heart Failure	0.022	0.016-0.031	Wright et al, 2015[9]
CVD death	0.017	0.012-0.024	Wright et al, 2015[9]
No CV event	0.906	-	Calculation
Hazard ratio of patients in TTR for Systolic BP 26-50%			
Nonfatal MI	0.83	0.57-1.18	Fatani et al, 2021[8]
Stroke	0.83	0.55 -1.27	Fatani et al, 2021[8]
Heart Failure	1.30	0.94-2.01	Fatani et al, 2021[8]
CVD death	0.69	0.42-1.15	Fatani et al, 2021[8]

No CV event	1.03	-	Calculation
Hazard ratio of patients in TTR for Systolic BP 51-75%			
Nonfatal MI	0.87	0.61-1.24	Fatani et al, 2021[8]
Stroke	0.58	0.36 -0.93	Fatani et al, 2021[8]
Heart Failure	0.84	0.54-1.29	Fatani et al, 2021[8]
CVD death	0.53	0.30-0.92	Fatani et al, 2021[8]
No CV event	1.12	-	Calculation
Hazard ratio of patients in TTR for Systolic BP 76-100%			
Nonfatal MI	0.69	0.46-1.04	Fatani et al, 2021[8]
Stroke	0.40	0.22-0.73	Fatani et al, 2021[8]
Heart Failure	0.59	0.34-1.02	Fatani et al, 2021[8]
CVD death	0.45	0.23-0.86	Fatani et al, 2021[8]
No CV event	1.25	-	Calculation
Programmatic Costs			
Annual PPCCM Pharmacist Visits, No.	6	4-12	Dixon et al, 2020[13]
PPCCM cost per visit	$24	$19-$29	ASHP, 2019[34]
Annual Physician Visits, No.			
PPCCM Group	1	1-2	Assumption
Usual Care Visits	3	1-6	Dixon et al, 2020[13]
Physician cost per visit	$90	$72-$108	CMS, 2019[35]
Total cost of PPCCM	$702	$562-$842	ASHP, 2019[34]
Total cost of usual care	$810	$648-$972	CMS, 2019[35]
Downstream Healthcare Costs			
One-time cost of nonfatal MI	$24,089	$15,372-$32,306	Bress et al, 2017[32]
One-time cost of stroke	$15,678	$6,001-$42,039	Bress et al, 2017[32]
One-time cost of heart failure	$11,678	$11,669-$16,580	Bress et al, 2017[32]
One-time cost of CVD death	$19,514	$12,560-$33,024	Bress et al, 2017[32]

Abbreviations Used: ASHP, American Society for Health Systems Pharmacists; CMS, Centers for Medicare and Medicaid Services; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; PPCCM, pharmacist-physician collaborative care model; TTR, time in target range; BP, blood pressure

Sensitivity Analyses

One-way deterministic sensitivity analyses were performed on all model variables to account for uncertainty in the parameter estimates for the two hypertensive management options. Additionally, threshold analyses were performed varying the cost per pharmacist visit, the number of annual pharmacist visits among patients in the PPCCM program, and the number of annual physician visits among patients in usual care to assess the values at which the programmatic costs of the two models would be equal.

Section 3.2: Results

In base case analyses, PPCCM hypertension management was associated with lower total program costs (difference: $-108.00) and lower downstream medical expenditures (difference: -

$162.86) when compared to usual care (Table 4). For every 10,000 hypertension patients managed with PPCCM vs. usual care over a three-year time horizon, approximately 27 CVD deaths, 29 strokes, 21 non-fatal MIs, and 12 incident HF diagnoses are expected to be averted.

PPCCM was associated with lower downstream medical expenditures across all parameter ranges tested in the deterministic sensitivity analysis. The expected downstream healthcare savings were most sensitive to the likelihood that patients receiving usual care spend little to no TTR for systolic BP (0-25%) (Figure 2). PPCCM was expected to reduce healthcare expenditures even as the proportion of usual care patients with TTR for systolic BP 0-25% was varied from its base case value of 55%, the probability observed by Dixon et al.,[13] to the lowest probability tested, 40%.

The program costs of hypertension management with PPCCM, while lower than those of usual care in base case analyses, were sensitive to the number of visits with a physician (usual care patients) and pharmacist (PPCCM patients) (Figure 3). Due to the substantial difference in CPT code reimbursement for pharmacist vs. usual care visits, a patient in the PPCCM program that was seen six times per year by a pharmacist and once per year by a physician was still cheaper than a patient in the usual care group that was seen three times per year by a physician. However, in one-way sensitivity analysis, the cost of PPCCM hypertension management exceeded the cost of usual care when independently varying the number of both types of provider visits. First, if the number of hypertension-related physician visits each year was reduced from three to one while holding the number of PPCCM-related visits constant, the cost of the PPCCM hypertension management exceeded the cost of usual care by $432 over the 3-year study period. Second, when the number of pharmacist visits among patients enrolled in PPCCM increased from six per year to twelve while the number of physician visits in the usual care group (n = 3) was held constant, PPCCM was associated with an incremental program cost of $324 over usual care.

In threshold analysis, the costs of the PPCCM and usual care programs became equal when the unit cost of pharmacist visits increases 62.5% to $39. The program costs were also equal when the number of PPCCM patient visits increased from six to 10 pharmacist visits per year or the number of usual care patient visits decreased from three to two physician visits per year.

Table 4: Cost-Effectiveness Results for Decision Analysis Model

	PPCCM	Usual care	Difference
Cardiovascular Events			
Nonfatal MI	0.0300	0.0321	21 per 10,000
Stroke	0.0149	0.0178	29 per 10,000
Heart failure	0.0225	0.0237	12 per 10,000
CVD death	0.0116	0.0143	27 per 10,000
Total downstream healthcare expenditures	$1,535.82	$1,698.64	- $162.82
Total program costs	$702.00	$810.00	- $108.00
Cost-benefit ratio	Dominant		

Abbreviations Used: PPCCM, pharmacist-physician collaborative care model; MI, myocardial infarction; CVD, cardiovascular disease

Figure 2: Tornado Diagram of Incremental Downstream Healthcare Expenditures among Patients Receiving PPCCM vs. Usual Care for Decision Analysis Model

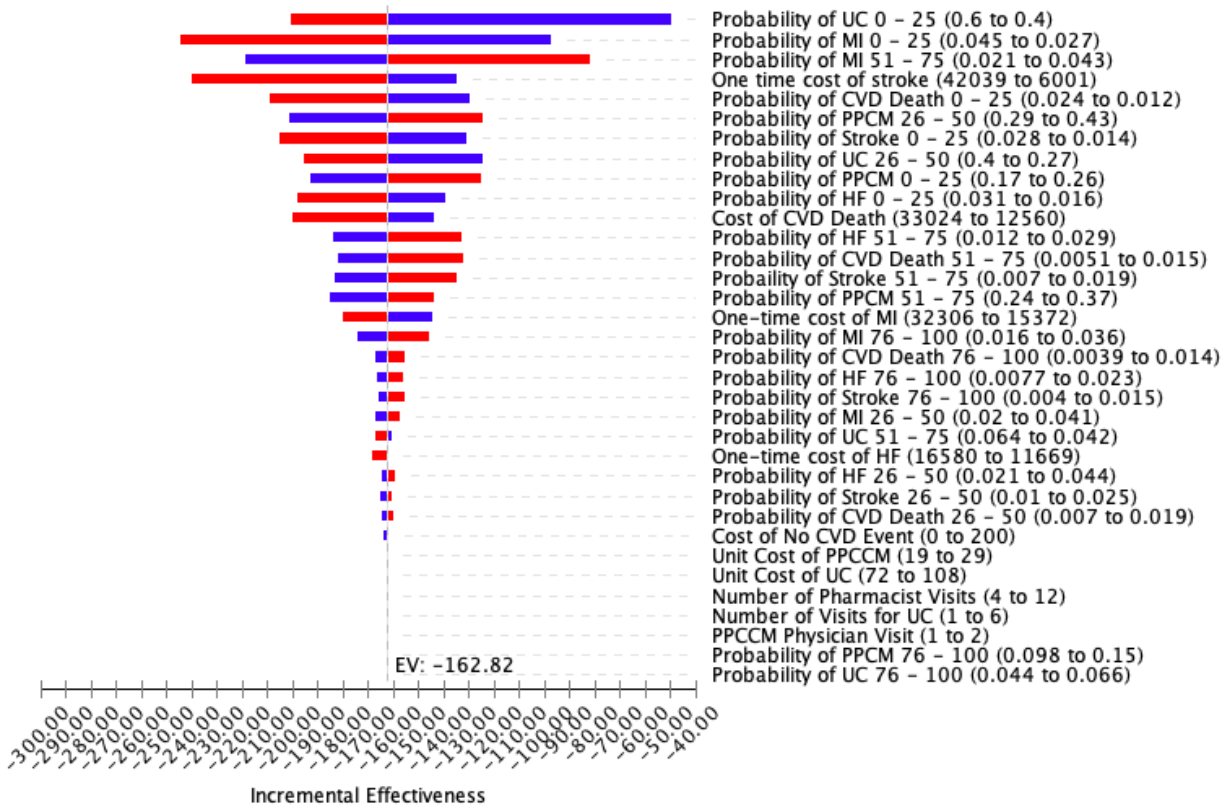
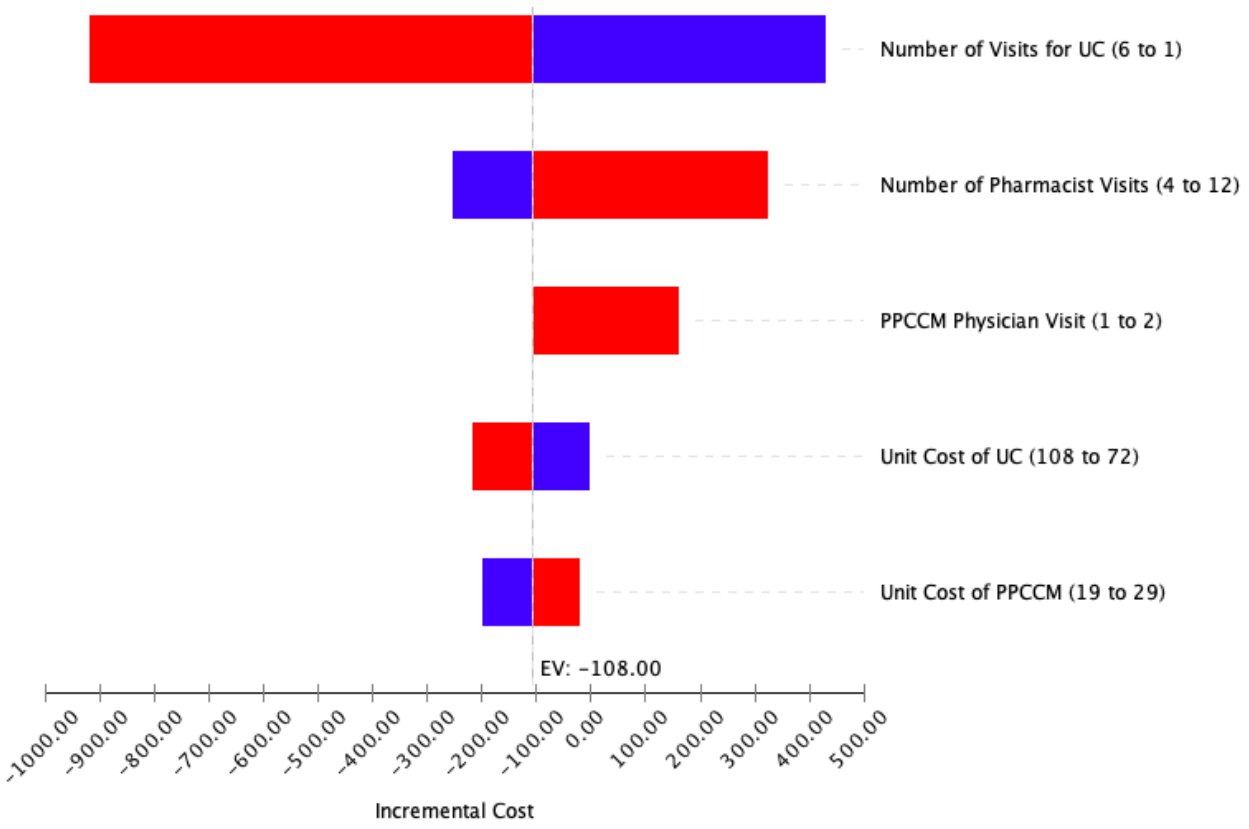


Figure 3: Tornado Diagram of Incremental Cost of PPCCM vs. Usual Care for Decision Analysis Model



CHAPTER 4: SPECIFIC AIM 2

Specific Aim 2:

2a. To assess the cost-benefit and cost-effectiveness of PPCCM relative to usual care in patients with hypertension with a TTR for systolic BP-based Markov model.

2b. To compare the cost-benefit and cost-effectiveness of PPCCM relative to usual care in patients with hypertension as assessed by the decision analysis and Markov models.

Section 4.1: Methods

Model Overview:

For specific aim 2, we used a Markov model (Figure 4) to evaluate the cost-effectiveness of two hypertension management practices, PPCCM and usual care. The population studied in this analysis consisted of adult patients who were previously diagnosed with hypertension (defined as office-based BP ≥ 140/90 mmHg) or were receiving antihypertensive medication(s).[13] A three-year time horizon was chosen, reflecting the time frame of available data linking TTR for systolic BP (0-25%, 26-50%, 51-75%, and 76-100%) to CV outcome measures (nonfatal MI, stroke, HF, and CVD death).[8,9] The time horizon is consistent with the follow-up duration from the SPRINT trial, which was terminated early given the clinical benefit of intensive BP control within three years of treatment.[9,32] Like the decision analysis model, the time horizon aligns with the shorter time frame utilized in cost-effectiveness models from the payer perspective.[33]

The primary differences between the decision analysis model and the Markov model are that the Markov model incorporates (1) the probability of the recurrence of an initial CV event, (2) probability of death after a specific CV event over the three-year time horizon,[37] and (3) the inclusion of incremental costs in patients with a past event beyond the initial cost of an event. Specific methodological differences are highlighted in Table 5. The Markov model was developed

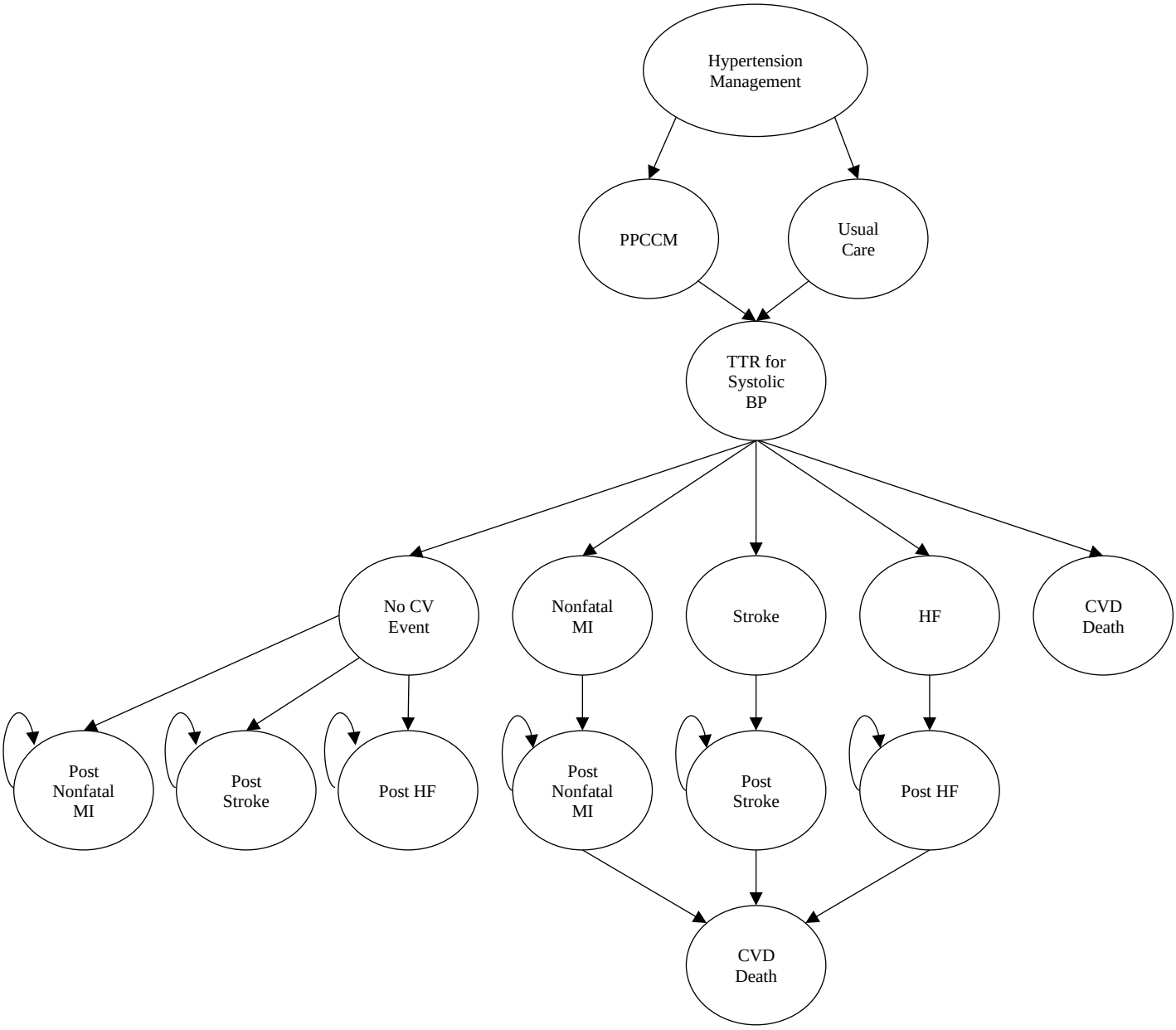
in TreeAge Pro (TreeAge Software Inc, Williamstown MA). Institutional Review Board approval was not required as this research did not qualify as human subjects research.

Table 5: Methodological Differences between Decision Analysis Model and Markov Model

Methodological Attribute	Decision Analysis Model	Markov Model
Recurrent CV Events	Not included	Included for recurrences of the same type of CV event
CVD Death	Included as a CV event among patients who did not have the other included CV events (e.g., MI, stroke)	Included as a CV event among both those who did not have the other included CV events (e.g., MI, stroke) and those who had an initial non-fatal event but later died
Cost of Events	One-time costs of treating the one CV event	One-time costs of treating a CV event plus incremental future costs among patients with a past event

Abbreviations Used: CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction

Figure 4: Markov Model for the Cost-Benefit of PPCCM Compared with Standard Usual Care on Time in Target Range for Systolic Blood Pressure in Hypertension Management



Abbreviations Used: PPCCM, pharmacist-physician collaborative care model; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; HF, heart failure

Effectiveness: Time in Target Systolic Blood Pressure Range and CV Event Outcomes

Base case parameters for the Markov model are listed in Table 6. The probabilities that patients managed with PPCCM and usual care would achieve levels of BP control within each of the 4 TTR for systolic BP quartiles were based on previously published data.[13] Although the published data on the effectiveness of PPCCM had a one-year study duration,[13] subjects in the model were assumed to stay in the same quartile of target BP range over the 3-year time horizon to facilitate linking the PPCCM effectiveness data to the clinical data on the association between TTR for systolic BP and CV events. Four CV events (nonfatal MI, stroke, HF, and CVD death) were selected for model inclusion based on available probabilities and hazard ratios from published data on CV outcomes associated with TTR for systolic BP quartiles.[8,9] Specifically, data on TTR for systolic BP quartiles and CV outcomes were derived from a post-hoc analysis of the SPRINT trial, a randomized, controlled, open-label trial of intensive versus standard BP control.[9]

Unlike the decision analysis model where patients were censored after their first CV event precluding analysis of subsequent events, we incorporated the probability of recurring CV events and death following an initial CV event in the Markov model. We utilized published data to determine the probability of the recurrence of the same CV event that the patient first had and the probability of death after their specific CV event.[37]

Hypertension Management and CV Event Costs

The Markov model incorporated direct medical costs, including both programmatic costs (i.e., direct costs for provider time) and downstream healthcare utilization associated with CV events (Table 6). Refer to Specific Aim 1 for a detailed explanation of the programmatic costs included. Cost data were obtained from publicly available data and recently published cost-effectiveness analysis.[32,34,35,37] Like the decision analysis model, one-time costs of treating each

CV event were obtained from the cost-effectiveness analysis of the SPRINT trial[32] and costs of hypertensive medications were assumed to be the same for both PPCCM and usual care. The core difference between the decision analysis model and the Markov model is that in the Markov model, we included long-term incremental costs of treating each CV event from a previously published cost-effectiveness analysis.[37] These long-term incremental costs included all inpatient and outpatient costs during the 3-month period following a CV event.[37] All costs were inflated to 2020 USD using the medical care component of the Consumer Price Index.

Table 6: Effectiveness and Cost Inputs for Markov Model

Variables	Base-case value	Range	Reference
Probability of TTR for Systolic BP by Hypertension Management Approach			
PPCCM			
0-25%	0.210	0.170-0.260	Dixon et al, 2020[13]
26-50%	0.360	0.290-0.430	Dixon et al, 2020[13]
51-75%	0.310	0.240-0.370	Dixon et al, 2020[13]
76-100%	0.120	0.098-0.150	Dixon et al, 2020[13]
Usual Care			
0-25%	0.550	0.400-0.600	Dixon et al, 2020[13]
26-50%	0.340	0.270-0.400	Dixon et al, 2020[13]
51-75%	0.050	0.042-0.064	Dixon et al, 2020[13]
76-100%	0.060	0.044-0.066	Dixon et al, 2020[13]
Probability of CV Events by TTR for Systolic BP			
Outcome event rates of patients in TTR for Systolic BP 0-25%			
Nonfatal MI	0.035	0.027-0.045	Wright et al, 2015[9]
Stroke	0.020	0.014-0.028	Wright et al, 2015[9]
Heart Failure	0.022	0.016-0.031	Wright et al, 2015[9]
CVD death	0.017	0.012-0.024	Wright et al, 2015[9]
No CV event	0.906	-	Calculation
Hazard ratio of patients in TTR for Systolic BP 26-50%			
Nonfatal MI	0.83	0.57-1.18	Fatani et al, 2021[8]
Stroke	0.83	0.55 -1.27	Fatani et al, 2021[8]
Heart Failure	1.30	0.94-2.01	Fatani et al, 2021[8]
CVD death	0.69	0.42-1.15	Fatani et al, 2021[8]
No CV event	1.03	-	Calculation
Hazard ratio of patients in TTR for Systolic BP 51-75%			
Nonfatal MI	0.87	0.61-1.24	Fatani et al, 2021[8]
Stroke	0.58	0.36 -0.93	Fatani et al, 2021[8]
Heart Failure	0.84	0.54-1.29	Fatani et al, 2021[8]
CVD death	0.53	0.30-0.92	Fatani et al, 2021[8]
No CV event	1.12	-	Calculation
Hazard ratio of patients in TTR for Systolic BP 76-100%			
Nonfatal MI	0.69	0.46-1.04	Fatani et al, 2021[8]

Stroke	0.40	0.22-0.73	Fatani et al, 2021[8]
Heart Failure	0.59	0.34-1.02	Fatani et al, 2021[8]
CVD death	0.45	0.23-0.86	Fatani et al, 2021[8]
No CV event	1.25	-	Calculation
Probability of Recurring CV Events			
Events, probability of (per month)			
Nonfatal MI	0.000598	0.00048-0.00072	Richman et al, 2016[37]
Stroke	0.000260	0.00021-0.00031	Richman et al, 2016[37]
Heart Failure	0.000449	0.00036-0.00054	Richman et al, 2016[37]
Death after MI	0.008355	0.00668-0.01003	Richman et al, 2016[37]
Death after Stroke	0.022691	0.01815-0.02723	Richman et al, 2016[37]
Death after Heart Failure	0.009084	0.00727-0.01090	Richman et al, 2016[37]
Programmatic Costs			
Annual PPCCM Pharmacist Visits, No.	6	4-12	Dixon et al, 2020[13]
PPCCM cost per visit	$24	$19-$29	ASHP, 2019[34]
Annual Physician Visits, No.			
PPCCM Group	1	1-2	Assumption
Usual Care Visits	3	1-6	Dixon et al, 2020[13]
Physician cost per visit	$90	$72-$108	CMS, 2019[35]
Total cost of PPCCM	$702	$562-$842	ASHP, 2019[34]
Total cost of usual care	$810	$648-$972	CMS, 2019[35]
Downstream Healthcare Costs			
One-time cost of nonfatal MI	$24,089	$15,372-$32,306	Bress et al, 2017[32]
One-time cost of stroke	$15,678	$6,001-$42,039	Bress et al, 2017[32]
One-time cost of heart failure	$11,678	$11,669-$16,580	Bress et al, 2017[32]
One-time cost of CVD death	$19,514	$12,560-$33,024	Bress et al, 2017[32]
Long-term incremental cost of nonfatal MI	$685	$548-$822	Richman et al, 2016[37]
Long-term incremental cost of stroke	$408	$326-$490	Richman et al, 2016[37]
Long-term incremental cost of heart failure	$754	$603-$905	Richman et al, 2016[37]

Abbreviations Used: ASHP, American Society for Health Systems Pharmacists; CMS, Centers for Medicare and Medicaid Services; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; PPCCM, pharmacist-physician collaborative care model; TTR, time in target range; BP, blood pressure

Sensitivity Analyses

One-way deterministic sensitivity analyses were performed on all model variables to account for uncertainty in the parameter estimates for the two hypertensive management options.

Section 4.2: Results

In base case analyses, PPCCM hypertension management was associated with lower downstream medical expenditures (difference: -$173.05) when compared to usual care (Table 6). Like the decision analysis model, PPCCM hypertension management was associated with lower total program costs (difference: $-108.00) since we utilized the same time horizon and number of patients visits. For every 10,000 hypertension patients managed with PPCCM vs. usual care over

a three-year time horizon, approximately 16 CVD deaths, 51 strokes, 42 non-fatal MIs, and 48 incident HF diagnoses are expected to be averted.

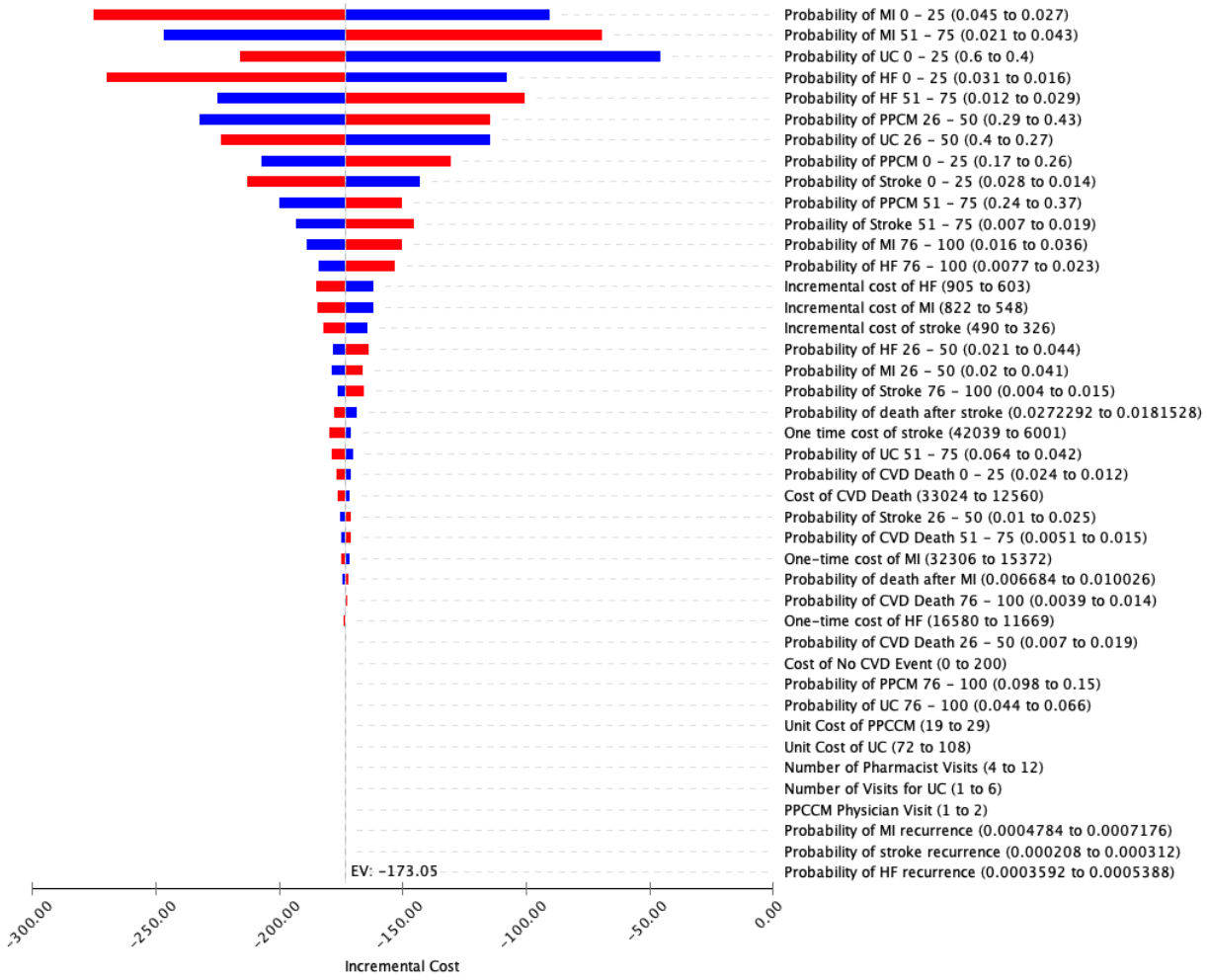
PPCCM was associated with lower downstream medical expenditures across all parameter ranges tested in the deterministic sensitivity analysis. The expected downstream healthcare savings were most sensitive to the probability of MI in TTR for systolic BP 0-25%. (Figure 5).

Table 7: Cost-Effectiveness Results of Markov Model

	PPCCM	**Usual care**	**Difference**
Cardiovascular Events			
Nonfatal MI	0.0707	0.0749	42 per 10,000
Stroke	0.0273	0.0324	51 per 10,000
Heart failure	0.0494	0.0542	48 per 10,000
CVD death	0.0388	0.0404	16 per 10,000
Total downstream healthcare expenditures	$2,084.85	$2,257.90	- $173.05
Total program costs	$702.00	$810.00	- $108.00
Cost-benefit ratio	Dominant		

Abbreviations Used: PPCCM, pharmacist-physician collaborative care model; MI, myocardial infarction; CVD, cardiovascular disease

Figure 5: Tornado Diagram of Incremental Downstream Healthcare Expenditures among Patients Receiving PPCCM vs. Usual Care for Markov Model



CHAPTER 5: DISCUSSION

Section 5.1: Main Findings

This study quantifies the cost-effectiveness of PPCCM for hypertension management to improve BP control and CV outcomes. Previous studies evaluated the impact of PPCCM on TTR for systolic BP[13] and the association between TTR for systolic BP and CV outcomes,[8] but no pharmacoeconomic analysis had combined these findings to model the cost-effectiveness of PPCCM from the payer perspective.

Both the decision analysis model and Markov model found that patients enrolled in the PPCCM incurred fewer costs associated with their direct hypertension management. The lower PPCCM program costs reflect the significantly lower cost of pharmacist time as billed by "incident to" CPT codes than physician visits for hypertension. In threshold analysis for the decision analysis model, the direct cost of provider time was lower for usual care if patients receiving usual care had fewer than two physician visits per year. However, previous studies suggests that approximately 80% of adult patients with hypertension have two or more hypertension-focused physician visits per year.[38] Nonetheless, given that the cost of PPCCM hypertension management exceeded the cost of usual care among patients with only one hypertension-related physician visit each year, payers concerned with the immediate budget impact of PPCCM reimbursement may focus on coverage for patients with at least two or three hypertension-related physician visits annually, as PPCCM is cost-neutral and cost-savings, respectively, in these populations. A second threshold analysis for the decision analysis model found that the direct program cost of PPCCM would equal that of usual care if patients met 10 times with a pharmacist annually. This well exceeds the number of previously observed pharmacist appointments for patients in two different PPCCM

programs,[13,29] suggesting that the PPCCM model is likely to save upfront hypertension management costs from the payer perspective.

While this study found that the direct intervention costs of the PPCCM were lower than that of usual care in both models, several past cost-effectiveness analyses on pharmacist-physician collaborative care for the management of hypertension found increased costs for patients in PPCCM.[29,31] A previous cost-effectiveness analysis from a societal perspective on a physician–pharmacist collaboration to improve hypertension control conducted by Polgreen et al. reported that provider costs over a 9-month period were $238.96 for PPCCM patients and $113.67 for usual care patients managed only by a physician.[29] Rather than using CPT billing codes, that study determined costs based on time spent with pharmacists and providers and their average compensation rates, likely due to its societal, rather than payer, perspective. Thus, while usual care patients had the same number of physician visits (median: three visits) as was assumed for our analyses, the cost of those three visits was calculated to be only $113.67. Kulchaitanaroaj et al. similarly reported higher costs for PPCCM in two analyses,[30,31] but, like Polgreen,[29] used time-based costing, resulting in higher provider costs among PPCCM patients ($345.25) than those in usual care ($111.84).[30] The use of CPT codes in this analysis generated higher expected costs for physician visits but more accurately reflects hypertension management costs from the payer perspective.

Current Procedural Terminology "incident-to" billing, in which the physician bills, receives payment, and reimburses the pharmacist, offers payers an opportunity to implement payment for services within existing frameworks of physician reimbursement. The use of incident-to billing and CPAs may also reduce barriers to PPCCM implementation from the pharmacy perspective, as a lack of clear reimbursement was cited by study authors as a potential barrier to

more widespread PPCCM dissemination. Physician champions for the model can help to facilitate reimbursement efforts and streamline referrals, as the pharmacists practicing under the CPAs in the collaborative care model routinely reported encountering new complaints from patients.

When compared to usual care, PPCCM was associated with lower downstream healthcare expenditures, saving an expected $162.82 over a three-year time horizon in our decision analysis model. Within our Markov model, PPCCM was associated with lower downstream healthcare expenditures, saving an expected $173.05 over a three-year time horizon. Our finding of downstream healthcare savings is consistent with the majority of economic evaluations of clinical pharmacy services for chronic disease state management that incorporate long-term healthcare expenditures.[39] Pharmacist-delivered medication management and hypertension education have consistently been shown to reduce BP,[40] which, in turn, is associated with CV events. Further, the more frequent pharmacist interactions in the PPCCM model may have facilitated the development of a stronger patient-pharmacist relationship and higher levels of trust, thereby enabling patients to better manage their chronic diseases.[41]

Our goal in conducting a decision analysis model and a Markov model was to determine if the decision analysis model substantially underestimated the value of pharmacist services due to its simplicity. Overall, both models resulted in similar expected cost savings per patient over a three-year time horizon ($162.82 for the decision analysis model vs. $173.05 for the Markov). The Markov model results did predict that PPCCM would be associated with more prevented CV events. However, given that there were few CV events over the short, 3-year time horizon, the Markov model did not result in substantially more cost savings attributed to PPCCM. Therefore, for short time horizons within the hypertension disease state, we do not expect that the use of the decision analysis model would substantially underestimate cost savings attributed to pharmacists.

For longer time horizons, where repeat CV events may come more into play, a Markov model will be able to capture more of the pharmacists' value for patient health outcomes and downstream healthcare costs.

While QALYs were not utilized as an outcome in this study, past cost-utility analyses of pharmacist-led or collaborative hypertension management have reported such programs to be cost-effective. Bryant et al. modeled 10-year health outcomes and one-year healthcare costs associated with pharmacist-led hypertension care in Black-owned barbershops in the Los Angeles Barbershop Blood Pressure Study from a healthcare sector perspective.[14] They reported a mean cost of $42,717 per QALY gained. Kulchaitanaroaj et al. similarly reported a PPCCM to be highly cost effective from the payer perspective ($26,807 per QALY gained). This study thus adds to a growing body of literature suggesting that pharmacist collaboration in the management of chronic conditions not only benefits the health outcomes of the patient but does so in a cost-effective manner.[42–44] PPCCM may have other benefits not captured in economic evaluations, including decreased physician workload and an ability to reach underserved populations.[25] There is a significant health professional shortage in rural areas and people living in these areas rely heavily on pharmacists for their healthcare needs. Therefore, pharmacists are in a unique position to fill the shortage gap and reach these underserved populations.

Section 5.2: Limitations

This research included several limitations. The TTR for systolic BP data was collected from a study with a small population of 112 patients (56 patients in both PPCCM and usual care), which may limit generalizability,[13] though the impact of the PPCCM model on hypertension management reported by Dixon et al.[13] was similar to that reported elsewhere.[17,18]

This study did not incorporate the cost of medications due to the lack of information on medication utilization among patients in the two groups. The post hoc analysis of SPRINT data by Fatani et al. indicated the number of BP-lowering agents based on the participants TTR for systolic BP,[8] but it is not known whether pharmacist involvement to promote higher TTR for systolic BP would systematically change the number of BP-lowering agents required to improve BP control. While Dixon et al. did not report specific medication utilization in the PPCCM and usual care groups,[13] the antihypertensives used by both PPCCM and usual care patients were predominately low-cost generics, minimizing the effect of drug costs on the cost-effectiveness of the program. Additionally, indirect costs were not included in our analysis due to a lack of data linking TTR for systolic BP to changes in productivity, absenteeism, and other indirect costs; similarly, utility values have not yet been established by TTR for systolic BP ranges However, given that numerous adverse CV outcomes have been associated with indirect costs of lost productivity due to morbidity and mortality,[45] it is likely that the lack of indirect costs in this study resulted in an underestimation of the downstream savings associated with PPCCM. Future research is needed to assess indirect costs and potential changes in QALYs associated with improvements in TTR for systolic BP. Furthermore, costs for payer oversight, including quality assurance (QA)/auditing of the benefit were not considered; substantial QA costs may reduce the reported savings associated with PPCCM implementation.

This study evaluated the impact of hypertension management with PPCCM on CV outcomes and associated costs over a three-year time frame. Hypertension is a chronic disease and is linked to health consequences including multiple MIs, strokes, HF exacerbations. The data we utilized for the Markov model only included the probability of recurrence of the same CV event.[37] However, a patient can experience different CV events over their lifetime. For example, a patient

can initially have a nonfatal MI and then later on in life experience a stroke or get diagnosed with HF. Therefore, our study may have underestimated the impact of PPCCM on long-term adverse CV events associated with TTR for systolic BP in hypertension management.

Finally, this study used effectiveness estimates from a real-world study on PPCCM for hypertension management.[13] However, a recent nationwide survey found that only about half of patients considered themselves likely to participate in clinical pharmacy services under a CPA, despite their perceptions that such services improve physician-pharmacist coordination.[46] If eligible patients choose not to participate in PPCCM services where available, the scope of downstream benefits realized by widespread programmatic access would be more limited than with widespread adoption.

Section 5.3: Future Directions

This research reports the cost-benefit of PPCCM versus usual care on TTR for systolic BP for four CV outcomes. The data for TTR for systolic BP and CV outcomes was from previously published data. The direct effect of PPCCM and usual care as it relates to patient outcomes and costs has not been reported. The first aim of our study with the decision analysis model was designed to evaluate only the first occurrence of CV event or death. Although for our second aim we conducted a Markov model, we were only able to find the probability of recurrence of the same CV event within published literature. Additionally, both the decision analysis model and Markov model only had a three-year time horizon to align with the payer perspective. Therefore, future research that includes a Markov model investigating different subsequent CV events over a patient's lifetime should be conducted. Also, the cost-benefit of PPCCM with the addition of hypertensive medication costs should also be explored. Different CV outcomes can result in additional hypertensive medications, which can impact the costs from the payer perspective. Since

TTR for systolic BP is a novel measure of BP control, there has not been any published literature that links TTR for systolic BP with health-related utilities. If TTR for systolic BP becomes widely accepted and studied, we can then incorporate its health-related utilities into both the decision analysis model and Markov model to better understand its impact on a patient's quality of life.

Section 5.4: Conclusion

In summary, this was the first study to evaluate the cost-effectiveness and cost-benefit of PPCCM and usual care on TTR for systolic BP in patients with hypertension. Even though the Markov model included recurrent CV events, the cost savings attributed to PPCCM over a three-year time horizon were similar between the decision analysis model and Markov model. Therefore, our findings suggest that the decision analysis model did not meaningfully underestimate the value of pharmacist services despite its simplicity relative to the Markov model. Overall, PPCCM was less costly to administer and resulted in reduced downstream adverse CV events as well as healthcare savings relative to usual care. Although further research is needed to evaluate the long-term costs and outcomes of PPCCM, payer coverage of PPCCM services may prevent future healthcare costs and improve patient CV outcomes.

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