Original Article

Cost-utility analysis of physician–pharmacist collaborative intervention for treating hypertension compared with usual care

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Objective: To estimate long-term costs and outcomes attributable to a physician–pharmacist collaborative intervention compared with physician management alone for treating essential hypertension.

Methods: A Markov model cohort simulation with a 6-month cycle length to predict acute coronary syndrome, stroke, and heart failure throughout lifetime was performed. A cohort of 399 patients was obtained from two prospective, cluster randomized controlled clinical trials implementing physician–pharmacist collaborative interventions in community-based medical offices in the Midwest, USA. Framingham risk equations and other algorithms were used to predict the vascular diseases. SBP reduction due to the interventions deteriorated until 5 years. Direct medical costs using a payer perspective were adjusted to 2015 dollar value, and the main outcome was quality-adjusted life years (QALYs); both were discounted at 3%. The intervention costs were estimated from the trials, whereas the remaining parameters were from published studies. A series of sensitivity analyses including changing patient risks of vascular diseases, probabilistic sensitivity analysis, and a cost-effectiveness acceptability curve were performed.

Results: The lifetime incremental costs were $26 807.83 per QALY (QALYs gained = 0.14). The intervention provided the greatest benefit for the high-risk patients, moderate benefit for the trial patients, and the lowest benefit for the low-risk patients. If a payer is willing to pay $50 000 per QALY gained, in 48.6% of the time the intervention would be cost-effective.

Conclusion: Team-based care such as a physician–pharmacist collaboration appears to be a cost-effective strategy for treating hypertension. The intervention is most cost-effective for high-risk patients.

Keywords: cardiovascular diseases, cost-effectiveness, cost-utility, hypertension, physician–pharmacist collaboration, quality-adjusted life years, team-based care

Abbreviations: ACS, acute coronary syndrome; BP, blood pressure; CCC, clinical classification categories; HCUP, Healthcare Cost and Utilization Project; ICD-10, the 10th revision of the International Statistical Classification of Diseases and Related Health Problems; ICERs, Incremental cost-effectiveness ratios; JNC7, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; MEPS, Medical Expenditure Panel Survey; mmHg, millimeters of mercury; QALYs, quality-adjusted life years; QPC, quality priority condition

INTRODUCTION

One in three American adults has hypertension. The combined direct and indirect cost of hypertension was estimated at $46.4 billion [1]. Three major vascular diseases attributable to hypertension include acute coronary syndrome (ACS), stroke, and heart failure [2], which cost $271.6 billion [1]. Systematic reviews and meta-analyses suggest that team-based care is a promising intervention to improve the outcomes of hypertension care [3,4], but little is known about long-term costs and effectiveness of team-based care [4,5].

A previous study evaluated the long-term effect of a pharmacist-led teamwork program treating patients with poor diabetes control by considering blood pressure (BP) as one of the outcomes [6]. Although it was shown to be likely cost-effective, the intervention had specific characteristics, namely average SBP reduction by 3 mmHg from

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the baseline and the pharmacists having their leading roles of solely managing the patients with poor control of diabetes and sending them back to the primary care team [7]. With these characteristics, generalizability to other settings was unclear and further research was needed.

Collaborative interventions between physicians and pharmacists treating patients with essential hypertension from two prospective, cluster randomized controlled clinical trials by Carter *et al.* [8,9] resulted in a higher number of patients achieving BP goals and mean SBP reduction by 9 mmHg [10] compared with physician management alone. Those trials were not restricted to only patients with diabetes, and physicians and pharmacists used face-to-face communication most of the time [8,9]. When the intervention cost was comprehensively evaluated by including costs related to physician and pharmacist time on direct patient care and collaboration, laboratory tests, medications, and overheads, the intervention was more costly than usual care in (average adjusted cost per person: \$774.90 vs. \$445.75, $P < 0.001$) [10]. The high short-term costs may be offset by improved long-term outcomes. Such potential long-term outcomes have not been evaluated. The objective of this study was to use a Markov model to estimate long-term costs and utility attributable to a physician–pharmacist collaborative intervention compared with physician management alone for treating essential hypertension.

METHODS

Background of the intervention and settings

Two physician–pharmacist collaborative interventions by Carter *et al.* [8,9] were implemented in community-based medical offices in the Midwest, USA. The interventions involved pharmacists with PharmD degrees collaborating with primary care physicians through face-to-face, phone, and/or written communication. The pharmacists and physicians were located in the same medical offices and had worked together for many years. The pharmacists provided recommendations addressing suboptimal therapy (i.e. clinical inertia) reported in the previous studies [11–14] to physicians and provided counseling about medication and lifestyle therapy to patients based on The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines [15]. The usual care groups represented hypertension managed by primary care physicians alone. We previously reported that the primary reason for the success of the intervention was that there were far more antihypertensive medications added or dosages increased in the intervention group (primarily added angiotensin-converting enzyme inhibitors, thiazide-type diuretics, calcium channel blockers, or spironolactone) [16]. The first study by Carter *et al.* implemented the intervention for 9 months, whereas the second study implemented the intervention for 6 months. Both trials had similar study methods, cohorts, care processes such as changes in medication regimens, and consistency of the collaborative intervention effects. The homogeneity test results showed that the variability in the intervention effects such as BP change was likely to be because of chance alone. Therefore, the first 6-month data of both studies were combined [17].

The follow-up studies of the trials showed that even though the intervention was finished, there was still a sustainability effect of lowered BP until 2 years [18–20]. Therefore, the cost-utility analysis for this study is based on the combined cohort and will model that the intervention effect lasted only for the first 2 years.

Markov model

A Markov model using cohort simulation was created to estimate long-term outcomes of patients with hypertension. Before entering the Markov model, patients with hypertension faced a decision node of receiving either the physician–pharmacist collaborative intervention or usual care treatment of physician management alone. From hypertension, patients may develop ACS, stroke, heart failure, death, or none (hypertension state). From each vascular event (i.e. ACS, stroke, and heart failure), patients may survive having a state of post vascular event, die during hospitalization, or die after hospitalization. From each post vascular event, patients may have a recurrence of the same disease or die. The three vascular diseases were chosen as they are strongly associated with hypertension [2] and are the major causes of cardiovascular death and costs [1].

The study used a recurring 6-month-long Markov cycle to be consistent with the intervention duration and reflect clinically meaningful occurrences of the vascular diseases [21–24]. The time horizon to evaluate long-term effects was lifetime. Shorter time horizons, including 5 and 10 years, were also performed to show some intermediate outcomes. The calculation of the Markov model was accomplished by Microsoft Excel 2013. This study was approved by the University of Iowa Institutional Review Board.

Cohorts

The base-case analysis (Table 1) used the subset of the combined cohort of Carter's trials [8,9] by including patients 30–74 years old with complete 6-month measures of healthcare utilization. The criteria were chosen to be consistent with a previous study evaluating the intervention cost [10] and to match risk prediction ability of risk estimation algorithms and equations. The base-case cohort included 354 patients without any previous cardiovascular conditions and 45 patients with cardiovascular conditions before enrolling in the trials. The cohort of 399 patients originally from both intervention and usual care groups from the trials was utilized in simulations to evaluate long-term costs and utilities. The whole cohort of 399 patients was assigned to be a simulated intervention group and a simulated usual care group one at a time. The difference between the two cohorts was SBP at 6 months.

Six hypothetical cohorts with modified risk profiles were created (Table 1) to explore heterogeneous effects of the intervention on individuals who had high and low risks of vascular diseases for sensitivity analyses. Unmodified risk factors had the same values as in the base-case cohort. The modified values of cholesterol and BMI were assigned randomly by a uniform distribution by SAS version 9.2 software (SAS Institute Inc., Cary, North Carolina, USA).

TABLE 1. Modified risk factors in the base-case and sensitivity cohorts

No.	Cohort name	Modified risk factors		
		% Of patients with diabetes	% Of patients who are current smokers	Cholesterol profiles/BMI
1	Base-case cohort from the combined Carter's trials	31.3	22.6	Average TC = 196.0 mg/dl; Average HDL = 49.6 mg/dl; Average BMI = 32.9 kg/m^2
2	High risk 1	100	As in the base-case cohort	As in the base-case cohort
3	High risk 2	100	100	As in the base-case cohort
4	High risk 3 (highest risk)	100	100	TC = 250–280 mg/dl; HDL = 25–34 mg/dl; BMI = 30–39 kg/m^2
5	Low risk 1	0	As in the base-case cohort	As in the base-case cohort
6	Low risk 2	0	0	As in the base-case cohort
7	Low risk 3 (lowest risk)	0	0	TC = 110–160 mg/dl; HDL = 60–70 mg/dl; BMI = 19–25 kg/m^2

TC, total cholesterol.

The intervention effectiveness and sustainability

SBP at 6 months was calculated from the trials [8,9] by subtracting the average SBP reduction from each patient's SBP at baseline. The average SBP reductions in the usual care and intervention groups were 6.8 and 18.8 mmHg, respectively, in the original 6-month collaboration trial [9]. The average SBP reduction was assumed to be maintained for only the first 2 years as a worst case scenario after the 6-month intervention was discontinued. This assumption was based on a recent prospective study evaluating the effect of a physician–pharmacist collaborative intervention [20] and 27-month and 24-month retrospective follow-up studies from the two original trials [18,19]. There are no data for past 24 months following the discontinuation of a pharmacist intervention. Therefore, it was assumed to deteriorate evenly during year 3 (15.8 mmHg), year 4 (12.8 mmHg), and year 5 (9.8 mmHg) and, eventually, to become equal to that in the usual care group for the remaining years based upon the 27-month and 24-month follow-up studies from the two original trials [18,19].

Transition probabilities

To estimate transition probabilities of ACS, stroke, and heart failure given hypertension, 34 published studies of vascular risk algorithms/equations were reviewed after searching from PubMed, Web of Science, and Google Scholar. Five were chosen (Table 2) on the basis of inclusion criteria: whether the risk models predicted incident or subsequent cases of vascular diseases, risk factors required by the risk estimation models were available from Carter's trials, and prediction ability of the risk models. The probabilities of the vascular events were estimated by applying the characteristics of the cohorts to the risk algorithms/equations. Framingham risk equation [25] estimated the vascular risks for 354 patients without any previous cardiovascular comorbidities, whereas the other four risk algorithms/equations [26–29] were used for 45 patients with previous cardiovascular conditions. These risk estimation algorithms/equations were validated and had reasonable predictability of vascular risks. The risk factors used by those algorithms/equations included SBP at 6 months, age, sex, total cholesterol, HDL cholesterol, smoking status, diabetes status, BMI, history of cardiovascular conditions, race, heart rate, BP-lowering medication use, and creatinine levels. SBP at 6 months resulting from the intervention was used for the first 2 years, and deteriorating SBP was used for the next 3 years. After that, there was no difference in SBP between the intervention and usual care simulations. After 5 years, patient age was the only factor that increased during each Markov cycle to reflect the age-dependent probabilities. Transition probability estimations by the risk algorithms/equations were accomplished by the use of SAS version 9.2 software.

The remaining transition probabilities of mortality and recurrence of vascular diseases were obtained from published studies and were the same for both the intervention and usual care simulations. Electronic searches of PubMed, Web of Science, and Google Scholar databases were conducted, and the quality assessment tool for observational cohorts and cross-sectional studies was utilized as guidance for study selection [30]. Probabilities of death given hypertension were estimated from the age-specific mortality rates of essential hypertension (the 10th revision of the International Statistical Classification of Diseases and Related Health Problems code of I10) [31], whereas the remaining probabilities of recurrence and mortality were assumed to be constant over time. The mortality rates of each vascular disease were obtained for the time of hospitalization used for the state of death during hospitalization at the beginning of the Markov cycle and the follow-up period used for the state of death after hospitalization at the end of the Markov cycle. In addition, mortality rates of individuals with a history of those diseases (i.e. post ACS, post stroke, and post heart failure) were estimated by multiplying the mortality rates during the follow-up period with the hazard ratios of mortality of the respective vascular events.

Costs

Direct medical costs were estimated on the basis of a payer perspective (Table 2). All analyses used a 3% discount rate of monetary values recommended by the Panel on Cost Effectiveness in Health and Medicine [32]. All costs presented were adjusted to the 2015 US dollar value using overall medical care price indexes in February obtained from the Bureau of Labor Statistics [33].

Using the information from their own trials [10], treatment costs of the intervention were estimated from time

TABLE 2. Input parameters

Input parameters	Point estimate		Posterior distribution parameter/SE		Distribution in PSA[a]	Reference(s)	Note
	The intervention group	The usual care group	The intervention group	The usual care group			
Probabilities							
HTN[b] to HTN	0.99149	0.99077	992.49	991.77	Dirichlet		
HTN to ACS[c]	0.00231	0.00259	3.31	3.59	Dirichlet	Framingham risk equations by D'Agostino *et al.* [25] to predict ACS among patients who had no previous cardiovascular conditions	
						Framingham risk equations by D' Agostino *et al.* [26] to predict ACS among patients with previous cardiovascular conditions	
HTN to stroke	0.00345	0.00385	4.45	4.85	Dirichlet	Framingham risk equations by D'Agostino *et al.* [25] to predict stroke among patients who had no previous cardiovascular conditions	
						Essen Stroke Risk Score (ESRS) by Diener *et al.* [27] to predict stroke among patients with previous cardiovascular conditions	
HTN to heart failure	0.00274	0.00279	3.74	3.79	Dirichlet	Framingham risk equations by D'Agostino *et al.* [25] to predict heart failure among patients who had no previous cardiovascular conditions	
						The Atherosclerosis Risk in Communities (ARIC) by Agarwal *et al.* [28] to predict incident heart failure among patients with previous other cardiovascular conditions	
						An algorithm by Krumholz *et al.* [29] to predict readmission for heart failure among patients with a history of heart failure	
HTN to death	0.000001		1.00	1.00	Dirichlet	National Center for Health Statistics [31]	The estimate represented the mortality of essential hypertension and hypertensive renal disease
ACS to death	0.10390		0.01082		Beta	Chen *et al.* [45]	
ACS to death at hospitals	0.09710				Beta	Chen *et al.* [45]	This parameter was not included in the probability sensitivity analysis
Stroke to death	0.15150		0.00335		Beta	Lee *et al.* [46]	
Stroke to death at hospitals	0.10770				Beta	Lee *et al.* [46]	This parameter was not included in the probability sensitivity analysis
Heart failure to death	0.13757		0.00054		Beta	Chen *et al.* [47]	
Heart failure to death at hospitals	0.05100				Beta	Goldberg *et al.* [48]	This parameter was not included in the probability sensitivity analysis
Post ACS to ACS	0.06054		0.00205		Beta	Brown *et al.* [49]	
Post ACS to death	0.18078		0.01114		Beta	Brown *et al.* [49], Battes *et al.* [50]	A hazard ratio of 1.74 was multiplied by the probability of death given ACS
Post stroke to stroke	0.01414		0.00110		Beta	Lee *et al.* [46]	
Post stroke to death	0.17725		0.00340		Beta	Lee *et al.* [46], Rajan *et al.* [51]	A hazard ratio of 1.17 was multiplied by the probability of death given stroke
Post heart failure to heart failure	0.25696		0.00494		Beta	Korves *et al.* [52]	
Post heart failure to death	0.24762		0.02125		Beta	Chen *et al.* [47], Norton *et al.* [53]	A hazard ratio of 1.80 was multiplied by the probability of death given heart failure assuming that patients had stage-B heart failure and moved to stage-C heart failure
Costs at 6 months adjusted to 2015 US dollars							
Hypertension treatment	$857.23	$493.11	$214.61		Gamma	Kulchaitanaroaj *et al.* [10]	

TABLE 2 (*Continued*)

Input parameters	Point estimate		Posterior distribution parameter/SE		Distribution in PSA[a]	Reference(s)	Note
	The intervention group	The usual care group	The intervention group	The usual care group			
Hypertension treatment after the 6-month intervention completed	$599.19	$493.11	$214.61		Gamma	Kulchaitanaroaj *et al.* [10]	
ACS	$23 047.81		$3457.17		Gamma	H-CUP Projections [34], Chen *et al.* [45], The Merck Manual of Diagnosis and	Hospitalization cost: 11 237.37; Physician fees: $3156.95; Outpatient cost: $1970.92; Medication cost: $1681.84
						Therapy [35], Medicaid physician fees from Arizona [39], Medicaid-to-Medicare fee index [40]	Home-healthcare cost: $2901.40; Nursing home cost: $2099.33; SE was calculated from 15% of the costs
Stroke	$27 138.39		$4070.76		Gamma	H-CUP Projections [34], Godwin *et al.* [54], Scientific American Surgery [36]	Hospitalization cost: $8725.49; Physician fees: $2944.81
						Medicaid physician fees from Arizona [39], Medicaid-to Medicare fee index [40], Demaerschalk *et al.* [55]	Outpatient cost and home-healthcare: $6662.22; Medication cost: $3073.20; Nursing home cost: $5732.67; SE was calculated from 15% of the costs
Heart failure	$10 578.94		$1586.84		Gamma	H-CUP Projections [34], Korves *et al.* [52], Scientific American Surgery [37], Medicaid physician fees from Arizona [39]	Hospitalization cost: $6345.81; Physician fees: $514.89; Outpatient cost: $517.51; Medication cost: $684.19; Home-healthcare cost: $1029.50
						Medicaid-to-Medicare fee index [40], Braunschweig *et al.* [56]	Nursing home cost: $1487.05; SE was calculated from 15% of the costs
Post ACS	$8653.50		$1298.02		Gamma	Chen *et al.* [45]	Outpatient cost + medication cost + home-healthcare cost + nursing home cost
Post heart failure	$3718.25		$557.74		Gamma	Korves *et al.* [52], Braunschweig *et al.* [56]	
Post stroke	$15 468.10		$2320.21		Gamma	Godwin *et al.* [54], Demaerschalk *et al.* [55]	
Utility weights							
Hypertension	0.787		0.0001		Beta	Sullivan *et al.* [41]	Hypertension was identified by QPC[d] representing conditions present at any time in the past
ACS	0.724		0.0008		Beta	Sullivan *et al.* [41]	This is the utility of coronary heart disease identified by CCC[e] reflecting conditions generally present during the individual's participation in the survey
Stroke	0.655		0.0009		Beta	Sullivan *et al.* [41]	Stroke was identified by CCC reflecting conditions generally present during the individual's participation in the survey
Heart failure	0.636		0.0010		Beta	Sullivan *et al.* [41]	Heart failure was identified by CCC reflecting conditions generally present during the individual's participation in the survey
Post ACS	0.725		0.0002		Beta	Sullivan *et al.* [41]	This is the utility of coronary heart disease identified by QPC representing conditions present at any time in the past
Post stroke	0.694		0.0002		Beta	Sullivan *et al.* [41]	Stroke was identified by QPC representing conditions present at any time in the past
Post heart failure	0.636		0.0002		Beta	Sullivan and Ghushchyan [42]	The utility was obtained from heart failure identified by International Classification of Diseases-9 (ICD-9)

SE, standard error.
[a]PSA, probability sensitivity analysis.
[b]HTN, hypertension.
[c]ACS, acute coronary syndrome.
[d]QPC, quality priority condition.
[e]CCC, clinical classification categories.

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. Specialists included cardiologists and nephrologists. It was assumed that after the completion of the 6-month intervention, patients in the intervention simulation continued to receive usual care but still took antihypertensive medications that were prescribed during the intervention. Thus, the costs subsequent to the withdrawal of the intervention included the *usual care* costs of physician time, laboratory tests, and overhead and the *intervention* costs of antihypertensive medications. Treatment costs in the usual care group included the same elements as in the intervention group except that they excluded the pharmacist time cost and the cost related to collaboration activities.

Costs of each vascular disease incorporated the cost of hospitalization, physician fees during hospitalization, outpatient visits after hospitalization, medications after hospitalization, home healthcare, and nursing home care. Costs of the post vascular events included costs related to outpatient visits, medications, home healthcare, and nursing home care.

Hospitalization costs were obtained from the Healthcare Cost and Utilization Project (HCUP) [34]. The study used the average total hospital costs projected for year 2012, which did not include physician fees. Therefore, physician fees were added into the hospitalization costs by using data from published articles. The fees were estimated from assumed diagnoses and procedures for one-time hospitalization and inpatient stay. Average length of stay was obtained from HCUP (2.4 days for ACS, 2.9 days for stroke, and 2.7 days for heart failure) [34], and it was assumed that there was one physician visit per day. The physician fee for a 55-min inpatient visit was $114.53. Diagnoses and procedures for ACS included stress testing with echocardiography or imaging, coronary angiography, percutaneous coronary intervention, and insertion of stent [35]. For stroke, those included computed tomography and MRI, assumed 50% chance of performing surgical evacuation of hematoma, and assumed 50% chance of thrombolysis [36]. For heart failure, it was assumed that 88% of the time patients had an emergency department visit, and 12% of the time they received an implantable defibrillator [37,38]. Physician fees for these procedures were obtained from publicly available Arizona Medicaid fees [39]. These Medicaid physician fees were converted to national Medicare physician fees using the Medicaid-to-Medicare fee index [40].

Outpatient and medication costs after hospitalization were the postevent costs of vascular diseases and were obtained from published studies with estimates based on Medicare reimbursements. The cost was assumed to distribute evenly every month when estimating 6-month costs from the published statistics. The costs of home healthcare and nursing home care were obtained from published studies or calculated from the published fractions of the total costs.

Outcomes

Quality-adjusted life years (QALYs) were selected to be a primary outcome of the intervention to represent both survival and health-related quality of life. The US community preference-based EQ-5D index scores or utility weights associated with each health state were obtained from a single study that was a nationally representative catalog using the information from the Medical Expenditure Panel Survey in the United States [41,42]. The utility weights for the vascular diseases were taken from the clinical classification categories reflecting conditions generally present during the individual's participation in the MEPS, whereas most of the post states of vascular diseases were obtained from quality priority condition representing conditions present at any time in the past [41].

A secondary outcome was the number of prevented vascular disease cases. This measure represents the health outcome attributable to hypertension control. The number of cases of each vascular disease between the intervention and the usual care simulations were discounted and compared. All outcomes were discounted by a 3% rate [32].

Base-case and sensitivity analyses

The base-case analysis and sensitivity analyses involved a scenario in which patients received the one-time intervention for 6 months. The scenario of deterioration of SBP reduction was conservative and favored usual care. Incremental cost-effectiveness ratios (ICERs) were estimated at 5-year, 10-year, and lifetime horizons. Sensitivity analyses were conducted by changing the probabilities of vascular events given hypertension because they were the main drivers of differences between the two treatments.

To assess uncertainty of the model parameters, a probabilistic sensitivity analysis that altered all parameters simultaneously given specified distributions (Table 2) was run 1000 times. A cost-effectiveness acceptability curve was performed to suggest the probability that the intervention was cost-effective given different values of willingness to pay ranging from $50 000 to $100 000 per QALY gained [7]. If the ICERs from the 1000-time simulation were less than the willingness to pay thresholds, the intervention would be considered cost-effective.

RESULTS

The base-case cohort included 399 patients. The mean age was 56.7 years (range 30–74), and approximately 47.9% of the patients had one comorbidity. Their risk profile is exhibited in Table 1. On average, an individual from this cohort took 1.4 medications and had a BP of 151.4 mmHg for SBP and 86.9 for DBP at baseline. The majority were white (86%), female (57.4%), married or living with a partner (63.2%) and did not drink alcohol (84.5%).

Table 3 shows the vascular risk reductions in the base-case cohorts. The base-case analysis demonstrated that the average discounted costs of the hypertension treatment and vascular diseases in the intervention simulation were greater than the costs in the usual care simulation by $3817.54 per person over a lifetime horizon (Table 4). The intervention compared with usual care increased QALYs by 0.14 per person. The ICER of the physician–pharmacist collaborative intervention was $26 807.83 per QALY gained. In shorter horizons of 5 and 10 years, the ratios were $78 547.07 and $39 084.65, respectively.

TABLE 3. Probabilities of vascular events given the state of hypertension of the base-case cohorts for the first 5 years

Year	Probabilities of the vascular events given hypertension state						Absolute risk reduction by the intervention		
	The intervention simulation			The usual care simulation					
	ACS (%)	Stroke (%)	Heart failure (%)	ACS (%)	Stroke (%)	Heart failure (%)	ACS (%)	Stroke (%)	Heart failure (%)
0	0.2311	0.3450	0.2744	0.2590	0.3846	0.2794	−0.0279	−0.0396	−0.0050
0.5	0.2370	0.3468	0.2754	0.2660	0.3868	0.2807	−0.0290	−0.0400	−0.0053
1.0	0.2430	0.3487	0.2765	0.2731	0.3891	0.2820	−0.0301	−0.0404	−0.0055
1.5	0.2491	0.3506	0.2776	0.2804	0.3915	0.2833	−0.0313	−0.0409	−0.0057
2.0	0.2555	0.3526	0.2788	0.2879	0.3939	0.2847	−0.0324	−0.0413	−0.0059
2.5	0.2700	0.3680	0.2814	0.2956	0.3964	0.2861	−0.0256	−0.0284	−0.0047
3.0	0.2769	0.3702	0.2827	0.3034	0.3989	0.2876	−0.0265	−0.0287	−0.0049
3.5	0.2929	0.3777	0.2857	0.3115	0.4015	0.2891	−0.0186	−0.0238	−0.0034
4.0	0.3004	0.3801	0.2872	0.3197	0.4041	0.2906	−0.0193	−0.0240	−0.0034
4.5	0.3180	0.3959	0.2903	0.3281	0.4068	0.2922	−0.0101	−0.0109	−0.0019
5.0	0.3262	0.3985	0.2919	0.3367	0.4096	0.2938	−0.0105	−0.0111	−0.0019
5.5[b]	0.3454	0.4125	0.2954	0.3454	0.4125	0.2954	0.0000	0.0000	0.0000

[a]ACS, acute coronary syndrome.
[b]For year 5.5 and onward, both intervention and usual care simulations had the same probabilities yielding 0% difference in absolute risk reduction.

Moreover, with the lifetime horizon, the discounted number of prevented ACS cases attributable to the intervention was 140 per 100 000 populations and that of stroke was 210 per 100 000 populations. However, the benefit of heart failure cases prevention due to the intervention finished at 21.5 years. The discounted numbers of prevented ACS, stroke, and heart failure cases due to the intervention were more evident in earlier years, at the time when the intervention contributed to greater BP reduction than the usual care. For instance, the number of prevented ACS, stroke, and heart failure cases at 5 years was 246, 285, and 49 cases per 100 000 populations.

The intervention showed heterogeneous effects by reducing risks of vascular diseases to a higher extent for individuals with higher risk, and it lowered the risks to a smaller extent for those with smaller risk. The ICERs at 5

TABLE 4. Incremental cost-effectiveness ratios of all cohorts

	Cohort						
	HR3[d]	HR2[c]	HR1[b]	Base case	LR1[e]	LR2[f]	LR3[g]
Horizon: lifetime							
Total costs of the intervention simulation	$54 743.01	$53 181.15	$52 012.21	$50 811.97	$50 160.96	$49 561.77	$47 982.68
Total costs of the usual care simulation	$52 086.58	$50 025.89	$48 553.64	$46 994.42	$46 075.92	$45 342.24	$43 411.44
QALYs of the intervention simulation	21.13	24.34	26.48	29.03	30.85	31.72	34.06
QALYs of the usual care simulation	20.89	24.17	26.33	28.89	30.72	31.60	33.95
Incremental costs (per person)	$2656.43	$3155.26	$3458.57	$3817.54	$4085.04	$4219.53	$4571.24
QALY gained (per person)	0.23	0.17	0.15	0.14	0.13	0.12	0.11
ICER[a]	$11 493.20	$18 535.20	$22 807.89	$26 807.83	$30 444.66	$34 115.19	$43 330.85
Horizon: 5 years							
Total costs of the intervention simulation	$12 783.87	$11 129.06	$10 338.21	$9534.72	$9010.87	$8826.34	$8482.90
Total costs of the usual care simulation	$12 084.22	$10 211.27	$9357.83	$8508.30	$7947.63	$7736.22	$7348.83
QALYs of the intervention simulation	7.7197	7.7999	7.8365	7.8787	7.9084	7.9164	7.9328
QALYs of the usual care simulation	7.6897	7.7810	7.8209	7.8657	7.8970	7.9063	7.9247
Incremental costs (per person)	$699.65	$917.79	$980.38	$1026.42	$1063.25	$1090.12	$1134.07
QALY gained (per person)	0.0299	0.0189	0.0155	0.0131	0.0114	0.0101	0.0080
ICER	$23 365.85	$48 538.47	$63 076.00	$78 547.07	$93 232.95	$107 922.82	$141 476.64
Horizon: 10 years							
Total costs of the intervention simulation	$25 313.25	$21 756.38	$19 984.11	$18 237.11	$17 117.39	$16 673.21	$15 830.95
Total costs of the usual care simulation	$24 025.98	$20 208.23	$18 350.28	$16 535.35	$15 360.48	$14 880.67	$13 975.21
QALYs of the intervention simulation	12.7598	13.1426	13.3186	13.5154	13.6511	13.6915	13.7757
QALYs of the usual care simulation	12.6639	13.0803	13.2676	13.4718	13.6126	13.6572	13.7486
Incremental costs (per person)	$1287.27	$1548.15	$1633.84	$1701.76	$1756.91	$1792.54	$1855.74
QALY gained (per person)	0.0959	0.0623	0.0510	0.0435	0.0385	0.0343	0.0272
ICER	$13 418.89	$24 842.51	$32 007.49	$39 084.65	$45 636.55	$52 190.60	$68 298.26

[a]ICERs (incremental cost-effectiveness ratios) were calculated from the estimates with four decimal points.
[b]HR1: high-risk cohort 1 assumed that all patients were diabetic.
[c]HR2: high-risk cohort 2 assumed that all patients were diabetic and smoked.
[d]HR3: high-risk cohort 3 assumed that all patients were diabetic, smoked, and had poor cholesterol or were obese.
[e]LR1: low-risk cohort 1 assumed that none of the patients were diabetic.
[f]LR2: low-risk cohort 2 assumed that no patients were diabetic and no patients smoked.
[g]LR3: low-risk cohort 3 assumed that no patients were diabetic, no patients smoked, and all patients had good cholesterol or good BMI.

years, 10 years, and lifetime (Table 4) show that the highest risk cohort had the lowest ICER, the lowest risk cohort had the highest ICER, and the base case had the ICER falling in between. This suggests that the intervention was the most cost-effective for the high-risk patients, was moderately cost-effective for the patients who had moderate levels of risk factors, and was less cost-effective for low-risk patients.

For the multivariable sensitivity analysis, the cost-effectiveness plane with the incremental costs as a *Y* axis and the incremental QALYs as an *X* axis revealed that the joint coordinates were in all quadrants. Almost half of the plots (49.6%) were in the north-east (31.5%) and south-east (18.1%) quadrants meaning that the intervention was likely to be more effective and costlier, and more effective and less costly, respectively. In 30.4% of the plots, the intervention was less effective and costlier. At the willingness-to-pay threshold at $50 000, the intervention was assessed to be cost-effective approximately 48.6% of the time.

DISCUSSION

The current study evaluated the long-term costs and outcomes including QALYs and prevented vascular events attributable to a 6-month physician–pharmacist collaborative intervention for treating essential hypertension compared with usual care. Despite the deteriorating effect 5 years after the intervention was stopped and the lack of effect thereafter, the benefit of preventing vascular disease and saving lives of patients with hypertension from earlier years still had a significant effect throughout lifetime. With the lifetime horizon and the widely used willingness to pay $50 000–$100 000 [7], the intervention appeared to be cost-effective because the ICERs from the base-case and sensitivity analyses were under $50 000. The findings were consistent across all hypothetical cohorts for a lifetime horizon.

With the scenario of a deteriorating effect 2 years after the intervention was stopped, this study presented the worst case scenario. The intervention may have had further sustainability to maintain SBP reduction for more than 2 years based on the sustainability trends reported in the follow-up studies [18–20], and the ICER would then be lower. In addition, in the real-world office practice, patients whose BP deteriorated after the intervention stopped might well have been referred back to the pharmacist for further adjustments of the medication regimen. Without more long-term data and a desire not to add more assumptions, the 2-year sustainability was used. In addition, the costs used in the present analysis were relatively modest but are similar to those found in a larger multicentered trial of a physician–pharmacist collaborative intervention [43]. Moreover, the intervention simulation had higher intervention costs due to the lifetime medications although there was no BP reduction. The analysis has taken into account the problems of adherence to medications that may occur when using medications for a long time.

Compared with the pharmacist–nurse intervention [44], this study had lower absolute risk reductions for ACS, stroke, and heart failure and did not find cost savings as reported in the previous study. Our absolute risk reductions were around the lower bounds of the previously reported ranges. The extrapolation methods to calculate the vascular risks were different. Their risks of vascular diseases were derived from a larger pool of eight randomized trials, whereas our study maintained high internal validity by using the patient characteristics from our original data. Moreover, the base-case cohort of this study tended to be a healthy cohort, which may explain why the absolute risk reduction was not very high. Therefore, the estimates of this study may be the lower bound effects of the intervention.

Another previous study evaluating a primary-care-team intervention led by a clinical pharmacist for managing type-2 diabetes and other outcomes such as high BP found that the team-based care was a dominant strategy (less costly and more effective) compared with usual care of primary care physicians in a 10-year evaluation period [6]. The results from this study show that the intervention was more costly and more effective at 10 years. The difference between the previous study and this study could be the different scenarios of the absolute risk reductions of vascular events. In the previous study, the absolute risk reductions between the team-based care and the usual care increased over time (e.g. fatal coronary heart disease risk was 0.1% in year 1 and that was 4.6% in year 10), whereas those in the present study were different only the first 5 years and then were equal for the remaining years through lifetime. However, the results suggested the similar direction. That is, the team-based care including pharmacists appeared to be cost-effective when a longer time horizon is considered. This study found that over a lifetime, the ICERs were less, and this was applied for both high-risk and low-risk patients.

Some limitations of the study are recognized. Because the intervention pharmacists had been working with physicians for many years in the same offices, and the sample was from community-based medical offices, the results cannot be extrapolated to different settings or conditions. Moreover, this analysis was an ad-hoc analysis of the original trials, clinical data, which could have improved the prediction of cardiovascular diseases in newer risk prediction models and algorithms, were not available. However, the risk prediction systems chosen in this study were at their possible best. Furthermore, the Markov model did not account for a complex disease pathway such as the possibility of a patient with ACS having a recurrent ACS, stroke, heart failure, the same condition, or die in the same cycle. Rather, the present model simplified the pathway; thus a patient with ACS may have a recurrent ACS, the same condition, or die. Last, a model simulation offers reasonable estimation of long-term effect of a team-based care intervention for decision makers in a timely manner, but it probably will not replace a prospective longitudinal study. Further studies may try to evaluate a team-based care intervention in different settings, scenarios, or patient groups to compare the results, or conduct a long-term study.

In conclusion, team-based care such as a physician–pharmacist collaboration appears to be a cost-effective strategy for treating hypertension for all patients with different levels of risks in a lifetime horizon. The intervention is the most cost-effective for high-risk patients.

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Reprints will not be made available.

Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

The study by Kulchaitanaroaj, *et al.* estimated the long-term costs and outcomes attributable to a physician-pharmacist collaborative intervention compared with physician management alone for treating essential hypertension. Using mathematical modelling for lifetime the authors reported that the high-risk patients may benefit from this collaboration more than the low-risk patient. The model is limited a little bit to the USA healthcare system, where the pharmacist working at the hospital can diagnose and treat patients and it cannot be extrapolated to other healthcare systems. The collaboration of hospital healthcare providers and hypertension specialists with community pharmacists in Europe will probably also be useful to increase patient compliance to treatment and new studies in the field are also needed.

Reviewer 2

Team-based care such as a physician-pharmacist collaboration appears to be a cost-effective strategy for treating hypertension for all patients with different levels of risks in a lifetime horizon. The intervention is the most cost-effective for high-risk patients. The design of the study demonstrate that this topic is difficult to study with regards to approval of patients and that there is a need for quantification of the judgment if doses of drugs can be increased, kept constant or increased.