Supplementary methods

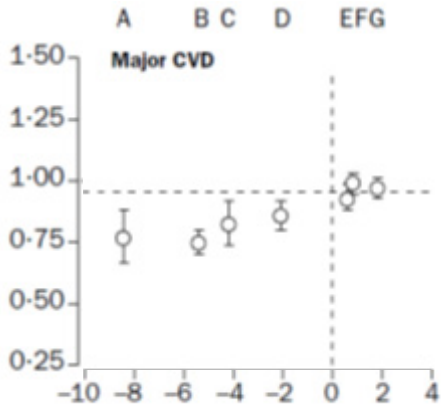
Blood pressure and cardiovascular disease

Two options were considered for assessing the impact of blood pressure change on cardiovascular disease (CVD) outcomes: Framingham risk equations, and Blood pressure lowering (BPL) Treatment Trialists' Collaboration published results.

For the Framingham risk equation option, the 30-year risk equations were simply re-calculated based on the blood pressure associated with the pharmacist intervention, and all other characteristics consistent with the control group.

For the BPL Treatment Trialists' Collaboration option, the relationship described in Figure S 1, was extrapolated to generate a relative risk of CVD for a given blood pressure change. The data in Figure S 1 was digitized, and a linear regression model was fit to the resulting data points. The fitted regression model intercept was 0.976 (standard error [SE] = 0.036), and linear systolic blood pressure coefficient of 0.045 (SE = 0.008) per mmHg. Using this regression equation, the estimated relative risk was 0.499 for an 18.3 mmHg decrease in systolic blood pressure, and 0.775 for a 7.6 mmHg decrease in systolic blood pressure. In probabilistic sensitivity analysis, the variance-covariance matrix of regression parameters was used to sample stochastic values. The correlation between the two fitted regression coefficients was 0.569.

Figure S 1: Observed relationship between blood pressure difference and relative risk for major cardiovascular disease from Blood Pressure Lowering Treatment Trialists' Collaboration[1]



Blood pressure and renal disease

For the risk of end stage renal disease (ESRD), reported incidence by blood pressure category (Table S 1) was initially used to derive an annual probability of disease for baseline treatment characteristics. A regression model was fit using the midpoint of each category to extrapolate a continuous relationship between systolic blood pressure and incidence of ESRD, with an estimated coefficient of 0.197 (SE=0.073) per mmHg. Incidence per 100,000 person-years was then converted to an annual probability by assuming an exponential distribution.[2] Using this methodology, the estimated annual probability of ESRD for a baseline systolic blood pressure of 149.5 was 0.000194.

To further estimate the relationship between systolic blood pressure changes and impact on ESRD, the reported relative risk by blood pressure category (Table S 1) was extrapolated to derive a relationship between blood pressure on a continuous scale and risk of disease.3 The continuous relationship was derived by assuming the midpoint of each category with respect to systolic blood pressure, and a linear regression model was fit. The resulting equation yielded a systolic blood pressure coefficient of 0.020 (SE = 0.007). Based on this equation, the relative risk of ESRD relative to optimal blood pressure was 2.57 for the control group and 1.98 for the intervention group, resulting in a relative risk of 0.771 for the intervention group relative to the control group.

Table S 1: Relationship between blood pressure category and relative risk of end stage renal disease incidence[3]

Category (JNC V)	Incidence per 100,000	95% confidence interval for incidence	Relative risk (vs. Optimal)	95% confidence interval for relative risk
Optimal	4.5	3.6-5.8	1.00	NA
Normal, not optimal	9.3	7.5-11.5	1.61	1.27-2.05
High normal	12.9	10.3-16.0	1.97	1.54-2.52
Hypertension				
Stage 1	19.5	15.8-24.1	2.57	2.06-3.22
Stage 2	31.7	24.6-41.0	3.82	2.97-4.92
Stage 3	34.5	24.7-48.0	3.88	2.82-5.33
Stage 4	43.7	26.9-71.1	4.18	2.59-6.76

JNC V = Fifth Joint National Committee report[4]

Supplementary Results

The model base case and all one-way sensitivity analyses considered indicated that the pharmacist intervention was a dominant strategy, i.e. less expensive and associated with better health outcomes. However, the magnitude of the benefits varied with specific sensitivity analyses. More detailed results are presented below with respect to cardiovascular events (Table S 2), ESRD incidence (Table S 3), life years (Table S 4), quality-adjusted life years (QALYs) (Table S 5), and costs (Table S 6).

With the exception of the sensitivity analysis regarding age-specific background costs, all sensitivity analyses impact the pharmacist intervention arm only, with the usual care outcomes remaining constant. The most notable impact on effectiveness results was associated the assumption that the intervention would have no additional benefits after three years. In this sensitivity analysis, the reduction in CVD events dropped from 0.21 to 0.01. Undiscounted life years gained were reduced from 0.8 to 0.1 in this analysis, while undiscounted QALYs gained were reduced from 0.9 to 0.1. Other sensitivity analysis results were closer to base case results, including a scenario in which the efficacy of the intervention was reduced by 50% after three years, and the two treatment arms were assumed to be equivalent after ten years. Thus, while the magnitude of clinical and cost benefits vary based on assumption, the overall interpretation of a cost-effective and potentially cost-saving intervention with clinical benefits was consistent across all plausible scenarios considered.

Table S 2: Cardiovascular events in base case and one-way sensitivity analyses

	Cardiovascular events		
	Usual care	Pharmacist intervention	Difference
Base case	0.61	0.40	-0.21
Framingham risk equations for blood pressure impact	0.61	0.57	-0.05
Blood pressure reduction based on partial intervention	0.61	0.53	-0.08
Age-specific background cost estimates	0.61	0.40	-0.21
10-year time horizon	0.32	0.17	-0.15
5-year time horizon	0.09	0.04	-0.04
Doubled cost of pharmacist intervention plus $33.33 per patient training costs incorporated	0.61	0.40	-0.21
Reduced background annual medical costs in intervention group	0.61	0.40	-0.21
Efficacy reduced: 100% after year three	0.61	0.50	-0.11
Efficacy reduced: 50% after year three, 100% after year ten	0.61	0.57	-0.04
"Optimistic" scenario regarding intervention costs	0.61	0.40	-0.21

Table S 3: End-stage renal disease (ESRD) incidence in base case and one-way sensitivity analyses

	ESRD events		
	Usual care	Pharmacist intervention	Difference
Base case	0.0039	0.0031	-0.0008
Framingham risk equations for blood pressure impact	0.0039	0.0030	-0.0009
Blood pressure reduction based on partial intervention	0.0039	0.0039	0.0000
Age-specific background cost estimates	0.0039	0.0031	-0.0008
10-year time horizon	0.0017	0.0013	-0.0014
5-year time horizon	0.0008	0.0006	-0.0002
Doubled cost of pharmacist intervention plus $33.33 per patient training costs incorporated	0.0039	0.0031	-0.0008
Reduced background annual medical costs in intervention group	0.0039	0.0031	-0.0008
Efficacy reduced: 100% after year three	0.0039	0.0038	-0.0001
Efficacy reduced: 50% after year three, 100% after year ten	0.0039	0.0030	-0.0009
"Optimistic" scenario regarding intervention costs	0.0039	0.0031	-0.0008

Table S 4: Life years in base case and one-way sensitivity analyses

	Life years		
	Usual care	Pharmacist intervention	Difference
Undiscounted			
Base case	20.0	20.7	0.8
Framingham risk equations for blood pressure impact	20.0	20.2	0.2
Blood pressure reduction based on partial intervention	20.0	20.3	0.3
Age-specific background cost estimates	20.0	20.7	0.8
10-year time horizon	9.5	9.5	0.0
5-year time horizon	4.9	4.9	0.0
Doubled cost of pharmacist intervention plus $33.33 per patient training costs incorporated	20.0	20.7	0.8
Reduced background annual medical costs in intervention group	20.0	20.7	0.8
Efficacy reduced: 100% after year three	20.0	20.0	0.1
Efficacy reduced: 50% after year three, 100% after year ten	20.0	20.2	0.2
"Optimistic" scenario regarding intervention costs	20.0	20.7	0.8
Discounted 5%			
Base case	12.4	12.7	0.3
Framingham risk equations for blood pressure impact	12.4	12.5	0.1
Blood pressure reduction based on partial intervention	12.4	12.5	0.1
Age-specific background cost estimates	12.4	12.7	0.3
10-year time horizon	7.7	7.7	0.0
5-year time horizon	4.5	4.5	0.0
Doubled cost of pharmacist intervention plus $33.33 per patient training costs incorporated	12.4	12.7	0.3
Reduced background annual medical costs in intervention group	12.4	12.7	0.3
Efficacy reduced: 100% after year three	12.4	12.4	0.0
Efficacy reduced: 50% after year three, 100% after year ten	12.4	12.5	0.1
"Optimistic" scenario regarding intervention costs	12.4	12.7	0.3

Table S 5: Quality-adjusted life years in base case and one-way sensitivity analyses

	Quality-adjusted life years		
	Usual care	Pharmacist intervention	Difference
Undiscounted			
Base case	16.5	17.4	0.9
Framingham risk equations for blood pressure impact	16.5	16.7	0.3
Blood pressure reduction based on partial intervention	16.5	16.8	0.4
Age-specific background cost estimates	16.5	17.4	0.9
10-year time horizon	8.2	8.2	0.0
5-year time horizon	4.3	4.3	0.0
Doubled cost of pharmacist intervention plus $33.33 per patient training costs incorporated	16.5	17.4	0.9
Reduced background annual medical costs in intervention group	16.5	17.4	0.9
Efficacy reduced: 100% after year three	16.5	16.6	0.1
Efficacy reduced: 50% after year three, 100% after year ten	16.5	16.8	0.3
"Optimistic" scenario regarding intervention costs	16.5	17.4	0.9
Discounted 5%			
Base case	10.4	10.8	0.3
Framingham risk equations for blood pressure impact	10.4	10.5	0.1
Blood pressure reduction based on partial intervention	10.4	10.6	0.1
Age-specific background cost estimates	10.4	10.8	0.3
10-year time horizon	6.7	6.7	0.0
5-year time horizon	3.9	3.9	0.0
Doubled cost of pharmacist intervention plus $33.33 per patient training costs incorporated	10.4	10.8	0.3
Reduced background annual medical costs in intervention group	10.4	10.8	0.3
Efficacy reduced: 100% after year three	10.4	10.5	0.0
Efficacy reduced: 50% after year three, 100% after year ten	10.4	10.6	0.2
"Optimistic" scenario regarding intervention costs	10.4	10.8	0.3

Table S 6: Cost outcomes in base case and one-way sensitivity analyses

	Costs		
	Usual care	Pharmacist intervention	Difference
Undiscounted			
Base case	$261,444	$252,582	-$8,862
Framingham risk equations for blood pressure impact	$261,444	$266,817	$5,372
Blood pressure reduction based on partial intervention	$261,444	$261,444	$3,600
Age-specific background cost estimates	$362,871	$365,928	$3,056
10-year time horizon	$85,374	$81,556	-$3,818
5-year time horizon	$36,227	$37,232	$1,006
Doubled cost of pharmacist intervention plus $33.33 per patient training costs incorporated	$261,444	$256,811	-$4,633
Reduced background annual medical costs in intervention group	$261,444	$251,200	-$10,244
Efficacy reduced: 100% after year three	$261,444	$261,137	-$307
Efficacy reduced: 50% after year three, 100% after year ten	$261,444	$259,794	-$1,650
"Optimistic" scenario regarding intervention costs	$261,444	$244,134	-$17,311
Discounted 5%			
Base case	$140,641	$134,277	-$6,364
Framingham risk equations for blood pressure impact	$140,641	$143,494	-$2,853
Blood pressure reduction based on partial intervention	$140,641	$142,372	$1,730
Age-specific background cost estimates	$179,441	$176,574	-$2,867
10-year time horizon	$67,863	$65,364	-$2,500
5-year time horizon	$32,710	$33,719	$1,009
Doubled cost of pharmacist intervention plus $33.33 per patient training costs incorporated	$140,641	$136,894	-$3,747
Reduced background annual medical costs in intervention group	$140,641	$133,432	-$7,209
Efficacy reduced: 100% after year three	$140,641	$132,400	-$98
Efficacy reduced: 50% after year three, 100% after year ten	$140,641	$139,640	-$1,001
"Optimistic" scenario regarding intervention costs	$140,641	$129,132	-$11,509

References

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3. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. *Arch Intern Med*. 2005;165(8):923-928.
4. Pogue VA, Ellis C, Michel J, Francis CK. New staging system of the fifth Joint National Committee report on the detection, evaluation, and treatment of high blood pressure (JNC-V) alters assessment of the severity and treatment of hypertension. *Hypertension* 1996;28(5):713-718.

Appendix to: Marra C, Johnston K, Santschi V, et al. Cost-effectiveness of pharmacist intervention for managing hypertension in Canada. Can Pharm J (Ott) 2017;150(3). DOI: 10.1177/1715163517701109.