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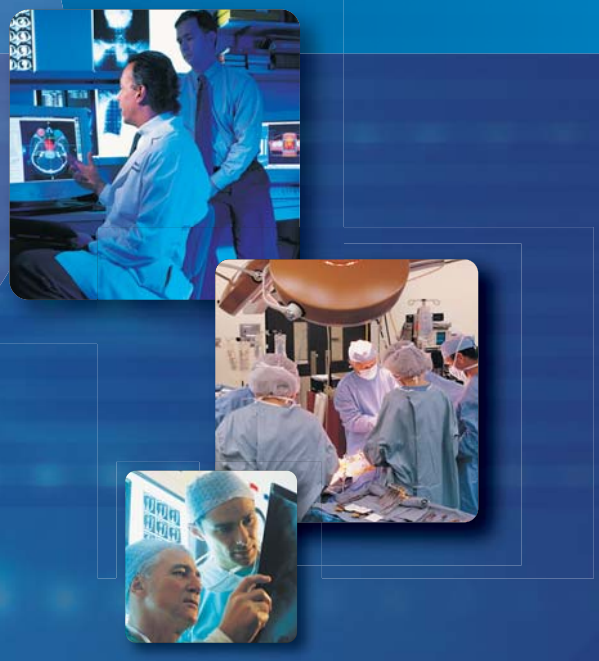
Thiazide Diuretics as First-Line Treatment for Hypertension: Meta-analysis and Economic Evaluation



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Thiazide Diuretics as First-Line Treatment for Hypertension: Meta-analysis and Economic Evaluation

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December 2007

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Khai Tran, the overall research lead, coordinated the research project and wrote the clinical sections of the report. Khai Tran and Chuong Ho selected trials; and extracted, tabulated, and analyzed data.

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Conflicts of Interest

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REPORT *IN BRIEF*

December 2007

Thiazide Diuretics as First-Line Treatment for Hypertension: Meta-analysis and Economic Evaluation

Technology and Condition

Thiazide diuretics (TZD) chlorthalidone, hydrochlorothiazide, indapamide, and metolazone for primary hypertension (at least 140 mm Hg systolic or 90 mm Hg diastolic blood pressure).

Issue

Despite their demonstrated clinical effectiveness and low cost, the rate of first-line TZD use in newly treated hypertensive patients remains lower than that of angiotensin-converting enzyme (ACE) inhibitors, α-blockers (AB), angiotensin II receptor blockers (ARB), β-blockers (BB), and calcium channel blockers (CCBs). There is also uncertainty about the evidence supporting blood pressure targets.

Methods and Results

A systematic review and a meta-analysis were conducted. Clinical and quality-of-life impacts were derived from 44 RCTs. Evidence of targeting blood pressure was derived from nine trials. TZDs reduced stroke events relative to ACE inhibitors and reduced heart failure events relative to CCB, but total cardiovascular and cerebrovascular events were not significantly different. For all patient groups, TZDs represent the least costly therapeutic option and are the second most effective option behind CCB.

Implications for Decision Making

- **Compelling evidence suggests that TZDs are effective first-line agents.** TZDs are comparable with ACE inhibitors, BB, and CCB in reducing the risks of many adverse outcomes, including mortality. No evidence comparing TZDs with AB or ARB was found. Overall differences in quality of life were not evident.
- **TZDs are least costly.** Based on a simulation model of treating newly diagnosed hypertensive patients 55 and 65 years of age, TZDs represent the least costly option and the second most effective option behind CCBs. CCBs are cost-effective for those willing to pay from $400,000 to $3 million for a quality-adjusted life-year, depending on the patient's risk of future disease.
- **First-line TZDs will curb increased expenditures.** If TZDs are used first-line, future increases in spending will be lower and, for some provinces, may decrease in the short term.
- **No compelling evidence for lower blood pressure targets was identified.** It is unclear if intensive lowering of blood pressure below the standard target (140/90 mm Hg) can significantly alter health outcomes important to patients.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Tran K, Ho C, Noorani HZ, Cimon K, Hodgson A, Coyle D, Coyle K, Myers MG, Wright JM. *Thiazide diuretics as first-line treatment for hypertension: meta-analysis and economic evaluation.*

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EXECUTIVE SUMMARY

Issue

The rate of thiazide use in hypertensive patients remains lower than that of other anti-hypertensive drug classes. There is a need to systematically evaluate the health outcomes and relative costs of first-line thaizide use in hypertensive therapy compared to other drug classes in patients with or without co-morbitities.

Objective

The aim of this health technology assessment is to evaluate the evidence for the clinical effects and the economic implications of thiazide diuretics when used as a first-line treatment for hypertension. This assesement is intended to inform those who must decide on an optimal choice of anti-hypertensive drug therapy in a patient diagnosed with hypertension for the first time. The economic implications of treating a typical newly diagnosed 55- or 65-year-old patient, with no significant additional risk factors such as heart disease, abnormal blood cholesterol, or diabetes are also examined.

The effects of reducing blood pressure below the standard target of 140/90 mm Hg are also evaluated.

Clinical Review

Methods: Bibliographic databases and grey literature sources were searched until May 2007 to obtain literature. Studies were selected systematically by two reviewers using defined criteria.

Results: There were 44 unique randomized controlled trials (RCTs), consisting of 26 clinical and 18 quality of life (QoL) trials, selected for inclusion. Of the RCTs, eight had QoL data. Nine unique trials related to target blood pressure were included. About one-third of the trials were of high quality.

Thiazide diuretic treatment reduced all cardiovascular and cerebrovascular events in subjects with uncomplicated essential hypertension as compared to placebo or no treatment. There were no significant differences for total cardiovascular and cerebrovascular morbidity and mortality when comparing thiazide diuretics with angiotensin-converting enzyme (ACE) inhibitors, β-blockers (BB), or calcium channel blockers (CCB). Thiazide diuretics were better in reducing stroke events relative to ACE inhibitors and in reducing heart failure events relative to CCB. No studies comparing thiazide diuretics with α-blockers or with angiotensin II receptor blockers (ARB) were identified.

The reduction of blood pressure below a target 140/90 mm Hg in the general population or in patients with diabetic or kidney disease showed no significant differences for all-cause death, death related to cardiovascular events, or renal failure.

Review of Economic Studies

***Methods*:** A review was conducted of economic evaluations that compared the use of thiazide diuretics to other drug therapies, as a first-line therapy for the treatment of hypertension. The literature search strategy identified 1,740 possible studies, of which 16 were found to be relevant for

inclusion in the literature review. No attempt was made to quantitatively synthesize the study results, so the review of studies was presented in narrative form.

Results and Conclusions: In most of the studies, the authors concluded that thiazide diuretics were the most cost-effective therapy for the initial treatment of hypertension. In the few studies where authors did not conclude that thiazide diuretics were the most cost-effective, BB or CCB were found to be more cost-effective. Although several economic evaluations were identified, none addressed the issue that was relevant to this report from a Canadian perspective. Thus, the completion of a full economic evaluation was considered to be appropriate.

Economic Evaluation

Methods: The objective of the economic evaluation was to determine the cost-effectiveness of starting the treatment of newly diagnosed hypertension with thiazide diuretics as compared with alternative anti-hypertensive drug classes. A Markov model was created and used to estimate the long-term costs and quality-adjusted life-years (QALY) associated with cerebrovascular and cardiovascular disease in the study populations. The model was populated with the most appropriate estimates of transition probabilities, costs, and QoL. Differences among treatments were assessed by adjusting the transition probabilities using relative risks. Analyses were conducted for eight groups of patients based on combinations of the following characteristics: men or women, 55 or 65 years of age, with a baseline systolic blood pressure of 150 mm Hg or 180 mm Hg.

Results: For all patient groups, thiazide diuretics represent the least costly therapeutic option and are the second most effective option behind CCB. Thus, all other treatment options (BB; either ACE inhibitors or ARB; or no therapy) are dominated by thiazide diuretics. The incremental cost per QALY gained for CCB versus thiazide diuretics is greater than $400,000 for all groups of patients. These conclusions are unaltered by the results of the sensitivity analysis.

Health Services Impact

Although the number of prescriptions for thiazide diuretics increased between 2000 and 2006 in some Canadian provinces, the proportion in 2005-2006 for thiazide diuretics relative to other antihypertensive drug classes remains low (from 8% to 22%). Except for α-blockers, the use of other antihypertensive dug classes increased during the past five years. The rates of increase for ARB and ARB plus thiazide were the highest. ACE inhibitors are the most commonly prescribed therapy and accounted for 30% to 40% of the total expenditure.

If prescribing trends continue as they have over the past five years, the expenditure for anti-hypertensive medications will increase yearly. On the other hand, if anti-hypertensive therapy is started with thiazide diuretics rather than other therapeutic classes, the yearly increase in expenditure will be reduced.

Ethical, Equity, and Psychosocial Issues

The advent of newer anti-hypertensive drugs such as ACE inhibitors, adrenergic blocking agents, and CCB leads to questions about the allocation of health care resources, because thiazide diuretics are cost-effective and less expensive compared to the other classes. There are differences in utilization patterns between provinces in the use of thiazide diuretics, despite no difference in the evidence and costs of therapy between jurisdictions. Patients should be adequately informed about the benefits and risks of diuretic therapy and educated about the benefits of lifestyle modification. Physicians and

other caregivers should discuss the impact of thiazide diuretics on a patient's quality of life or general well-being, especially sexual dysfunction. Patients' attitudes are influenced by cultural differences, beliefs, and previous experiences.

Conclusion

TZD-based therapy is superior to placebo or no treatment in reducing the risks of all-CV and CRV events in subjects with uncomplicated hypertension. No significant differences for all-CV and CVR-related mobidity and mortality were found when TZD were compared with other antihypertensive medications. TZD, however, were better in reducing the risk of stroke than ACE inhibitors and in reducing the risk of HF than CCB.

The economic analysis found little difference between therapies in terms of effectiveness and found TZD to be the most cost-effective initial therapy fo patients in all study populations, unless society is willing to pay more than $400,000 for a QALY gained from the use of CCB.

Evidence from a limited number of trials, most of which were low quality, showed that the intensive lowering of blood pressure below the standard target of 140/190 mm Hg in patients with hypertension did not result in a difference in the risks of all-cause death, death related to cardiovascular events, and renal failure.

ABBREVIATIONS

AB	α-blockers
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitors
AE	adverse event
ARB	angiotensin II receptor blockers
BB	β-blockers
BFTZ	bendroflumethiazide or bendrofluazide
b.i.d.	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CC	creatinine clearance
CCB	calcium channel blocker
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CHHS	Canadian Heart Health Survey
CI	confidence interval
CLTD	chlorthalidone
CLTZ	chlorothiazide
CRV	cerebrovascular
CV	cardiovascular
DBP	diastolic blood pressure
DM	diabetes mellitus
GFR	glomerular filtration rate
HCTZ	hydrochlorothiazide
HF	heart failure
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
MAP	mean arterial pressure
MCS	Monte Carlo simulation
MCTZ	methyclothiazide
MI	myocardial infarction
NNT	number needed to treat
NR	not reported
NS	not statistically significant
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomized controlled trial
RF	renal failure
RR	relative risk

RRD	relative risk difference
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
TZD	thiazide diuretics
t.i.d.	three times daily
TMTZ	trichlomethiazide
WMD	weighted mean difference

TABLE OF CONTENTS

TABLES (Tables 1 to 32 are located in the report)

FIGURES (All figures are located in the appendices)

APPENDICES

1 INTRODUCTION

1.1 Background

Hypertension, which is persistently elevated arterial blood pressure (BP), is a public-health concern in developed countries. It is common, asymptomatic, detectable, usually treatable, and can lead to lethal complications if unidentified or untreated. Although the pathophysiology of hypertension is increasingly understood, its etiology is unknown in 90% to 95% of cases (primary, essential, or idiopathic hypertension). The most common causes of death in patients with hypertension are due to effects on the heart (i.e., cardiac decompensation after an excessive work-load imposed by increased systemic blood pressure), cardiovascular system (i.e., long-standing effects on blood vessels throughout the body leading to stroke, myocardial infarction, and peripheral vascular disease), and kidney (i.e., renal failure).[1]

BP increases with age.[2] Systolic and diastolic blood pressure (SBP and DBP) gradually increase in men and women from 18 to 50 years of age. After the age of 50 years, SBP continues to increase throughout life while DBP tends to level or drop off. Thus, elevated SBP is a risk factor of cardiovascular disease throughout life, while elevated DBP is more commonly identified as a risk factor until the age of 50 years.

The prevention and management of hypertension is a public-health challenge in Canada. Hypertension is the most common diagnosis in Canada. The number of primary diagnoses at physicians' offices reached up to 21.3 million in 2004, a 24% increase from that in 2001.[3] Of those diagnosed with hypertension, 80% received drug prescriptions. The Canadian Heart Health Survey indicates that approximately 22% of Canadian adults (18- to 70-years-old) have hypertension, and 75% of Canadians with hypertension are younger than 65-years-old.[4]

The goal of therapy is to reduce hypertension-associated morbidity and mortality. The lowering of blood pressure (BP) can be achieved by a combination of healthy lifestyles and pharmacological treatment. The classes of antihypertensive drugs include thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, adrenergic blocking agents [including α-blockers (AB) and β-blockers (BB)], calcium channel blockers (CCB), and angiotensin II receptor blockers (ARB). Among commonly used drug classes, thiazide diuretics have been suggested as first-line agents for the management of hypertension. The cost per day of therapy was lowest for thiazide diuretics and highest for ARB.[5]

1.2 Overview of Technology

All anti-hypertensive drugs lower BP, although the mechanisms of action vary (Table 1).

1.2.1 Thiazide diuretics

The term "thiazide diuretic" is used for drugs with a thiazide chemical structure, and for those with a similar pharmacological action on the kidney but which are not chemically a thiazide, such as chlorthalidone, indapamide, and metolazone. Thiazide diuretics are recommended as first-line agents for adults with hypertension who do not have indications that call for the use of specific agents, and for those with other indications (isolated systolic hypertension, left ventricular hypertrophy, and

diabetes with normal urinary albumin excretion).[6] Second-line anti-hypertensive drugs from other classes can be added if the patient's hypertension is still uncontrolled. Depending on the indications, other first-line agents may be considered.

Table 1: Oral anti-hypertensive drugs available in Canada

Class	Drug (Trade Name)	Daily Dose Range (mg/d)	Daily Frequency
Thiazide and thiazide-like diuretics			
	Chlorthalidone (Apo-Chlorthalidone)	6.25 – 50	1
	Hydrochlorothiazide (Apo-Hydro®, Novo-Hydrazide, PMS-Hydrochlorothiazide)	12.5 – 100	1
	Indapamide (Apo-Indapamide ®, Gen-Indapamide, Lozide ®, Novo-Indapamide, PMS-Indapamide)	1.25 – 2.5	1
	Metolazone (Zaroxolyn)	2.5 – 5	1
Adrenergic blocking agents			
β-blockers (cardioselective)	Acebutolol (Apo-Acebutolol, Gen-Acebutolol, Gen-Acebutolol (Type S), Novo-Acebutolol, Nu-Acebutolol, Rhotral, Sandoz Acebutolol, Sectral)	100 – 800	2
	Atenolol (Apo-Atenol, CO Atenolol, Gen-Atenolol, PMS-Atenolol, Novo-Atenol, RAN-Atenolol, ratio-Atenolol, Sandoz Atenolol, Tenormin)	25 – 100	1
	Bisoprolol (Apo-Bisoprolol ®, Monocor ®, Novo-Bisoprolol, Sandoz Bisoprolol)	2.5 – 20	1
	Metoprolol (Apo-Metoprolol, Apo-Metoprolol (Type L), Betaloc, Betaloc Durules, Gen-Metoprolol (Type L), Lopresor, Metoprolol Tartrate Injection USP, Novo-Metoprol, Nu-Metop, PMS-Metoprolol-L, Sandoz Metoprolol (Type L))	25 – 200	1 – 2
β-blockers (non-selective)	Nadolol (Apo-Nadol®, Novo-Nadolol)	40 – 160	1
	Pindolol (Apo-Pindol, Gen-Pindolol, Novo-Pindol, Nu-Pindol, Sandoz Pindolol, Visken)	10 – 40	2
	Propranolol (Apo-Propanolol, Inderal-LA, Novo-Pranol)	40 – 160	2
	Timolol (Apo-Timol, Novo-Timol)	20 – 40	2
α-blockers	Doxazosin (Apo-Doxazosin®, Cardura™, Gen-Doxazosin, Novo-Doxazosin)	1 – 16	1
	Prazosin (Apo-Prazo®, Novo-Prazin)	2 – 20	2 – 3
	Terazosin (Apo-Terazosin, Hytrin, Novo-Terazosin, PMS-Terazosin, Ratio-Terazosin)	1 – 20	1 – 2
Combined α-blockers and β-blockers	Carvedilol (Apo-Carvedilol, PMS-Carvedilol, RAN-Carvedilol, ratio-Carvedilol)	3.125 – 50	2
	Labetalol (Apo-Labetalol®, Labetalol Hydrochloride Injection, Trandate®)	100 – 1200	2
ACE inhibitors			
	Benazepril (Apo-Benazepril, Lotensin)	10 – 40	1 – 2
	Captopril (Apo-Capto®, Capoten™, Gen-Captopril, Novo-Captopril, PMS-Captopril)	25 – 100	2
	Cilazapril (Inhibace, Novo-Cilazapril, PMS-Cilazapril)	1.0 – 10	1 – 2
	Enalapril (Vasotec)	5 – 40	1 – 2

Table 1: Oral anti-hypertensive drugs available in Canada			
Class	**Drug (Trade Name)**	**Daily Dose Range (mg/d)**	**Daily Frequency**
	Fosinopril (Apo-Fosinopril, Gen-Fosinopril, Monopril, Novo-Fosinopril)	10 – 40	1
	Lisinopril (Prinivil, Zestril)	10 – 40	1
	Perindopril (Apo-Perindopril, Coversyl)	4 – 8	1
	Quinapril (Accupril,)	10 – 40	1
	Ramipril (Altace, Apo-Ramipril)	2.5 – 20	1 – 2
	Trandolapril (Mavik)	1 – 4	1
Angiotensin II receptor blockers			
	Candesartan (Atacand)	8 – 32	1
	Eprosartan (Teveten)	400 – 800	1 – 2
	Irbesartan (Avapro)	150 – 300	1
	Losartan (Cozaar)	25 – 100	1 – 2
	Telmisartan (Micardis)	20 – 80	1
	Valsartan (Diovan)	80 – 320	1 – 2
Calcium channel blockers			
Dihydropyridines	Amlodipine (Norvasc)	2.5 – 10	1
	Felodipine (Plendil, Renedil, Sandoz Felodipine)	2.5 – 20	1
	Nifedipine (Adalat XL, Apo-Nifed, Apo-Nifed PA)	30 – 60	1
Non-Dihydropyridines	Diltiazem (Apo-Diltiaz, Cardizem, Cardizem CD, Gen-Diltiazem, Gen-Diltiazem CD, Novo-Diltiazem, Novo-Diltiazem CD, Novo-Diltiazem HCl ER, Nu-Diltiaz, Nu-Diltiaz CD**,** ratio-Diltiazem CD **,** Sandoz Diltiazem CD **,** Sandoz Diltiazem T, Tiazac®, Tiazac® XC)	120 – 540	1 – 2
	Verapamil (Apo-Verap®, Apo-Verap® SR, Covera-HS®, Gen-Verapamil**,** Gen-Verapamil SR, Isoptin® SR, Novo-Veramil SR, Nu-Verap, Verapamil Hydrochloride Injection USP)	100 – 480	1 – 2
Direct vasodilators			
	Minoxidil (Loniten)	2.5 – 80	1 – 2

ACE=angiotensin-converting enzyme.

The mechanisms for the lowering of BP by thiazides are incompletely understood. Thiazide diuretics inhibit sodium chloride reabsorption from the kidney. Thiazides also induce a loss of potassium (hypokalemia) and an increase of uric acid in the serum. Thiazide-induced hypokalemia is partly due to the inhibition of sodium chloride reabsorption and activation of the renin-angiotensin system, which stimulates aldosterone secretion and subsequently elevates potassium excretion. Significant hypokalemia occurs infrequently. When it does occur, it can usually be corrected by using potassium- sparing diuretics or potassium supplements. ACE inhibitors can be used with thiazides, because the former inhibits angiotensin II production and, therefore, aldosterone secretion. Other side effects of thiazide diuretics include hypomagnesemia, hypercalcemia, hyperurecemia, hyperglycemia, hyperlipidemia, and sexual dysfunction. Diuretic-induced hyperurecemia can cause gout. Low-dose therapy with thiazide diuretics is less likely to produce these metabolic abnormalities.

Thiazides also lower calcium excretion in the urine by promoting calcium reabsorption at the distal tubule; thus, they are used to prevent calcium-containing kidney stones. The reduced calcium excretion causes a positive calcium balance and is associated with increased bone density in post-menopausal women.[7]

1.2.2 Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors inhibit the conversion of angiotensin I to angiotensin II, a substance that induces the constriction of blood vessels and secretion of aldosterone, which causes retention of sodium and water. ACE inhibitors also block the degradation of bradykinin, which is a substance that can lower BP and stimulate the synthesis of vasodilators such as prostaglandin E2 and prostacyclin. ACE inhibitors decrease aldosterone and can increase the potassium concentration in serum (hyperkalemia). The primary differences among the ACE inhibitors that are on the market are the time to onset and the duration of action. Some adverse effects that occur in <1% of patients are neutropenia, agranulocytosis, proteinuria, glomerulonephritis, and acute kidney failure. Angioedema, with symptoms including lip and tongue swelling and difficulty breathing, occurs in <2% of patients, more likely in African-Americans and smokers. ACE inhibitors commonly cause dry cough in up to 20% of patients.

1.2.3 Adrenergic blocking agents

The α- and β-adrenergic blockers are groups of drugs that inhibit α- and β-adrenergic receptors in the arteries, veins, heart, and kidney. There are also non-selective adrenergic blocking agents. β-adrenergic blocking agents can be non-selective (for example, propranolol) or β-1 selective (for example, atenolol). The side effects of β-blockers (BBs) can be heart failure, bronchospasm, and decreased peripheral blood flow. The abrupt cessation of BB can cause unstable angina, myocardial infarction, and death in patients with coronary heart disease.

1.2.4 Calcium channel blockers

The calcium channel blockers (CCBs) inhibit the movement of ionic calcium across membranes. This movement has effects on the heart (pace-maker activity, conduction, and contractility) and arteries. Different chemical classes, such as dihydropyridines and non-dihydropyridines, vary in activity. For instance, nifedipine of the dihydropyridine group has the greatest effect on the blood vessels, while verapamil and diltiazem of the non-dihydropyridine group have a greater effect on the heart. High doses of diltiazem and verapamil can cause bradycardia or atrioventricular block. These drugs can cause anorexia, nausea, peripheral edema, or hypotension.

1.2.5 Angiotensin II receptor blockers

The angiotensin II receptor blockers (ARBs) directly inhibit the effects of angiotensin II on the angiotensin II type 1 (AT1) receptor that mediates the hypertensive effects of vasoconstriction, aldosterone release, sympathetic nervous system activation, anti-diuretic hormone release, and constriction of the efferent arterioles of the glomerulus. ARBs have less of an effect on the AT2 receptor that mediates vasodilation, tissue repair, and inhibition of cell growth. ARBs may cause hyperkalemia and may acutely adversely affect renal function in predisposed patients.

1.2.6 Others: direct vasodilators

Peripheral vasodilators, such as hydralazine and minoxidil, relax the smooth muscle of blood vessels. One side effect of hydralazine is a lupus-like syndrome. Compared to hydralazine, minoxidil increases the risk of sodium and water retention, which can lead to heart failure events.

1.2.7 Utilization and cost data

Table 2 shows utilization data for different drug classes in Canadian provinces. Data from Prince Edward Island, New Brunswick, British Columbia, Manitoba, and Nova Scotia were for 2005-2006; data from Saskatchewan were for 2004-2005; and data from Alberta were from 2000-2001 to 2005-2006. Data from preceding years appear in Appendices 1a to 1f. Data from Ontario, Quebec, and Newfoundland and Labrador were unavailable. The information on the use of these drug classes was not restricted to hypertension. The estimated numbers of drug recommendations made by Canadian office-based physicians for hypertension appear in Table 3. Although the numbers do not reflect the entire picture of drug prescriptions for hypertension in Canada (i.e., including hospitals and hypertension clinics), the proportion of drugs used for hypertension should not be too much of a deviation from the true values, because the primary diagnosis of hypertension is made in physicians' offices, and 80% of these patients received anti-hypertensive drug prescriptions.

We estimated the amount of money spent in one fiscal year for the indicated number of persons. The expenditure per person shows that thiazide diuretics were the least expensive. The percentage of prescriptions was second lowest among the drug classes.

Appendix 2 shows the formulary data for some Canadian jurisdictions. The table shows the therapeutic category and corresponding Anatomical Therapeutic Chemical (ATC) description for all anti-hypertensive drugs. The status of formulary coverage across several public formularies is enumerated by drug identification number (DIN). Most drugs are open-listed, except ARBs in some provinces.

2 THE ISSUE

The rate of thiazide use in hypertensive patients remains lower than that of other anti-hypertensive drug classes. There is a need to systematically evaluate the health outcomes and relative costs of first-line thiazide use in hypertensive therapy compared to other drug classes in patients with or without co-morbidities.

3 OBJECTIVES

The aim of this health technology assessment is to evaluate the evidence for the clinical effects and the economic implications of thazide diuretics when used as a first-line treatment for hypertension. This assessment is intended to inform those who must decide on an optimal choice of anti-hypertensive drug therapy in a patient diagnosed with hypertension for the first time. The economic implications of treating a typical newly diagnosed 55- or 65-year-old patient, with no significant additional risk factors such as heart disease, abnormal blood cholesterol, or diabetes are also examined.

Table 2: Utilization data for some drug classes from Canadian provinces								
Class	**Category**	**PEI***	**NB†**	**BC‡**	**SK****	**MB††**	**NS‡‡**	**AB*****
TZD	No. of persons (%)	1,862 (9.3)	21,115 (19.0)	148,122 (24.7)	27,126 (18.6)	24,701 (16.5)	29,138 (17.6)	235,332 (18.0)
	No. of prescriptions (%)	6,239 (7.8)	92,433 (17.9)	656,862 (22.2)	133,883 (12.7)	112,035 (13.7)	136,285 (16.3)	2,217,816 (17.7)
	Unit cost†††	--	$0.13	$0.13	--	--	--	--
	Expenditure‡‡‡ (%)	$30,569 (0.6)	$497,702 (2.1)	$5,865,398 (5.4)	$982,324 (3.7)	$1,282,437 (3.7)	$1,371,091 (3.8)	$20,876,200 (3.5)
	Expenditure/person	$16	$24	$40	$36	$52	$47	--
α-blockers	No. of persons (%)	87 (0.4)	2,271 (2.0)	2,859 (0.5)	1,426 (1.0)	1,843 (1.2)	4,957 (3.0)	35,485 (2.7)
	No. of prescriptions (%)	368 (0.5)	9,746 (1.9)	12,084 (0.4)	10,591 (1.0)	10,088 (1.2)	22,378 (2.7)	268,788 (2.1)
	Unit cost	--	$0.43	$0.34	--	--	--	--
	Expenditure (%)	$8,553 (0.2)	$308,424 (1.3)	$400,007 (0.4)	$181,553 (0.7)	$357,050 (1.0)	$753,198 (2.1)	$9,024,049 (1.5)
	Expenditure/person	$98	$136	$140	$127	$194	$152	--
β-blockers	No. of persons (%)	5,050 (25.2)	24,916 (22.4)	125,188 (20.8)	26,232 (18.0)	30,790 (20.5)	40,078 (24.2)	269,249 (20.6)
	No. of prescriptions (%)	20,646 (25.8)	119,115 (23.1)	644,731 (21.8)	197,608 (18.8)	172,507 (21.2)	211,884 (25.3)	2,313,606 (18.4)
	Unit cost	--	$0.37	$0.48	--	--	--	--
	Expenditure (%)	$440,124 (8.6)	$2,736,997 (11.4)	$12,972,628 (12.0)	$2,375,896 (8.9)	$3,768,503 (11.0)	$4,951,383 (13.6)	$47,846,117 (8.1)
	Expenditure/person	$87	$110	$104	$91	$122	$124	--
β-blockers + TZD	No. of persons (%)	--	460 (0.4)	412 (0.1)	1,103 (0.8)	397 (0.3)	--	4,419 (0.3)
	No. of prescriptions (%)	--	2,057 (0.4)	1,390 (0.1)	8,587 (0.8)	1,824 (0.2)	--	53,829 (0.4)
	Unit cost	--	$0.68	$0.78	--	--	--	--
	Expenditure (%)	--	$78,084 (0.3)	$80,189 (0.1)	$186,055 (0.7)	$60,080 (0.2)	--	$2,210,379 (0.4)
	Expenditure/person	--	$170	$195	$169	$151	--	--
ACEI	No. of persons (%)	5,571 (27.8)	31,445 (28.3)	165,455 (27.6)	35,417 (24.3)	36,468 (24.3)	41,358 (24.9)	343,221 (26.2)
	No. of prescriptions (%)	20,929 (26.2)	148,589 (28.8)	859,708 (29.1)	277,429 (26.4)	219,379 (26.8)	213,491 (25.5)	3,461,664 (27.6)

Table 2: Utilization data for some drug classes from Canadian provinces								
Class	**Category**	**PEI***	**NB†**	**BC‡**	**SK****	**MB††**	**NS‡‡**	**AB*****
	Unit cost	--	$0.77	$0.77	--	--	--	--
	Expenditure (%)	$1,766,958 (34.4)	$9,368,967 (39.0)	$42,216,122 (39.1)	$8,145,905 (30.6)	$10,397,632 (30.3)	$11,793,666 (32.4)	$198,052,449 (33.5)
	Expenditure/person	$317	$298	$255	$230	$285	$285	--
ACEI + TZD	No. of persons (%)	80 (0.4)	548 (0.5)	5,221 (0.9)	4,991 (3.4)	3,278 (2.2)	361 (0.2)	13,827 (1.1)
	No. of prescriptions (%)	325 (0.4)	2,337 (0.5)	19,938 (0.7)	37,648 (3.6)	15,558 (1.9)	1,899 (0.2)	128,599 (1.0)
	Unit cost	--	$0.94	$0.91	--	--	--	--
	Expenditure (%)	$19,417 (0.4)	$152,617 (0.6)	$1,147,531 (1.1)	$1,016,390 (3.8)	$750,100 (2.2)	$93,935 (0.3)	$7,994,192 (1.4)
	Expenditure/person	$243	$278	$220	$204	$229	$260	--
ARB	No. of persons (%)	1,977 (9.9)	6,129 (5.5)	26,173 (4.4)	13,212 (9.1)	13,134 (8.8)	18,260 (11.0)	133,059 (10.2)
	No. of prescriptions (%)	8,332 (10.4)	27,160 (5.3)	124,499 (4.2)	99,564 (9.5)	68,532 (8.4)	87,516 (10.5)	1,248,007 (9.9)
	Unit cost	--	$1.12	$1.17	--	--	--	--
	Expenditure (%)	$662,522 (12.9)	$2,025,222 (8.4)	$8,119,119 (7.5)	$3,332,687 (12.5)	$4,035,941 (11.8)	$5,551,939 (15.3)	$88,905,102 (14.7)
	Expenditure/person	$335	$330	$310	$252	$307	$304	--
ARB + TZD	No. of persons (%)	378 (1.9)	948 (0.9)	7,338 (1.2)	8,549 (5.9)	7,553 (5.0)	--	48,828 (3.7)
	No. of prescriptions (%)	1,447 (1.8)	3,814 (0.7)	27,521 (0.9)	63,157 (6.0)	34,414 (4.2)	--	425,332 (3.4)
	Unit cost	--	$1.17	$1.18	--	--	--	--
	Expenditure (%)	$110,737 (2.2)	$284,978 (1.2)	$2,091,599 (1.9)	$1,979,095 (7.4)	$2,130,337 (6.2)	--	$31,893,183 (5.4)
	Expenditure/person	$293	$301	$285	$232	$282	--	--
CCB	No. of persons (%)	5,027 (25.1)	23,453 (21.1)	119,669 (19.9)	27,454 (18.9)	31,763 (21.2)	32,003 (19.3)	226,048 (17.3)
	No. of prescriptions (%)	21,699 (27.1)	111,317 (21.5)	612,558 (20.7)	223,760 (21.3)	184,438 (22.5)	165,138 (19.7)	2,433,643 (19.4)
	Unit cost	--	$0.96	$1.09	--	--	--	--
	Expenditure (%)	$2,102,750 (40.9)	$8,595,317 (35.7)	$35,118,731 (32.5)	$8,462,641 (31.7)	$11,544,365 (33.6)	$11,944,096 (32.8)	$186,723,728 (31.6)
	Expenditure/person	$418	$366	$293	$308	$363	$373	--

Table 2: Utilization data for some drug classes from Canadian provinces								
Class	**Category**	**PEI***	**NB†**	**BC‡**	**SK****	**MB††**	**NS‡‡**	**AB*****
Total	No. of persons (%)	20,032 (100)	111,285 (100)	600,437 (100)	145,510 (100)	149,927 (100)	165,794 (100)	1,309,468 (100)
	No. of prescriptions (%)	79,985 (100)	516,568 (100)	2,959,291 (100)	1,052,227 (100)	818,775 (100)	836,692 (100)	12,551,284 (100)
	Expenditure (%)	$5,141,630(100)	$24,048,309 (100)	$108,011,325 (100)	$26,662,545 (100)	$34,326,446 (100)	$36,365,373 (100)	$591,525,398 (100)

AB=Alberta; ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin II receptor blockers; BC=British Columbia; CCB=calcium channel blockers; MB=Manitoba; NB=New Brunswick; NS=Nova Scotia; PEI=Prince Edward Island; SK=Saskatchewan; TZD=thiazide diuretics
*data obtained from Prince Edward Island Ministry of Health (Patrick Crawford, Prince Edward Island Drug Programs, Department of Social Services and Seniors: personal communication, 2007 Mar 5)
†data obtained from New Brunswick Ministry of Health (Brenda Currie, New Brunswick Prescription Drug Program: personal communication, 2007 Mar 15)
‡data obtained from British Columbia Ministry of Health (Brett Wilmer, Pharmaceutical Services, PharmaNet and Evaluation: personal communication, 2007 Mar 19)
**data were in 2004-05 and obtained from the Canadian Institute for Health Information (Ruzica Subotic-Howell, CIHI: personal communication, 2007 Apr 4)
††data obtained from the Canadian Institute for Health Information (Ruzica Subotic-Howell, CIHI: personal communication, 2007 Apr 4)
‡‡ data obtained from Nova Scotia Department of Health (Judy McPhee, Nova Scotia Drug Programs: personal communication, 2007 April 20)
***data were from 2000/01 to 2005/06 and obtained from Alberta Health & Wellness (Marylin Thornton, Pharmaceutical Policy and Programs Branch, Population Health Division: personal communication, 2007 April 27)
†††indicates average unit cost
‡‡‡indicates drug cost plus markup cost plus dispensing fee minus beneficiary contribution

Table 3: Anti-hypertensive drug use in Canada for hypertension and other indications			
Drug Class	**Estimated Numbers of Drug Recommendations Made by Canadian Office-based Physicians for Hypertension in 2006**		
	Total (%)*	**For hypertension (%)†**	**For others (%)†**
TZD	3,738,250 (10.6)	3,073,540 (82.2)	664,710 (17.8)
α-blockers	305,020 (0.9)	81,930 (26.9)	223,090 (73.1)
β-blockers	6,144,280 (17.5)	2,581,120 (42.0)	3,563,160 (58.0)
ACEI	8,541,430 (24.3)	5,754,980 (67.4)	2,786,450 (32.6)
ACEI + TZD	932,840 (2.7)	832,610 (89.3)	100,230 (10.7)
ARB	3,724,660 (10.6)	3,038,180 (81.6)	686,480 (18.4)
ARB + TZD	2,480,010 (7.0)	2,255,310 (90.9)	224,700 (9.1)
CCB	6,004,410 (17.1)	4,259,010 (70.9)	1,745,400 (29.1)
Others	3,165,160 (9.0)	495,340 (15.6)	2,669,820 (84.4)
Total	35,193,670 (100)	--	--

ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin II receptor blockers; CCB=calcium channel blockers;TZD= thiazide diuretics; *as a % of all drug classes
† as a % of its class; Source: IMS Health Canada, Canadian Disease and Therapeutic Index (CDTI)

The effects of reducing blood pressure below the standard target of 140/90 mm Hg are also evaluated.

The objective is accomplished by addressing three questions.

- Does the use of first-line thiazide diuretics change morbidity and mortality as compared to no treatment or placebo and other first-line anti-hypertensive drug classes for treatment of the following populations:
  - patients with uncomplicated primary hypertension (primary prevention)
  - patients with primary hypertension and comorbidities (primary prevention)
  - patients with primary hypertension and an existing cardiovascular event or disease (secondary prevention)?
- What are the economic implications of the use of first-line thiazide diuretics in the treatment of hypertension as compared with no treatment or placebo and other first-line anti-hypertensive drug classes in newly diagnosed 55- or 65-year-old patients with no significant additional risk factors?
- Does aiming for BP targets lower than 140/90 mm Hg result in a difference in morbidity and mortality as compared to the standard target of 140/90 mm Hg in patients with hypertension?

4 CLINICAL REVIEW

4.1 Methods

A protocol for the systematic review was written a priori and followed throughout the review.

4.1.1 Literature search strategy

The bibliographic databases that were searched were OVID's MEDLINE (1966 to the present; In-Process & Other Non-Indexed Citations), EMBASE (1980 to the present), and BIOSIS Previews (1985 to the present); DIALOG's EMBASE (1974 to 1979), and BIOSIS Previews (1969 to 1984); PubMed; and The Cochrane Library. The controlled vocabulary and keywords for the primary search included terms for "thiazide diuretics," "sodium chloride symporter inhibitors," the brand and generic names of specific pharmacological agents, and "hypertension" (Appendix 3). Methodological filters were applied to limit retrieval to controlled trials, meta-analyses, and systematic reviews. Retrieval was limited to the human population for the clinical search, with no language restrictions. Update searches were performed at predefined intervals during the project. A supplemental search was performed to retrieve controlled trials, meta-analyses, and systematic reviews for the research question on the aim to lower blood pressure targets. Retrieval for the supplemental search was limited to 1990 to 2006, the human population, and the English language. Update searches were performed until May 18, 2007. Grey literature was obtained through searching the web sites of health technology assessment and related agencies, and their associated databases.

Google™ and other Internet search engines were used to search for additional materials and information. The web sites of professional associations such as the Canadian Hypertension Society, Canadian Cardiovascular Society, American Society of Hypertension, American College of Cardiology, American Heart Association, American Stroke Association, and European Stroke Initiative and their associated conference sites were searched for additional information.

4.1.2 Selection criteria and method

a) Selection criteria

Eligibility criteria for trials involving thiazide diuretics versus placebo and other drug classes (question 1)

A study was eligible for inclusion only if it satisfied each of the following criteria:

***Study design*:** The trials were randomized controlled trials (RCTs) having a thiazide diuretic as first-line drug therapy in one group and active-treatment comparison or no treatment (including placebo) in the other group. The study duration was at least one year, and BP was measured at baseline and at ≥1 time points during the study period. Trials were included if the patients received concurrent drugs that were not for hypertensive treatment. The study duration was unrestricted in the selection of trials for quality of life (QoL).

***Population*:** Inclusion was not restricted by age, gender, or co-morbid conditions. Participants were required to have primary (essential) hypertension defined by a baseline of at least 140 mm Hg systolic BP or 90 mm Hg diastolic BP.

***Intervention*:** The intervention was a drug of the thiazide diuretic family including bendrofluazide, bendroflumethiazide, benzthiazide, chlorothiazide, chlorthalidone, cyclopenthiazide, hydroflumethiazide, methyclothiazide, hydrochlorothiazide, quinethazone, indapamide, metolazone, trichlormethiazide, polythiazide, and xipamide.

Comparators: The comparators were placebo, no treatment, or other recommended first-line agents including α-blockers (AB), β-blockers (BB), angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCB), and angiotensin II receptor blockers (ARB).

***Outcomes*:**

- total mortality, cardiovascular (including heart failure, myocardial infarction, coronary heart disease) and cerebrovascular events (including stroke), and kidney disease (including renal failure)
- change in systolic and diastolic BP
- QoL

Eligibility criteria for trials involving BP target (question 3)

A study was eligible for inclusion only if it satisfied each of the following criteria:

***Study design*:** Evidence was limited to RCTs where patients were randomized to aim for different BP targets. There were no exclusions based on the anti-hypertensive treatment used to achieve the target.

***Population*:** Inclusion was not restricted by age, gender, or co-morbid conditions. Participants were required to have primary (essential) hypertension defined by a baseline of at least 140 mm Hg systolic BP or 90 mm Hg diastolic BP.

***Intervention*:** Standard BP target of <140/90 mm Hg**.**

Comparators: BP targets lower than the standard target.

***Outcomes*:**

- total mortality, cardiovascular (including heart failure, myocardial infarction, coronary heart disease) and cerebrovascular events (including stroke), and kidney disease (including renal failure)
- change in systolic and diastolic BP
- QoL

b) Selection method

Two reviewers (KT, CH) independently selected trials for inclusion. The citations that were downloaded in Reference Manager (bibliographic software) were exported into Microsoft Excel (spreadsheet software). First, titles and abstracts were screened and potentially relevant articles were ordered, then articles were re-screened using selection criteria. The selected trials were verified by a third reviewer (KC). Differences in decisions between reviewers were resolved by consensus.

4.1.3 Data extraction strategy

Data from each included trial were extracted by three reviewers (KT, CH, KC) working independently, using a structured form (Appendix 4). Data were verified for discrepancies and tabulated by KT and KC. Disagreements were resolved by consensus.

4.1.4 Strategy for quality assessment

The reporting quality of the included RCTs was evaluated by two reviewers (KT and CH) using the Jadad five-point scale.[8] The quality of trials is rated on a scale of 0 to 5, with higher scores associated with better quality. Low quality trials (≤2) can contribute to overall increased estimates of benefit in meta-analysis.[9,10] The ratings are based on reporting of randomization, double-blinding, withdrawals, and dropouts (Appendix 5). Information on concealment of allocation,[11] blinding of assessors, and intention-to-treat (ITT) analyses was also recorded.

4.1.5 Data analysis methods

Data synthesis and analysis were performed using Review Manager software (RevMan 4.2). Dichotomous data were combined using the relative risk (RR) and the relative risk difference (RRD). The number needed to treat (NNT) was calculated based on the RR using Visual Rx software, which is available at http://www.nntonline.net/ebm/visualrx/try.asp, and was reported only if the RR was statistically significant. Continuous data with variances (i.e., standard deviation or standard error) were combined using a weighted mean difference (WMD) method. Where no variance was reported, a value was imputed based on data from similar trials. In the case of BP, for example, values of 15 and 10 were assigned as the standard deviation (SD) for SBP and DBP respectively. Where the BP was reported as a change (Δ) from baseline, the calculated value was the difference between baseline and change values. All standard error (SE) values were converted to SD. Where the quantitative pooling of results was appropriate, the random effects model was used to compute treatment efficacy. The heterogeneity of treatment effect between trials was detected using the common chi-square test with $P < 0.10$ indicating significant heterogeneity. Forest plots were generated wherever appropriate. A qualitative systematic review was performed for outcomes relating to QoL, because it was inappropriate to combine those data statistically.

Attempts were made to examine the differences between trials that were included in the review. If significant heterogeneity existed, the reasons for heterogeneity (e.g., study design, population characteristics, study quality) were explored. Where significant variation between studies was observed, an analysis of subgroups that were based on the factors potentially responsible for heterogeneity was performed, and the influence of these factors was assessed. If outliers were present, then results were pooled with or without the outliers to investigate the impact on the overall result. When necessary, a sensitivity analysis was performed to investigate the robustness of the results of statistical synthesis by estimating and comparing the effects of the intervention in different subgroups, including trial quality, publication year, age, gender, race, co-morbid conditions, baseline severity of hypertension, and dose.

4.2 Results

4.2.1 Quantity of research available

For trial selection related to question 1 (Figure 1), 6,167 citations were identified during the original literature search. From these, 378 potentially relevant reports were retrieved for further scrutiny. A total of 145 reports describing 44 unique trials (26 clinical trials and 18 trials having QoL data only) were selected for inclusion. Of the 26 clinical trials, eight had QoL data.

For trial selection related to question 3 (Figure 2), 1,379 citations were identified during the original literature search. From these, 72 potentially relevant reports were retrieved for further scrutiny. Forty-five reports describing nine unique trials were selected for inclusion. The lists of included and excluded trials appear in Appendices 6 and 7 respectively.

Most of the included trials had multiple publications that described different aspects of the trials or preliminary results. Unless otherwise indicated, the main publication for each trial, which provided the most comprehensive report of the trial outcomes, is the article that we have chosen to cite throughout the report when referring to that trial. It is also the article that was assessed for quality using the Jadad scale.

4.2.2 Trial characteristics

The characteristics of the clinical trials selected for question 1, of the clinical trials measuring QoL, and of the clinical trials selected for question 3 appear in Appendices 8a, 8b, and 8c respectively. The characteristics of the patients in trials selected for question 1, for QoL, and for question 3 are shown in Appendices 9a, 9b, and 9c respectively. The inclusion criteria, exclusion criteria, and methods of treatment in trials selected for question 1, in trials measuring QoL, and in trials selected for question 3 are shown in Appendices 10a, 10b, and 10c respectively. The quality assessment results of trials selected for question 1, trials measuring QoL, and trials selected for question 3 are shown in Appendices 11a, 11b, and 11c respectively. The term “thiazide diuretics” is used in this report to mean “thiazide diuretic-based therapy.” The same holds true for the other drug classes.

a) Clinical trials related to thiazide diuretics versus placebo and other drug classes

Of the 26 trials[12-37] selected for question 1,[13,15-18,20,21,25,26,28-30,32-36] 17 compared thiazide diuretics with placebo or no treatment, three[12,14,21]compared thiazide diuretics with ACE inhibitors, four[19,23,25,26] compared thiazide diuretics with BB, and six[12,22,24,27,31,38] compared thiazide diuretics with CCB. Some trials had >1 comparator.

Most trials were multicentre and multinational, had a mean follow-up of 1.1 to >7 years, and were supported by government funding. Seven trials[14,18,19,22-25] reported having industry financial sponsorship, while five trials[12,16,25,26,32] obtained study medications from pharmaceutical industries. Five[27,28,34,35,38] did not report on sponsorship. The size of the study populations varied from 99 to 33,357 patients at randomization. The quality assessment revealed that one trial[12] scored 5, three trials[29,34,35] scored 4, six trials[18,20,21,25,30,38] scored 3, 11 trials[13,16,17,22,24,26-28,32,33,36] scored 2, and five trials[14,15,19,23,31] scored 1 on the Jadad scale (Appendix 10a). Scores of 3 to 5 were considered to be high while scores ≤2 were low. The allocation concealment was unclear in all trials. One trial[12] reported blinding of the outcome assessor. Twelve trials[12-14,18,19,21,22,25,26,29,32,38] stated the use of an ITT approach in their data analyses.

Seventeen trials[13,15-18,20,21,25,26,28-30,32-36] involving thiazide diuretics versus placebo or no treatment had a total patient population of 34,360. Six trials[15,18,21,26,32,33] had a patient population of hypertensive elderly individuals with a mean age of >60 years. Three trials[17,20,29] had a patient population consisting of stroke or transient ischemic attack survivors who had normal or high BP. The remaining trials had a patient population with a broader range of ages, with mild to moderate hypertension, and with no co-morbidities. Three trials[34-36] had a male study population. The ratio of men to women was close to one in most trials. Many trials did not report the race or ethnicity of the study population. Those that did report race had more Caucasians, except one trial,[20] which had 80% African-Americans. Patients who had previous cardiovascular events or other diseases were excluded from most trials. The BP goals for the treatment groups were <140 to 160 mm Hg for SBP and <90 to 100 mm Hg for DBP. Additional information appears in Appendices 9a and 10a.

Three trials[12,14,21] involving thiazide diuretics versus ACE inhibitors had a total patient population of 31,249 consisting of hypertensive subjects aged ≥55 years (mean age 67 to 84 years), who had received prior treatment for hypertension. One trial[12] included subjects having at least one additional risk factor for coronary heart disease (CHD) events, and patients who had previous cardiovascular events or other diseases. One trial[12] reported race and ethnicity of the population. The ratio of men to women was close to one in two trials.[12,14] The BP goals for both treatment groups were <140 to 160 mm Hg for SBP and <80 to 90 mm Hg for DBP. The treatments were started with thiazide diuretics or ACE inhibitors, followed by step-care, which involves using other anti-hypertensive drugs to attain BP goals.

Four trials[19,23,25,26] involving thiazide diuretics versus BB had a total population of 19,413, which consisted of 35- to 64-year-old hypertensive subjects in three trials[19,23,25] and 65- to 74-year-old subjects in one trial.[26] Patients who had previous treatment for hypertension, secondary hypertension, previous cardiovascular events, or other diseases were excluded. None of the trials reported the race or ethnicity of the study population. Two trials[19,23] had only male patients, while the other two[25,26] had equal numbers of men and women in the study population. The BP goals for both treatment groups were <90 to 95 mm Hg DBP in three trials[19,23,25] and an SBP of 150 or 160 mm Hg in the trial involving older patients.[26] Treatment was initiated with thiazide diuretics or BB followed by step-care using other anti-hypertensive drugs to attain BP goals.

Six trials[12,22,24,27,31,38] involving thiazide diuretics versus CCB had a total population of 35,471, which consisted of ≥40-year-old subjects in three trials,[12,22,24] ≥60-year-old subjects in two trials,[27,31] and 40- to 65-year-old hypertensive subjects in one trial.[38] One trial[12] did not exclude patients who had secondary hypertension, previous cardiovascular events, or other diseases. Two trials[12,24] reported the race or ethnicity of the study population. Three trials[12,22,38] had equal numbers of men and women, while the others had more men[24] or more women[27,31] in the study population. The BP goals for both

treatment groups were <140 mm Hg SBP and <90 mm Hg DBP in two trials,[12,22] <90 or 95 mm Hg DBP in one trial,[24] and <160 mm Hg in the trial involving older patients.[31] Treatments were started with thiazide diuretics or CCB, followed by step-care using other anti-hypertensive drugs to attain BP goals.

No trials involving thiazide diuretics versus ARB met the inclusion criteria.

b) Clinical trials related to quality of life (QoL)

The selection of trials related to QoL was less stringent with respect to outcomes and follow-up time. Of the 26 trials[19,31,32,35-37,39-58] having QoL data, nine[18,25,32,35,36,40,42,56,58] compared thiazide diuretics with placebo, nine[41,44-48,53,54,56] compared thiazide diuretics with ACE inhibitors, 12[19,40,41,44,48,49,51,52,54,56-58] compared thiazide diuretics with AB or BB, seven[31,38,41,48,50,54,56] compared thiazide diuretics with CCB, and three[39,46,55] compared thiazide diuretics with ARB. Some trials had >2 comparators.

Many trials were multicentre and multinational, and the follow-up time varied from three months to >7 years. Sixteen trials[18,19,31,32,39-41,44,46,48,49,52,53,56-58] received drugs or funding from industry. Nine trials[34,35,38,45,47,50,51,54,55] did not report the sources of funding. The study population varied from 30 to 17,354 patients at randomization. The quality assessment revealed that three trials[35,42,46] scored 4, seven trials[32,37,39,43,49,56,57] scored 3, and the rest scored 2 and 1 on the Jadad scale (Appendix 11b). The allocation concealment was clear in one trial.[52] One trial[42] reported the blinding of the outcome assessor. Ten trials[19,32,37,39,43,46,49,53,56,57] stated the use of an ITT approach in the data analysis.

The patient population in all trials related to QoL consisted of mainly mild to moderate hypertensive subjects with an age range from 19 to 90 years. Those having secondary hypertension, pregnancy, or other diseases were excluded. Eleven trials[32,38-41,45,47,49,51,56,57] had equal numbers of men and women, one trial[46] had women only, and four trials[35,42,48,54] had men only in the study population. Most trials used a DBP of <90 or 95 mm Hg as the BP goal. Treatments were started with thiazide diuretics, other anti-hypertensive drug classes, or placebo. If the BP goal was not attained, dose doubling was usually implemented.

c) Clinical trials related to BP target

Of the nine trials[59-67] that fulfilled our selection criteria, six[59-62,65,67] were from the US, one[63] was multinational, one[64] was from Japan, and one[66] was from Italy. All trials except the one from Japan,[64] which did not report the source of sponsorship, were sponsored by the pharmaceutical industry. The length of follow-up was two to six years. The smallest study population had 56 patients,[64] and the largest one had 18,790 patients[63] at randomization. One trial[67] had 77 patients. The population of other trials[59-62,65,66] was from 100 to 600 patients. The quality assessment revealed that two trials[59,63] scored 3 and 5 respectively, four trials[62,65-67] scored 2, and three trials[60,61,64] scored 1 on the Jadad scale (Appendix 11c). The allocation concealment was unclear in all trials. One trial[63] reported the blinding of outcome assessors. Five trials[59,62,65-67] stated the use of an ITT approach in the data analysis.

Patients with diabetes were the main participants in three trials (two[60,61] of type 2 diabetes and one[62] of type 1 diabetes). Five trials[59,64-67] had a patient population consisting of subjects with kidney disease. Subjects who had diseases other than the one selected were excluded. One trial[63] included hypertensive patients who were 50 to 80 years old, with no mention of restriction regarding other disease types. Patients with type 2 diabetes[60,61] were between 40 to 74 years old, while those with type 1[62] were 18 to 40 years old. The age range of patients with kidney disease was broader: 18 to 73

years old in four trials[59,65-67] or 44 to 84 years old in one trial.[64] Patients were randomized to aim for a moderate lowering of BP to <140/90 mm Hg in one arm of the trial and a more intensive lowering of BP to <130/80 mm Hg in the other trial arm. The pharmacological methods of treatment differed among, and in, trials.

4.2.3 Data analyses and synthesis

Where possible, data from all included and relevant trials were entered into each appropriate meta-analysis. Because of the incomplete reporting of data for specific subgroups or outcomes, not all trials could be included in each relevant meta-analysis to derive summary estimates. Summary estimates [relative risk (RR) or weighted mean difference (WMD)] were computed using the random effects model, because the results obtained with the fixed and random effects model were similar when there was little to no heterogeneity (indicated by p >0.1 in the chi-squared test). Subgroup analyses were performed for some outcomes with an attempt to identify the source of heterogeneity. In trials having >1 comparator, the populations of patients receiving thiazide diuretics were counted more than once in the forest plots.

a) Does use of thiazide diuretics change morbidity, mortality, and QoL as compared to placebo, no treatment, or other anti-hypertensive drug classes?

The data that were extracted from selected trials (Appendix 12) are classified according to the comparator. The summary estimates including RR, relative risk reduction (RRR), and number needed to treat (NNT) appear in Table 4. The NNT was calculated when RR was statistically significant. The data on QoL from 26 trials comparing the effects of thiazide diuretics with other treatments are shown in Appendix 13.

Thiazide diuretics versus placebo or no treatment

Ten dichotomous and two continuous outcomes were extracted from 17 trials[13,15-18,20,21,25,26,28-30,32-36] comparing thiazide diuretics versus placebo or no treatment. The 10 dichotomous outcomes were cardiovascular events, coronary heart disease, myocardial infarction, heart failure, stroke, cerebrovascular events, renal failure, cardiovascular death, all death, and withdrawal. The two continuous outcomes were SBP and DBP.

Table 4: Clinical outcomes of thiazide diuretics versus placebo or no treatment and other anti-hypertensive drug classes

Dichotomous Outcomes	No. of Trials	No. of Patients	Heterogeneity, *P* Value	RR (95% CI)	RRR (95% CI)	NNT (95% CI)
Thiazide diuretics versus placebo/no treatment						
All CV (elderly only)	4	7,538	0.43	0.68 (0.62, 0.76)	0.32 (0.24, 0.38)	15 (12, 19)
All CV (stroke survivors)	2	6,117	0.46	0.77 (0.64, 0.91)	0.23 (0.09, 0.36)	50 (32, 128)
All CV (others)	3	14,748	0.03	0.94 (0.59, 1.50)	0.06 (-0.50, 0.54)	NS
All CV (low-quality trials)	5	8,495	0.07	0.76 (0.63, 0.93)	0.24 (0.07, 0.37)	24 (16, 80)
All CV (high-quality trials)	4	19,908	0.13	0.71 (0.60, 0.85)	0.29 (0.15, 0.40)	58 (42, 112)
All CV (all)	**9**	**28,403**	**0.07**	**0.73 (0.65, 0.83)**	**0.27 (0.17, 0.35)**	**40 (31, 63)**
CHD (elderly	3	6,698	0.47	0.72	0.28	35

Table 4: Clinical outcomes of thiazide diuretics versus placebo or no treatment and other anti-hypertensive drug classes						
Dichotomous Outcomes	**No. of Trials**	**No. of Patients**	**Heterogeneity, *P* Value**	**RR (95% CI)**	**RRR (95% CI)**	**NNT (95% CI)**
only)				(0.61, 0.85)	(0.15, 0.39)	(25, 65)
CHD (others)	4	22,828	0.80	1.07 (0.88, 1.30)	-0.07 (-0.30, 0.12)	NS
CHD (low-quality trials)	5	10,910	0.26	0.76 (0.62, 0.95)	0.24 (0.05, 0.38)	60 (38, 286)
CHD (high-quality trials)	2	29,526	0.65	1.04 (0.85, 1.28)	-0.04 (-0.28, 0.15)	NS
CHD (all)	**7**	**29,526**	**0.07**	**0.87 (0.71, 1.07)**	**0.13 (-0.07, 0.29)**	**NS**
MI (elderly only)	3	6,127	0.62	0.63 (0.48, 0.84)	0.37 (0.16, 0.52)	67 (48, 154)
MI (others)	4	5,053	0.97	0.91 (0.71, 1.16)	0.09 (-0.16, 0.29)	NS
MI (low-quality trials)	5	9,951	0.63	0.79 (0.65, 0.96)	0.21 (0.04, 0.35)	96 (58, 500)
MI (high-quality trials)	2	1,229	0.17	0.69 (0.27, 1.79)	0.31 (-0.79, 0.73)	NS
MI (all)	**7**	**11,180**	**0.58**	**0.78 (0.65, 0.94)**	**0.22 (0.06, 0.35)**	**101 (64, 368)**
HF	**3**	**1,843**	**0.36**	**0.42 (0.20, 0.89)**	**0.58 0.11, 0.80)**	**52 (38, 274)**
Stroke (elderly only)	5	4,359	0.45	0.64 (0.54, 0.77)	0.36 (0.23, 0.46)	37 (29, 58)
Stroke (stroke survivors)	2	6,117	0.80	0.80 (0.62, 1.03)	0.20 (-0.03, 0.38)	NS
Stroke (others)	3	14,125	0.80	0.32 (0.20, 0.52)	0.68 (0.48, 0.80)	121 (101, 169)
Stroke (low-quality trials)	4	7,452	0.62	0.65 (0.54, 0.78)	0.35 (0.22, 0.46)	36 (28, 57)
Stroke (high-quality trials)	6	21,149	0.02	0.58 (0.38, 0.91)	0.42 (0.09, 0.62)	120 (81, 556)
Stroke (all)	**10**	**28,601**	**0.09**	**0.62 (0.50, 0.77)**	**0.38 (0.23, 0.50)**	**79 (60, 103)**
CRV	**4**	**5,634**	**0.38**	**0.61 (0.41, 0.90)**	**0.39 (0.10, 0.59)**	**100 (66, 390)**
RF	**4**	**9,383**	**0.51**	**1.10 (0.34, 3.51)**	**-0.10 (-2.51, 0.66)**	**NS**
CV death (elderly only)	5	8,390	0.54	0.78 (0.67, 0.91)	0.22 (0.09, 0.33)	50 (33, 121)
CV death (others)	3	16,477	0.07	0.66 (0.37, 1.17)	0.34 (-0.17, 0.63)	NS
CV death (low-quality trials)	5	10,224	0.46	0.73 (0.61, 0.87)	0.27 (0.13, 0.39)	62 (43, 129)
CV death (high-quality trials)	3	14,643	0.20	0.90 (0.69, 1.16)	0.10 (-0.16, 0.31)	NS
CV death (all)	**8**	**24,867**	**0.27**	**0.79 (0.68, 0.92)**	**0.21 (0.08, 0.32)**	**121 (80, 318)**
All death (elderly only)	6	8,941	0.70	0.90 (0.82, 1.00)	0.10 (0.00, 0.18)	NS
All death (stroke	3	6,216	0.27	0.87	0.13	NS

Table 4: Clinical outcomes of thiazide diuretics versus placebo or no treatment and other anti-hypertensive drug classes						
Dichotomous Outcomes	**No. of Trials**	**No. of Patients**	**Heterogeneity, *P* Value**	**RR (95% CI)**	**RRR (95% CI)**	**NNT (95% CI)**
survivors)				(0.67, 1.11)	(-0.11, 0.33)	
All death (others)	8	19,203	0.26	0.85 (0.63, 1.16)	0.15 (-0.16, 0.37)	NS
All death (low-quality trials)	11	13,211	0.49	0.85 (0.76, 0.95)	0.15 (0.24, 0.05)	67 (42, 200)
All death (high-quality trials)	6	21,149	0.80	0.97 (0.87, 1.09)	0.03 (-0.09, 0.13)	NS
All death (all)	**17**	**34,360**	**0.55**	**0.91 (0.84, 0.98)**	**0.09 (0.02, 0.16)**	**170 (96, 763)**
Withdrawals due to AE (elderly only)	2	6,116	<0.00001	2.70 (1.28, 5.73)	-1.70 (-0.28, -4.73)	NNH: 8 (3, 48)
Withdrawals due to AE (others)	3	595	0.01	0.59 (0.08, 4.21)	0.41 (-3.21, 0.92)	NS
Withdrawals due to AE (all)	**5**	**6,711**	**<0.00001**	**1.58 (0.77, 3.22)**	**-0.58 (-2.22, 0.23)**	**NS**
Thiazide diuretics versus ACE inhibitors						
All CV	**2**	**30,392**	**0.01**	**0.99 (0.87, 1.12)**	**0.01 (-0.12, 0.13)**	**NS**
CHD	**2**	**30,392**	**0.33**	**1.03 (0.96, 1.11)**	**-0.03 (-0.11, 0.04)**	**NS**
HF	**2**	**30,392**	**0.09**	**0.94 (0.71, 1.24)**	**0.06 (-0.24, 0.29)**	**NS**
Stroke	**3**	**31,249**	**0.44**	**0.88 (0.80, 0.98)**	**0.12 (0.02, 0.20)**	**83 (50, 497)**
All death	**3**	**31,249**	**0.66**	**1.00 (0.95, 1.07)**	**0.00 (-0.07, 0.05)**	**NS**
Withdrawals due to AE	**1**	**24,309**	**NA**	**0.99 (0.96, 1.01)**	**0.01 (-0.01, 0.04)**	**NS**
Thiazide diuretics versus β-blockers						
All CV	**3**	**12,844**	**0.0010**	**0.96 (0.69, 1.33)**	**0.04 (-0.33, 0.31)**	**NS**
CHD	**4**	**19,413**	**0.001**	**0.97 (0.73, 1.28)**	**0.03 (-0.28, 0.27)**	**NS**
Stroke	**3**	**16,179**	**0.003**	**0.80 (0.45, 1.42)**	**0.20 (-0.42, 0.55)**	**NS**
CV death	**3**	**12,844**	**0.02**	**0.99 (0.67, 1.46)**	**0.01 (-0.46, 0.33)**	**NS**
All death	**4**	**19,413**	**0.05**	**1.02 (0.83, 1.25)**	**-0.02 (-0.25, 0.17)**	**NS**
Withdrawals due to AE	**2**	**7,479**	**<0.00001**	**0.75 (0.30, 1.87)**	**0.25 (-0.87, 0.70)**	**NS**
Thiazide diuretics versus calcium channel blockers						
All CV (low-quality trials)	3	3,179	0.16	0.80 (0.55, 1.17)	0.20 (-0.17, 0.45)	NS
All CV (high-quality trials)	2	25,717	0.77	0.96 (0.92, 1.00)	0.04 (0.00, 0.08)	NS
All CV (all)	**5**	**28,896**	**0.35**	**0.95 (0.86, 1.04)**	**0.05 (-0.04, 0.14)**	**NS**
CHD	**3**	**26,600**	**0.33**	**0.88**	**0.12**	**NS**

Table 4: Clinical outcomes of thiazide diuretics versus placebo or no treatment and other anti-hypertensive drug classes						
Dichotomous Outcomes	**No. of Trials**	**No. of Patients**	**Heterogeneity, *P* Value**	**RR (95% CI)**	**RRR (95% CI)**	**NNT (95% CI)**
				(0.47, 1.67)	**(-0.67, 0.53)**	
MI	**5**	**11,168**	**0.98**	**0.92 (0.72, 1.19)**	**0.08 (-0.19, 0.28)**	**NS**
HF	**4**	**33,174**	**0.25**	**0.71 (0.54, 0.95)**	**0.29 (0.05, 0.46)**	**62 (39, 358)**
Stroke (low-quality trials)	4	9,754	0.63	1.04 (0.80, 1.35)	-0.04 (-0.35, 0.20)	NS
Stroke (high-quality trials)	2	25,717	0.77	1.06 (0.94, 1.20)	-0.06 (-0.20, 0.06)	NS
Stroke (all)	**6**	**35,471**	**0.87**	**1.06 (0.95, 1.18)**	**-0.06 (-0.18, 0.05)**	**NS**
CRV	**2**	**1,828**	**0.79**	**0.69 (0.33, 1.43)**	**0.31 (-0.43, 0.67)**	**NS**
RF	**2**	**30,878**	**0.19**	**1.03 (0.62, 1.71)**	**-0.03 (-0.71, 0.38)**	**NS**
All death (low-quality trials)	3	9,340	0.54	0.92 (0.79, 1.08)	0.08 (-0.08, 0.21)	NS
All death (high-quality trials)	2	25,717	0.69	1.04 (0.98, 1.11)	0.04 (-0.11, 0.02)	NS
All death (all)	**5**	**35,057**	**0.50**	**1.02 (0.96, 1.08)**	**-0.02 (-0.08, 0.04)**	**NS**
Withdrawals due to AE	**4**	**32,706**	**0.0007**	**0.92 (0.67, 1.28)**	**0.08 (-0.28, 0.33)**	**NS**

Continuous Outcomes	**No. of Trials**	**No. of Patients**	**Heterogeneity, *P* Value**	**WMD (95% CI)**
Thiazide diuretics versus placebo or no treatment				
SBP (elderly only)	6	9,841	<0.00001	-15.58 (-19.66, -11. 51)
SBP (others)	5	19,528	<0.00001	-21.85 (-28.88, -14.82)
SBP (all)	11	28,369	<0.00001	-18.28 (-22.09, -14.47)
DBP (elderly only)	6	8,941	<0.00001	-6.52 (-9.52, -3.51)
DBP (others)	7	23,071	<0.00001	-12.36 (-15.64, -9.07)
DBP (all)	13	32,012	<0.00001	-9.61 (-11. 80, -7.42)
Thiazide diuretics versus ACE inhibitors				
SBP	3	31,249	<0.00001	-0.07 (-2.48, 2.34)
DBP	3	31,249	1.00	0.00 (-0.22, 0.22)
Thiazide diuretics versus β-blockers				
SBP	4	19,413	0.0001	-0.75 (-1.97, 0.47)
DBP	4	19,413	0.007	0.55 (-0.08, 1.18)
Thiazide diuretics versus calcium channel blockers				
SBP	5	33,589	0.0005	-1.19 (-2.18, -0.20)
DBP	6	35,471	<0.0001	0.02 (-0.52, 0.56)

AE=adverse events; CHD=coronary heart disease events; CI=confidence interval;CRV=cerebrovascular events; CV=cardiovascular events; DBP=diastolic blood pressure; HF=heart failure events; MI=myocardial infarction events; NNT=number needed to treat; NR=not reported; NS=not statistically significant; ; RD=risk difference; RF=renal failure; RR=relative risk; RRR=relative risk reduction; SBP=systolic blood pressure; WMD= weighted mean difference

All cardiovascular (CV) events: When all CV events were pooled from nine trials[15,18,20,25,26,28,29,32,36] with a total population of 28,403 subjects, the RR (95% CI) of thiazide diuretics compared to placebo or no treatment was 0.73 (0.65, 0.83), which was statistically significant (Figure 3). The chi-squared test revealed that there was some heterogeneity (p=0.07). Of the nine trials, four[15,18,26,32] exclusively involved ≥60-year-old subjects, two[20,29] had only stroke or transient ischemic survivors, and three[25,28,36] had mild to moderate hypertensive subjects (20- to 64-years-old) in the study population. Of the nine trials, five[15,26,28,32,36] were of low quality, and four were of high quality.[18,20,25,29]

The subgroup analyses showed that thiazide diuretics treatment for elderly (>60-years-old) and stroke survivor subjects significantly reduced the risk of CV events by 32% and 23% respectively, compared to placebo or no treatment. The RR of the remaining population, 0.94 (0.59, 1.50), was not statistically significant. Furthermore, the subgroup analyses showed that the results were unaffected by trial quality.

Coronary heart disease (CHD) events: When CHD events were pooled from seven trials[13,15,25,26,28,29,32] with a total population of 29,526 subjects, the RR was not statistically significant [0.87 (0.71, 1.07)], and the *P* value for heterogeneity was 0.07 (Figure 4). Of the seven trials, three[15,26,32] had only elderly subjects in the study population. Of the seven trials, five[13,15,26,28,32] were of low quality, and two[25,29] were of high quality.

Subgroup analyses showed that thiazide diuretics treatment of the elderly significantly reduced the risk of having CHD by 28%, compared to placebo or no treatment. The RR of the remaining population in three trials[13,25,28] and stroke survivors in one trial,[29] 1.07 (0.88, 1.30), was not statistically significant. Low-quality trials showed a statistically significant difference, while high-quality trials did not.

Myocardial infarction (MI) events: When MI events were pooled from seven trials[13,18,20,28,30,32,33] with a total population of 11,180 subjects, the RR (95% CI) was 0.78 (0.65, 0.94), and the *P* value for heterogeneity was 0.58 (Figure 5). Of the seven trials, five[13,20,28,32,33] are of low quality and two are of high quality.[18,30]

The subgroup analysis of trials[18,32,33] consisting of elderly subjects showed a statistically significant RR [0.63 (0.48, 0.84)], while the analysis of remaining trials[13,20,28,30] including one having stroke survivors had a non-statistically significant RR [0.91 (0.71, 1.16)] for MI. Thus, the effect of thiazide diuretics in the risk reduction of MI was more apparent in trials that included elderly patients only. Low quality trials showed a statistically significant difference, while high quality trials did not.

Heart failure (HF) events: Of the three trials[18,20,33] that reported HF events in a total population of 1,843 subjects, two trials[18,33] included elderly patients only and one[20] included stroke survivors. The RR (95% CI) for HF was 0.42 (0.20, 0.89), which was statistically significant (Figure 6). There was no significant heterogeneity among the three trials (p=0.36).

Stroke: When stroke events were pooled from 10 trials[18,20,21,25,26,28-30,32,33] with a total population of 28,601 subjects, the RR (95% CI) was 0.62 (0.50, 0.77), which was statistically significant (Figure 7). There was some heterogeneity among trials (p=0.09). Of those 10 trials, five[18,21,26,32,33] included elderly subjects only, two[20,29] included stroke survivors, and three[25,28,30] included mild to moderate hypertensive subjects who were 21- to 64-years-old. Of the 10 trials, four[26,28,32,33] are of low quality and six are of high quality.[18,20,21,25,29,30]

Subgroup analyses showed that the RR (95% CI) for stroke among the elderly and mild to moderate hypertensive subjects with a broader range of ages were 0.64 (0.54, 0.77) and 0.32 (0.20, 0.52), respectively. The RR for stroke in the stroke survivors subgroup was not statistically significant [0.80 (0.62, 1.03)]. Further subgroup analyses showed that the results were not affected by trial quality.

Cerebrovascular (CRV) events: When the CRV events were pooled from four trials[13,15,18,28] with a total population of 5,634 subjects, the RR (95% CI) was 0.61 (0.41, 0.90), which was statistically significant (Figure 8). There was no significant heterogeneity among trials (p=0.38).

Renal failure (RF) events: Four trials[13,18,32,35] reported RF events, of which the RR (95% CI) was not statistically significant [1.10 (0.34, 3.51)] (Figure 9). The *P* value for heterogeneity was 0.51.

Cardiovascular (CV) death: When CV deaths were pooled from eight trials[13,15,17,18,21,25,26,32] with a total population of 24,867 subjects, the RR (95% CI) was 0.79 (0.68, 0.92), which was statistically significant (Figure 10). Of the eight trials, five[15,18,21,26,32] included elderly subjects only, and three[13,17,25] included stroke survivors and mild to moderate hypertensive subjects who were 30- to 69-years-old. Of the eight trials, five[13,15,17,26,32] are of low quality and three are of high quality.[18,21,25]

Subgroup analyses revealed that the RR (95% CI) for CV death in the elderly population (8,390 subjects) was statistically significant [0.78 (0.67, 0.91)], while that of the remaining population (16,477 subjects), including stroke survivors in one trial[17] and mild to moderate hypertensive patients with a broader range of ages in two trials,[13,25] was not statistically significant [0.66 (0.37, 1.17)]. Low-quality trials showed a statistically significant difference, while high-quality trials did not.

All death: When deaths due to any cause (all-death) were pooled from 17 trials[13,15-18,20,21,25,26,28-30,32-36] with a total population of 34,360 subjects, the RR (95% CI) was significant [0.91 (0.84, 0.98)] (Figure 11). Of those 17 trials, six trials involved elderly patients only (8,941 subjects), three trials involved stroke survivors (6,216 subjects), and eight trials involved mild to moderate hypertensive subjects with a broader range of ages (19,203 subjects). Of the 17 trials, 11[13,15-17,26,28,32-36] are of low quality and six[18,20,21,25,29,30] are of high quality.

The analyses based on the population difference revealed that none of the RR values for the three subgroups was statistically significant. The *P* values for heterogeneity among all trials and trials in each subgroup were >0.1, indicating no heterogeneity. Low-quality trials showed a statistically significant difference, while high-quality trials did not.

Withdrawal: Many trials did not report the number of withdrawals due to adverse events. When the number of patients who withdrew because of adverse events during treatment were pooled from five trials[16,17,26,32,35] with a total population of 6,711 subjects, the RR (95% CI) was not statistically significant [1.58 (0.77, 3.22)], and the *P* value for heterogeneity was <0.00001 (Figure 12). The subgroup analyses revealed that the RR (95% CI) for withdrawals due to adverse events in the elderly population (6,116 subjects) in two trials[26,32] was statistically significant [2.70 (1.28, 5.73)], indicating that more elderly patients withdrew from thiazide diuretics treatment than from placebo or no treatment.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP): The weighted mean differences (WMD) for SBP and DBP were all negative and statistically significant (Figures 13 and 14), indicating that thiazide diuretics effectively lowered BP compared to placebo or no treatment. The *P*

values for heterogeneity were all < 0.00001. The subgroup analyses of elderly patients and the rest of the population also showed negative and statistically significant WMD values for SBP and DBP.

Quality of life (QoL): Nine trials[25,32,35,36,40,42,43,56,58] compared thiazide diuretics with placebo, with a sample size ranging from 176[42] to 12,951 patients[32] and a follow-up time ranging from two months[42] to 7.5 years.[36] The results from these studies are conflicting, with two trials showing no significant differences between treatment and placebo[35,40] and seven trials[25,32,36,42,43,56,58] indicating a higher incidence of male sexual dysfunction in the group taking thiazide diuretics. One[42] of the seven trials showed a statistical difference (with a *P* value of <0.01), while the rest showed numbers without providing a statistical analysis.

Thiazide diuretics versus angiotensin-converting enzyme (ACE) inhibitors

Six dichotomous and two continuous outcomes were extracted from three trials[12,14,21] comparing thiazide diuretics versus ACE inhibitors, for a meta-analysis. The dichotomous outcomes of all-CV, CHD, and HF were reported from two trials[12,14] with a total population of 30,392 subjects, while stroke and all-death were reported from three trials with a total population of 31,249 subjects. The numbers of withdrawals due to adverse events were reported in one trial.[12] The two continuous outcomes of SBP and DBP were reported from all three trials.

The meta-analyses revealed that the RR for all-CV (Figure 15), CHD (Figure 16), HF (Figure 17), and all-death (Figure 19) were not statistically significant. The WMD for SBP (Figure 21) and DBP (Figure 22) were also not statistically significantly different. The RR (95% CI) for stroke was 0.88 (0.80, 0.98) (Figure 18), indicating that subjects treated with thiazide diuretics were 12% less likely than ACE inhibitor-treated subjects to have stroke events. Withdrawals due to adverse events (Figure 20) were not statistically significant between treatments.

QoL: The QoL in patients on thiazide diuretics compared with those on ACE inhibitors was reported in nine trials,[41,44-48,53,54,56] with study populations ranging in size from 30[45] to 1,182 patients,[47] and with follow-up times from one year[45] to four years[56]. Thiazide diuretics were found to cause male sexual dysfunction in two trials;[54,56] ACE inhibitors were reported to result in better QoL in two trials;[47,48] while four trials showed no differences between treatments.[44,45,46,53] The outcome data were mostly descriptive without numbers or with numbers, but no statistical analysis.

Thiazide diuretics versus β-blockers (BB)

Six dichotomous and two continuous outcomes were extracted from four trials[19,23,25,26] comparing thiazide diuretics to BB, for a meta-analysis. The dichotomous outcomes were all-CV, CHD, stroke, CV death, all-death, and withdrawal, while the continuous outcomes were SBP and DBP. Not every trial reported all outcomes.

The meta-analyses revealed that the RR for all six dichotomous outcomes (Figures 23 to 28) and the WMD for SBP (Figure 29) and DBP (Figure 30) were not statistically significant. The *P* values for heterogeneity of all outcomes were <0.1.

QoL: Twelve trials[19,40,41,44,48,49,51,52,54,56-58] compared thiazide diuretics with AB or BB, with a study population ranging from 29[51] to 8,700 patients[25] and follow-up times from four weeks[51] to four years.[56] No differences in QoL between treatments were reported in seven trials;[40,41,44,48,51,52,57] three trials[49,56,58] showed a higher incidence of male sexual dysfunction with thiazide or chlorthalidone treatment; and one trial[19] showed that patients on BB experienced a higher incidence of QoL

disturbances. One trial[54] showed that both treatments were associated with an increased incidence of sexual dysfunction. There were no statistical analyses for the sexual dysfunction data.

Thiazide diuretics versus calcium channel blockers (CCB)

Nine dichotomous and two continuous outcomes were extracted and meta-analyzed from six trials[12,22,24,27,31,38] comparing thiazide diuretics versus CCB. The dichotomous outcomes were all-CV, CHD, MI, HF, stroke, CRV, RF, all-death, and withdrawal, while the continuous outcomes were SBP and DBP. Not every trial reported all outcomes.

The meta-analyses revealed that the RR values for all-CV (Figure 31), CHD (Figure 32), MI (Figure 33), stroke (Figure 35), CRV (Figure 36), RF (Figure 37), all-death (Figure 38), and withdrawal (Figure 39) were not statistically significant. The SBP (Figure 40) in the thiazide group was significantly lower than that in the CCB group, while the DBP (Figure 41) was not different. The RR (95% CI) for HF was 0.71 (0.54, 0.95) (Figure 34), indicating that subjects who were treated with thiazide diuretics were 29% less likely than CCB-treated subjects to have a heart failure event. The *P* values for heterogeneity of all outcomes were >0.1, except for the outcomes of withdrawals, SBP, and DBP.

The subgroup analyses based on trial quality where it was applicable – such as for all-CV, stroke, and all-death – revealed that the results were unaffected by trial quality.

QoL: Thiazide diuretics were compared with CCB in seven trials,[31,38,41,48,50,54,56] with a study population ranging from 172[48] to 1,882 patients[31] and a follow-up time of eight months[48] to five years.[50] No significant differences between treatments were found in four trials;[31,41,48,50] one trial[38] showed that verapamil was associated with a higher rate of sexual dysfunction, while another trial[56] showed the same for men who were treated with chlorthalidone. One trial[54] showed that both treatments caused sexual dysfunction. QoL outcome data were descriptive or presented without statistical analysis.

Thiazide diuretics versus ARB

No studies comparing the effects of thiazide diuretics with those of angiotensin receptor blockers (ARB) on morbidity and mortality were identified.

The QoL in patients on thiazides and ARB was compared in three trials,[39,46,55] covering 392, 429, and 69 patients, with follow-up times of one year, 12 weeks, and 28 months respectively. No difference was found between candesartan and thiazide in two trials,[39,46] while one trial found that losartan improved QoL.[55]

b) Does aiming for blood pressure targets <140/90 mm Hg result in a difference in morbidity and mortality compared to the standard blood pressure target of 140/90 mm Hg?

Clinical outcomes from trials related to question 3 appear in Appendix 14. Of the dichotomous outcomes extracted from nine trials, five outcomes (all-death, CV death, RF, stroke, and MI) could be meta-analyzed (Table 5).

When all-death events were pooled from eight trials[59-61,63-67] with a total population of 15,878 subjects, the RR (95% CI) was 0.99 (0.78, 1.26), which was not statistically significant (Figure 42). Of those eight trials, five[59,64-67] included patients with kidney disease, and two[60,61] included patients with diabetes in the study population. The subgroup analyses showed that the RR for all-death in

chronic kidney disease (Figure 43) and diabetic patients (Figure 44) were not statistically significant. The *P* values for heterogeneity in all cases were >0.1.

When CV death events (Figure 45) were pooled from two trials,[61,63] with 13,006 subjects, the RR (95% CI) was not statistically significant [0.88 (0.67, 1.15)]. The *P* value for heterogeneity was 0.51. For stroke (Figure 46) and MI (Figure 47), the RR were not statistically significant.

Table 5: Clinical outcomes in moderate versus intensive lowering of BP

Dichotomous Outcomes	Number of Trials	Number of Patients	Heterogeneity, *P* Value	RR (95% CI)
All death (all)	8	15,878	0.22	0.99 (0.78, 1.26)
All death (chronic kidney disease)	5	2,402	0.43	0.85 (0.62, 1.18)
All death (diabetics)	2	950	0.19	1.44 (0.81, 2.57)
CV death	2	13,006	0.51	0.88 (0.67, 1.15)
Stroke	2	13,006	0.06	1.60 (0.56, 4.55)
MI	2	13,006	0.23	1.07 (0.74, 1.54)
RF	5	2,402	0.23	1.09 (0.91, 1.31)

Continuous Outcomes	Number of Trials	Number of Patients	Heterogeneity, *P* Value	WMD (95% CI)
SBP	8	15,878	<0.00001	7.25 (3.96, 10.53)
DBP	8	15,878	<0.00001	5.33 (4.11, 6.56)

BP=blood pressure; CI=confidence interval;CV=cardiovascular events; MI=myocardial infarction; RF=renal failure; RR=relative risk

For the assessment of kidney function after patients underwent treatments to reach moderate or intensive BP lowering, six trials[59-62,66,67] of eight showed no significant differences in glomerular filtration rate, serum creatinine, or creatinine clearance. One study by Ikeda *et al*.,[64] with 28 patients in each arm, showed that patients in the intensive BP reduction arm had significantly lower serum creatinine and better creatinine clearance than those in the moderate BP arm. When RF (Figure 48) were pooled from five trials[64-68] with a total population of 2,402 chronic kidney disease subjects, the RR (95% CI) was not statistically significant [1.09 (0.91, 1.31)]. The *P* value for heterogeneity was 0.23.

Two trials[60,61] of type 2 diabetic patients (hypertensive or normotensive patients) reported that the intensive lowering of BP below the target did not make any significant difference in terms of MI, CHD, or retinopathy. There was no difference between the two BP targets for kidney function measured using creatinine clearance. In type 1 diabetic subjects, creatinine clearance did not differ between intensive and moderate BP lowering, although proteinuria was significantly reduced by the intensive approach.

The WMD (95% CI) for SBP (Figure 49) and DBP (Figure 50) were 7.25 (3.96, 10.53) and 5.33 (4.11, 6.56), respectively. The intensive lowering of BP reduced SBP and DBP by 7.25 mm Hg and 5.33 mm Hg, respectively – more than that which was achieved by treating to the moderate target of 140/90 mm Hg.

Based on the available information from the included RCTs, no evidence was found that lowering BP <140/90 mm Hg target had any benefit in reducing the risks of morbidity and mortality, despite different treatment modalities or groups of patients.

4.2.4 Discussion

The clinical part of this report aims to answer two questions. The first question is whether first-line treatment with thiazide diuretics changes morbidity and mortality compared to placebo or to first-line treatment with other anti-hypertensive drug classes. The second question is whether reducing BP below the standard target of 140/90 mm Hg for the general population or for hypertensive patients with diabetes or renal disease, using any treatment, affects morbidity and mortality.

a) Thiazide diuretics versus placebo and other drug classes

In the clinical trials of thiazide diuretics versus placebo and other drug classes, four comparators were identified: placebo or no treatment, ACEI, BB, and CCB. No evidence related to thiazide diuretics versus AB or ARB was found. In addition to outcomes related to cardiovascular, cerebrovascular, and renal morbidity and mortality, data were collected from trials reporting the QoL of patients who were treated with thiazide diuretics compared to placebo, ACEI, AB, BB, CCB, and ARB.

b) Thiazide diuretics versus placebo or no treatment

Compared to placebo or no treatment, thiazide diuretics significantly reduced the risks of all-CV events (27%), stroke (38%), CRV (39%), and CV death (21%) in a population of mild to moderate hypertensive subjects. Similar findings were reported in a meta-analysis.[69] The reduced risk reduction of all-CV events, including MI and CHD, and CV death, which was achieved with thiazide diuretics, seems to be significant in higher mortality risk populations such as seniors, but not in low risk populations such as middle-aged subjects without co-morbidities. A meta-analysis by Hoe *et al.*[70] using weighted linear regression showed that thiazide diuretics treatment reduced all-cause death and CV death in the high mortality risk populations, but had no, or negative, effect on patients at lower mortality risk. No significant difference for risk of stroke was found in the population of stroke survivors.

RF was not the primary outcome of most trials. Therefore, the meta-analysis of four trials showed no significant differences between active treatment and placebo. For all-cause death, there was no significant difference between treatments in subgroup analyses based on population differences. The follow-up time could be a factor (i.e., not long enough) in revealing any difference regarding mortality in the selected hypertensive population. Although overall withdrawals due to adverse events during the study were not significantly different between treatments, more seniors withdrew from the thiazide diuretics treatment arm than from placebo. The causes of the higher withdrawal of seniors in the thiazide diuretics arm were not reported.

The QoL results are conflicting among trials. The trials of short-term follow-up (few months to one year) often reported no significant difference in QoL between treatment and placebo. On the other hand, the trials of long-term follow-up (≥2 years) showed a higher incidence of psychosocial problems (i.e., fatigue, sleep dysfunction, anxiety, memory trouble, depression, nightmares, loss of appetite) in the active treatment group than in the placebo group. Seven of nine trials indicated a higher incidence of male sexual dysfunction in the thiazide diuretics group. Although it was less frequent at low doses, other significant side effects of thiazide diuretics including hypokalemia, hyponatremia, renal dysfunction, dyslipidemia, hyperglycemia, and gout have been reported.[71,72] Elderly hypertensive patients might be more susceptible to these side effects and to psychosocial problems leading to a high incidence of withdrawal.

In summary, thiazide diuretics reduced the risk of all-CV events including MI, HF, and cerebrovascular events including stroke in subjects with uncomplicated essential hypertension compared to placebo or no treatment. The risk reduction induced by thiazide diuretics for certain cardiovascular events such as CHD, MI, and CV death was more significant in seniors than in middle-aged subjects. Psychosocial problems that could affect the QoL of subjects treated with thiazide diuretics were identified.

c) Thiazide diuretics versus ACE inhibitors

There were no significant differences between thiazide diuretics and ACE inhibitors for all-CV events including CHD and HF, all-cause death, RF, withdrawal, and BP reduction. Thiazide diuretics, however, significantly reduced the risk of stroke by 12% relative to ACE inhibitors.

The combined study population consisted of ≥55-year-old subjects with mild to moderate hypertension. In the three trials that met the inclusion criteria for thiazide diuretics versus ACE inhibitors, the combined population was 31,249. More than two-thirds of the population were from one trial (ALLHAT)[12] and had at least one additional cardiovascular risk factor. African-Americans, who were more than half of the population in ALLHAT, had higher risks of developing stroke and combined CVD with lisinopril than with chlorthalidone.[73] This is because the African-American population has comparatively low plasma rennin activity and may respond better to thiazide diuretics than to ACE inhibitors. No significant differences in RF rates were found between treatments based on the findings reported from this large trial.

The QoL results showed no significant differences between treatments or were favourable with ACE inhibitors in trials with short-term follow-up (i.e., <1 year). In trials with long-term follow-up, evidence showed that thiazide diuretics might be associated with sexual dysfunction in men.

Thus, although there were no significant differences for the risks of cardiovascular morbidity and mortality between treatments, thiazide diuretics seem to be better than ACE inhibitors in reducing the risk of stroke. The effect of long-term treatment with thiazide diuretics on male sexual function should be considered.

d) Thiazide diuretics versus BB

Four trials with middle-aged and elderly subjects showed no significant differences between treatments for all-CV events including CHD and stroke. The reduction in BP, incidence of withdrawal, all-cause death, and CV death were not statistically significant between treatments. In general, the QoL results showed no significant differences between treatments. Both treatments might be associated with male sexual dysfunction, although thiazide diuretics appear to be associated with a higher incidence.

e) Thiazide diuretics versus CCB

The study population of trials comparing thiazide diuretics and CCB consisted of middle-aged and elderly subjects, 87% of whom had at least one CV risk factor. There were no significant differences between treatments for all-CV events including CHD and MI, and CRV events including stroke. The reduction in BP, incidence of withdrawal, RF, and all-cause death were not statistically significant between treatments. Thiazide diuretics, however, significantly reduced the risk of HF by 29% relative to CCB treatment. HF was higher with amlodipine versus chlorthalidone in the ALLHAT trial[12] population, which was 69% of the total population. In black and non-black patients, the rates of HF were higher for amlodipine than for chlorthalidone.[73] This was unlikely due to the poor response to BP reduction by CCB, because no difference in BP reduction was observed between

CCB and thiazide diuretics. Therefore, these findings suggest that CCBs are less effective than thiazide diuretics in the prevention of HF.

The QoL results and side effects showed no significant differences between treatments. Both treatments might be linked with male sexual dysfunction.

f) Comments

This meta-analysis assumed that anti-hypertensive treatments based on each drug class were constant across trials. Given that some subjects did not respond to first-line treatment, a step-care or combination therapy approach was followed in most trials to achieve the BP goal. The goal also varied between trials and was usually higher for seniors than for middle-aged hypertensive subjects. In each drug class, the doses and drug types differed among trials. Some trials included seniors exclusively in the study population, while others included middle-aged males only or subjects with a range of ages. Most trials excluded subjects who had secondary hypertension or previous CV events and other diseases. The population in two trials[12,22] consisted of hypertensive subjects having at least one additional CV risk factor. Three trials[17,20,29] included only stroke or transient ischemic survivors. These factors might be sources of heterogeneity. A random-effects model was used to compute summary estimates with the assumption that variability existed in and between trials. Whenever heterogeneity occurred, an attempt was made to identify its source by conducting subgroup analysis based on the age of the population. This could be a limitation of this meta-analysis, because heterogeneity might also be derived from a variation in methods. Because most trials used a selected population that might not be generalizable, the results from this report should be interpreted cautiously, because they might be inapplicable to hypertensive subjects having concomitant CV diseases.

The quality assessed using the Jadad scale varied among trials. Because of the limited number of trials and the irregularity of outcome reporting among trials, a subgroup analysis based on trial quality was not possible for some comparisons such as thiazide diuretics versus ACE inhibitors and thiazide diuretics versus BB. For thiazide diuretics versus placebo or no treatment, there were enough trials to perform subgroup analyses based on trial quality for outcomes such as all-CV, CHD, MI, stroke, CV death, and all-death. The results were unaffected by trial quality (all-CV, stroke) or there were significant differences with low quality trials only (CHD, MI, CV death, all-death). For thiazide diuretics versus CCB, the subgroup analyses of outcomes such as all-CV, stroke, and all-death showed that the results were unaffected by trial quality. It was uncertain whether trials with a low score were poorly conducted or poorly reported. Two-thirds of the trials were of low quality. Most trials had inadequate or unclear allocation concealment, and this has been associated with biased estimates of effectiveness.[10]

The limitations of the QoL analyses included the use of non-standardized tools, the subjective conclusion of the unpublished data in some cases, the non-blinding in trials, and the lack of statistical analyses of some QoL outcome data. These limitations made it impossible to pool the data and derive a point estimate.

One limitation of this review is the lack of identification of the effect of thiazide diuretics on subpopulations with specific comorbidities. Hypertensive patients often have comorbidities, and most need >1 drug to achieve optimal BP control. Which monotherapy is most appropriate for first-line use is part of the clinical question. The European guidelines[74] regarding the management of arterial hypertension emphasize the selection of a first-line agent according to patients'

comorbidities. Thus, systematic reviews should be conducted to examine which agent is suitable as first-line therapy for hypertensive patients with specified comorbidities or diseases.

g) BP target

There is no evidence that the reduction of BP below the standard target of 140/90 mm Hg for the general population, for diabetic patients, or for chronic kidney disease subjects changes morbidity and mortality. The total study population of included trials consisted of hypertensive nephropathic subjects, hypertensive or normotensive diabetic subjects, and mild to moderate hypertensive subjects without comorbidities. In all cases, the intensive lowering of BP below the standard target did not result in any risk reduction of all-cause death, death related to CV events, or RF. No differences in renal function were found after intensive and moderate lowering of BP. No significant differences in health-related QoL were seen between intensive and moderate lowering of BP in groups of African-Americans with hypertensive kidney disease.[75] The HOT study[76] showed that the lowering of DBP <80 mm Hg or <85 mm Hg resulted in improved well-being, but was associated with a deterioration of sex life in male patients and an increase in the number of swollen ankles and dry cough.

5 ECONOMIC REVIEW AND ANALYSIS

5.1 Review of Economic Studies

A review of economic evaluations compared the use of thiazide diuretics to the use of other drugs as first-line therapy of hypertension.

5.1.1 Methods

a) Literature search strategy

The bibliographic databases searched for the review were OVID's MEDLINE (1966 to present; In-Process & Other Non-Indexed Citations), EMBASE (1980 to present), and BIOSIS Previews (1985 to present); PubMed; The Cochrane Library; and the Health Economic Evaluations Database HEED. Controlled vocabulary and keywords for the primary search included "thiazide diuretics," "sodium chloride symporter inhibitors," the brand and generic names of specific pharmacological agents, and "hypertension" (Appendix 15). A methodological filter was applied to limit the retrieval to studies with economic components. Only English-language publications were included in the criteria. Update searches were performed at predefined intervals during the project.

Grey literature was obtained through searching the web sites of health technology assessment and related agencies and their associated databases. Google™ and other Internet search engines were used to search for additional information. The web sites of professional associations such as the Canadian Hypertension Society, Canadian Cardiovascular Society, American Society of Hypertension, American College of Cardiology, American Heart Association, American Stroke Association, European Stroke Initiative, International Society for Pharmacoeconomics and Outcomes Research, the International Health Economics Association, and their associated conference sites were searched for additional information.

b) Selection criteria

Studies were included in this review if they met the following criteria:

- they were related to the initial treatment of primary hypertension in an adult population – excluding studies that were related to specific disease subgroups
- they were full economic evaluations: cost-effectiveness, cost-utility, or cost-benefit analyses; or cost-minimization analyses with a statement that the effectiveness of comparative therapies was assumed to be the same (There is debate about whether cost-minimization analyses should be considered to be full economic evaluations. To be comprehensive, they are included in this review, although this is not an endorsement for their use or appropriateness.)
- they were published in the English language
- they were published as full reports, either as peer reviewed publications or as technical reports, i.e., no abstracts
- they were studies comparing thiazide diuretics monotherapy to at least one other class of anti-hypertensive therapy or to no therapy.

c) Selection method

The literature search was used to identify 1,740 studies. The abstracts and titles of these studies were reviewed, and 103 were identified as potentially relevant. Full papers and reports for the 103 studies were examined, and 16 were found to be relevant for inclusion in the literature review (Figure 51).

d) Data extraction strategy

The following data were extracted from studies: authors, country of origin, year of study, type of analysis, study population, comparators, whether the study was funded by the pharmaceutical industry, outcome measures for the economic analysis, and the main results. No attempt was made to synthesize the results. The review of studies was presented in a narrative form rather than as a formal quantitative review.

What is an acceptable incremental cost-effectiveness ratio is open to interpretation and will vary by jurisdiction, and possibly by year and medical area. Thus, it is difficult to interpret published studies in this respect. In this report, where reference is made to a therapy being the most cost-effective, this is as defined by the authors of the studies. Cost-effectiveness relates to a therapy being less costly and more effective or to a therapy being more effective at an increased cost with an incremental cost per unit of effectiveness gained that is considered to be acceptable.

5.1.2 Results

Appendix 16 details the 16 relevant studies. Six studies were from the US, three from Sweden, and one from each of Spain, UK, Canada, Greece, Italy, and New Zealand. One further study was conducted for several jurisdictions.

Three studies were cost-utility studies incorporating quality adjusted life-years (QALYs).[77-79] Ten studies were cost-effectiveness analyses with the following outcomes used as effectiveness measures: life-years gained,[80-83] deaths prevented,[84,85] cardiovascular events prevented,[86,87] control of BP,[88] and compliance.[89] Three studies were cost-minimization analyses that assumed an equal benefit between treatment options.[90-92]

Thiazide diuretics were compared to BB in 14 studies, ACE inhibitors or ARB in 14 studies, and CCB in 13 studies. In seven studies, the thiazide diuretic used in the analysis was stated: three with hydrochlorothiazide, three with chlorthalidone, and one with indapamide.

In two cost-minimization analyses, thiazide diuretics were the least costly initial therapy. In the other study, BB were the least costly strategy, followed by thiazide diuretics. In two of the three cost-utility analyses, treatment with thiazide diuretics was considered by the study authors to be cost-effective. In the UK NICE study, CCB were considered by the study authors to be the most cost-effective, mainly because of the inclusion of diabetes as an outcome of interest.[77] In seven of the 10 cost-effectiveness analyses, thiazide diuretics were considered by the study authors to be the most cost-effective option. In two studies, BB were considered by the study authors to be more cost-effective.[81,83] Another study seemed to favour the use of an ARB (losartan), although there were concerns about the outcome measure used (probability of potential effectiveness) and the choice of diuretic (indapamide).[89]

Three[83,88,89] of the 16 studies were funded by a pharmaceutical company.[89] In two[83,89] of these studies, the study authors concluded that a non-thiazide drug, which was manufactured by the sponsor of the study, was cost-effective.[89]

5.1.3 Discussion

According to the study authors, most studies found that thiazide diuretics provided the most cost-effective initial treatment of hypertension. In the few studies where authors did not find thiazide diuretics to be the most cost-effective, BB or CCB were more cost-effective. Two of the studies favouring drugs other than thiazides were sponsored by the pharmaceutical industry.

Although several economic evaluations were identified, none addressed the question that is relevant to this report from a Canadian perspective. Thus, the completion of a full economic evaluation was considered to be appropriate.

5.2 Primary Economic Evaluation

The objective of the study was to determine the cost-effectiveness of starting treatment of newly diagnosed hypertension with thiazide diuretics compared with alternative anti-hypertensive drugs. The study did not consider the cost-effectiveness of alternative strategies based on the switching of therapies or the use of adjunct therapies. Thus, the study focused on the impact of long-term costs and outcomes using four single-drug therapies (thiazide diuretics, CCB, BB and ACE inhibitors, or ARB compared to no therapy.

5.2.1 Methods

a) Study population

For the base case analysis, eight study populations were considered. The cohorts included men and women, 55- or 65-years-old, with a baseline SBP of 150 mm Hg or 180 mm Hg. The base case scenario included non-smokers with no history of diabetes or left ventricular hypertrophy with normal cholesterol and high density lipoprotein (HDL) levels (5.0 and 1.3 respectively).

b) Model structure

A Markov model was created to estimate the long-term costs and QALYs associated with cerebrovascular and cardiovascular disease in the study populations (Figure 52). The model adopts a time horizon of 10 years with a cycle length of one year. A 10-year time horizon was chosen, because it was sufficient to determine the long-term effects of initial monotherapy, given that it is

unlikely that any patient would stay on such therapy after 10 years, and that the incidence of events beyond this time would likely not be directly related to initial therapy.

The model was populated with estimates of transition probabilities, treatment effects, costs, and utilities. Published studies, including previous economic models, were searched to identify the most recent reliable estimates for all parameters in the model, based on their relevance to the study question, study population, and study perspective.

In the model, all patients are assumed to start in a "well" state, which represents no previous additional CV or CRV events. Patients can transit from the well state to states representing the progression of CV and CRV diseases. Transition probabilities from the well state are a function of gender, age, SBP, and other risk factors. States relate to unstable angina, MI, CV disease, stroke, and HF. Once a patient experiences one of these events, the annual risks of further events are a function of the previous disease history.

The model was developed in a Microsoft Excel spreadsheet. Monte Carlo simulation (MCS) involved obtaining several outcome estimates by re-running the model using different values for each data input randomly selected from the variable's probability density function.[93]

c) Transition probabilities

Transition probabilities for no treatment

For each study population, assuming no drug therapy, the transition probabilities relating to the transition from the well state were calculated. These were derived from a Canadian nomogram used in clinical practice to predict cardiovascular and cerebrovascular risks.[94] The nomogram was derived by using Framingham equations to calculate the 10-year risk of initial cardiovascular and cerebrovascular events based on the cohort risk factors. This was then converted into annual transition probabilities for cerebrovascular and CV events. The probability of the specific event (unstable angina, MI, CV disease, stroke, and HF) was calculated based on the proportion of initial events that relate to these complications.[77]

Once the individual had experienced an initial event, the risk of experiencing a subsequent event would be affected by history. The probabilities of future events were derived from the most pertinent clinical trial data and followed the methods adopted in a NICE report.[77] The probabilities of having unstable angina and HF after MI were taken from the secondary prevention trial (HOPE).[95] The HOPE trial compared the efficacy of ramipril with that of placebo in preventing cardiovascular events among high risk patients with evidence of vascular disease or diabetes and one other cardiovascular risk factor. The probabilities of unstable angina, MI, stroke, heart failure, and CV death after the onset of heart failure were taken from the placebo arm of the SOLVD trial.[96] SOLVD was a double-blind trial that examined patients with reduced left ventricular ejection fraction to determine the effect of enalapril versus placebo on mortality and morbidity. It was also assumed that transitions from unstable angina to HF and stroke, and from stroke to unstable angina, were the same as those seen in the MI population and as assumed in the NICE report.[77] The risk of HF after a stroke was assumed to be half that after an MI.[77]

For tertiary or subsequent events (after more than one previous event), the transition probability for subsequent events was based on the previous event with the highest associated transition probability. This assumption avoided the problems that can arise with transition probabilities when assuming an additive relationship and can be considered to be conservative.

Treatment effects
To incorporate the effects of treatment on the transition of patients, the transition probabilities identified were weighted by the RR of MI, stable angina, stroke, HF, and death associated with treatment with four types of anti-hypertensive drugs including thiazide diuretics, CCB, BB, and ACE inhibitors or ARB. In the base analysis, the risk reductions were applied to the transition probabilities for primary events in the Markov model. The same risk reductions are used for all patient cohorts.

RRs were obtained from the CADTH review of the effectiveness of thiazides compared to no treatment, CCB, BB, and ACE inhibitors or ARB detailed in this report and from a UK review of the effectiveness of all four therapies compared to no therapy.[77] The analysis was conducted for ACE inhibitors and ARB together rather than independently, because this followed the design of both the CADTH and UK clinical reviews. The CADTH report excluded unstable angina as an outcome. There was a lack of studies comparing thiazide diuretics to all classes of anti-hypertensive drugs. This meant that for certain outcomes, there were no data in the CADTH report.

d) Costs
All costs are presented in 2006 Canadian dollars with costs from other years inflated using the Canadian Price Index. The direct cost of drug therapy and the costs associated with the long-term complications of hypertension were incorporated in the model. All costs included in the model were Canadian. In the base case scenario, the annual cost of drug therapy was calculated based on the most commonly used drug and dosage in each class of medications. The annual drug costs were obtained from the Ontario Drug Benefit Formulary Comparative Drug Index and included four dispensing fees of $6.54 based on a maximum 90-day supply. It was assumed that ARB would only be used in those patients who did not tolerate ACE inhibitors (20% of the population). Therefore, 20% of the annual cost was calculated to be due to the use of ARB and 80% due to the use of ACE inhibitors.

The Canadian costs associated with the complications of hypertension were obtained from the literature.[97,98] The costs were based on those of the incident event and to the incremental costs of long-term management. Thus, the costs associated with MI (initial year of event and subsequent years), unstable angina (initial year of event and subsequent years), stroke (initial year of event and subsequent years), and HF (initial year of event and subsequent years) were needed. The costs related to stroke and MI were derived from a Canadian study that measured the costs of complications from diabetes.[97] The costs related to angina and HF were derived from a Canadian analysis of costs in the HOPE trial.[98] For patients with more than one previous complication, an additive model was assumed with respect to costs.

e) Utilities
For patients in the well state, the Canadian population age-specific norms from the National Population Health Survey were used as input into the model.[99] For the other disease states in the model, the utility values were derived from the literature – specifically, a UK economic model for the analysis of statins and the Harvard Cost-Effectiveness Analysis database.[100,101] For patients with disease complications, the impact of further disutilities was modelled using a multiplicative assumption: i.e., the utility of an individual was the product of his or her age-specific utility value and the utility value associated with any complications. This assumption is accepted as a more conservative assumption than the use of an additive function.

f) Analytical framework

Base analysis

The model allows for the conduct of a cost-utility analysis, where outcomes are expressed in terms of QALYs. The analysis is presented in terms of the incremental cost per outcome gained. ICERs are reported for all comparisons. In interpreting results, all treatments that are dominated (higher cost, less QALYs) by at least one other treatment are excluded. Then, ICERs are discussed for the remaining treatment options.

The analysis is conducted from the perspective of a provincial ministry of health. For the base case analysis, the costs and benefits were discounted at 5% per annum.[102] A sensitivity analysis was conducted with discounting at 0% and 3%.[102]

Analysis of variability

The analysis is presented for eight population cohorts based on gender, age, and SBP. This will allow the determination of any variation in cost-effectiveness by patients' characteristics. In addition, the analysis was conducted assuming different baseline cholesterol levels and for current smokers.

Analysis of uncertainty

A sensitivity analysis was conducted to assess the robustness of the study's results to changing assumptions in the model:

- costs associated with complications
- disutility associated with complications
- application of RRRs associated with treatment to primary and secondary events.

The base analysis was conducted through a deterministic analysis whereby the point estimates for each parameter are entered into the model, and an estimate of the cost-effectiveness of treatment is obtained.

In addition, a probabilistic analysis was conducted by using MCS in relation to the RRR associated with treatment.[93,102] As the relationship between input parameters and outcomes can be non-linear, the expected values of outcomes obtained from a MCS can differ from those from a deterministic analysis.[103] Thus, the analysis based on MCS avoids the potential for non-optimal decisions that can occur with deterministic analyses because it accounts for uncertainty regarding important clinical outcomes.

For the MCS, probability distributions were specified for the RRR based on the CADTH report. Probability distributions took the form of a log-normal distribution. Thus, the estimates of costs and QALYs associated with each treatment option were obtained by re-running the model using values for each RR that were randomly selected from the probability distribution around clinical variables. In this study, 3,000 replications were conducted; i.e., a set of 3,000 outcome estimates were obtained.

In the MCS, the cost-effectiveness of treatment is presented in terms of the incremental cost per QALY gained, which is the ratio of the mean incremental costs and incremental QALYs.[104] In addition, cost-effectiveness acceptability curves (CEACs) were derived for each of the eight study populations.[105] In a CEAC, the probability that a therapy is the optimal treatment (i.e., the net monetary benefit of a therapy is positive in all comparisons) is depicted for each potential value of λ (the threshold value for a QALY). In the CEACs, the probabilities are presented for values between \$0 and \$100,000. A maximum value of \$100,000 was chosen because, given previous funding

decisions, it is unlikely that a treatment option will be accepted based on economic arguments with an ICER greater than this value.

5.2.2 Results

a) Data inputs

Tables 6 to 13 detail the data inputs for the economic model.

Transition probabilities

Tables 6 and 7 contain the transition probabilities relating to the no-therapy option. Tables 8 and 9 provide the RR of each event associated with each therapy. Table 8, which is taken from the NICE report, provides the RRs of events for all treatment options versus no treatment.[77] Table 9 provides the same data from the CADTH report. In the CADTH report, the RRs were calculated versus thiazide diuretics. The RRs for treatments other than thiazide diuretics versus placebo were derived as the product of the RR versus thiazide diuretics and the RR of no treatment versus thiazide diuretics. Table 10 provides the RR estimates and 95% confidence intervals used in the MCS. The probability distributions for RRs were assumed to take the form of log-normal distributions. For instances where there were no data available, an RR of 1 with no uncertainty is assumed.

Table 6: Transition probabilities for primary events with no therapy[77,94]

Transition State	Age 55 SBP 150	Age 55 SBP 180	Age 65 SBP 150	Age 65 SBP 180
Males				
UA	0.0013	0.0016	0.0022	0.0029
MI	0.0031	0.0038	0.0046	0.0060
Stroke	0.0037	0.0046	0.0073	0.0094
CVD death	0.0024	0.0030	0.0043	0.0056
Well	0.99	0.99	0.98	0.98
Females				
UA	0.00037	0.00059	0.00048	0.00070
MI	0.00046	0.00075	0.0011	0.0016
Stroke	0.0014	0.0023	0.0035	0.0051
CVD death	0.00054	0.00086	0.0016	0.0023
Well	0.997	0.99	0.99	0.99

Table 7: Transition probabilities for secondary events with no therapy

Initial State	Transition State	Transition Probability	Source
UA	MI	0.030	NICE[77]
	Stroke	0.0095	Yusuf[95]
	HF	0.023	Yusuf[95]
	CVD death	0.020	NICE[77]
	Previous UA	0.92	Complement
MI	UA	0.0077	NICE[77]
	MI	0.072	NICE[77]
	Stroke	0.0095	Yusuf[95]
	HF	0.023	Yusuf[95]
	CVD death	0.011	NICE[77]
	Previous MI	0.88	Complement

Table 7: Transition probabilities for secondary events with no therapy			
Initial State	**Transition State**	**Transition Probability**	**Source**
Stroke	UA	0.0018	Yusuf[95]
	MI	0.0016	NICE[77]
	Stroke	0.29	NICE[77]
	HF	0.011	Yusuf[95]
	CVD death	0.34	NICE[77]
	Previous stroke	0.36	Complement
HF	UA	0.023	SOLVD[96]
	MI	0.023	SOLVD[96]
	Stroke	0.010	SOLVD[96]
	HF	0.054	SOLVD[96]
	CVD death	0.062	SOLVD[96]
	Previous HF	0.83	Complement

Complement means that probability of health state where no additional event occurs (e.g., previous stroke) equals one minus the sum of all other probabilities from this state
*transition probabilities have been rounded to two digits
+for subsequent transitions for patients with a history of two or more health states, highest transition probability used for subsequent transitions.

Table 8: RRs for events versus no therapy by primary treatment from NICE report[77]				
Outcome	**Thiazide diuretics**	**CCB**	**BB**	**ACE inhibitors or ARB**
Unstable angina	0.893	0.881	0.984	0.970
MI	0.780	0.796	0.855	0.816
Stroke	0.690	0.656	0.851	0.731
HF	0.530	0.731	0.761	0.642
Death	0.910	0.883	0.939	0.902

Table 9: RRs for events versus no therapy by primary treatment from CADTH report				
Outcome	**Thiazide diuretics**	**CCB#**	**BB#**	**ACE inhibitors or ARB#**
Unstable angina	1*	1*	1*	1*
MI	0.78	0.85	0.78*	0.78*
Stroke	0.62	0.58	0.78	0.70
HF	0.42	0.59	0.42*	0.45
Death	0.79	0.79*	0.80	0.79*

For analysis based on CADTH report, data based on studies comparing TZDs to other treatment options.
*RR of 1 was assumed when no data available.

Table 10: RRs and 95% confidence intervals for events versus thiazide diuretics by primary treatment from CADTH report				
Outcome	**No treatment**	**CCB#**	**BB#**	**ACE inhibitors or ARB#**
Unstable angina	1*	1*	1*	1*
MI	0.78 (0.65, 0.94)	0.92 (0.72, 1.19)	1*	1*
Stroke	0.62 (0.50, 0.77)	1.06 (0.95, 1.18)	0.80 (0.45, 1.42)	0.88 (0.80, 0.98)
HF	0.42 (0.20, 0.89)	0.71 (0.54, 0.95)	1*	0.94 (0.71, 1.24)
Death	0.79 (0.68, 0.92)	1*	0.99 (0.67, 1.46)	1*

Figures in parenthesis are 95% confidence intervals. Probability distributions assumed to take form of log normal distributions
*RR of 1 assumed when no data available.

Costs

Table 11 contains the annual costs associated with disease states derived from previous Canadian studies.[97,98] Table 12 contains the annual drug costs associated with each treatment option.

Table 11: Annual costs for each health state in model		
Health State	**Cost ($)**	**Source**
MI initial year	22,700	Coyle[97]
MI subsequent years	8,400	Coyle[97]
Unstable angina initial year	4,000	Lamy[98]
Unstable angina subsequent years	4,000	Lamy[98]
Stroke initial year	47,800	Coyle[97]
Stroke subsequent years	4,700	Coyle[97]
HF initial year	6,300	Lamy[98]
HF subsequent years	6,300	Lamy[98]

Table 12: Annual drug therapy costs[112]	
Drug Therapy	**Cost ($)**
ACE inhibitors or ARBs*	418
Thiazides	29
BB	205
CCB	789

Utilities

Table 13 contains the values used to derive utility values for each health state in the model. Age-gender specific utility values were obtained from the National Population Health Survey.[99] The utilities associated with each disease event were derived from the NICE analysis.[77] An example of how utility values were calculated for a specific state appears in Table 14.

Table 13: Utility values			
Health State	**Age or Timeframe**	**Utility value**	**Source**
Healthy male	50 to 59	0.90	Statistics Canada[99]
	60 to 69	0.89	Statistics Canada[99]
	70 to 79	0.85	Statistics Canada[99]
Healthy female	50 to 59	0.89	Statistics Canada[99]
	60 to 69	0.88	Statistics Canada[99]
	70 to 79	0.85	Statistics Canada[99]
MI	First 6 months	0.76	Harvard School of Public Health,[100] NICE[101]
	Subsequently	0.88	Harvard School of Public Health,[100] NICE[101]
Unstable angina	First 6 months	0.77	Harvard School of Public Health,[100] NICE[101]
	Subsequently	0.80	Harvard School of Public Health,[100] NICE[101]
Stroke		0.63	Harvard School of Public Health,[100] NICE[101]
Diabetes		0.90	Harvard School of Public Health,[100] NICE[101]
HF		0.71	Harvard School of Public Health,[100] NICE[101]
Death		0	Harvard School of Public Health,[100] NICE[101]

Table 14: Example of derivation of utility values for composite states	
Example: Utility value for 60-year-old woman with unstable angina and stroke	
Utility values for each component of composite state	
Healthy female aged 60	0.88
Unstable angina	0.77
Stroke	0.63
Utility value for composite health state	
$0.88 \times 0.77 \times 0.63 =$	0.43

b) Primary analysis

Tables 15 to 22 detail the results of the economic analysis based on the RRs obtained from the NICE report for each of the eight population cohorts. For all groups, thiazide diuretics represent the least costly therapeutic option and are the second most effective option behind CCB. Thus, all other treatment options (BB, ACE inhibitors or ARB, and no therapy) are dominated by thiazide diuretics. The incremental cost-effectiveness ratio (ICER) expressed as an incremental cost per QALY gained for CCB versus thiazide diuretics ranges from $450,000 for men aged 65 with a SBP of 180 mm Hg to $1.1M for men aged 55 with a SBP of 150 mm Hg. The range is from $400,000 for women aged 65 with a SBP of 180 mm Hg to $2M for women aged 55 with a SBP of 150 mm Hg. Thus, the ICER is higher in patients with a lower risk of hypertension-related events (younger and lower initial SBP).

Tables 23 to 30 detail the results of the economic analysis based on the RR obtained in this report for each of the eight population cohorts. Again, thiazide diuretics represent the least costly therapeutic option and are the second most effective option behind CCB. The ICERs associated with CCB compared to thiazide diuretics are higher – ranging from $1M to $5.2M.

Table 15: Results for males aged 55 SBP 150 based on NICE RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$4,189	$5,187	$6,514	$3,163	$9,265
QALYs	7.08	7.10	7.12	7.12	7.13
Incremental Cost per QALY					
versus no treatment		$39,000	$54,000	Dominant	$94,000
versus BB			$77,000	Dominant	$146,000
versus ACE inhibitors or ARBs				Dominant	$257,000
versus thiazides					$1.1 million

Table 16: Results for males aged 55 SBP 180 based on NICE RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$5,174	$6,021	$7,255	$3,859	$9,946
QALYs	7.02	7.06	7.08	7.08	7.09
Incremental Cost per QALY					
versus no treatment		$27,000	$39,000	Dominant	$72,000
versus BB			$58,000	Dominant	$114,000
versus ACE inhibitors or ARBs				Dominant	$204,000
versus thiazides					$887,000

Table 17: Results for males aged 65 SBP 150 based on NICE RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$7,341	$7,851	$8,843	$5,345	$11,380
QALYs	6.82	6.87	6.90	6.91	6.92
Incremental Cost per QALY					
versus no treatment		$11,000	$19,000	Dominant	$42,000
versus BB			$31,000	Dominant	$69,000
versus ACE inhibitors or ARB				Dominant	$130,000
versus thiazides					$581,000

Table 18: Results for males aged 65 SBP 180 based on NICE RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$9,353	$9,564	$10,361	$6,772	$12,772
QALYs	6.71	6.77	6.81	6.82	6.83
Incremental Cost per QALY					
versus no treatment		$4,000	$10,000	Dominant	$28,000
versus BB			$20,000	Dominant	$50,000
versus ACE inhibitors or ARB				Dominant	$97,000
versus thiazides					$453,000

Table 19: Results for women aged 55 SBP 150 based on NICE RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$1,304	$2,750	$4,331	$1,110	$7,244
QALYs	7.11	7.12	7.13	7.13	7.13
Incremental Cost per QALY					
versus no treatment		$171,000	$209,000	Dominant	$325,000
versus BB			$263,000	Dominant	$458,000
versus ACE inhibitors or ARB				Dominant	$769,000
versus thiazides					$3.2 million

Table 20: Results for women aged 55 SBP 180 based on NICE RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$2,088	$3,406	$4,898	$1,640	$7,755
QALYs	7.07	7.09	7.10	7.10	7.10
Incremental Cost per QALY					
versus no treatment		$97,000	$121,000	Dominant	$194,000
versus BB			$155,000	Dominant	$277,000
versus ACE inhibitors or ARB				Dominant	$472,000
versus thiazides					$2 million

Table 21: Results for women aged 65 SBP 150 based on NICE RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$3,011	$4,171	$5,552	$2,252	$8,343
QALYs	6.87	6.89	6.90	6.91	6.91
Incremental Cost per QALY					
versus no treatment		$58,000	$75,000	Dominant	$125,000
versus BB			$98,000	Dominant	$184,000
versus ACE inhibitors or ARB				Dominant	$326,000
versus thiazides					$1.3 million

Table 22: Results for women aged 65 SBP 180 based on NICE RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$4,350	$5,293	$6,520	$3,308	$9,216
QALYs	6.80	6.83	6.85	6.85	6.86
Incremental Cost per QALY					
versus no treatment		$33,000	$44,000	Dominant	$79,000
versus BB			$60,000	Dominant	$120,000
versus ACE inhibitors or ARB				Dominant	$218,000
versus thiazides					$418,000

Table 23: Results for men aged 55 SBP 150 based on CADTH RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$4,189	$4,924	$6,419	$3,032	$9,195
QALYs	7.08	7.13	7.14	7.14	7.15
Incremental Cost per QALY					
versus no treatment		$15,000	$38,000	Dominant	$73,000
versus BB			$171,000	Dominant	$232,000
versus ACE inhibitors or ARB				Dominant	$287,000
versus thiazides					$3.2 million

Table 24: Results for men aged 55 SBP 180 based on CADTH RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$5,174	$5,699	$7,139	$3,698	$9,861
QALYs	7.02	7.09	7.10	7.11	7.11
Incremental Cost per QALY					
versus no treatment		$8,000	$27,000	Dominant	$55,000
versus BB			$133,000	Dominant	$183,000
versus ACE inhibitors or ARB				Dominant	$227,000
versus thiazides					$2.5 million

Table 25: Results for men aged 65 SBP 150 based on CADTH RRs					
	No Treatment	**BB**	**ACE inhibitors or ARBs**	**TZDs**	**CCB**
Costs	$7,341	$7,406	$8,688	$5,092	$11,207
QALYs	6.82	6.91	6.93	6.94	6.95
Incremental Cost per QALY					
versus no treatment		$1,000	$13,000	Dominant	$31,000
versus BB			$78,000	Dominant	$107,000
versus ACE inhibitors or ARB				Dominant	$132,000
versus thiazides					$1.4 million

Table 26: Results for men aged 65 SBP 180 based on CADTH RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$9,353	$9,007	$10,169	$6,454	$12,555
QALYs	6.71	6.82	6.84	6.86	6.87
Incremental Cost per QALY					
versus no treatment		$87,000	$158,000	Dominant	$254,000
versus BB			$492,000	Dominant	$681,000
versus ACE inhibitors or ARB				Dominant	$598,000
versus thiazides					$5.2 million

Table 27: Results for women aged 55 SBP 150 based on CADTH RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$1,304	$2,669	$4,304	$1,053	$7,191
QALYs	7.11	7.13	7.13	7.14	7.14
Incremental Cost per QALY					
versus no treatment		$171,000	$209,000	Dominant	$325,000
versus BB			$262,000	Dominant	$458,000
versus ACE inhibitors or ARB				Dominant	$769,000
versus thiazides					$3.2 million

Table 28: Results for women aged 55 SBP 180 based on CADTH RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$2,088	$3,277	$4,855	$1,549	$7,671
QALYs	7.07	7.10	7.10	7.11	7.11
Incremental Cost per QALY					
versus no treatment		$48,000	$91,000	Dominant	$151,000
versus BB			$297,000	Dominant	$363,000
versus ACE inhibitors or ARB				Dominant	$415,000
versus thiazides					$3.2 million

Table 29: Results for women aged 65 SBP 150 based on CADTH RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$3,011	$3,982	$5,486	$2,109	$8,209
QALYs	6,87	6.91	6.91	6.92	6.92
Incremental Cost per QALY					
versus no treatment		$26,000	$55,000	Dominant	$94,000
versus BB			$194,000	Dominant	$241,000
versus ACE inhibitors or ARB				Dominant	$277,000
versus thiazides					$2.2 million

Table 30: Results for women aged 65 SBP 180 based on CADTH RRs					
	No Treatment	**BB**	**ACE inhibitors or ARB**	**TZDs**	**CCB**
Costs	$4,350	$5,022	$6,427	$3,121	$9,023
QALYs	6.80	6.85	6.86	6.87	6.88
Incremental Cost per QALY					
versus no treatment		$12,000	$32,000	Dominant	$59,000
versus BB			$126,000	Dominant	$158,000
versus ACE inhibitors or ARB				Dominant	$183,000
versus thiazides					$491,000

c) Analysis of uncertainty and variability

The results of the univariate sensitivity analysis were similar to those of the primary analysis. The analysis shows that the results are robust to all changes in parameters and that thiazides continue to dominate BB, no treatment, and ACE inhibitors or ARB. Thus, the only result of interest is how the sensitivity analysis affected the ICER for CCB versus thiazide diuretics.

To illustrate the impact of the changes in assumptions, Table 31 presents the ICER for CCB compared to thiazide diuretics in each sensitivity analysis for the population cohorts (assuming the RRs from NICE) with the lowest or highest risks of events: women aged 55 with a SBP of 150 mm Hg and men aged 65 with a SBP of 180 mm Hg.

Table 32 compares the incremental cost per QALY gained for CCB based on the deterministic analysis and based on the MCS.

Figure 53 contains the cost-effectiveness acceptability curves for all eight study populations. Based on a threshold value of a QALY of $50,000, the probability that thiazide diuretics are the optimal treatment choice ranges from 87.6% to 100%.

Table 31: Results of sensitivity analysis: Incremental cost per QALY gained for CCB compared to TZDs based on NICE RRs

Assumption	Women aged 55 SBP 150 mm Hg	Men aged 65 SBP 180 mm Hg
1 point increase in cholesterol	$3,156,475	$425,000
2 point increase in cholesterol	$2,623,990	$379,000
Double the cost of long term complications	$3,140,100	$441,000
Half the cost of long term complications	$3,164,662	$460,000
Disutility doubled	$3,378,001	$501,000
Disutility halved	$3,091,019	$434,000
Application of RRs to subsequent events	$3,140,141	$450,000
Assuming all patients are smokers	$1,744,524	$294,000
Genericization of calcium channel blockers	$1,565,004	$220,000
0% discount	$2,900,600	$419,000
3% discount	$3,472,088	$500,000

Table 32: Comparison of incremental cost per QALYs for CCB versus TZDs based on CADTH RRs

Study Population	ICER based on Deterministic Analysis	ICER based on MCS
Men aged 55, SBP 150 mm Hg	$3.2 million	$4.9 million
Men aged 55, SBP 180 mm Hg	$2.5 million	$4.5 million
Men aged 65, SBP 150 mm Hg	$1.4 million	$1.7 million
Men aged 65, SBP 180 mm Hg	$5.2 million	$1.5 million
Women aged 55, SBP 150 mm Hg	$3.2 million	$6.8 million
Women aged 55, SBP 180 mm Hg	$3.2 million	$3.9 million
Women aged 65, SBP 150 mm Hg	$2.2 million	$2.6 million
Women aged 65, SBP 180 mm Hg	$491,000	$528,000

5.2.3 Discussion

The economic analysis found little to choose from between each drug treatment regarding effectiveness, with the results mainly driven by drug costs. In terms of cost-effectiveness, the results of the main analysis were consistent with those of the literature review in that the most cost-effective drugs compared to no treatment were thiazide diuretics and BB. However, thiazide diuretics were dominant over BB (cost-saving and more effective), and with respect to ACE inhibitors or ARB and no treatment. For all study populations, CCBs were more effective in having greater QALYs than thiazide diuretics. However, the incremental cost per QALY gained was >$400,000 for all study populations.

The univariate sensitivity analysis showed that the results were not sensitive to changes in parameters. The two scenarios that most significantly affected the ICER were the analysis based on assuming all patients were smokers and the analysis based on assuming a generic price of CCB. For both analyses, the ICERs were >$200,000, showing that these factors were unlikely to affect the conclusions about optimal treatment.

The model adopted in this study is similar to that adopted in a UK report .[77] The model was considered to have a high degree of face validity in its design and in the appropriateness of the study's findings. The analysis found that CCBs were associated with a marginal benefit over thiazides, but were not considered to be cost-effective. This does not mean that the economic analysis is inconsistent with the clinical review. Although the clinical review found no statistically significant differences between thiazides and CCBs, it is important in economic evaluation to incorporate point estimates and degrees of uncertainty from the available data, regardless of the levels of statistical significance. Thus, the results occur because of a marginal difference between CCBs and thiazides with respect to stroke (RR of 0.656 versus 0.690 from the NICE report and 0.58 versus 0.62 from the CADTH review). Although statistical inference is not considered in this context, the uncertainty around the RRs is considered in the probabilistic sensitivity analysis.

This study has several limitations.

There was a lack of head-to-head studies comparing all treatment options. Thus, the results were often based on indirect comparisons, which can lead to false inference. Given the paucity of data, however, there are few other options available.

Given the degree of uncertainty around estimates of RRs, a limited probabilistic sensitivity analysis was conducted. This analysis addressed the effect of the uncertainty on the confidence in the study results. The uncertainty around other parameters was not considered in the analysis, mainly because estimates for most of these parameters were presented in the literature as point estimates. This is a limitation of the analysis, although the uncertainty around costs and utilities would not affect the point estimates of the ICERs.

Relating to the RRs, the RRs come from randomized controlled clinical trials where patients may more on to second line combination therapy. In addition the clinical trials focused on patients for whom thiazide diuretics were an appropriate first line therapy. Thus, the results of this analysis can not provide any indication relating to what is the appropriate second line therapy for patients nor can it provide insight into the most appropriate first line therapy for patients with specific co morbidities.

Analysis is conducted for patients aged 65 and 75. Thus results for patients both older and younger need to be inferred from these results. It is likely in both instances that results would remain consistent – i.e. thiazide diuetics would be dominant over all therapies except calcium channel blockers. The ICER for calcium channel blockers is likely to be greater for younger patients and lower for older patients.

Another limitation is that the study focused on the impact of initial monotherapy and did not model the choice of switches in monotherapy or initiation of combination therapy. There were two reasons for this. First, there are little if any clinical trial data assessing the optimal secondary treatment options after each monotherapy. Thus, modelling beyond initial monotherapy is likely to require the use of weaker assumptions. Second, it is unclear whether the analysis would incorporate secondary therapy as adopted in Canada or optimal secondary therapy if that could be established. In other instances, the analysis was conducted adopting conservative assumptions biased against more effective treatment, e.g., the assumptions relating to utility values for composite states and the probabilities of tertiary events. Related to this, it was assumed that patients would be equally adherent to therapies. This may lead to some bias in the results, but because thiazides are the lowest cost option, it is unlikely that there be would any changes in the conclusions of the report if differential adherence was assumed.

The report only included disutility related to events. There is evidence from the clinical review that there may be differential QoL for patients on different therapies. The data, however, were insufficient to be incorporated into utility values. It is unclear whether any differences found in the review would translate into different utility values – hence, utility was assumed to vary by health state, not treatment.

Another limitation is that the study only included the outcomes directly related to hypertension and did not model other long-term conditions such as diabetes. This is the primary reason why the conclusions differ from those of the National Collaborating Centre for Chronic Conditions report, which included diabetes, and for which there are more favourable outcomes with respect to CCB. Diabetes, however, is a complicated disease, and modelling in terms of a binary outcome (diabetes or no diabetes), as in the National Collaborating Centre for Chronic Conditions report, may be too simplified an approach.

6 HEALTH SERVICES IMPACT

6.1 Population Impact

The Canadian Heart Health Surveys (CHHS)[4] between 1986 and 1992 revealed that the prevalence of hypertension in the Canadian population for 18- to 74-year-olds was 22% and was higher in men (26%) than in women (18%). The hypertension prevalence increased with age. At ages 18 to 34 years, men had a higher hypertension prevalence than women (11% versus 2%). The prevalence was lower in men (56%) than women (58%) in the age group of 65 to 74 years.

A cohort analysis of a Canadian population of >150,000 patients (age range 18 to 97 years) in southwestern Ontario between 2000 and 2003 showed that the prevalence of hypertension was 17.3%.[106] The prevalence was higher in women than in men in all age groups. The overall prevalence in women and men were 19% and 15.5%, respectively. Of the hypertensive patients, 71% were

untreated, 13% were treated but not controlled, and 16% were treated and controlled. Compared with previous surveys,[4] the recent survey showed that the prevalence of hypertension in Canada had decreased. Although the proportions of treated and controlled patients were unchanged, the proportion of untreated patients was higher in the recent survey.

The Canadian awareness of hypertension and the understanding of the consequences of high BP were low.[4,107] Overall, 66% to 98% were unaware of the association between hypertension and cardiovascular diseases. Most people (63%) could identify the signs and symptoms of hypertension, but had limited knowledge of lifestyle issues and believed that hypertension was not a serious medical condition. More than half (59%) believed that they would not have hypertension, and if they did, 38% thought that they would be able to control it themselves. Among hypertensive individuals between 18 and 74 years of age, 42% were not aware of their hypertension, 19% were not treated or controlled, 23% were treated but not controlled, and 16% were treated and controlled.

A Canadian study[108] on prescribing practices between 1994 and 2002 for a cohort of 194,761 seniors (≥66 years old) in Ontario found that one-third (35%) of initial anti-hypertensive prescriptions were for thiazides. The rates of thiazide use as first-line anti-hypertensive treatment in the elderly increased with age (from 31% at the age of 66 to 69 years, to 51% at ≥85 years). Prescriptions for thiazides as first-line treatment were written less for males (28%) than females (40%), and less for diabetic (15%) than non-diabetic subjects (39%). Similar findings were shown in a study on a cohort of seniors in British Columbia.[5] Women, older patients, and patients with no comorbidities were more likely to receive thiazides as first-line treatment than their counterparts. ACE inhibitors remained the most prescribed anti-hypertensive drug followed by diuretics, BB, and CCB in 2002.[108] From 1994 to 2002, the prescribing rates increased by 81% for ACE inhibitors, 10% for diuretics, and 27% for BB, but decreased by 22% for CCBs.[108]

The aforementioned cohort analyis[106] showed that ACE inhibitors were the predominant choice among drug classes. For patients receiving combination therapy, the primary combination was ACE inhibitors and diuretics (78%), followed by ARB and diuretics (16%), and ACE inhibitors and CCB (6%).

Utilization data between 2000 and 2006 for anti-hypertensive drug classes from provincial drug programs showed that the numbers of prescriptions for thiazide diuretics increased by 42%, 53%, 72%, and 19% in New Brunswick, British Columbia, Manitoba, and Nova Scotia, respectively (Appendices 1b, 1c, 1e, 1f), while it was unchanged in Saskatchewan (Appendix 1d). The numbers of prescriptions of other anti-hypertensive drug classes also increased, except for combinations of BB and thiazide diuretics. Prescriptions for ARB and ARB plus thiazide diuretics increased two- to three-fold from 2000 to 2006. ACE inhibitors are the most commonly prescribed therapy and accounted for about 30% to 40% of the total expenditure.

6.2 Budget Impact

a) Objective

The objective of the budget impact analysis is to forecast the expenditure for single-agent anti-hypertensive drugs for 2006-2007, 2007-2008, and 2008-2009 in each province under different assumptions about changes in prescribing patterns.

Under the base case scenario, we assumed that prescribing patterns will follow the trends of the previous years and incorporated the observed proportional changes in prescribing for each class. Given the findings of the economic analysis, alternative scenarios relate to proportional declines in the volume of prescriptions for drugs other than thiazide diuretics, and a subsequent increase in prescribing for thiazide diuretics.

b) Methods

Forecasts for the expenditure under the base case were obtained using the following stepped approach:

- Each participating province gave estimates for the total costs and total volume for each class of anti-hypertensive for the past three to five years.
- The proportions of prescriptions for each class in 2005-2006 for hypertension were estimated based on data provided by IMS.
- The proportions for each class were applied to the data from step 1 to estimate the volume and cost of prescriptions for hypertension by class for each of the past five years.
- The rate of increase in the number of claims in each class for each province was obtained by analyzing data from the most recent and least recent years provided by the province. This rate of increase was used to estimate volume by class for 2006-2007, 2007-2008, and 2008-2009 for each province.
- The forecasted claims for the year are weighted by the average cost per claim by class for each province in the most recent year to provide the forecasted cost by class for 2006-2007, 2007-2008, and 2008-2009.

The base case forecast is compared to alternative scenarios relating to switching to thiazide diuretics as first-line therapy from other therapies. This is done by assuming a different proportional reduction in total prescriptions for each of the other classes: 5%, 10%, and 25%. These alternatve estimates are obtained as follows:

- The volume and cost of prescriptions for the other classes are reduced in each of 2006-2007, 2007-2008, and 2008-2009 by the relevant percentage.
- The decrease in the total volume of prescriptions for the other classes compared to the base case is estimated.
- The volume of thiazide diuretic prescriptions in the alternative scenarios is the volume in the base case scenario plus the volume identified in step 2.

The forecasted claims for the year from step 3 are weighted by the average cost per claim by class for each province in the most recent year to provide the forecasted cost by class for 2006-2007, 2007-2008, and 2008-2009.

c) Results

The annual number of prescriptions and expenditure for anti-hypertensive therapies in British Columbia, New Brunswick, Prince Edward Island, Nova Scotia, Manitoba, and Saskatchewan are presented in Tables 33 to 38. Although all five therapeutic classes are used in the treatment of hypertension, they are also used in the treatment of other diseases. IMS data were analyzed to estimate the proportion of claims for the treatment of hypertension (Table 39). This allowed for the calculation of the expenditure for medications used in the treatment of hypertension and an estimate of the annual increase in prescribing.

The projected increase in expenditure for 2006-2007, 2007-2008, and 2008-2009 appears in Table 40. If prescribing trends continue as they have over the past five years, the expenditure for anti-hypertensive medications increases yearly. If, on the other hand, anti-hypertensive therapy is started with thiazide diuretics rather than other therapeutic classes, the yearly increase in expenditure is reduced. In Table 40, the impact of a 5%, 10%, and 25% reduction in non-thiazide prescriptions and corresponding increase in thiazides on the overall budget is presented. For instance, the projected budget impact in BC for 2008-2009 is $82M, $79 million, and $69M at 5%, 10%, and 25%, respectively.

d) Discussion

Given the current trends, expenditures on anti-hypertensive medications are forecasted to increase yearly. If antiihypertensive therapy is started with thiazide diuretics, the forecasted increase will be lower, and for some provinces, the expenditures may decrease in the short term. The projected budget savings are modest; i.e., a 5% reduction in prescribing for classes other than thiazides in BC would lead to savings of approximately $3M per annum, but this could allow resources to be allocated to other therapies without any detriment in the effectiveness of the management of hypertension.

One limitation of a budget impact analysis is that it is designed to illustrate the potential impact of changes in prescribing patterns, rather than the actual impacts that will occur. The reductions in prescribing for specific classes are not based on the actual estimates of possible changes in practice, but are designed to depict what financial savings could be obtained from changes of such magnitude. If changes in prescribing patterns did occur, it would be possible to determine the net financial impact.

6.3 Ethical, Equity, and Psychosocial Issues

The findings of this report show a disparity between the evidence and the choice of drugs in Canada for the treatment of hypertension. Based on the evidence of the clinical efficacy and cost-effectiveness, thiazide diuretics are suitable as first-line choice in the treatment for hypertension compared to other classes.

The evidence of this comprehensive compilation is available and not new. Others assessing the evidence have come to similar conclusions previously. Assuming that the clinical evidence and cost were considered, it is estimated that 80% to 90% of patients being treated with anti-hypertensive drugs would be receiving a thiazide diuretic as first-line treatment. Data from seven provinces, however, show that the percentage of thiazide prescriptions ranges from 8% to 22%. The disparity among provinces is surprising given that the evidence and costs do not differ between jurisdictions.

Prescribing practices are likely influenced by industry marketing and little influenced by the passive diffusion of robust evidence and costing information in isolation. Specialty societies should undertake knowledge transfer strategies on prescribing habits among physicians. These strategies should go beyond the passive dissemination of clinical practice guidelines and policy statements, if they are to promote the use of lower-cost, evidence-based treatments for hypertension.[109,110] Furthermore, cost savings achieved through anti-hypertensive therapy can be translated into health benefits from new effective, but costly, therapies (e.g., cancer care) for smaller populations.

As part of the process of informed consent, as with other health care technologies, the physician has a responsibility to discuss with every patient the advantages and disadvantages of using thiazide diuretics compared to other classes. To give valid informed consent to treatment, patients need to be adequately informed about the benefits and risks of such therapy (e.g., potential impact on sexual function; influence of age, sex, and comorbidities on health benefits).[108] All patients should be educated on the benefits of lifestyle modification (e.g., smoking cessation, weight loss, sodium restriction).

Any consideration of the benefits and risks of therapy must include the psychosocial dimensions and a discussion of the clinical and economic outcomes. Physicians and other caregivers need to discuss the impact of anti-hypertensive therapy on a patient's quality of life or well-being.[111] To ensure good physician-patient relations and adherence to therapy, physicians need to be aware of changes in patients' health perceptions, energy levels, physical functioning, and overall satisfaction with treatment.[111] Patients' attitudes are influenced by cultural differences, beliefs, and previous experiences with the health system.[1]

7 CONCLUSIONS

Thiazide diuretic-based therapy is superior to placebo or no treatment in reducing the risks of all-cardiovascular and cerebrovascular events in subjects with uncomplicated hypertension. No significant differences for all-cardiovascular and cerebrovascular-related morbidity and mortality were found when thiazide diuretics were compared with other anti-hypertensive medications. Thiazide diuretics, however, were better in reducing the risk of stroke than ACE inhibitors, and in reducing the risk of heart failure than CCBs.

The economic analysis found little difference between therapies in terms of effectiveness and found that thiazide diuretics are the most cost-effective initial therapy for patients in all study populations, unless society is willing to pay more than $400,000 for a QALY gained from the use of CCBs.

Evidence from a limited number of trials, most of which were of low quality, showed that the intensive lowering of blood pressure below the standard target of 140/90 mm Hg in patients with hypertension did not result in a difference in the risks of all-cause death, death related to cardiovascular events, and renal failure.

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APPENDICES

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