Identification of factors driving differences in cost effectiveness of first-line pharmacological therapy for uncomplicated hypertension

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BACKGROUND: Published practice guidelines and economic evaluations have come to different conclusions regarding optimal pharmacotherapy for the treatment of uncomplicated hypertension. The drivers of these disparities are not clear. Greater understanding is needed for clinicians, researchers and policy makers to determine the most effective and sustainable strategies.

OBJECTIVES: To identify how cost and cost-effectiveness considerations are used to generate recommendations by major hypertension guidelines, and determine key drivers of cost-effectiveness conclusions in available economic evaluations.

METHODS: A systematic search and narrative review of major hypertension guidelines and health technology assessments of first-line antihypertensive therapy were performed.

RESULTS: Of the eight guidelines identified, formal cost-effectiveness analysis was rarely integrated in the formulation of recommendations. When guidelines considered costs, recommendations remained incongruent. Two economic evaluations were identified (United Kingdom and Canada); however, these differed in their conclusion of the most cost-effective agent and attractiveness of calcium channel blockers. Review of these economic evaluations suggests that cost-effectiveness conclusions are strongly influenced by relative costs of drug classes; when relative differences in drug costs are lower, the impact on associated conditions such as heart failure and diabetes influences cost-effectiveness conclusions.

CONCLUSION: In the setting of finite health care resources and significant budget impact due to high population prevalence, cost effectiveness is an important consideration in the treatment of uncomplicated hypertension. Identification of key drivers of cost effectiveness will assist interpretation and conduct of current and future economic evaluations.

Key Words: *Clinical practice guidelines; Cost; Cost effectiveness; Hypertension; Pharmacotherapy*

It is well accepted that identification and treatment of hypertension with pharmacological therapy is effective at preventing future adverse clinical events. However, numerous pharmacological agents exist, with varying costs and impacts on health. Hypertension is a common disorder affecting 18% of the adult population (1), with more than 4.8 million Canadians diagnosed in 2007 (2). As such, even

La détermination des facteurs à l'origine des différences de rapport coût-efficacité des traitements pharmacologiques de l'hypertension non compliquée

HISTORIQUE : Les lignes directrices publiées et les évaluations économiques arrivent à des conclusions différentes quant à la pharmacothérapie optimale de l'hypertension non compliquée. On ne comprend pas clairement les facteurs responsables de ces disparités. Les cliniciens, les chercheurs et les décideurs doivent mieux les comprendre pour déterminer les stratégies les plus efficaces et les plus durables.

OBJECTIFS : Déterminer comment les questions de coûts et de rapport coût-efficacité sont utilisées dans les principales lignes directrices sur l'hypertension pour produire des recommandations et déterminer les principaux moteurs des conclusions à l'égard du rapport coût-efficacité dans les évaluations économiques.

MÉTHODOLOGIE : Les chercheurs ont procédé à une recherche systématique et à une analyse narrative des principales lignes directrices sur l'hypertension et des évaluations des antihypertensifs de première intention en technologie de la santé.

RÉSULTATS : Dans les huit lignes directrices repérées, l'analyse coût-efficacité officielle était rarement intégrée à la formulation des recommandations. Lorsque les lignes directrices tenaient compte des coûts, les recommandations demeuraient non congruentes. Deux évaluations économiques ont été repérées (Royaume-Uni et Canada), mais leur conclusion différait quant au médicament le plus rentable et à l'attrait des inhibiteurs calciques. D'après une analyse de ces évaluations économiques, les conclusions en matière de rapport coût-efficacité dépendent largement du coût relatif de catégories de médicaments. Lorsque les différences relatives du coût des médicaments sont plus faibles, leurs répercussions sur des troubles connexes comme l'insuffisance cardiaque et le diabète ont une incidence sur les conclusions en matière de rapport coût-efficacité.

CONCLUSION : Compte tenu des ressources de santé limitées et des conséquences considérables sur les budgets en raison de la forte prévalence de la population, le rapport coût-efficacité est un élément important du traitement de l'hypertension non compliquée. La détermination des principaux facteurs du rapport coût-efficacité contribuera à l'interprétation et à la tenue des futures évaluations économiques.

small differences in incremental costs and health outcomes may have a substantial impact from a population perspective.

While frequently cited as important factors when selecting appropriate antihypertensive therapy, it is unclear to what extent costs and cost-effectiveness data are used in the development of treatment guidelines, and if this accounts for differences in treatment recommendations

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between guidelines. Furthermore, it has been noted that health technology assessments (HTAs) and economic evaluations have come to discordant conclusions regarding the most cost-effective agent (3). The reasons for these differences are not clear, nor is there a description in the literature of what the major drivers of cost effectiveness are. This leads to confusion for practitioners and policy makers alike as they attempt to interpret and reconcile differences. A greater understanding will facilitate effective and efficient management of this large patient population in the face of finite health care resources, and guide future analyses.

We determined whether cost effectiveness was an implicit or explicit consideration in the formulation of major clinical practice guidelines of first-line therapy of uncomplicated hypertension. We also systematically searched HTA and economic evaluations of first-line pharmacological therapy for hypertension produced by major HTA organizations, and assessed quality, summarized results, and identified important model differences and drivers of cost effectiveness.

METHODS

Guidelines produced by national hypertension societies were identified using the International Society of Hypertension Web site (4). Organizations were restricted to countries of G8 nations and Australia because these countries best reflect considerations relevant to Canada. One reviewer (MH) abstracted information from guidelines and accompanying documentation for country, year, organization, first-line anti-hypertension treatment recommendations, integration of cost and cost-effectiveness data, and conduct of de novo economic evaluation. The abstracted information was verified by a second reviewer (SWK). Disagreements were resolved by consensus.

A systematic literature search of the HTA database produced by the Centre for Reviews and Dissemination, and the International Network of Agencies for Health Technology Assessment was conducted, informed by an MLIS-qualified librarian with expertise in systematic reviews. References of articles were scrutinized for additional studies. Studies were included if a formal economic evaluation (where incremental costs and health benefits of two or more strategies are determined) of first-line treatment of uncomplicated hypertension in adult subjects was conducted, with at least one comparison including pharmacotherapy. Non-English language, abstract-only publications, and studies published before 2000 were excluded. Two reviewers (MH, SWK) applied selection criteria to the title and abstract of each citation. Full-text articles were obtained for citations that could not be unequivocally excluded by the title and abstract alone. Disagreements among reviewers were resolved by consensus.

One reviewer (MH) used a standard data extraction form to extract and record relevant information, which was verified by a second reviewer (SWK). Information captured included intervention, comparators, study population, study design, time horizon, perspective, data sources for effects, data sources for costs, health-related quality of life (HRQOL), currency, year, base-case incremental cost-effectiveness ratio results or incremental net benefit, sensitivity analysis and conclusions. Costs were converted to a common currency and year (2006 Canadian dollars), accounting for currency conversion and inflation adjustment (5-7). Study quality was independently assessed by two reviewers (SWK, MH) using an adapted checklist (8). It was anticipated a priori that a small number of articles would be identified. Therefore, a qualitative synthesis of included studies was planned, with specific emphasis on identification of model inputs that led to changes in conclusions between and within studies.

RESULTS

One international and seven country-specific guidelines for first-line treatment of hypertension were identified (Table 1). Cost was discussed in the majority of guidelines (seven of eight). However, only one guideline – by the National Collaborating Centre for Chronic Conditions and National Institute for Clinical Excellence (9) – reported on a complete economic evaluation and specifically

incorporated the findings into recommendation development. Two guidelines – the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (10) and the World Health Organization (11) – explicitly suggested thiazide diuretics only as first-line therapy, citing equal efficacy among commonly used agents and lowest acquisition cost of thiazides as important factors. Of the remaining four guidelines mentioning cost, all listed multiple potential first-line therapies (Table 1). In these four guidelines, discussion focused on drug acquisition costs as a potential barrier to adherence. A discussion of cost effectiveness was provided in the World Health Organization guideline (11), stating that while the medication with the lowest cost is appropriate under the assumption of similar efficacy, there may be selected patient populations in which more costly agents may be considered cost effective if clinical benefit is substantially greater than those associated with a lower-cost agent, although formal analyses to quantify these arguments were not performed.

In the search for economic evaluations, 64 citations were identified, three underwent further scrutiny and two met selection criteria. Reviewers agreed on all articles, and the quality (8) of both studies was determined to be high. Details of the models and their results are shown in Table 2.

The National Collaborating Centre for Chronic Conditions/National Institute for Clinical Excellence analysis (9) estimated the cost effectiveness of four blood pressure-lowering drug classes in patients with essential hypertension, using a stated cost-effectiveness threshold of £20,000 (CAN\$45,000) per quality-adjusted life year (QALY), below and above which strategies would be considered attractive and unattractive, respectively. Effectiveness data were based on a meta-analysis of 20 trials comparing at least one drug with another, and not with a placebo. Effectiveness, as measured by the development of myocardial infarction, stroke, angina, diabetes and heart failure, was translated into HRQOL using various sources. Costs included drug acquisition costs as well as United Kingdom (UK) cost estimates associated with the five health states. The authors concluded that thiazide diuretics and calcium channel blockers dominated (were less costly and more effective) over beta-blockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. It is noted that the absolute magnitude of difference in effectiveness between calcium channel blockers and ACE inhibitors or angiotensin receptor blockers was small. At an added cost of £12,250 (CAN\$27,600) per QALY, calcium channel blockers were found to be more cost effective than thiazide diuretics in a population of 65-year-old individuals with intermediate risk for diabetes (1.1%/year), heart failure (1.0%/year) and cardiovascular disease (2.0%/year). The authors concluded that in a younger cohort (55-year-old individuals), thiazides became the preferred option, while calcium channel blockers were preferred when 65- and 75-year-old cohorts were considered.

The most cost-effective agent did change in sensitivity analyses, where model inputs were varied throughout plausible ranges. If calcium channel blockers were greater than six times the cost of thiazides, thiazides became the preferred agent. Furthermore, calcium channel blockers were assumed to increase the risk of developing heart failure but lower the risk of developing diabetes compared with thiazide based on results of the meta-analysis conducted. If the baseline annual risk of developing diabetes was assumed to be zero, thiazides became more effective and less costly (dominant). However, if the risk of diabetes exceeded 3% per annum, ACE inhibitors or angiotensin receptor blockers became a cost-effective alternative to calcium channel blockers. As the risk of heart failure increases, and as the risk of cardiovascular events associated with heart failure increases, the cost-effectiveness ratio of calcium channel blockers becomes less favourable. Relative effectiveness was based on a primary meta-analysis, and use of upper and lower ranges of the CIs also led to changes in conclusions. Finally, while side effects of medications were not included in the base-case analysis, inclusion had a large impact on cost-effectiveness conclusions. In sensitivity analysis, if the decrement in HRQOL due to medication side effects alone was 4% or greater,

TABLE 1
First-line therapy recommendations and integration of cost in hypertension guidelines

Country	Guideline	Source (year)	First-line treatment for uncomplicated hypertension	Cost or cost effectiveness discussed in guideline	Cost-effectiveness analysis performed	Reference
Australia	Guide to management of hypertension 2008	National Heart Foundation (2008)	ACEI (or ARB), CCB Diuretics for age ≥65 years only	Mention of costs as a factor to consider for access to medications	No	27
Canada	2009 Canadian Hypertension Education Program recommendations	Canadian Hypertension Society (2009)	Thiazide diuretic, BB (age <60 years), ACEI, CCB or ARB	No	No	17,28
Europe	2007 European Society of Hypertension/ European Society of Cardiology practice guidelines for the management of arterial hypertension	European Society of Hypertension/European Society of Cardiology (2007)	Based on CV risk profile, concomitant conditions, drug interactions, cost (to patient or health provider)	While costs listed as consideration when choosing treatment, "cost considerations should never predominate over efficacy, tolerability and protection"	No	29
France	Management of adults with essential hypertension	Haute Autorité de santé (2005)	Thiazide diuretics or BB in absence of other specific indications	Diuretics and BB highlighted as "not expensive"; diuretics noted to have lowest daily cost	No	30
International	2003 World Health Organization/ International Society of Hypertension statement on management of hypertension	World Health Organization/ International Society of Hypertension (2003)	Thiazide diuretic Potential use of other drug classes in high-risk patients	Implicit dominance of diuretics based on comparative trial data (similar effectiveness) and lower costs. Specific discussion regarding cost effectiveness: more costly drugs may be cost effective in selected patient populations	No	11
Japan	The Japanese Society of Hypertension guidelines for the management of hypertension	Japanese Society of Hypertension (2009)	All six classes (CCB, ACEI/ARB, thiazide diuretics, BB, alpha-blockers)	Thiazide diuretics described as "inexpensive, to the advantage of pharmaco-economics"	No	31
United Kingdom	Hypertension. Management in adults in primary care: Pharmacological update	National Collaborating Centre for Chronic Conditions (funded to produce guidelines for the NHS by NICE) (2006)	Age ≥55 years or black: CCB or thiazide Age <55 years: ACEI	Recommendations group had access to detailed health economic analysis, which was used in conjunction with other considerations to formulate guidelines	Yes – primary economic analysis performed	9
United States	Management of Hypertension: Update in Therapeutics (JNC 7)	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2003)	Thiazide diuretics as first-line therapy (alone or in combination with ACEI, ARB, BB or CCB)	Minimizing patient cost described as strategy to optimize control and minimize economic barriers. Implicit dominance of diuretics based on clinical trial data and lower drug costs	No	10

ACEI Angiotensin-converting enzyme inhibitors; ARB Angiotensin receptor blockers; BB Beta-blockers; CCB Calcium channel blockers; CV Cardiovascular; JNC 7 Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NHS National Health Service; NICE National Institute for Health and Clinical Excellence

treatment (compared with no pharmacological therapy) was no longer cost effective, and differences in HRQOL of as small as 0.1% between agents due to side effects could lead to reordering of the most cost-effective agent.

The Canadian Agency for Drugs and Technologies in Health analysis (3) used a similar approach and model (Table 2). Effectiveness was based on transitions to the same health states, with the exception that diabetes was not included in the model (and was acknowledged by the authors as a potential cause of differences from other reports). RRs were computed from a meta-analysis of 26 trials. However, trial selection criteria specified that thiazides must be included as a treatment arm (compared with placebo or another drug class); thus, only 10 trials were common to both evaluations. Despite this, the effectiveness estimates inputted into the model were similar to the UK study (no differences in overall mortality, but a reduction in stroke for thiazide compared with ACE inhibitors, and a reduction in heart failure for thiazide compared with calcium channel blockers), although the relative difference between agents for development of diabetes was not

included. The relative cost differences at 2006 prices among agents were also markedly different (Table 3). The results of this analysis indicate that thiazide diuretics dominated (were less costly and led to greater health benefits) over all other strategies (including no treatment), with the exception of calcium channel blockers. However, calcium channel blockers were associated with a cost-effectiveness ratio of more than \$400,000/QALY and were therefore considered unlikely to be attractive.

DISCUSSION

Different guidelines generate nonuniform recommendations for first-line therapy in patients with uncomplicated hypertension, despite use of the same evidence base. While there may be various explanations for this (12), we sought to determine whether consideration of cost or cost effectiveness played a role. It is surprising that in the three guidelines in which recommendations appear to be influenced by cost or cost-effectiveness considerations, the recommendations still have major differences. The only guideline that integrates findings from a

TABLE 2
Summary of identified economic evaluations of first-line therapy for hypertension

	NICE: Hypertension. Management in adults in primary care (2006) (9)	CADTH: Thiazide diuretics as first-line treatment for hypertension: Meta-analysis and economic evaluation (2007) (3)
Objective	To estimate the cost effectiveness of various blood pressure-lowering drug classes for the management of hypertension in primary care	To estimate the cost effectiveness of first-line thiazide diuretics compared with placebo and other drug classes in the treatment of hypertension in newly diagnosed patients
Population	Patients with essential hypertension and no pre-existing CVD, HF or DM	Newly diagnosed 55- or 65-year-old patients with no significant additional risk factors
Setting	Cohorts classified by age, sex, baseline CVD risk, HF risk and DM risk No intervention	Eight cohorts classified by sex, age and systolic blood pressure No therapy
Comparators	Thiazide diuretics, CCB, BB or ACEI/ARB (80% to 20% mix)	Thiazide diuretics, CCB, BB or ACEI/ARB (80% to 20% mix)
Form of economic analysis	Cost-utility analysis	Cost-utility analysis
Perspective	Health care payer (United Kingdom)	Health care payer (Canada)
Timeframe	Lifetime	10 years
Clinical effectiveness data source	Meta-analysis (20 trials) Trials with placebo control excluded	Meta-analysis (26 trials) Only trials comparing thiazide diuretics with other therapy/placebo included
Quality of life	QALYs based on published data Utility decrement for MI, angina, stroke, DM, HF Utility adjusted for age No utility decrement for side effects	Baseline age-specific utilities based on Canadian National Population Health Survey Adjusted for disease complications
Direct costs	Health states: Angina, MI, stroke, HF, DM Annual drug cost (see Table 3)	Health states: Angina, MI, stroke, HF Annual drug cost (see Table 3): Includes estimated drug dispensing fees
Indirect costs	N/A	N/A
Data modelling details	Treatment effects attributed to first-line drug 6-month cycles Probability of events are independent of previous events Patients can transition to any health state	Monotherapy only 1-year cycles Patients transition according to sex, age, systolic blood pressure, other risk factors Risk of event is a function of disease history
Decision modelling details	Markov model (model diagram provided)	Markov model (model diagram provided)
Sensitivity analysis approach	Magnitude of treatment effects Use of ARB relative to ACEI Cost of CCB Baseline risk of developing DM and HF	Cholesterol levels Smoking status Costs of complications Disutility of complications RRs of events according to treatment Probabilistic sensitivity analysis
Currency and year	£, 2005	CAN\$, 2006
Important findings from sensitivity analysis	Results sensitive to age, baseline CVD risk, DM risk and HF risk Results sensitive to cost of CCB (no longer cost effective if CCB more than 6 times the cost of thiazides) Results sensitive to uncertainty around treatment effects	Results not sensitive to changes in parameters
Base-case results	All treatments are cost effective compared with no treatment At intermediate risk for HF and diabetes, BB and ACEI/ARB are dominated, and CCB have an ICER of £12,250 (2006 CAN\$27,600) compared with diuretics At high risk for HF: Thiazide diuretics are most cost effective At high risk for HF and diabetes: ACEI/ARB are most cost effective	Thiazide diuretics dominate over BB, ACEI/ARB and no treatment CCB have an ICER >\$400,000 compared with diuretics
Conclusions	"Beta-blockers are the class of drug least favoured, and CCB and thiazide-type diuretics appear the most cost-effective choices in most scenarios"	"The economic analysis found little difference between therapies in terms of effectiveness and found thiazide diuretics to be 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 CCB"

ACEI Angiotensin-converting enzyme inhibitors; ARB Angiotensin receptor blockers; BB Beta-blockers; CADTH Canadian Agency for Drugs and Technologies in Health; CCB Calcium channel blockers; CVD Cardiovascular disease; DM Diabetes mellitus; HF Heart failure; ICER Incremental cost-effectiveness ratio; MI Myocardial infarction; N/A Not applicable; NICE National Institute for Health and Clinical Excellence; QALY Quality-adjusted life year

primary economic evaluation (9) does not list thiazide diuretics, the drug class with the lowest acquisition costs, as the single preferred agent. Furthermore, two recently published high-quality economic evaluations performed by major government-associated HTA agencies came to differing conclusions regarding the attractiveness of treatment with calcium channel blockers. This review identifies several factors

that are key drivers of cost and cost effectiveness, including relative drug acquisition costs, impact on development of associated conditions, and chronic adverse drug side effects affecting HRQOL of the various drug classes.

Differences in drug acquisition costs among antihypertensive classes can be a major driver of both cost and cost effectiveness. This

TABLE 3
Relative annual costs of antihypertensive treatment in health technology assessments

	Cost			
	Thiazide diuretics	Calcium channel blockers	Beta-blockers	ACEI/ARB
NICE: Hypertension. Management in adults in primary care (2006)* (9)	Reference £13 (CAN\$29)	5× £70 (CAN\$158)	1× £13 (CAN\$29)	5× £67 (CAN\$151)
CADTH: Thiazide diuretics as first-line treatment for hypertension: Meta-analysis and economic evaluation (2007) [†] (3)	Reference \$29	27× \$789	7× \$205	14× \$418

All costs are presented in relation to the reference values (ie, thiazide diuretics) and as a monetary value. *Annual drug costs from Prescription Pricing Authority, 2005 (2006 Canadian cost provided in parentheses); [†]Annual drug costs from Ontario Drug Benefit Formulary Comparative Drug Index, 2006 (includes dispensing fee). ACEI Angiotensin-converting enzyme inhibitors; ARB Angiotensin receptor blockers; CADTH Canadian Agency for Drugs and Technologies in Health; NICE National Institute for Health and Clinical Excellence

TABLE 4
Relative annual costs of antihypertensive treatment in Alberta in 2006 and 2009

	Cost	
	2006	2009
Thiazide diuretics (hydrochlorothiazide 25 mg QD)	Reference (\$25)	1× (\$25)
Calcium channel blockers (amlodipine 5 mg QD)	22× (\$542)	11× (\$283)
ACEI/ARB (ramipril 5 mg QD 80%/losartan 50 mg QD 20%)	14× (\$362)	11× (\$278)
Beta-blockers (atenolol 25 mg QD)	4× (\$106)	4× (\$106)

All costs are presented in relation to the reference value (ie, thiazide diuretics) and as a monetary value. Annual drug costs from the 2006 and 2009 Alberta Health and Wellness Drug Benefit List (14); includes a dispensing fee of \$10.22 four times per year based on the Alberta Health and Wellness dispensing fee for April 2009 (32). ACEI Angiotensin-converting enzyme inhibitor; ARB Angiotensin receptor blocker; QD Once daily

is evident in the Canadian economic evaluation, where annual drug costs for other classes were seven to 27 times higher than a thiazide diuretic (Table 3). When very large cost differences exist, more expensive agents need to demonstrate a substantial advantage over thiazide diuretics in health outcomes and attendant downstream health care costs to be considered attractive within a cost-effectiveness framework. While a cost-minimization approach (where effectiveness is assumed to be equal and the lowest cost treatment strategy is deemed optimal) has been criticized (13), this approach may be reasonable for uncomplicated hypertension because effectiveness has generally been found to be similar between drug classes. Indeed, this framework has been informally applied in some of the identified guidelines, leading to recommendations for thiazide diuretics as first-line therapy in uncomplicated patients.

However, a cost-minimization approach is not appropriate when the relative differences in annual drug costs among classes falls, as small differences in effectiveness begin to have a greater impact on conclusions. In the UK economic evaluation, where the cost of alternate medication classes are only one- to fivefold greater than thiazide diuretics, thiazides were not considered to be the most cost-effective agents in uncomplicated hypertension and, under some scenarios, ACE inhibitors or angiotensin receptor blockers became a cost-effective alternative. These analyses were driven by the relative differences in some drug classes on development of heart failure and diabetes, as well as different assumptions on the baseline risk of developing these conditions. While this reflects drug pricing in the UK at the time of the analysis, this scenario may also occur in other jurisdictions as drugs become generic and prices fall. For example, the cost of the commonly used dihydropyridine calcium channel blocker amlodipine has decreased by 50% from 2006 to 2009 in Alberta (14), leading to substantially lower estimated annual drug acquisition costs relative to thiazide diuretics (Table 4). It should

also be noted that actual drug acquisition costs may vary within Canada (15,16), which may lead to differing optimal approaches between and within each province. As such, it is important to update economic evaluations with geographically specific data to reflect current cost realities for each jurisdiction.

Certain classes of medications have been found to have an advantage over others with respect to development of associated conditions such as heart failure, stroke and diabetes. While the relative effect size is of moderate magnitude (20% to 40% difference), the relatively low absolute risk of development of de novo conditions in subjects with uncomplicated hypertension translates into small absolute effects. However, the UK economic evaluation confirms that the impact on development of these conditions is important. In addition, the efficacy among drug classes may vary by age or ethnicity (17) and, therefore, may also impact economic conclusions. The baseline risk of developing heart failure or diabetes altered conclusions due to the HRQOL decrement and health care costs associated with these conditions. Because calcium channel blockers are associated with an increased risk of heart failure but a lower risk of diabetes compared with thiazide diuretics, altering the risk of development over a small range (0% to 3%) led to changes. These were not seen in the Canadian analysis, most likely due to much greater differences in drug costs (although diabetes was not considered as a health state in the Canadian model).

In settings with smaller differences in cost among the drug classes, considerations other than relative effectiveness may alter results. The UK model suggested that while the quality of life decrements associated with chronic pharmacological therapy for hypertension are unknown, relatively small changes for all agents and between agents can alter results. While not specifically evaluated in either model, factors such as side effects that impact persistence (adherence) of therapy may also have a substantial impact on cost-effectiveness conclusions (18). Observational studies have found that persistence is lowest with diuretics and beta-blockers, and is higher with angiotensin receptor blockers and ACE inhibitors, which may impact the relative cost effectiveness of therapy (19-21). It is also possible that other potential drivers of cost effectiveness may play a role, such as costs of laboratory monitoring with each medication class (22) or other potential side effects that may lead to hospitalization such as hyponatremia or hyperkalemia, neither of which were included in the two reports.

The present review has several limitations that warrant acknowledgment. First, given the lack of information in guidelines, it was often not clear to what extent cost and cost effectiveness played a role in formulating recommendations. This contrasts sharply with more explicit descriptions of processes for how efficacy evidence is used in the creation of recommendations for practice guidelines. Second, the review of economic evaluations was limited to a single database, and did not include other peer-reviewed publications. However, this database captures HTAs conducted by members of the International Network of Agencies for Health Technology Assessment and other major HTA organizations, which are likely to be used to influence health care policy and decision making. In addition, we did not have access to the economic models used, and the identification of key drivers of cost effectiveness was

limited to what was presented by the authors and our interpretation. For example, cases of heart failure and diabetes attributed to medication use were assumed to have the same quality of life and cost impact as typical cases, and we were not able to further test this and other assumptions used in the models. We also could not definitively determine to what extent drug cost differences, or inclusion or exclusion of the health state of diabetes altered study conclusions. In addition, the models only considered monotherapy; however, most patients with hypertension require at least one agent to meet optimal blood pressure targets (21,23,24). The choice of subsequent lines of therapy, if varying in effectiveness and costs, may also impact ranking conclusions.

While information from cost-effectiveness studies is rarely formally integrated into guideline development (25), given the reality of finite health care resources, it is imperative to explicitly integrate findings from such analyses into recommendations to ensure health system sustainability. Relying on drug acquisition costs alone may not be reliable to estimate cost effectiveness, particularly in jurisdictions where the relative differences among drug class costs have decreased. In these

settings, differential effects on development of comorbid conditions such as heart failure and diabetes, medication-related changes in HRQOL, or persistence with therapy may be important factors. We advocate further study on the relative differences between drug classes on outcomes, quality of life and adherence (20), particularly for different patient subgroups (26), to determine optimal and efficient treatment. Identification of key drivers of cost effectiveness will assist in the interpretation of current economic evaluations, and should be incorporated into future economic evaluations that inform treatment guidelines.

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