Cost-effectiveness of dutasteride-tamsulosin combination therapy for the treatment of symptomatic benign prostatic hyperplasia: A Canadian model based on the CombAT trial

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Abstract

Introduction: Benign prostatic hyperplasia (BPH) is common in men 50 years old and older. The main treatment options are alpha-blockers (such as tamsulosin), which reduce symptoms, and 5-alpha reductase inhibitors (such as dutasteride), which reduce symptoms and slow disease progression. Clinical studies have demonstrated that dutasteride-tamsulosin combination therapy is more effective than either monotherapy to treat symptomatic BPH. We studied the cost-effectiveness in Canada of the dutasteride (0.5 mg/day) and tamsulosin (0.4 mg/day) combination compared with tamsulosin or dutasteride monotherapy.

Methods: A Markov model was developed which follows a cohort of male BPH patients ≥50 with moderate to severe lower urinary tract symptoms (LUTS). The model estimates costs to the Canadian health care system and outcomes (in terms of quality adjusted life years [QALYs]) at 10 years and over a patient's lifetime. The dutasteride-tamsulosin combination was compared to each of tamsulosin monotherapy and dutasteride monotherapy.

Results: Compared with tamsulosin, the combination was more costly and produced better patient outcomes. Over a lifetime, the incremental cost-effectiveness ratio was CAN$25 437 per QALY gained. At a willingness to pay CAN$50 000 per QALY, the probability of combination therapy being cost-effective was 99.6%. Compared with dutasteride, the combination therapy was the dominant option from year 2, offering improved patient outcomes at lower cost. The probability that combination therapy is more cost-effective than dutasteride was 99.8%.

Conclusion: Combination therapy offers important clinical benefits for patients with symptomatic BPH, and there is a high probability that it is cost-effective in the Canadian health care system relative to either monotherapy.

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases in men aged 50 and older.[1,2] The number of Canadian men aged ≥50 years is projected to grow by over 37% to 6.5 million by 2018, and the number of men with moderate-severe lower urinary tract symptoms (LUTS) is expected to increase by 41% to 2.6 million.[3] BPH can manifest itself through LUTS and, if left untreated, can lead to complications, such as acute urinary retention (AUR), BPH-related surgery, incontinence, recurrent urinary tract infections and, in some cases, renal failure.[4,5] The main objective of treatment for LUTS/BPH is to alleviate symptoms and to reduce the risk of disease progression.[6] For patients with mild symptoms, watchful waiting with lifestyle modifications are acceptable. However, for patients with moderate to severe symptoms, surgical or pharmacological therapies are recommended.[7] The main pharmacological treatment options for LUTS caused by BPH are alpha-blockers (ABs) and 5-alpha reductase inhibitors (5ARIs).[4] Alpha-blockers, such as the uro-selective tamsulosin, relax the muscles of the bladder neck and the prostate, thus increasing urinary flow rates;[8] 5ARIs, such as dutasteride, decrease the risk of BPH-related long-term complications by reducing cellular growth and, subsequently, reducing prostate size.[8]

The Canadian BPH guidelines recommend alpha-blockers for symptomatic relief in BPH patients who do not have an enlarged prostate, while highlighting that these agents do not alter the natural progression of the disease. 5ARIs, administered as monotherapy or in combination with alpha-blockers, are recommended for symptomatic men with an enlarged prostate and are associated with decreased risk of urinary retention and/or prostate surgery.[7] The guidelines also state that combination therapy effectively delays symptomatic disease progression.[7]

The 4-year Combination of Avodart and Tamsulosin (CombAT) study was designed to evaluate whether combination therapy was more effective than monotherapy in reduc-

ing the relative risk of clinical progression in men with BPH with moderate to severe LUTS who were predicted to be at increased risk of disease progression (defined by a prostate volume ≥30 cc and prostate-specific antigen [PSA] ≥1.5 ng/mL[9]). The results showed that combination therapy significantly reduced the risk of AUR and surgery over tamsulosin by 67.6% and 70.6%, respectively.[10] The combination also significantly reduced symptoms and the risk of clinical progression versus both therapies, and clinical benefits were sustained over 4 years.[10]

The objective of our study was to evaluate the long-term cost-effectiveness of a fixed dose combination therapy (0.5 mg dutasteride + 0.4 mg tamsulosin) compared to tamsulosin 0.4 mg monotherapy or dutasteride 0.5 mg monotherapy (all administered once daily) in Canada.

Methods

Model structure

A cost-effectiveness model was developed based on a discrete Markov process with annual cycle length (Table 1). Cost-effectiveness was analysed at 10 years and at a lifetime horizon (up to 25 years). The perspective was that of the Canadian health system. A Markov process was selected because BPH is a chronic condition with repeated clinical events over time.

The Markov structure includes 6 mutually exclusive health states: (1) mild BPH symptoms; (2) moderate BPH symptoms; (3) severe BPH symptoms; (4) AUR; (5) post-surgery following transurethral resection of the prostate (TURP); and (6) death (Fig. 1). Symptom severity in this study is defined by the International Prostate Score System (IPSS) (Table 2). The IPSS is most commonly used in assessing BPH symptom severity in clinical trials; other inclusion criteria in CombAT have been previously described, and include age, prostate volume, PSA and maximum urinary flow rate (Qmax).[9] While these definitions of mild, moderate and severe symptoms are common in Canada, we have used these cutoffs to be consistent with those used in the CombAT trial. AUR was modelled as a temporary health state because it is a short-term complication requiring emergency treatment. Patients can enter the AUR state from any of the BPH symptom states in a half cycle.

The patient pathway following AUR depended on the treatment success: the two treatment options were emergency catheterization and trial without catheter (TWOC). After a successful TWOC, patients returned to their previous health states. Patients with unsuccessful TWOC required BPH-related surgery and entered the post-surgery health state. In this model, BPH-related surgery was transurethral resection of the prostate (TURP), which resulted in one of two outcomes: TURP success or TURP failure. TURP failure was declared when a patient's IPSS was not reduced by more than 50% after surgery. TURP was assumed as the most common surgery

Table 1. Cost-effectiveness model overview

Aspect	Details	Justification/references
Analytical methods	Markov state transition model with tunnel state and embedded decision tree	Long-term chronic condition, clear and reproducible, quick evaluation of sensitivity analyses.
Software used	Microsoft Excel 2007	Transparent and accessible platform
Model perspective(s)	Canadian heath system payer	
Time horizon	Lifetime (up to 25 years in practice)	Reflects long-term analysis of outcomes
Cycle length	Annual cycles	Long term analysis
Patient population	Men aged ≥50 years with moderate to severe BPH at baseline	Reflects CombAT trial and current indications
Treatment arms	Combination therapy of dutasteride and tamsulosin	
Comparator arms	Tamsulosin monotherapy Dutasteride monotherapy (each comparator arm contained within separate models versions)	Comparing to cheapest comparator (tamsulosin) will give the largest possible net impact on costs. Dutasteride is a relevant comparator since the study treatment is a combination including dutasteride, which is currently used for the treatment of BPH in Canada.
Outcomes	Costs of drug treatment Costs of consultations Costs of AUR Costs of BPH-related surgery Total costs Total QALYs Incremental cost Incremental QALY Incremental cost per QALY	Accepted and widely used measures of cost-effectiveness.

BPH: benign prostatic hyperplasia; CombAT: Combination of Avodart and Tamsulosin trial; AUR: acute urinary retention; QALYs: quality adjusted life years.

Table 2. Symptom severity score defined by the IPSS

Clavien	Definition
Mild	0-11
Moderate	12-23
Severe	24-35

IPSS: International Prostate Score System

choice for men in Canadian clinical practice. Patients who had a successful first TURP may have later relapsed and thus required a second procedure, as would have patients whose first TURP was unsuccessful. In this study, it was assumed that patients did not undergo more than two TURP procedures.

Outcomes

The model estimated the following outcomes: costs of drug treatment, costs of consultations, costs of AUR, costs of BPH-related surgery, total costs (including hospitalizations and home care post-surgery or in the event of complications such as incontinence), total quality adjusted life years (QALYs), incremental cost, incremental QALYs, and incremental cost per QALY gained. Costs and outcomes were discounted at 5% per annum.

Patient population

To calculate BPH-related costs in Canada, we set the number of men entering the model at 1.313 million, which is the estimate of the prevalence of moderate-severe BPH in men over 50 (23%).[11-14] The model cohort was representative of the population of the CombAT trial,[10] which included men ≥50 diagnosed with moderate to severe BPH, as measured by the IPSS. The starting distribution of patients in each of the BPH symptom health states entering the model was established by the baseline IPSS of the CombAT trial population: mild = 7%; moderate = 63%; and severe = 30%. The classification of severity is the one used in the trial. Although the trial enrolled men with moderate or severe symptoms, some had improved before starting treatment, hence there is a small proportion of patients with mild symptoms.

Treatment effects

The efficacy of the comparator interventions was derived from the CombAT clinical study report. This was a 4-year, multicentre, randomized, double-blind, parallel-group study in 4844 men ≥50 years of age with a clinical diagnosis of BPH, IPSS score ≥12, prostate volume ≥30 cm^3, PSA 1.5-10 ng/mL, and Qmax >5 and ≤15 mL/s with minimum voided volume ≥125 mL.[10] Interventions were oral daily tamsulosin 0.4 mg, dutasteride 0.5 mg or a combination of both. Combination therapy was significantly superior to tamsulosin monotherapy, but not dutasteride monotherapy, at reducing the relative risk of AUR and BPH-related surgery. Combination therapy was also significantly superior to both monotherapies at reducing the relative risk of BPH clinical progression. Combination therapy provided significantly greater symptom benefit than either monotherapy at 4 years.[10]

Transition probabilities between BPH symptom states were calculated using cohort-level data from the CombAT trial. Average annual transitions between symptom states were derived for the combination therapy and each of the tamsulosin and dutasteride monotherapies, from three monthly observations in the trial. The relative risks of AUR and BPH-related surgery were estimated from the number of yearly events observed in the trial using standard methods (Table 3).[15]

Patients transitioning to the temporary AUR health state had their next transition determined by the success or failure of TWOC. This care pathway was not reported in the CombAT trial, and for the model we assumed that 50% of patients had a successful TWOC based on a clinical review by Emberton and colleagues.[16] Similarly, the care pathway of patients undergoing BPH-related surgery was not reported in the CombAT trial, and we determined the care pathway from published literature.[7,17-19] Unsuccessful TURPs consisted of those resulting in total permanent incontinence and those where re-treatment with a second TURP was possible (defined as "failed TURP"). The probability of having a failed TURP was calculated as: 1 – (probability of success) – (probability of total incontinence) (Fig. 1).

Table 3. Event rates and transition probabilities for AUR and BPH-related surgery based on the CombAT study

	AUR event rates and transition probabilities			
	No. events	No. at risk	4-year probability	Annual probability
Combination	36	1610	0.0224	0.0056
Tamsulosin	109	1611	0.0677	0.0173
Dutasteride	44	1623	0.0271	0.0066
	BPH-related surgery event rates and transition probabilities			
	Number of events	Number at risk	4-year probability	Annual probability
Combination	38	1610	0.0236	0.0060
Tamsulosin	126	1611	0.0782	0.0202
Dutasteride	56	1623	0.0345	0.0087

Adapted from Roehrborn et al.[10] AUR: acute urinary retention; BPH: benign prostatic hyperplasia.

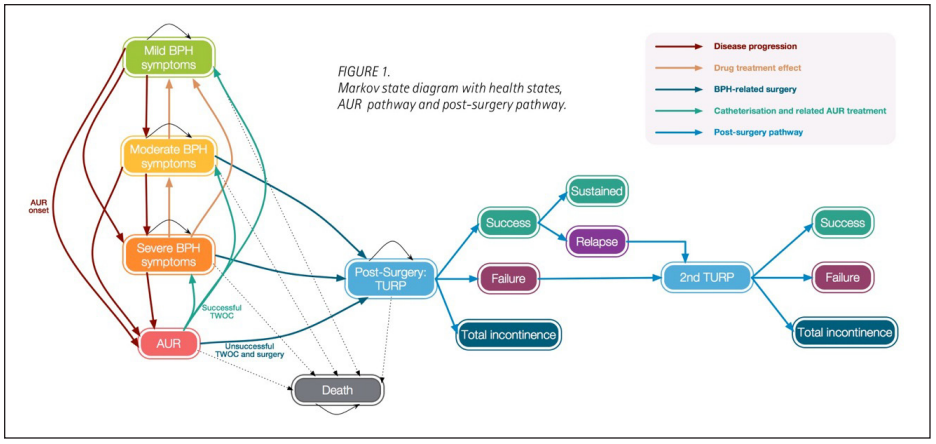

Fig. 1. Markov state diagram with health states, acute urinary retention pathway, and post-surgery pathway.

Adverse events

While the costs of treatment-related adverse events (AEs) may not be relevant in terms of overall budget impact, the (dis)utility induced by drug-related AEs may have a significant impact on the cost-effectiveness of combination therapy. As such, the cost of treating these AEs was also included.

The probability of any TURP-related AE was extracted from the 2009 European Urology Association BPH treatment guidelines (Table 4).[20] This total probability was applied to all patients in the post-surgery state (first or second TURP), whether or not the procedure was a success. Pharmacotherapy-related AEs were based on the CombAT trial data. Only common drug-related AEs (more than 1% of the population) in any treatment arm were included to capture the most frequently occurring ones (Table 5). AEs were assumed to be mutually exclusive.

Discontinuation

Patients may have discontinued treatment at the end of a cycle due to AEs or lack of efficacy. The percentage of patients who discontinued treatment per year due to treatment-related AEs for combination therapy, tamsulosin, and dutasteride monotherapy were 1.44 %, 0.91 %, and 0.97%, respectively.[10] The percentage of patients discontinuing treatment per year due to lack of efficacy for combination, tamsulosin, and dutasteride monotherapy was 0.83%, 1.65%, and 1.11 % respectively.[10]

Mortality

Mortality data were taken from Statistics Canada[21] for men 50 years old and older for 2007 (the most recent year available at the time of the analysis). Discontinuous data in the primary source were fitted by exponential regression to estimate a continuous relationship between age and rates of mortality. The equation for the rate of mortality as a function of age was: mortality rate = 2.9984 exp (0.0946 × age in years)

Resource use

Costs included all primary care and hospital/surgery costs, based on: (a) resource use associated with disease severity states (maintenance healthcare visits or routine care), (b) resource use associated with AUR, and (c) resource use associated with TURPs. Clinical pathways and resource use were estimated by Canadian clinical experts. The number of visits to health professionals per year was assumed constant over time. For drug-related adverse events, it was assumed that patients visited their general practitioner for an additional appointment per cycle. Resource use for AUR follow-up and BPH-related surgery was based on a number of assumptions provided by Canadian clinicians.

The cost year was 2010/2011. Unit costs were taken from costs/prices in Quebec and Ontario, as representative of Canada as a whole, and were derived from the Ministry of Health and Long Term Care, Ontario Schedule of benefits[22] (district nurse visit, hospital nurse visit, GP consultation, urologist consultation), and Quebec Liste de Medicaments, July 2011[23] (drug prices). Other costs (urodynamic test, flexible cystoscopy, cost of prostate-related surgery and the cost of AUR) were taken from published literature,[24] and inflated using the Pay and Prices Index.[25]

Table 4. TURP-related adverse events in the CombAT study

Event	Probability
TUR syndrome	2.0 %
Blood transfusion	5.0 %
Stress incontinence	2.2 %
Bladder neck contracture	4.0 %
Urethral stricture	3.8 %
Probability of any adverse event (used in model)	17.0 %

Adapted from Roehrborn et al.[10] TURP: transurethral resection of the prostate

Table 5. Annual risk of adverse events reported in CombAT (≥1% in any group)

Adverse event	Combination	Tamsulosin	Dutasteride
Dizziness	0.44%	0.44%	0.23%
Ejaculatory abnormality	1.81%	0.53%	0.32%
Impotence/erectile dysfunction	2.28%	1.33%	1.80%
Gynecomastia (breast enlargement)	0.47%	0.23%	0.59%

Adapted from Roehrborn et al.[10] CombAT: Combination of Avodart and Tamsulosin trial.

Health state utility

We assumed that the utility of a patient benefiting from a successful TURP was the same as a patient with moderate BPH symptoms. Likewise, the utility of a patient undergoing an unsuccessful TURP was the same as a patient with severe BPH symptoms. The disutility of the AUR temporary health state was evaluated from published utilities,[26] and it was assumed that the disutility of being catheterized while waiting for a TURP was the same as the disutility of AUR. Patients may have experienced waiting time before receiving surgery, therefore enduring the disutility of a health state until it was resolved. Thus, the model included the waiting time of a patient with AUR before receiving a TURP, as well as the time taken to resolve an AUR without surgery (Table 6).

Probabilistic sensitivity analysis

Cost inputs were varied according to a log-normal distribution. Default means came from the associated default cost inputs for the deterministic model and values were varied by ±20% to obtain standard errors. Utility inputs were varied according to a normal distribution, default means came from the associated default utility inputs for the deterministic model and values were varied by ±50% to obtain standard errors. Binomial probabilistic inputs were varied according to a beta distribution and default means came from the associated default inputs for the deterministic model.

Results

Cost-effectiveness

We compared the cost-effectiveness of combination therapy tamsulosin monotherapy at 10 years and at a lifetime horizon of 25 years (Table 7). The discounted cumulative costs associated with combination and tamsulosin therapies over 10 years were CAN$7.400 billion and CAN$3.445 billion, respectively, a difference of CAN$3.955 billion ($3013 per patient). The cumulative total of discounted QALYs associated with treatment with combination therapy was 9.229 million over 10 years, compared to 9.090 million for tamsulosin monotherapy, a difference of 138 671 QALYs. At 10 years, the incremental cost-effectiveness ratio (ICER) was CAN$28 523 per QALY gained (CAN$3.955bn/138 671). At a lifetime horizon, the incremental cost-effectiveness ratio was CAN$25 437.

We compared combination therapy to dutasteride monotherapy (Table 8). The discounted cumulative costs associated with combination and dutasteride over 10 years were CAN$7.400 billion and CAN$7.435 billion respectively, a difference of CAN$35.318 million. The cumulative total of discounted QALYs associated with treatment with combination therapy was 9.229 million over 10 years, compared to 9.179 million for dutasteride monotherapy. Compared with dutasteride monotherapy, combination therapy was a dominant option at 10 and 25 years, offering better patient outcomes at lower cost.

Table 6. Utility and disutility values used in the cost-effectiveness model

Health state	Utility value	Source
Mild	0.99	Baladi 1996[21]
Moderate	0.90	Baladi 1996[21]
Severe	0.79	Baladi 1996[21]
Post-TURP, successful	0.90	Assumption: same as moderate health state
Post-TURP, unsuccessful	0.79	Assumption: same as severe health state
Post-TURP, totally incontinent	0.70	Baladi 1996[21]
Disutility of AUR	-0.14	Ackerman 2000[20]
Disutility of being catheterised while waiting for TURP	-0.14	Assumption: same as AUR
Adverse event associated with TURP	**Disutility**	**Source**
TUR syndrome	-0.17	Ackerman 2000[20]
Stress incontinence	-0.04	Ackerman 2000[20]
Bladder neck contracture / urethral stricture	-0.02	Ackerman 2000[20]
Adverse event associated with treatment	**Disutility**	**Source**
Dizziness	-0.22	Vera-Llonch 2008[22]
Ejaculatory abnormality	-0.01	Ackerman 2000[20]
Impotence / erectile dysfunction	-0.06	Ackerman 2000[20]
Gynecomastia (breast enlargement)	-0.05	Penson 2005[23]

BPH: benign prostatic hyperplasia; CombAT: Combination of Avodart and Tamsulosin trial; AUR: acute urinary retention; QALYs: quality adjusted life years.

Table 7. Costs, outcomes and incremental cost-effectiveness ratio for combination therapy compared with tamsulosin monotherapy*

	Total cost (CAN $)	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY gained (ICER)
10-year time horizon					
Tamsulosin	$3.445bn	9.090m			
Combination	$7.400bn	9.229m	+$3.955bn	+138,671	$28,523
Lifetime horizon (up to 25 years)					
Tamsulosin	$5.073bn	15.664m			
Combination	$11.497bn	15.917m	+$6.424bn	+252,551	$25,437

*Costs and outcomes are discounted at 5%. bn: billion; m: million.

Sensitivity analysis

Probabilistic sensitivity analysis was carried out (1000 iterations) for both comparisons, and results are shown at the lifetime horizon (25 years). We illustrate the cost-effectiveness planes (Fig. 2. Fig. 3) and the cost-effectiveness acceptability curves (Fig. 4, Fig. 5). At a willingness to pay CAN$50 000 per QALY, the probability of combination therapy being cost-effective relative to tamsulosin was about 99.6% (Fig. 4). The probability that combination therapy is more cost-effective than dutasteride monotherapy was about 99.8% (Fig. 5).

Discussion

The results of the CombAT trial suggest that the combination of tamsulosin and dutasteride offers important clinical benefits in terms of symptom relief and reduced clinical progression than either monotherapy alone.[10] The results of the present analysis suggest that there is a high probability that this combination therapy is also cost-effective relative to either monotherapy. At a willingness to pay CAN$50 000, the probability that combination therapy is cost-effective relative to either tamsulosin or dutasteride was more than 99%. A similar study evaluating a different combination therapy of doxazosin (an AB) and finasteride (a 5-ARI) compared to doxazosin monotherapy found a baseline ICER less than CAN$40 000.[24]

Many patients take both tamsulosin and dutasteride and experience the benefits of combination therapy. The cost-effectiveness of a fixed-dose combination turns on the relative prices of the individual drugs, and on the prescribing costs. In Canada, the new marketed fixed-dose combination product, Jalyn (GlaxoSmithKline) (0.5 mg dutasteride + 0.4 mg tamsulosin) is the same price as dutasteride (Avodart, GlaxoSmithKline) alone, so that once the additional cost of tamsulosin is eliminated, the fixed-dose combination must be less expensive than the two drugs separately. Reducing two sets of prescription fees to one increases the cost advantage of the fixed-dose presentation. In normal clinical practice, the fixed-dose combination therapy is likely to be more cost-effective than the baseline values in this analysis.

This study has a number of limitations. There is a lack of data for some inputs and, as a result, a number of assumptions had to be made based on current clinical practice. The clinical burden of AUR patients and/or patients awaiting or undergoing a TWOC may be underestimated due to the model treatment of AUR as a tunnel state: the time spent in this state by

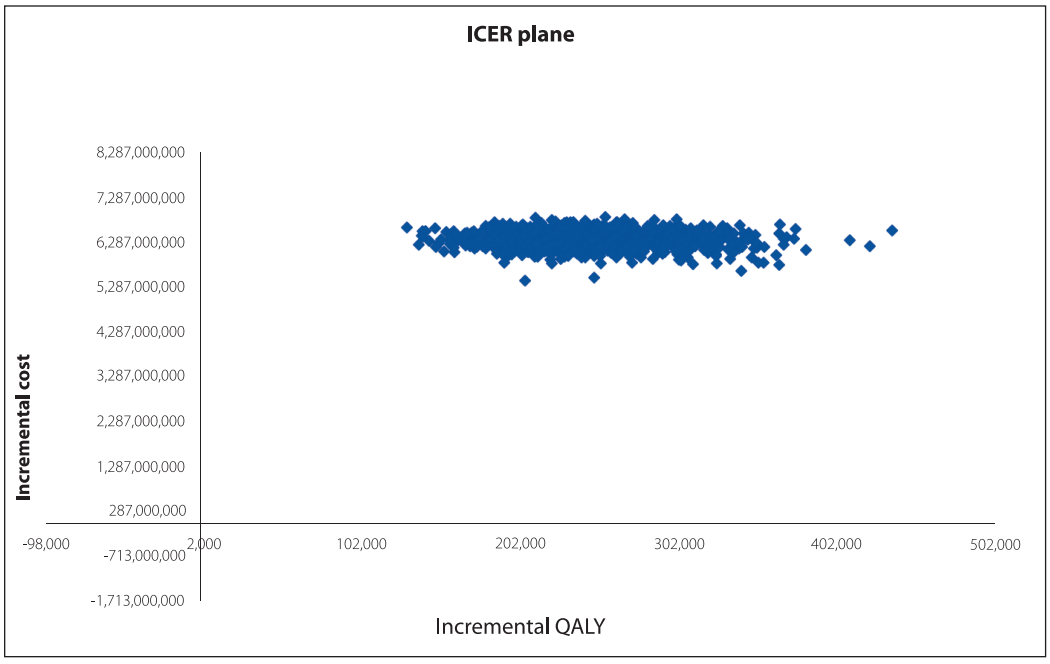

Fig. 2. Cost-effectiveness plane for combination therapy compared with tamsulosin.

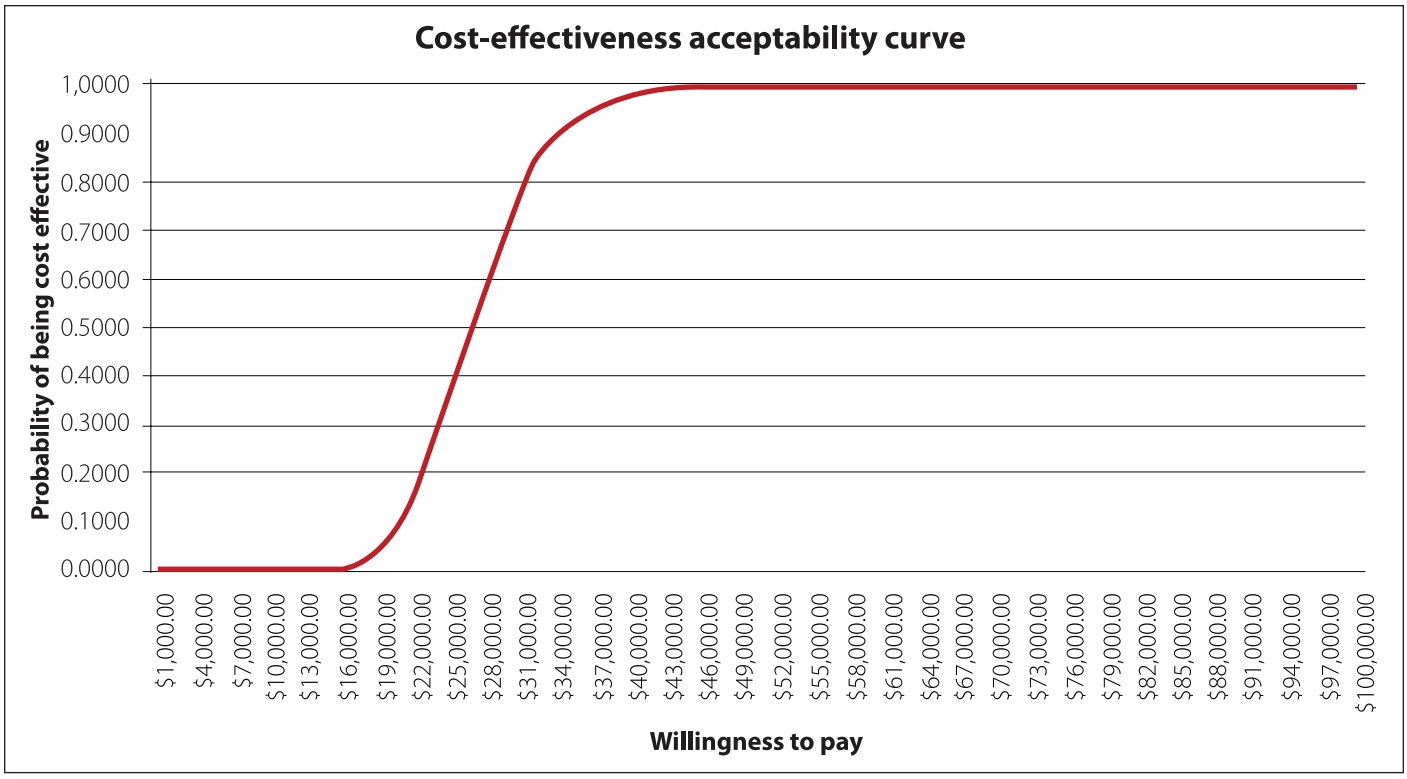

Fig. 3. Cost-effectiveness acceptability curve for combination therapy compared with tamsulosin.

patients is underestimated, as is mortality. Assuming patients returned to their previous symptom state following successful TWOC may have underestimated the utility costs to these patients. Other surgical interventions (other than TURP) are available to treat BPH, but these were not included in the model. Treatment switching only occurred at the end of an annual cycle, whereas in practice treatment switching occurs throughout the year. In practice, patients who regress to a mild symptom state may be withdrawn from treatment, but the model assumed that all patients remained on treatment.

We assumed 100% compliance/persistence with pharmacotherapy and that withdrawals due to drug-related adverse events were minimal or not significantly different between treatment regimens (based on the results of the CombAT trial). This may not be entirely consistent with general practice, where there are typically higher rates of discontinuation of ABs.

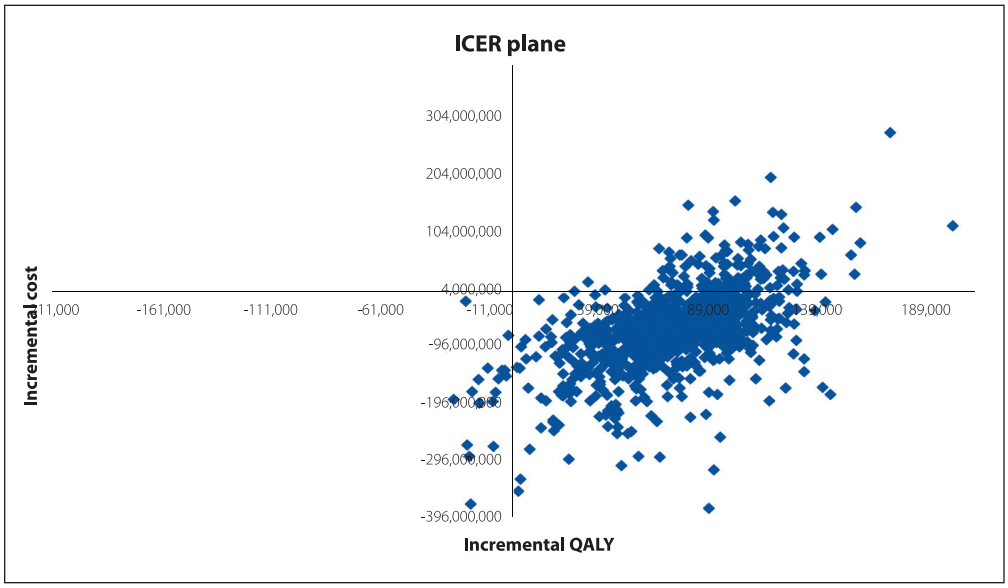

Fig. 4. Cost-effectiveness plane for combination therapy compared with dutasteride.

Conclusion

The combination of dutasteride and tamsulosin has been demonstrated to significantly reduce the risk of AUR, BPH-related surgery and clinical progression compared to tamsulosin monotherapy, but not dutasteride therapy, and significantly improves symptom scores compared with both monotherapies. Canadian guidelines place the combination as an appropriate and effective pharmacotherapy

Table 8. Costs, outcomes and incremental cost-effectiveness ratio for combination therapy compared with dutasteride monotherapy*

	Total cost (CAN $)	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY gained (ICER)
10-year time horizon					
Dutasteride	$7.435bn	9.179m			
Combination	$7.400bn	9.229m	-$35.318m	+49,414	Dominant
Lifetime horizon (up to 25 years)					
Dutasteride	$11.565bn	15.836m			
Combination	$11.497bn	15.917m	-$68.515m	+80,341	Dominant

*Costs and outcomes discounted at 5%. QALYs: quality adjusted life years. ICER: incremental cost-effectiveness ratio. bn: billion; m: million.

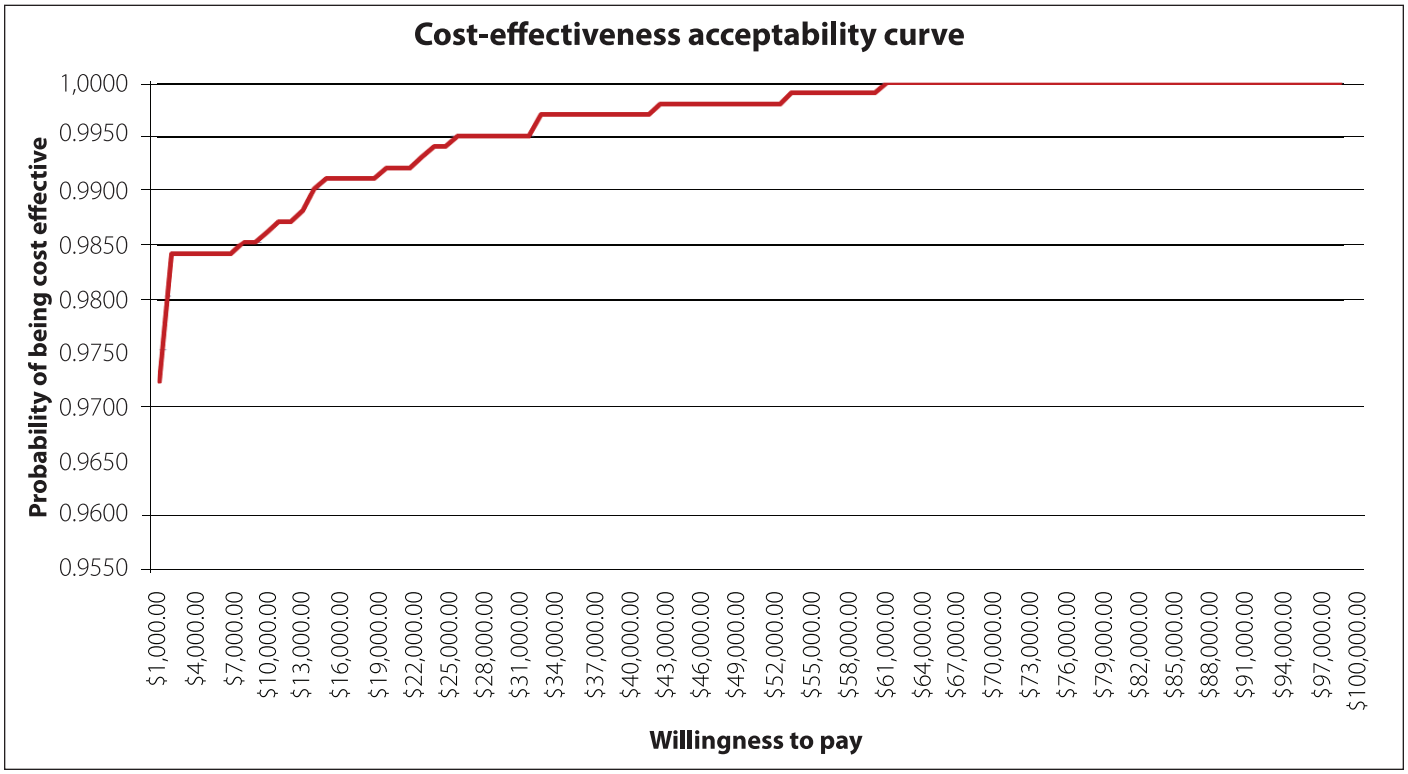

Fig. 5. Cost-effectiveness acceptability curve for combination therapy compared with dutasteride.

option for men with moderate to severe BPH symptoms who have an enlarged prostate. We showed that combination therapy is more cost-effective than either dutasteride or tamsulosin monotherapy in the Canadian healthcare system, suggesting that the introduction of a fixed-dose combination product would offer significant benefits in improving health outcomes, and at lower cost when patients would otherwise be prescribed both tamsulosin and dutasteride separately.

Competing interests: Afisi Ismaila, Amyn Sayani and Zhen Su are employees of GlaxoSmithKline (GSK), which markets and sells Avodart (dutasteride) and dutasteride-tamsulosin fixed combination therapy in Canada under the trade name Jalyn. Afisi Ismaila is also an assistant professor (part-time) in the Department of Clinical Epidemiology and Biostatistics at McMaster University, Hamilton, Ontario, Canada. Anna Walker and John Posnett are employees of Heron Evidence Development, which was funded by GlaxoSmithKline (GSK) to conduct an independent cost-effectiveness assessment of dutasteride-tamsulosin combination therapy. Dr. Nickel is a consultant and investigator for GSK. Dr. Laroche is a consultant for GSK.

This paper has been peer-reviewed.

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