An economic evaluation of doxazosin, finasteride and combination therapy in the treatment of benign prostatic hyperplasia

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Objective: *The Proscar Long-Term Efficacy and Safety Study (PLESS) and the Medical Therapy of Prostatic Symptoms (MTOPS) study provide new evidence regarding the benefits of finasteride in the treatment of benign prostatic hyperplasia (BPH). The objective of this study was to utilize data from the PLESS and MTOPS studies to assess the cost-utility of finasteride and finasteride in combination with doxazosin, compared to doxazosin alone in men with moderate to severe BPH symptoms.*

Methods: *A semi-Markov decision analytic model was constructed to estimate the clinical consequences, costs and cost-utility of doxazosin, finasteride, and combination therapy. Analyses were conducted for a 15-year time frame from the perspective of the Ontario Ministry of Health and Long Term Care (MOHLTC). Results are reported stratified by baseline serum prostate-specific antigen (PSA) level according to all baseline serum PSA levels, patients with baseline serum PSA > 1.3 ng/ml, and patients with baseline serum PSA > 3.2 ng/ml.*

Results: *Compared to doxazosin alone, combination therapy was more expensive but more effective. Cost-utility ratios ranged from $27,823/QALY for patients with PSA > 3.2 ng/ml to $34,085/QALY for all patients. Finasteride, although dominated by doxazosin, may be cost-effective compared to watchful waiting in patients who fail doxazosin and do not choose to proceed to surgery. Compared to watchful waiting, cost-utility ratios for finasteride ranged from $35,016/QALY for patients with PSA > 3.2 ng/ml to $44,336/QALY for all patients. Results were robust across a wide range of sensitivity analyses.*

Conclusions: *Combination therapy is cost-effective compared to doxazosin with cost-utility ratios under $40,000/QALY across a wide range of scenarios. The cost-effectiveness of combination therapy increases as serum PSA level increases.*

Key Words: cost-effectiveness analysis, decision analysis, benign prostatic hyperplasia, finasteride

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Introduction

Benign prostatic hyperplasia (BPH), a noncancerous enlargement of the prostate gland, is the most common benign neoplasm in the ageing human male.[1,2] Approximately one half of Canadian men 50 years of age or older have mild to severe symptoms of BPH, the prevalence of which increases with age.[3] For many men, BPH may cause bothersome symptoms that interfere with daily activities and

adversely affect their quality of life.[4,5] As the disease progresses, consequences may also include acute urinary retention (AUR), need for surgery, urinary incontinence, recurrent urinary tract infection or, in rare cases, renal failure due to obstruction.[6,7] Recent evidence suggests that clinical progression of BPH and the risk of urinary-related events may be correlated with prostate volume and serum prostate-specific antigen (PSA) level: men with larger prostate volumes and increased PSA levels have been shown to be at higher risk of further prostate growth, symptom deterioration, AUR, and BPH-related surgery.[8-10]

Options available for the treatment of BPH in Canada range from watchful waiting to pharmacologic therapies and surgical intervention. Watchful waiting involves reassessing the patient at regular intervals and monitoring for disease progression, and is generally recommended for men who are at an early or mild stage of disease and experiencing minor symptoms that do not interfere with normal daily activities. For patients developing progressive symptoms, moderate inconvenience or BPH-related complications, pharmacologic or surgical interventions are recommended.[1]

Surgical interventions, of which transurethral resection of the prostate (TURP) is currently considered to be the gold standard, have been shown to achieve long-term relief from symptoms of BPH.[1,11] Most patients with bothersome BPH, however, would prefer to avoid surgery[12] and the majority of urologists elect for a therapeutic trial of medication prior to resorting to surgical options.[13] Pharmacotherapy has been dominated by symptomatic treatment with alpha-adrenoceptor antagonists (alpha-blockers), which continue to be considered the most cost-effective monotherapy for symptom relief. Finasteride (Proscar®) is the first in a new class of 5-alpha-reductase inhibitors that inhibit the growth of glandular epithelial cells, preventing disease progression primarily through reduction of prostate volume and secondarily through symptom improvement.[14] Thus, in contrast to alpha-blockers, finasteride has been shown to treat the underlying cause (hyperplasia) as well as the symptoms of BPH. Finasteride has been shown to provide the greatest benefit in men with moderate to severe symptoms and an enlarged prostate, defined by a PSA > 1.3 ng/ml or a prostate volume > 30 ml.[8]

Finasteride has recently been the subject of several published studies examining the economic impact of therapies for BPH.[15-18] The most comprehensive evaluation for Canada was produced by Baladi et al[18] for the Canadian Coordinating Office of Health Technology Assessment (CCOHTA). The analysis compared finasteride to watchful waiting and TURP for first line treatment. The study found that the relative cost-effectiveness of finasteride was dependent on the severity of BPH symptoms and life expectancy. For severe symptoms, finasteride was the least effective initial treatment, though it was cheaper than either alternative if life expectancy was less than 3 years. For moderate symptoms, finasteride improved quality of life more than either alternative, and was cheaper than either alternative if life expectancy was less than 3 years. From 4 to 14 years, finasteride was more effective and cheaper than TURP, but more expensive than watchful waiting.

For each of these studies, many key model parameters were derived from the 1994 US clinical practice guidelines of the Agency for Health Care Policy and Research (AHCPR).[2] In particular, estimates of treatment failure rates provided in the 1994 guidelines were extrapolated from short-term clinical trial data, and the guidelines conceded the lack of clear documentation regarding finasteride and alpha-blocker failure rates and rates of surgery. Subsequent clinical trials of finasteride have shown lower re-treatment rates than those estimates derived from the AHCPR guidelines.[14,19] The guidelines have since been updated (2003) to reflect significant changes in the availability of treatment options and the availability of recent evidence regarding their efficacy and safety. In addition, these analyses did not consider the clinical and economic impacts associated with all relevant BPH-related outcomes (AUR), and did not stratify results by prostate volume or PSA level. The CCOHTA evaluation also did not consider alpha-blocker therapy as a comparator in their analysis.

Since the publication of the aforementioned analyses, two studies have significantly increased the breadth of data available regarding the clinical effectiveness of finasteride; the Proscar Long-Term Efficacy and Safety Study (PLESS)[14] and the Medical Therapy of Prostatic Symptoms (MTOPS) study.[19] The PLESS study compared finasteride to placebo in men with moderate to severe symptoms of BPH for a period of 4 years. Results from PLESS demonstrated that, in men with moderate to severe symptoms and enlarged prostates, finasteride was effective in reducing AUR events and the risk of proceeding to surgery. The PLESS study also demonstrated the importance of prostate volume and serum PSA as powerful predictors of the natural history of BPH and of response to treatment.[8-10, 20]

Based on the PLESS results, a cost-minimisation

analysis by Albertsen et al[21] showed that finasteride was cost saving compared to the alpha-blocker terazosin in men with prostate enlargement and moderate to severe BPH symptoms. The magnitude of the 2-year savings in men 65 years of age depended on PSA level, with savings increasing from US$137 for men with PSA > 1.3 ng/ml to US$373 for men with PSA > 3.2 ng/ml.

The MTOPS study directly compared finasteride, doxazosin and combination therapy (finasteride and doxazosin) to placebo in men with moderate to severe BPH. With an average follow-up of 4.5 years, MTOPS represents the longest study to date that directly compares BPH pharmacologic therapies, and is the first study to show that a combination of finasteride and an alpha-blocker is the most effective therapy in treating symptoms and progression of disease in patients. The risks of AUR and the need for invasive therapy were significantly reduced by combination therapy and finasteride, but not by doxazosin.[19] Doxazosin, finasteride and combination therapy each resulted in significant improvement in symptom scores with combination therapy being superior to both doxazosin and finasteride alone.[19] In support of the findings of PLESS, MTOPS also showed an increasing risk of BPH-related events with increasing serum PSA levels.[19]

The PLESS and MTOPS studies, which provide new clinical evidence demonstrating the benefits of finasteride (alone and in combination with an alpha-blocker), the emergence of less expensive, generic alpha-blockers and the limitations of previous economic studies support a re-evaluation of the cost-effectiveness of these medical options in the treatment of moderate to severe BPH.

Objective

The objective of this study was to assess the cost-effectiveness and cost-utility of finasteride and combination therapy relative to doxazosin alone for treatment of BPH in men with moderate to severe symptoms and an enlarged prostate. Since finasteride has demonstrated the greatest effectiveness in patients with increased prostate volume/serum PSA levels, results are presented for three populations: a) all BPH patients, b) BPH patients with baseline serum PSA > 1.3 ng/ml and c) BPH patients with baseline serum PSA > 3.2 ng/ml.

Methods

Decision analytic model

The basic premise underlying the model is that BPH is a progressive, symptomatic disease that will require ongoing treatment or surgical intervention for a significant proportion of patients. The cost-effectiveness of a given therapy is driven by its ability to provide symptom control over a sustained period of time and to delay or prevent the outcomes and costs associated with AURs and surgical interventions.

A decision analytic model was constructed to estimate the clinical consequences, costs and cost-utility (measured as cost per quality-adjusted life year gained) of various therapies compared to standard treatment for moderate to severe BPH. Clinical consequences were captured by measuring the number of AURs, BPH-related surgeries, deaths and QALYs for patients in each strategy. Quality-adjusted life year (QALY) is a measure that combines the duration and the quality of time spent in different states of health. Each health state in the model was assigned a QALY weight based on a rated preference for that health state relative to perfect health (defined as 1) and death (defined as 0), and the QALY weights were summed over the 15-year time frame of the evaluation. Symptom improvement was incorporated based on reductions in symptom score with each of the therapies and the associated improvements in quality of life.

Treatment comparators included doxazosin, finasteride, and combination therapy with doxazosin and finasteride. Finasteride and combination therapy are compared relative to doxazosin therapy for the main analyses, as alpha-blockers represent the dominant therapy for non-surgical treatment of moderate to severe BPH.[19] A strategy of watchful waiting was included in the model to facilitate comparison of active treatment groups based on studies that included a placebo comparator. The doxazosin dosage included in the model was 1mg OD, titrated to 4 mg and 8 mg OD. Finasteride treatment was assumed to be a 5 mg OD dosage and combination therapy consisted of finasteride 5 mg OD and doxazosin 4 mg OD.

The model, shown in Figure 1, employs a semi-Markov state transition structure in which patients can exist in one of a limited number of mutually exclusive health states. These states include receiving/remaining on medical treatment for moderate to severe prostatism, being in a 'post surgery' state following surgical intervention, and death, defined as peri-operative death or death due to natural causes. Patients in the model can transition between states at 6 months, 12 months, and annually thereafter. Movements between states in the model are triggered by AUR, BPH-related surgery and natural mortality. These events determine the health

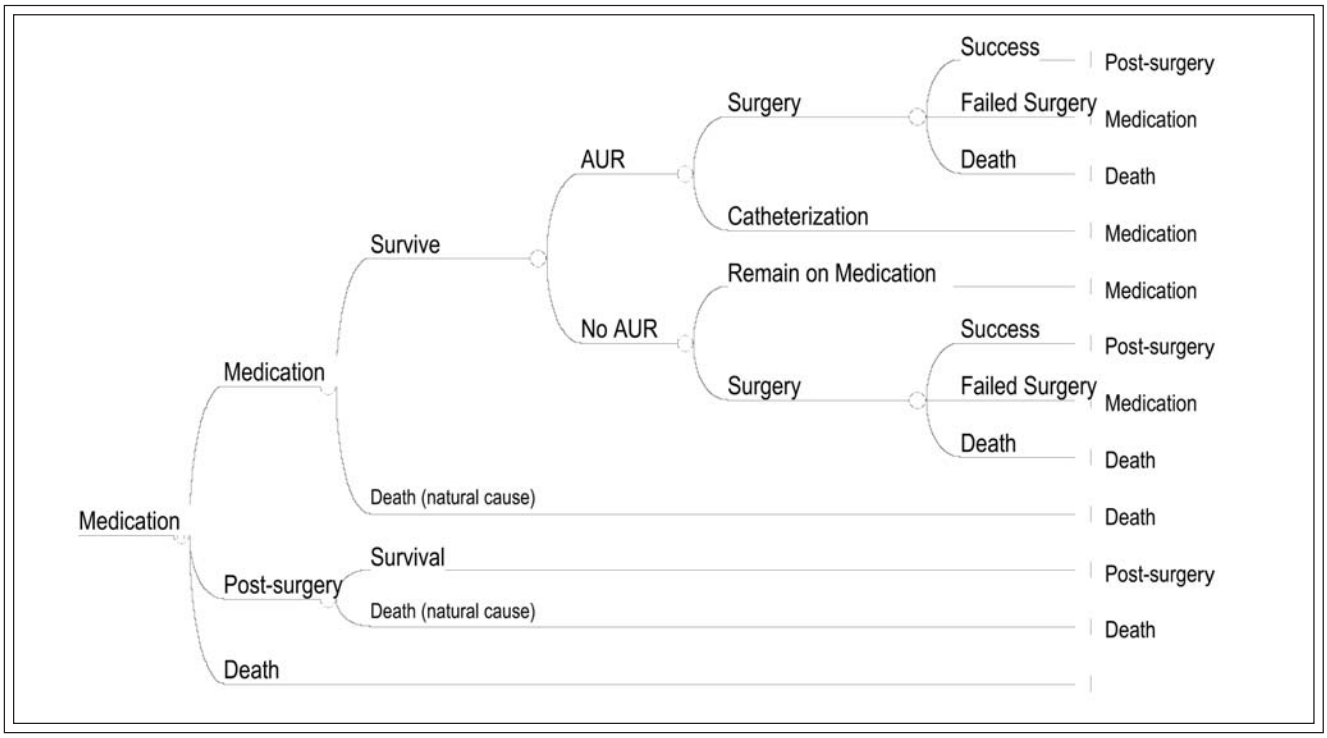

Figure 1. Model of BPH events within a model cycle. Medication involves adopting one of four strategies: finasteride, watchful waiting, doxazosin or combination therapy.

state in which the next cycle begins and the state from which costs and quality of life are derived for that cycle. In the event of an occurrence of AUR, the patient transitions to immediate surgery or is relieved non-surgically through catheterization. Costs and QALYs were calculated for patients in the post-surgical health state under the assumption that patients experience improved BPH symptoms along with some chance of post-surgical complications for each period of time spent in the post-surgery state. It was assumed that patients experiencing no improvement in symptoms following TURP were placed back on initial therapy and that the effectiveness of TURP was not conditional upon prior treatment with finasteride, doxazosin, or combination therapy. A patient experiencing AUR who is relieved non-surgically through catheterization may require or choose surgery over the remaining course of the time frame. A patient who does not experience AUR may remain on therapy or transition to elective surgery. Outcomes for patients undergoing elective surgery were assumed to be the same as those for AUR-related surgery.

Methodological framework

Cost consequence (cost per AUR avoided, cost per TURP avoided) and cost-utility (cost per QALY gained) analyses were conducted using the BPH decision analytic model described above. Analyses were conducted for a 15-year time frame from the perspective of the Ontario Ministry of Health and Long Term Care (MOHLTC). All costs are presented in 2003 Canadian dollars, and costs and outcomes occurring beyond the first year were discounted at a rate of 5% in the base case analysis, as recommended by the CCOHTA guidelines for the conduct of economic evaluations.[22]

Patient population

The population evaluated in the decision model includes men with moderate to severe symptoms of BPH and an enlarged prostate as determined by digital rectal examination (DRE) that choose not to undergo immediate surgical treatment, either due to contraindications or personal choice. The base-case patient was modelled on the PLESS study as a white male, aged 64 years with an average quasi-American Urologic Association (AUA) symptom score of 15, a prostate volume of 55 ml and a serum PSA of 2.8 ng/ml.

Model assumptions and data inputs

The majority of the data inputs for the model were derived from the PLESS and MTOPS studies. The PLESS and MTOPS studies were quite similar with

respect to study design and the characteristics of the patient population. Each of these studies was double-blinded, placebo-controlled, randomized, and multi-centre, with long-term follow-up. Participating patients were required to have moderate to severe symptoms of BPH (as determined by the AUA symptom score) and decreased maximal urinary flow rates. The primary distinction between patients included in PLESS and those included in MTOPS is that patients in PLESS were required to have an enlarged prostate upon DRE. This is reflected in the characteristics of the study populations where the baseline prostate volume in PLESS was 55 ml, compared to 36 ml in MTOPS. As finasteride's primary mode of action is to prevent disease progression and alleviate symptoms through reduction of prostate volume, and because the target population for the current analysis was patients with moderate to severe BPH and an enlarged prostate, the PLESS study provides the most appropriate data regarding finasteride's effectiveness in the most relevant patient population. PLESS also has the advantage of providing estimates of efficacy stratified by PSA (a proxy for prostate volume) that was an important consideration in the current economic evaluation. The analysis was, therefore, undertaken using the base rates of AUR and surgery for watchful waiting (placebo) and finasteride from PLESS.

MTOPS represents the most current source of data regarding the efficacy of alpha-blockers and the only source of data regarding the efficacy of combination therapy with respect to urologic events. Data from MTOPS was therefore used to estimate the effectiveness of alpha-blocker and combination therapy in the current analysis. The AUA symptom score data was also derived from MTOPS to provide estimates of year-to-year changes in symptoms for all treatments included in the model.

Model probabilities

Model probabilities of AUR and surgery for watchful waiting and finasteride were obtained directly from the PLESS study, which provided data based on stratification of men into three PSA groups (all patients, PSA > 1.3 ng/ml and PSA > 3.2 ng/ml). The probabilities of AUR and TURP for alpha-blockers and combination therapy were estimated from MTOPS by calculating the proportionate risk reduction for alpha-blockers and combination therapy versus placebo reported in the MTOPS study, and using these to derive the expected risk reduction in AUR and TURP for alpha-blocker and combination therapy for the PLESS-based population.

Based on the PLESS study, 74.5% of patients on

TABLE 1. **Probabilities of BPH-related outcomes for each therapy**

	Watchful waiting	Finasteride	Doxazosin	Combination
Probability of AUR at year 4[a]				
All patients	1.3%	0.7%	1.0%	0.4%
PSA > 1.3 ng/ml	1.6%	0.8%	1.1%	0.5%
PSA > 3.2 ng/ml	2.0%	0.9%	1.4%	0.6%
Probability of surgical intervention following AUR[b]	74.5%	40.0%	74.5%	40.0%
Probability of elective TURP at year 4[c]				
All patients	2.5%	1.4%	2.4%	0.8%
PSA > 1.3 ng/ml	3.0%	1.6%	2.9%	1.0%
PSA > 3.2 ng/ml	3.7%	1.8%	3.6%	1.2%

[a]The probabilities of AUR for doxazosin and combination therapy were estimated by determining the expected risk reductions in AUR relative to placebo in PLESS, based on the proportionate risk reduction between doxazosin/combination therapy and placebo reported in the MTOPS study.

[b]For watchful waiting and finasteride therapy, the proportion of patients who require surgical treatment following an AUR was taken from PLESS as 74.5% and 40%, respectively. The watchful waiting proportion of 74.5% was assumed for doxazosin and the finasteride proportion of 40% was assumed for combination therapy.

[c]The probabilities of elective TURP for doxazosin and combination therapy were estimated by determining the expected risk reductions in surgery relative to placebo in PLESS, based on the proportionate risk reduction between doxazosin/combination therapy and placebo reported in the MTOPS study.

TABLE 2. **Probabilities of surgical outcomes and QALY estimates**

Immediate surgical outcomes - proportion of patients (90% confidence interval)	
Mild prostatism (without incontinence or impotence)[a]	0.723[b] (0.540 – 0.900)[c]
Mild prostatism with incontinence	0.021[b] (0.018 – 0.025)
Mild prostatism with impotence	0.136[b] (0.034 – 0.324)
No improvement in symptoms of prostatism	0.095[d] (na)
Total urinary incontinence	0.010[b] (0.007 – 0.014)
Death	0.015[b] (0.005 – 0.033)
Longer-term surgical outcomes - proportion of patients (90% confidence interval)	
Urethral stricture	3.1[b] (0.5 – 9.7)
Bladder neck contracture	1.7[b] (1.3 – 2.1)
Re-treatment probability per year[e]	2.1[b] (1.9 – 2.3)
Utility estimates	
Average QALY at baseline	0.8743[f]
Change in QALY per change in AUA symptom score	0.0138[g]
Increment in QALY following successful TURP surgery	0.0440[h]

[a]With or without possible urethral stricture or bladder neck contracture.
[b]Estimates were derived from Baladi et al,[18] which in turn were based on McConnell et al.[2]
[c]Calculated by Baladi et al,[18] assuming mild prostatism with incontinence and mild prostatism with impotence are independent events.
[d]Calculated by Baladi et al[18] as a residual.
[e]Re-treatment probability includes the probability of immediate re-TURP due to severe urinary tract infection.
[f]Calculated using data from Baladi et al.[18]
[g]Calculated using data from MTOPS, Baladi et al and Kaplan et al.[20]
[h]Derived from Noble et al.[25]

watchful waiting and 40% of patients on finasteride experienced an AUR required surgery.[23] It was assumed that the proportion of patients on doxazosin experiencing the same event mirrored the watchful waiting rate and that the rate for combination therapy patients mirrored the finasteride rate.

Similar to Baladi et al,[18] surgical outcomes were based on data presented in the Agency for Health Care Policy and Research (ACHPR) guidelines.[1,2] Longer-term consequences of TURP requiring re-hospitalization or outpatient interventions were incorporated in cost calculations, and probability estimates for each selected event were derived from Baladi et al.[18]

Natural mortality estimates for men starting at age 65 and for the subsequent 15 years were taken from Statistics Canada data for 1997 all cause mortality.[24] Base-case transition probabilities are presented in Tables 1 and 2.

Quality-adjusted life years

The model evaluates the total number of QALYs associated with each treatment over the study time frame. Although not shown directly in the model schematic, symptom severity and improvement in symptoms are indirectly modelled within the states and transitions. Estimates of QALY weights for relevant health states were based on information available in the literature. The average QALY weight for a BPH patient with moderate to severe symptoms was estimated to be 0.874. QALY weight estimates for mild, moderate and severe BPH were derived from Baladi et al[18] and weighted by the proportion of patients in each disease severity category at the start of the PLESS trial. Changes in patient quality of life resulting from changes in symptom score during a cycle were also estimated from the literature. The average change in AUA symptom score occurring over the duration of each cycle was estimated from MTOPS clinical trial data. The average QALY increment per point change in AUA symptom score in moderate to severe BPH patients (estimated to be 0.014) was calculated using reported QALY-weight changes for progressing

from mild-moderate and moderate-severe symptom scores from Kaplan et al[20] and Baladi et al[18] and weighting them by the proportion of patients in each disease severity category in the PLESS trial. It was assumed that the average QALY increment per symptom point change was constant over the range of moderate to severe symptom severity.

Since patients undergoing surgery are expected to have an improvement in BPH symptoms and quality of life, a surgery-induced QALY weight improvement of 0.044 (estimated from Noble et al[25]) was added to the baseline QALY weight for patients undergoing TURP. The QALY estimates utilized in the base case analysis are shown in Table 2.

Resource utilization and costs

Resource utilization was estimated based on previous economic analyses of BPH[18] with the assistance of a clinical expert (JCN) for the following events; medical therapy with alpha-blocker and/or finasteride, patient monitoring, AUR treated with catheterization, AUR-related TURP, elective TURP (e.g. not occurring as a result of AUR), and medical care following surgery (related to management and post-surgical complications). Direct medical costs incurred as a result of these events and incorporated in the analysis included BPH-related drugs, professional visits, emergency room visits, hospitalisations, surgery, surgical complications, and laboratory tests and procedures. Only health care resources funded by the MOHLTC were included.

Health care resources were valued using relevant sources from Ontario, including the 2003 Ontario Health Insurance Plan (OHIP) Schedule of Benefits[26] for costs of services including physician visits, laboratory work and diagnostic procedures and the Ontario Ministry of Health Drug Benefit Formulary[27] for the costs of medications. The direct costs for events requiring an emergency room (ER) visit or hospitalization were obtained from the London Health Sciences Corporate Cost Model[28] as fully allocated costs that include all medications and treatments, laboratory tests, and health care professional services received in hospital, as well as overhead and opportunity costs. Tables 3 and 4 outline the costs related to medical therapy, TURP and treatment of AUR.

TABLE 3. **Estimated cost of BPH medical treatment and disease management**

	Watchful waiting		Finasteride		Doxazosin		Combination	
	First year	Subsequent years	First year	Subsequent years	First year	Subsequent years	First year	Subsequent years
Drug-related costs[a]	$0	$0	$679	$679	$285	$285	$920	$920
Urologist visits[b]	$58	$58	$58	$58	$97	$58	$97	$58
Diagnostic tests[c]	$57	$57	$57	$57	$57	$57	$57	$57
Total cost of therapy and patient monitoring	$115	$115	$794	$794	$439	$400	$1,074	$1,035

[a]The price for doxazosin was based on the Ontario Drug Benefit best available price (BAP) for 4 mg ($0.54), and the cost of finasteride ($1.63) was obtained from Merck Frosst. A full year of use, as well as a 10% pharmacy mark-up charge and a $4.11 dispensing fee per prescription (renewed every 3 months) were assumed. Based on expert opinion, it was assumed for the cost of doxazosin that 80% of patients are titrated to a daily dose of 4 mg OD (daily cost: $0.54) and 20% of patients are titrated to a dose of 8 mg OD (daily cost: $1.08). For combination therapy, it was assumed that all patients used a 4 mg OD dose of doxazosin.

[b]For each therapy, visits include one full and one partial assessment each year, and two additional partial assessments in the first year for doxazosin to allow for titration of medication. Unit prices for physician fees and services, laboratory work and diagnostic procedures were obtained from the 2003 Ontario Health Insurance Plan (OHIP) Schedule of Benefits. Resource utilization and costs associated with AUR and BPH-related surgery were obtained from a corporate hospital costing model (the London Health Sciences Corporate Cost Model). This source provided a fully allocated cost of an ER visit and/or hospitalization including all medications and treatments received in hospital, medical procedures, laboratory tests, health care professional services received in hospital, overhead and opportunity costs. The cost also included the fees associated with pre-admission clinic visits, where applicable.

[c]For all patients, one PSA test, two fluometry, two serum creatinine and two urinalysis tests were assumed, based on Baladi et al[18] and expert opinion.

TABLE 4. **Estimated resource utilization and costs associated with AUR and TURP**

	Average cost per event
Acute Urinary Retention (AUR)	
Direct cost of AUR[a]	$459.35
Follow-up of AUR[b]	$226.34
Total cost of AUR	$685.70
	Average cost per patient
Transurethral Resection of the Prostate (TURP)	
Direct cost of TURP in first year[c]	$3678.31
Cost in subsequent years[d]	$143.09
Cost of treating complications[e]	$52.41

[a]Includes one emergency room visit for a male (65 years or older) presenting with urinary symptoms (fully allocated cost obtained from London Health Sciences Corporate Cost Model), and ER physician fees for consultation and catheterization.
[b]Assumes that 60% of patients would require a home care visit every 3rd day for 3 weeks with bacterial cultures conducted, and that all patients would require 21 days of prophylactic antibiotic treatment.
[c]Includes a pre-admission clinic visit, hospital and operating room costs (fully allocated costs obtained from London Health Sciences Corporate Cost Model) and professional fees.
[d]Includes the cost of a re-TURP multiplied by the risk of occurrence as indicated in Table 2.
[e]Estimated as the cost of complications multiplied by the annual rate of occurrence. Assumes that bladder neck contracture is treated by admission to hospital and surgery, and 10%-25% of patients with total urinary incontinence receive an artificial sphincter (as reported by Baladi et al[18]).

Results

Clinical and cost consequences

Table 5 shows the outcome and cost results for all PSA levels for the base-case analysis. Finasteride, doxazosin and combination therapy all reduced the risk of AUR, TURP and death and produced a greater number of QALYs compared to watchful waiting. Across all PSA levels, combination therapy yielded the greatest reductions in rates of AUR, TURP and death, followed by finasteride, then doxazosin. Combination therapy also produced the greatest number of QALYs across all baseline levels of serum PSA, followed by doxazosin and finasteride. The most costly therapy at each PSA stratum was combination therapy, followed by finasteride, doxazosin and watchful waiting.

Using the data in Table 5, incremental ratios of cost per AUR averted and cost per TURP averted can be calculated. For finasteride relative to doxazosin, the incremental cost per AUR averted was $83,089 for all patients, $60,723 for patients with a PSA > 1.3 ng/ml and $38,721 for patients with a PSA > 3.2 ng/ml. The incremental cost per TURP averted was $14,047, $10,933 and $7,816 for all patients, patients with PSA > 1.3 ng/ml and patients with PSA > 3.2 ng/ml, respectively. For combination therapy, the incremental cost per AUR averted relative to doxazosin was $88,400, $74,469, and $62,358 for all patients, patients with a PSA > 1.3 ng/ml and patients with a PSA > 3.2 ng/ml, respectively. The incremental cost per TURP averted was $22,478, $18,902 and $15,682 for all patients, patients with a PSA > 1.3 ng/ml and patients with a PSA > 3.2 ng/ml, respectively.

Cost-utility analysis

For the cost-utility analysis, all results are presented relative to doxazosin. Table 6 shows the results of the 15-year, base-case analysis for patients at each level of PSA. These ratios represent, for each alternative medical therapy, the additional cost for each quality adjusted life year gained relative to doxazosin. Compared to treatment with doxazosin, treatment with finasteride produced less benefit at a greater cost across all PSA strata and is therefore considered to be 'dominated' compared to doxazosin. Relative to doxazosin, combination therapy was more expensive but more effective with cost per QALY gained ranging from $27,823 for patients with PSA > 3.2 ng/ml to $34,085 for patients at any level of prostate enlargement.

Sensitivity analyses

Several univariate sensitivity analyses were conducted to assess the robustness of the model results to uncertainty surrounding key model parameters. The results of the analyses showed that combination therapy had an incremental cost-utility ratio of less

TABLE 5. **Base case cost-consequence analysis, stratified by PSA: clinical and cost consequences associated**

	Watchful Waiting			Doxazosin			Finasteride		
	All PSA	PSA > 1.3	PSA > 3.2	All PSA	PSA > 1.3	PSA > 3.2	All PSA	PSA > 1.3	PSA > 3.2
Clinical consequences (% patients)									
AUR	14.83%	17.30%	20.30%	10.53%	12.34%	14.55%	7.94%	9.02%	9.78%
TURP	36.94%	42.87%	50.15%	33.63%	39.20%	46.13%	18.31%	20.76%	22.50%
Death	41.92%	41.98%	42.06%	41.89%	41.95%	42.02%	41.74%	41.76%	41.78%
QALYs gained	8.608	8.598	8.586	8.787	8.772	8.752	8.709	8.705	8.702
BPH-related costs ($CDN/patient)									
Medications	$866	$832	$787	$3,110	$2,999	$2,855	$6,167	$6,091	$6,036
Direct medical costs	$1,387	$1,622	$1,917	$1,505	$1,758	$2,075	$601	$683	$741
Total costs	$2,254	$2,454	$2,704	$4,615	$4,757	$4,930	$6,767	$6,773	$6,777

than $40,000 per QALY gained compared to doxazosin across a wide range of alternative scenarios Table 7. The only exceptions to this trend were observed when the analysis was conducted for a 4-year time frame, MTOPS rates of AUR and elective TURP were utilized without adjustment, QALY weights derived from the CCOHTA analysis were used, and treatment effect on symptom improvement was decreased by 50% relative to the base case. In all scenarios, the incremental cost per QALY gained for combination therapy was lowest in patients with a PSA level > 3.2 ng/ml. Finasteride was more expensive and less efficacious relative to alpha-blocker in all but two scenarios.

For the base case analysis, the probability of AUR and elective TURP for watchful waiting and finasteride were taken from the PLESS study, and the probabilities for combination therapy and alpha-blocker were derived from the MTOPS study and adjusted to the 'base rate' observed in the placebo group of PLESS. Since the observed probabilities of AUR and surgical events were lower in the MTOPS study compared to the PLESS study for the watchful waiting and finasteride treatment groups, a sensitivity analysis was performed in which probabilities observed in MTOPS were used for each therapy, without adjustment. In this analysis, finasteride remained dominated relative to doxazosin and the cost-utility ratios for combination therapy increased to $49,769, $47,685 and $45,092 for all patients, patients with a PSA > 1.3 ng/ml and patients with a PSA > 3.2 ng/ml, respectively.

In order to explore the effect of uncertainty regarding the QALY weight estimates on the model results, a number of sensitivity analyses were conducted. In all cases, the trends in cost/QALY for each PSA strata resembled those from the base case analysis. When QALY weights derived from the CCOHTA analysis were implemente d in a sensitivity analysis, the incremental cost/QALYs relative to

TABLE 6. **Base case cost-utility analysis, stratified by PSA: incremental cost-utility, versus doxazosin**

	Doxazosin			Finasteride		
	All PSA	PSA > 1.3	PSA > 3.2	All PSA	PSA > 1.3	PSA > 3.2
Mean costs ($CDN/patient)	$4,615	$4,757	$4,930	$6,767	$6,773	$6,777
Mean QALYs	8.787	8.772	8.752	8.709	8.705	8.702
Incremental costs	-	-	-	$2,152	$2,016	$1,847
Incremental QALYs	-	-	-	-0.078	-0.067	-0.050
Cost per QALY gained	-	-	-	dominated	dominated	dominated

Note: Dominated implies that a treatment is less effective and more costly than its comparator.

with BPH treatment, over 15 years

All PSA	Combination PSA > 1.3	PSA > 3.2
5.03%	6.03%	7.34%
12.00%	14.34%	17.46%
41.67%	41.69%	41.72%
8.930	8.923	8.914
$9,038	$8,930	$8,784
$439	$526	$643
$9,477	$9,456	$9,426

doxazosin was moderately higher than those for the base case scenario, ranging from $49,454/QALY for all patients to $44,912/QALY for patients with a PSA > 3.2.

Sensitivity analyses also showed that the model results were moderately sensitive to alternative assumptions regarding symptom improvement. The effect of increasing and decreasing the differences in symptom score change between treatment groups by 50% was evaluated in separate analyses. As shown in Table 7, when treatment effects were increased by 50%, the incremental cost/QALY relative to doxazosin was much lower than in the base case, ranging from $24,511/QALY for all patients to $20,386/QALY for patients with PSA > 3.2. When treatment effects were decreased by 50%, the cost/QALY for each PSA strata for combination therapy was higher than in the base case, ranging from $55,932/QALY for all patients to $43,805/QALY for patients with a PSA > 3.2.

over 15 years

All PSA	Combination PSA > 1.3	PSA > 3.2
$9,477	$9,456	$9,426
8.930	8.923	8.914
$4,862	$4,699	$4,496
0.143	0.151	0.162
$34,085	$31,108	$27,823

Since treatment with finasteride may be associated with continuing symptom improvement beyond 4 years, finasteride and combination therapy were assumed in separate sensitivity analyses to have an additional one-point improvement and an additional two-point improvement during year 5. In these analyses, finasteride was no longer dominated relative to doxazosin. Although the cost-utility ratios were very large for the analysis that utilized a one-point improvement in symptoms, ratios for the analysis that utilized a two-point improvement in symptoms beyond 4 years were below $40,000 across all PSA strata. Therefore, finasteride alone may prove to be a cost-effective therapy relative to alpha-blockers if its effects are shown to continue beyond 4 years of therapy.

Additional analyses explored the sensitivity of the model results to the rate of discounting, probability of AUR-related TURP, cost of TURP and cost of AUR. The model results were not sensitive to changes in these parameters.

Discussion

The objective of the present study was to use recent information from PLESS and MTOPS to assess the cost-utility of finasteride and combination therapy compared to doxazosin alone in men with moderate to severe BPH symptoms at different levels of serum PSA.

Benchmarks for using economic evaluations in clinical decision-making, such as those suggested by Laupacis et al,[29] are controversial but are often used to provide a framework to interpret the magnitudes of cost-effectiveness ratios. For example, Laupacis et al suggest that a cost/QALY of $20,000 or less provides strong evidence for adoption of a therapy, a cost/QALY between of $20,000 and $100,000 provides moderate support for adoption, and a cost/QALY above $100,000 provides weak evidence for adoption.[29]

The current economic analysis showed that, at every level of prostate enlargement, active pharmacotherapy was superior to watchful waiting and combination therapy resulted in the lowest rates of AUR and surgery, the greatest number of QALYs and the greatest cost. Compared to doxazosin, combination therapy resulted in improved quality of life over the 15-year time period with cost-utility ratios ranging from $27,823 to $34,085 per QALY gained for the PSA > 3.2 ng/ml and all PSA groups, respectively. For all comparisons, cost-utility ratios were lowest (indicating superior cost-effectiveness) for patients with the most enlarged prostates (PSA > 3.2 ng/ml).

The present evaluation also showed that, relative

TABLE 7. **Incremental cost per QALY gained for finasteride and combination therapy relative to doxazosin for various sensitivity analyses**

	Finasteride Incremental cost per QALY Gained			Combination therapy Incremental cost per QALY gained		
	All PSA	**PSA > 1.3**	**PSA > 3.2**	**All PSA**	**PSA > 1.3**	**PSA > 3.2**
Base case analysis	dominated	dominated	dominated	$34,085	$31,108	$27,823
4-year time frame	dominated	dominated	dominated	$51,876	$48,521	$44,354
Discounting – None	dominated	dominated	dominated	$33,967	$31,246	$28,264
– 3%	dominated	dominated	dominated	$34,071	$31,202	$28,046
MTOPS rates of AUR and elective (non-AUR) TURP	dominated	dominated	dominated	$49,769	$47,685	$45,092
Probability of TURP following AUR						
– 75% regardless of therapy	dominated	dominated	dominated	$35,141	$32,184	$28,893
– 90% regardless of therapy	dominated	dominated	dominated	$34,467	$31,505	$28,230
Finasteride and combination therapies improve AUA symptom score past year 4						
– by one point	dominated	$61,344,542	$116,832	$22,751	$21,273	$19,566
– by two points	$36,834	$30,134	$22,588	$17,073	$16,163	$15,089
Symptom improvement treatment effect						
– 50% increase	dominated	dominated	dominated	$24,511	$22,567	$20,386
– 50% decrease	dominated	dominated	dominated	$55,932	$50,055	$43,805
QALY weights						
– weights for post-surgery based						
– on changes in symptom score	dominated	dominated	dominated	$30,298	$27,330	$24,131
– Baseline weights from Noble[25]	dominated	dominated	dominated	$34,284	$31,313	$28,030
– CCOHTA weights	dominated	dominated	dominated	$49,454	$47,406	$44,912
– Lower weights for moderate BPH, severe BPH and impotence	dominated	dominated	dominated	$25,429	$23,447	$21,216
Cost of TURP						
– 50% increase	dominated	dominated	dominated	$30,454	$27,146	$23,517
– 50% decrease	dominated	dominated	dominated	$37,715	$35,071	$32,130
Cost of AUR						
– 50% increase	dominated	dominated	dominated	$33,978	$30,992	$27,698
– 50% decrease	dominated	dominated	dominated	$34,191	$31,224	$27,949

Note: Dominated implies that a treatment is less effective and more costly than its comparator.

to doxazosin, finasteride alone resulted in substantial clinical benefits with respect to AUR events and surgical outcomes averted. Nonetheless, since there were fewer QALYs overall and greater total costs for finasteride, it was 'dominated' by doxazosin. In patients who choose not to undergo surgery and for whom alpha-blocker therapy is not effective, finasteride may, however, be a cost-effective alternative compared to watchful waiting. Base case analyses indicated cost-utility ratios of $44,336, $40,329, and $35,016 per QALY for all patients, patients with PSA > 1.3 ng/ml and patients with PSA > 3.2 ng/ml, respectively.

As an alternative strategy for the treatment of BPH,

alpha-blockers could be discontinued following a year of combination therapy with patients remaining on finasteride alone for subsequent years. Although data demonstrating the clinical and economic impact of such a strategy is presently scarce, studies supporting this management option are beginning to emerge.[30,31] A strategy of combination therapy for the first year, followed by finasteride alone for subsequent years was also investigated in this economic evaluation as a secondary analysis. This strategy resulted in cost-utility ratios for combination therapy relative to doxazosin ranging from $16,697/QALY for patients with PSA > 3.2 ng/ml to $21,068/QALY for all patients.

Previous economic evaluations of finasteride have either failed to incorporate all relevant outcomes, assumed alpha-blocker therapy to be equivalent to placebo with respect to event rates, or relied on estimates of long-term treatment failure extrapolated from short-term clinical trial data.

The shortcomings of previous evaluations have been addressed in the present decision analytic model and the strengths of the current evaluation include the use of recently published long-term clinical trial data for all treatment comparators, incorporation of all relevant BPH-related outcomes (symptom improvement, AUR, surgery and QALYs), use of conservative assumptions for key parameters, and the conduct of extensive sensitivity analyses.

No long-term data regarding BPH-related outcomes was available for a Canadian specific population. The decision-analytic model incorporated data from the best available North American sources of evidence. The PLESS study provides the most appropriate data regarding finasteride in the most relevant patient population, stratified by prostate volume (PSA). MTOPS represents the most current source of data regarding the efficacy of alpha-blockers and the only source of data regarding the efficacy of combination therapy. There is no evidence in the literature to suggest, however, that patterns of practice with respect to the BPH-related outcomes observed within PLESS and MTOPS studies would be significantly different from those that would be observed in a comparable Canadian population.[32] Data from the PLESS and MTOPS studies was, therefore, combined to provide the majority of the data inputs for the model. Consequently, the current study represents the first evaluation to demonstrate the clinical and economic benefits of a combination strategy with finasteride and alpha-blocker in the treatment of BPH.

Assumptions employed in the current model were conservative in terms of estimating the cost-effectiveness of finasteride and combination therapy. Based on the lack of applicable data, AUR and TURP-related QALY weight decrements were not incorporated in the current analysis. However, AUR and TURP are undesirable events, which have been shown to have a considerable impact on quality of life. Recent work by Cher et al[33] demonstrate that the QALYs lost due to surgery change dramatically with risk attitude, with QALYs lost increasing as aversion to risk increases. The authors also note that risk aversion has a profound impact on QALYs when the potential outcomes of a therapy can include death or disability.[33] Since finasteride achieves a greater risk reduction for TURP events than do doxazosin or watchful waiting, exclusion of QALY decrements for AUR or TURP in our model is likely a conservative assumption.

The evidence regarding the risk of re-treatment in patients given alpha-blockers for lower urinary tract symptoms is somewhat conflicting. In a recent study conducted by De la Rosette et al[34] the authors reported that re-treatment rates for patients with mild, moderate and severe lower urinary tract symptoms were 27%, 33% and 70%, respectively after 5 years. Furthermore, patients with larger prostates (volume > 40 ml) had higher re-treatment rates than those with smaller prostates (volume < 40 ml) at 72% and 48%, respectively. The current analysis utilized rates from MTOPS, which were lower than those reported by de la Rosette, representing a conservative estimation of the benefit of finasteride compared to alpha-blockers, particularly for patients with large prostate volumes.

To maintain consistency with the MTOPS study, our analyses also assumed that the alpha-blocker used for treatment of BPH was doxazosin. However, tamsulosin now represents approximately half of all alpha-blocker prescriptions for the treatment of BPH in Canada.[35] Tamsulosin is considerably more expensive than doxazosin at a cost of $0.95-$1.90/day (compared to $0.59-$1.19/day for alternative alpha-blockers). As the acquisition cost of alpha-blocker therapy approaches that of finasteride, the relative cost-effectiveness of finasteride in the Canadian market will improve.

It is important to note that the current analysis assumed that all BPH-related surgeries were TURPs. Current options for the surgical treatment of moderate to severe BPH include a number of minimally invasive and invasive procedures such as transurethral incision of the prostate, holium laser resection, electrovaporization, laser vaporization, open prostatectomy and various thermotherapies.[1]

However, TURP is still viewed as the gold standard for surgical therapies and published long-term follow-up data was available from randomized clinical trials for inclusion in the model. The impact of this assumption was explored in extensive sensitivity analyses that accounted for less invasive and less expensive procedures. The model was insensitive to changes in the parameters related to TURP.

Extensive sensitivity analyses were also performed to assess the impact of both the uncertainty and variability in all other model parameters. The model results were shown to be quite robust, as combination therapy had an incremental cost-utility ratio of less than $40,000 per QALY gained compared to doxazosin across a wide range of alternative scenarios. In all scenarios, the incremental cost per QALY gained for combination therapy was lowest in patients with a PSA level > 3.2 ng/ml. Finasteride was more expensive and less efficacious relative to alpha-blocker in all but two scenarios. The sensitivity analyses showed that the results of the model were most sensitive to changes in symptom improvement.

Conclusion

Based on the findings of the two most influential studies regarding the pharmacologic treatment of moderate to severe BPH, we developed an innovative decision analytic model to estimate the clinical consequences, costs and cost-utility of doxazosin, finasteride, and combination therapy.

This study demonstrates that combination therapy for the treatment of BPH in men with moderate to severe symptoms and an enlarged prostate is cost-effective compared to alpha-blocker therapy with cost-utility ratios under $40,000/QALY across a wide range of scenarios. Finasteride therapy was also shown to be a cost-effective alternative compared to watchful waiting for patients who fail alpha-blocker therapy and choose not to proceed immediately to surgery.

The results of the present study also clearly demonstrate that greater effectiveness at higher PSA levels results in better cost-utility for finasteride, either alone or in combination with an alpha-blocker. □

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