ABSTRACT

OBJECTIVE: To estimate 8-year health and economic outcomes of the angiotensin II receptor blocker valsartan versus the calcium channel blocker amlodipine in therapy of patients with type 2 diabetes and microalbuminuria based on clinical endpoints from a 6-month randomized controlled clinical trial, the MicroAlbuminuria Reduction With VALsartan (MARVAL) study.

METHODS: We developed a Markov model that utilized urinary albumin excretion rate data to project patient distributions to 7 possible health states over 8 years. For each health state, we identified quality-adjustment weights (health utilities) and medical care costs from public sources. The model then calculated mean quality-adjusted survival, medical care costs, and cost-effectiveness ratios for each treatment arm. Treatment arms were compared with the incremental cost-effectiveness ratio.

RESULTS: Patients treated with valsartan gained 7 months (mean) per patient of quality-adjusted survival relative to patients treated with amlodipine (77 versus 70 months; \(P<0.01\)); valsartan patients also incurred $32,412 (mean) per patient lower medical costs than amlodipine patients ($92,058 versus $124,470; \(P<0.01\)). Model results were consistent for each year of analysis and robust to changes in key model parameters.

CONCLUSION: This research (1) extends 6-month clinical trial outcomes to an 8-year period, (2) translates health outcomes from technical clinical endpoints to quality-adjusted survival, and (3) estimates economic consequences of therapeutic outcomes. The results quantify the favorable long-term health (i.e., quality-adjusted survival) and economic benefits (i.e., lower total medical costs) of therapy with valsartan, an angiotensin II receptor blocker, versus amlodipine, a calcium channel blocker, in the treatment of patients with type 2 diabetes and microalbuminuria based on an extension of the results of a short-term clinical (MARVAL) trial. These research findings are important to the extent patients with type 2 diabetes and microalbuminuria reported therapeutic outcomes. The results quantify the favorable long-term health (i.e., quality-adjusted survival, medical care costs, and cost-effectiveness ratios for each treatment arm. Treatment arms were compared with the incremental cost-effectiveness ratio.

KEYWORDS: Amlodipine, Diabetes, End-stage renal disease, Markov model, Microalbuminuria, Outcomes research, Quality-adjusted survival, Valsartan

Markov Modeling Analysis of Health and Economic Outcomes of Therapy With Valsartan Versus Amlodipine in Patients With Type 2 Diabetes and Microalbuminuria

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Diabetic nephropathy is the leading cause of renal failure and end-stage renal disease.¹ Microalbuminuria as measured by overnight urinary albuminuria excretion rate (UAER) is the first sign of diabetic renal disease² and the best predictor of progressive failure.³ In addition to risk of renal failure, patients with diabetes are also at increased risk for hypertension and cardiovascular diseases.⁴⁻⁵ Blood pressure reduction alone is well known to play a major role in reducing the risk of cardiovascular events and delaying onset and progression of renal disease.⁶⁻⁸ Newer antihypertensive agents that block the renin-angiotensin system have been shown to confer additional benefits from UAER reduction.⁹⁻¹² Clinical evidence of renal protective effects of angiotensin-converting enzyme inhibitors (ACEIs) is well established,¹³⁻¹⁵ and similar effects have more recently been demonstrated with angiotensin II receptor blockers (ARBs).¹⁶⁻¹⁸

Expert guidelines endorse ACEIs as first-line therapy for persons with type 1 or type 2 diabetes and mild or severe hypertension; ARBs are also recommended as first-line therapy for patients with type 2 diabetes and microalbuminuria or clinical nephropathy.¹⁷ Yet, empirical research suggests that many patients who could benefit from these recommendations may also remain untreated with them.¹⁸⁻¹⁹ To highlight the benefits of appropriate treatment, we modeled long-term health and economic outcomes of therapy with valsartan (Diovan), an angiotensin II antagonist, versus amlodipine (Norvasc), a calcium channel blocker.

A recently published 6-month clinical trial of 332 of patients with type 2 diabetes and microalbuminuria reported therapeutic outcomes...
tic results achieved with valsartan (N=169) compared with amlodipine (N=163), a widely prescribed calcium channel blocker, in terms of blood pressure and UAER clinical endpoints. The trial findings showed a large and statistically significant reduction in UAER from baseline in patients treated with valsartan (absolute reduction = 25.6 mcg/min) compared with amlodipine (absolute reduction = 4.7 mcg/min), 56% of baseline versus 92% of baseline, respectively (P<0.001), despite similar reductions in blood pressure (absolute reduction of 6.6 mm diastolic with valsartan versus 6.5 mm with amlodipine) achieved by each treatment. Notably, twice as many patients on valsartan therapy returned to normoalbuminuria than amlodipine patients (29.9% versus 14.5%; P = 0.001). Consistently favorable results were observed in subgroups of study patients with type 2 diabetes and microalbuminuria with or without hypertension.

The objective of our modeling analysis was to extend the results of the above-described trial of valsartan versus amlodipine in type 2 diabetes with microalbuminuria by quantifying long-term health consequences of treatment in terms of quality-adjusted survival (QAS) and estimating the economic consequences of treatment outcomes. These data highlight the potential health and economic benefits that could be gained by timely adherence to expert prescribing guidelines for patients with type 2 diabetes and microalbuminuria. These data are relevant, as research suggests many patients who are prime candidates for agents that block the renin-angiotensin system may not be receiving them.

Our study employed a modeling approach. A well-designed model can potentially enhance the value of clinical trials by extending the time period studied, expressing outcomes not directly assessed in the trial, allowing cost estimation, and permitting sensitivity analysis. Our model extends a 6-month clinical trial to 8 years, expresses clinical outcomes in terms of QAS (rather than intermediate clinical endpoints such as UAER), quantifies associated economic costs of therapy, and enables sensitivity analysis to be conducted on all key model parameters. By presenting our model results, decision makers may perhaps more clearly see the long-term impact of important prescribing decisions.

Our investigation adds to the body of modeling research of interventions that mediate renal disease progression. Wu et al. developed a 10-year population simulation model to evaluate the impact of type 1 diabetes on quality-adjusted life-years (QALYs) and economic costs and found intensive therapy was associated with additional QALYs as well as cost savings. Rodby et al. developed a model to compare lifetime health outcomes and associated economic costs for patients with type 1 and type 2 diabetes and overt nephropathy treated with either captopril or placebo, based on clinical results of a randomized placebo-controlled trial, and concluded that treatment with captopril would result in substantial cost savings. Hogan et al. estimated the economic impact of health outcomes observed in a 3-year randomized trial plus its 3.6-year (median) extension study of adjunct benazepril versus placebo in patients with chronic renal insufficiency of any etiology (of which 10% was attributed to diabetes) who were managed for hypertension with agents excluding ACEIs and found that patients treated with adjunct benazepril enjoyed more QAS and lower medical costs than adjunct placebo-treated patients. The U.S. Centers for Disease Control and Prevention (CDC) Diabetes Cost-Effectiveness Group developed a model to evaluate the cost-effectiveness (CE) of various interventions (intensive glycemic control,
Markov Modeling Analysis of Health and Economic Outcomes of Therapy With Valsartan Versus Amlodipine in Patients with Type 2 Diabetes and Microalbuminuria

intensified hypertension control, and reduction in serum cholesterol level) for the treatment of type 2 diabetes using clinical outcomes data from the United Kingdom Prospective Diabetes Study over a median period of 10 years and found that intensified hypertension control was most cost effective.8

II Methods

Model Description

We developed a 7-state Markov model, which is summarized in Figure 1. Health states included the stages of renal disease, specifically (1) Stage 0 disease indicated by normal albumin levels, (2) Stage 1 disease characterized by microalbuminuria, (3) Stage 2 disease characterized by nephropathy, and (4) Stage 3 disease: kidney failure, also known as end-stage renal disease.7 Three additional health states completed the model structure: (5) cardiovascular disease, (6) death, and (7) withdrawal from the study for any reason.

The probabilities of patients transitioning to different health states over 8 years (Table 1) were extrapolated linearly based on data from the 24-week MicroAlbuminuria Reduction With VALsartan (MARVAL) study,15,24 recently published longer-term studies,10,13,14 and government documents.25 For each health state, quality weights (health utilities) were obtained from the medical literature and costs were obtained from publicly available sources. A third-party payer perspective was taken. Future costs were assumed to increase at a rate of 2.8% per year, equal to the average net increase in medical prices above the general price level from 1991 to 2001 based on the consumer price index.27 A 3% annual rate was used to discount future period costs and effectiveness units to present value equivalents. The model calculated outcomes on a quarterly (3-month) basis, but results are presented on an annual basis. Key model parameters were varied in sensitivity analysis.

Effectiveness (Quality-Adjusted Survival)

The effectiveness unit employed in the model was years (or equivalent months) of QAS. QAS was calculated by multiplying the time patients spent in each health state by the health state’s associated quality weight (health utility). Health utilities assigned to each health state were obtained from the medical literature (Table 2).

Costs

Costs were obtained from public sources and expressed in 2001 dollar values (Table 3). Medical care costs included the costs of study drugs, routine health care services, and aggregate estimates of medical care associated with the various health states. Aggregate costs were calculated by multiplying the time patients spent in different health states by the medical costs associated with those health states.

Cost-Effectiveness Ratios

Ratios of costs to effectiveness units were calculated for each treatment arm by dividing costs by years of QAS. The CE ratio describes
the relative cost to purchase the equivalent of 1 full year of QAS.

**Incremental Cost-Effectiveness Ratio**

The ratio of incremental costs to incremental effectiveness for 2 treatments is calculated as the difference in costs divided by the difference in effectiveness: \((C_a - C_b)/(E_a - E_b)\). The incremental CE ratio is a measure of economic efficiency. It describes the relative economic cost to purchase extra effectiveness yielded by a more effective agent, expressed in terms of 1 whole unit of effectiveness. If the incremental CE ratio has a negative value, it is important to note whether the negative arises in the numerator or denominator, because a negative in the numerator is favorable to valsartan (it would mean valsartan therapy results in lower medical care costs than amlodipine), but a negative value in the numerator is favorable to amlodipine (i.e., it would mean valsartan is less effective than amlodipine).

**Analyses**

Costs, years of QAS, and CE ratios were calculated for each treatment arm. The 2 treatment groups were compared with the incremental CE ratio. Bootstrap methods were employed to determine statistical significance of differences in QAS, costs, and the incremental CE ratio. Sensitivity analysis was performed on key model parameters to ascertain the stability of the results to changes in baseline values. Key parameters were health state transition probabilities, costs, and utilities; medical cost inflation; and the discount rate.

**Results**

**Health State Outcomes**

The model’s distribution of patients to health states over 8 years favored the valsartan group (Figure 2). More than twice as many patients in the valsartan arm returned to normal albuminuria—the best possible model outcome—as did patients in the amlodipine arm. Half as many valsartan patients were projected to reach end-stage renal disease as patients taking amlodipine (9.1% versus 18.6%), and mortality outcomes were similarly favorable to valsartan, at 8.5% versus 17.3% for amlodipine patients. Fewer valsartan patients progressed to cardiovascular disease than did their amlodipine patients (1.9% versus 2.3%, respectively). Rates of withdrawal were similar between the 2 arms (21.5% valsartan versus 23.7% amlodipine).

**Effectiveness (Quality-Adjusted Survival)**

Mean discounted years of QAS for each treatment arm are shown in Table 4. The advantage for the valsartan arm versus amlodipine was small in year 1 (0.011 years) but increased to 0.555 years per patient by the end of year 8. This is equivalent to 7 months per patient of additional survival in full health.

**Medical Care Costs**

Cumulative discounted mean per-patient medical care costs increased in both treatment arms over the model period, indi-
per-patient medical care costs were $1,006 lower for valsartan than amlodipine, which increased to $11,339 after 4 years, and $32,412 (P < 0.01) at the end of 8 years of analysis.

Cost-Effectiveness Ratios

In year 1, the CE ratio per year of QAS for valsartan was $12,444 compared with $13,653 for amlodipine. In year 8, the CE ratio for valsartan rose to $14,407 per year of QAS, and for amlodipine, to $21,332. (A lower CE ratio is better.)

Incremental Cost-Effectiveness Ratio

Both dimensions of outcome—costs and effectiveness—favored valsartan relative to amlodipine. Valsartan was less costly and more effective in terms of QAS than amlodipine. This scenario gives the incremental CE ratio a negative value (i.e., −$58,400 per QALY gained; P < 0.01), and indicates here that there is no trade-off between cost and effectiveness in this analysis because the same treatment option yields both lower costs and more effectiveness.

Sensitivity Analysis

Sensitivity analysis on key baseline model parameters (Table 6) shows model conclusions are stable given wide variation in key assumptions. The parameters with the greatest impact on model results are the costs and utility weights assigned to health states, but changes in these parameters modify the magnitude of the QAS and economic outcomes without changing the overall rank ordering of the treatment arms. Health state transition probabilities were analyzed by revising them to the lower and upper 95% confidence limits reported in the core clinical trial from which they were identified; these changes had relatively little impact on the relative outcomes of each treatment arm. Model outcomes were also analyzed with the direct drug price of amlodipine set equal to $0.30 per 5 mg tablet, a price considered to be equal to that of generically available ACEIs. This change reduced mean per-patient drug costs for the amlodipine arm from $773 to $161 and the difference in costs between valsartan and amlodipine treatment arms from $32,412 in the base-case analysis to $28,611, but the rank ordering of the treatments remained stable even at this low price. Direct drug costs represent a relatively small portion of total medical care costs for these patients, and this result highlights the importance of clinical effectiveness as the key driver of health and economic outcomes for these patients. Changes in the discount rate applied to future costs and QAS, as well as the time period of analysis, have little net effect on results.

Discussion

Our 8-year modeling analysis of the health and economic outcomes of valsartan versus amlodipine in the management of type 2 diabetes with microalbuminuria is the first to be performed in the United States. Results extend data from a 6-month clinical trial to 8 years, interpret health outcomes in terms of quality-adjusted patient survival, and estimate associated costs of medical care. Results highlight the potential long-term health and economic benefits of treating relevant patients with appropriate classes of pharmaceutical agents and the penalty of suboptimal prescribing practices.

These findings for amlodipine versus valsartan remain relevant today even in the presence of expert guidelines that recommend the use of agents that block the renin-angiotensin system (ACEIs or ARBs) for patients with type 2 diabetes and microalbuminuria because research suggests that more patients could benefit from these agents who are not yet receiving them. One managed care study showed that 51% of persons with chronic renal insufficiency—and 35% of persons with chronic renal insufficiency and diabetes—were not treated with either an ACEI or ARB. Another managed care study revealed that fewer than 50% of diabetic hypertensives were receiving an ACEI. These findings suggest ample opportunity to improve patient...
health while avoiding substantial medical care costs by treating high-risk patients with diabetes, microalbuminuria, and/or poorly managed hypertension with appropriate therapy.

Our findings of the economic benefits of valsartan relative to amlodipine are consistent with, though perhaps greater in magnitude than, findings of other models. The CDC diabetes CE group modeled 3 interventions for type 2 diabetes over a 10-year period and found intensified hypertension control yielded greater QAS and lower cost than either intensive glycemic control or cholesterol reduction, a finding that highlighted the CE of intensified antihypertensive therapy, in general, for patients with type 2 diabetes.8 Hogan et al.23 conducted an economic evaluation in the U.S. setting of results of the European Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency study11 in which persons with European Angiotensin-Converting-Enzyme inhibition in an economic evaluation in the U.S. setting of results of the European experience observed in the trial.23 The greater magnitudes were increased to reflect U.S. patterns rather than the increase to $16,794 per patient when dialysis and transplantation values) in the U.S. setting; medical care costs were estimated to cumulate mean medical care costs of $12,991 per patient (1999

denied the CE of intensified antihypertensive therapy, in general, for patients with type 2 diabetes.8 Hogan et al.23 conducted an economic evaluation in the U.S. setting of results of the European Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency study11 in which persons with chronic renal insufficiency of any etiology treated for hypertension with various agents (excluding ACEIs) were randomized to either an ACEI (benazepril) or placebo and followed for a median period of 6.6 years. Results of that analysis revealed more QAS enjoyed by the ACEI group than the placebo arm and cumulative mean medical care costs of $12,991 per patient (1999 values) in the U.S. setting; medical care costs were estimated to increase to $16,794 per patient when dialysis and transplantation rates were increased to reflect U.S. patterns rather than the European experience observed in the trial.23 The greater magnitude of cost savings reported in our study may be explained, at least in part, by a longer period of analysis, selection of a higher-risk group of patients for analysis, a greater difference in effectiveness of therapeutic agents, and/or use of more favorable model parameters.

Limitations

There are several potential limitations to our model analysis. The model is based on health state transition probabilities obtained from a 6-month clinical (MARVAL) study of valsartan versus amlodipine in the United Kingdom. These data were used to formulate the probabilities with which patients transitioned to various health states over an 8-year period. However, these data were compared with other longer-term trial results, and we believe the potential variation between the data we used in the model and other clinical evidence is minor.

A limitation common to modeling evaluations is the use of aggregate costs for each health state. The use of actual costs for different practice settings may be more representative of local conditions, and caution is recommended when evaluating aggregate model results with respect to a particular setting. For a range of proportional changes in input prices, analytical results of the model also changed roughly proportionately (Table 6). But altering input costs that do not reflect proportional changes across health states (e.g., higher prices associated with end-stage renal disease and lower prices associated with cardiovascular disease) could result in different CE ratios and incremental CE ratios than those shown.

Utilities associated with health states were obtained from the literature. While it would be unusual to have utility measures available at the local level, preferences for health states may vary over time and between people and should be carefully considered.

To the extent that readers would like to see a comparison of valsartan, an ARB, to an ACEI, particularly a generic ACEI, our model will be seen as limited by its derivation from a published clinical trial comparing valsartan and amlodipine, a calcium channel blocker. Further research comparing ARBs and ACEIs would be informative. However, our research objective was to highlight health and economic consequences of treatment with either valsartan or amlodipine. Given the evidence suggesting that many appropriate patients may still be receiving agents other than ARBs or ACEIs, this research is relevant.

Conclusion

Extending the results of a clinical trial using our model suggests...
that substantial health gains and cost savings can be realized by treating patients with type 2 diabetes and microalbuminuria with valsartan, an angiotensin II receptor blocker, rather than with amlodipine, a calcium channel blocker. Our study also demonstrated the value of using pharmacoeconomic modeling for purposes of extending the results available from clinical trials. By applying the data obtained from a clinical trial of central importance to data from related clinical trials and information on costs and utilities, a broader and richer set of results can be obtained by decision makers.

ACKNOWLEDGMENT

The authors wish to thank Thomas J. Hogan, president, Medtech, Morristown, NJ, for assistance in the preparation of this manuscript.

DISCLOSURES

Funding for this research was provided by Novartis Pharmaceuticals Corporation and was obtained by author Dean Smith. Smith and authors Anh Nguyen and Corey Peak are paid consultants for Novartis; author Feride Frech is an employee of Novartis. Smith served as principal author of the study. Study concept and design and analysis were contributed by Smith, Nguyen, and Frech. The manuscript was drafted by Smith, with critical revisions and important intellectual content contributed by Nguyen, Peak, and Frech. Statistical analysis was provided by Smith and Peak.

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