Economic impact of reduced incidence of atrial fibrillation in patients with left ventricular dysfunction treated with enalapril

Monika Wagner[1], Derek T. McLachlin[1], Donna Rindress[1], Brigitte Desjardins[2], Anique Ducharme[3], Jean-Claude Tardif[3]

[1]BioMedCom Consultants inc., Montreal, QC, [2]Merck Frosst Canada Ltd., Montreal, QC, [3]Montreal Heart Institute, Montreal, QC

ABSTRACT

Background: Atrial fibrillation (AF) in the setting of heart failure (HF) is linked to embolic stroke and exacerbation of HF. The rate of new-onset AF in patients with left ventricular dysfunction and mild to moderate HF enrolled in the Studies of Left Ventricular Dysfunction was significantly lower in those receiving enalapril in addition to standard treatment (5.4% vs 24% over 2.9 years; P<.0001). The objective of this study was to predict economic consequences over five and ten years, from a Canadian third party payer perspective, of reduced AF incidence in HF patients receiving enalapril.

Methods: The costs and consequences of AF prevention with enalapril were modeled over five or ten years using a Markov decision analytical model. Patients were assigned to one of four health states: "no AF", "AF", "post-stroke", and "death" and moved from one state to the other according to published incidence rates. The model considered increased incidence of stroke as the main consequence of AF and assumed that most patients developing AF would receive warfarin treatment for stroke prevention. Resource utilization and costs were mostly retrieved from published Canadian studies.

Results: Despite similar incidence of stroke between the two groups (standard treatment with or without enalapril) because of prophylactic treatment of AF patients with warfarin, reduced incidence of AF in enalapril-treated patients resulted in savings of $382 and $525 per patient over five and ten years, respectively. These savings stemmed from reduced hospitalization for AF, and less need for warfarin and amiodarone therapy, direct consequences of the lower incidence of AF in patients receiving enalapril. Sensitivity analyses demonstrated that enalapril becomes more cost-saving as the baseline risk of embolic stroke in patients with AF increases and the use of warfarin prophylaxis decreases.

Conclusion: We conclude that reduction in the incidence of AF with enalapril leads to both clinical and economic advantages, in addition to its already well-established benefits of reduced morbidity, mortality, and costs in patients with HF.

INTRODUCTION

- About 1% of Canadians aged 12 and over have heart failure (HF)[1]
- People with HF have 4.5 to 5.9 times increased risk of developing atrial fibrillation (AF)[2]
- AF increases risk of stroke up to 7-fold,[3] exacerbates HF[4] and may increase mortality in HF patients[5,6]
- Angiotensin-converting enzyme inhibitors reduce morbidity and mortality in HF patients[7]
- Analysis of 374 Canadian patients who participated in the Studies of Left Ventricular Dysfunction (SoLVD) found that use of the angiotensin-converting enzyme inhibitor enalapril reduced incidence of new-onset AF relative to standard care (5.4% vs 24%, P<.0001; hazard ratio 0.22, 95% confidence interval 0.11-0.44; mean follow-up 2.9 years)[8]

OBJECTIVE

This study determines the economic impact of reduced incidence of AF in HF patients treated with enalapril from a Canadian health care system perspective.

METHODS

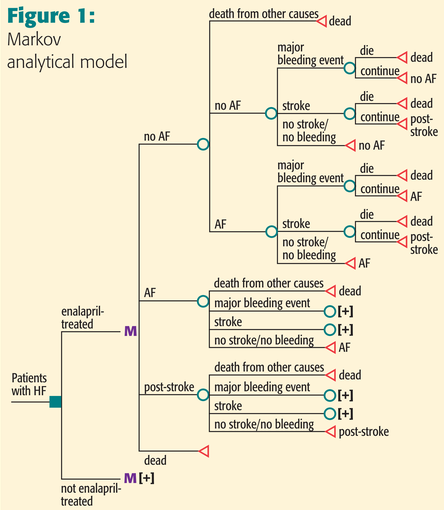
Model

- Markov decision model with 1-year cycle length (Figure 1) and 5- or 10-year horizon
- Standard care vs standard care plus enalapril
- Four health states: no AF, AF, post-stroke, dead
- During each cycle, a patient may die, have a stroke, have a major bleeding event, or have no event
- Years of life were not discounted
- Event probabilities were estimated based on published data (Table 1)
- Incidence of stroke in patients with AF was calculated by adjusting the baseline incidence using the proportion of patients receiving warfarin (78%[9]) and the stroke risk reduction afforded by warfarin (61%[10])

DISCLOSURE

This study was funded by Merck Frosst Canada Ltd, which manufactures enalapril. MW, DTM and DR received consulting fees from Merck Frosst Canada Ltd. BD is employed by Merck Frosst Canada Ltd. AD and JCT have nothing to disclose.

Figure 1: Markov analytical model



Only the enlapril (active treatment) arm is shown; the "not enalapril-treated" arm has analogous structure. **[+]** indicates nodes at which the tree is collapsed. **AF**: atrial fibrillation; **HF**: heart failure; **M**: Markov node; ■: decision node; ○: chance node; ◁: end node.

Table 1: Key event probabilities, base case

Parameter	With enalapril	Without enalapril	Source(s)
Incidence of AF (year[1])	0.019	0.083	8
Incidence of stroke in HF patients without AF (year[1])	0.02	0.02	11
Incidence of stroke in HF patients with AF (year[1])	0.045	0.045	12,13
Incidence of stroke after a previous stroke (year[1])	0.059	0.059	14
All-cause mortality (year[1])	0.067	0.074	15,16

Table 2: Key cost parameters, base case

Parameter	Value	Source(s)
Annual HF standard care cost ($)	1,575	17
Acute hospital cost of stroke ($)	9,575	18
Care outside the hospital during first year after stroke ($)	26,520	18
Care during the second and following years after stroke ($)	9,518	18
Cost of a major bleeding event not resulting in death ($)	7,595	19
Cost of a fatal major bleeding event ($)	11,639	19,20
Cost for AF as admitting diagnosis ($)	2,402	21

Costs

- All costs are in 2004 Canadian dollars and were discounted 3% annually
- Resource utilization and cost data were obtained from published studies of Canadian practice (see Table 2)
- One-time costs were assigned to transition from the "no AF" to the "AF" state, and to death or survival from stroke and major bleeding events
- Enalapril cost was not included because it is used to treat HF and not to prevent AF

Sensitivity analysis

- Twenty parameters were varied in one-way sensitivity analyses for the 5-year horizon, most by ±10%

RESULTS

Base case results

- Enalapril treatment resulted in savings of $383 per patient over five years and $525 over ten years (see Table 3)
- Most cost saving with enalapril resulted from reduced hospitalization for AF
- Stroke costs were similar in the two groups because warfarin is effective for preventing stroke in AF patients
- Over 10 years, patients receiving enalapril could expect to live 0.22 years (80 days) longer, on average
- After 10 years, almost 18% more patients in the enalapril group were still without AF

Table 3: Model output, base case

	After 5 years			After 10 years		
Outcome	Enalapril-treated	Not enalapril-treated	Difference*	Enalapril-treated	Not enalapril-treated	Difference*
Total cost per patient ($)	9,656	10,039	-383	17,125	17,650	-525
Average life-expectancy (years)	4.18	4.11	0.07	7.06	6.84	0.22
Percentage of patients in the "no AF state"	57.9	39.5	18.4	33.5	15.6	17.9

*enalapril-treated minus not enalapril-treated

Sensitivity analysis

- Only the parameters to which the model was most sensitive are shown (Figure 3)
- The model was robust to variation in parameters, and was most sensitive to changes in risk of stroke and all-cause mortality

Figure 3

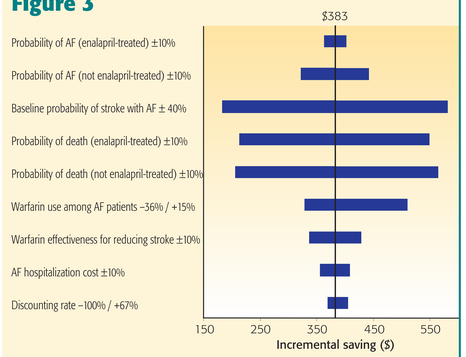
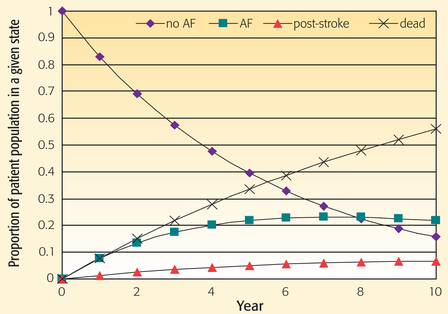


Figure 3. Sensitivity analysis for the 5-year horizon. Bars represent the change in incremental saving resulting from the indicated changes in model parameters. The vertical line indicates the base case result.

Distribution of patients in health states

- At 10 years, 34% of **all enalapril-treated patients** remained in the no AF state, but only 16% of all those not receiving enalapril did so (Table 3 and Figure 2)
- Of patients **who remained alive** at 10 years, 15% of those treated with enalapril had AF; 49% of those not treated with enalapril had AF (Figure 2)

Figure 2: Panel A – not enalapril-treated



Panel B – enalapril-treated

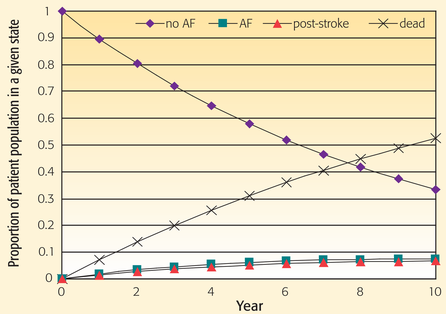


Figure 2. State probabilities for patients not receiving enalapril (Panel A) or receiving enalapril (Panel B). The probability that a patient will be in a particular state of the model is shown for each year.

CONCLUSION

- HF patients treated with enalapril incur substantially lower costs than those not treated with enalapril, mainly because of reduced morbidity associated with AF
- These benefits are in addition to the morbidity and mortality benefits of treating HF patients with enalapril, which has been previously shown to be cost-effective or cost-saving in these patients

ACKNOWLEDGEMENTS

The authors thank Marie-Claude Meilleur of Merck Frosst Canada Ltd. for assistance and helpful discussions.

Presented at the 54th Annual Scientific Session of the American College of Cardiology, Orlando, Florida, March 6-9, 2005

REFERENCES

1 Manuel DG, Leung M, Nguyen K, Tanuseputro P, Johansen H. Can J Cardiol. 2003;19(9): 997-1004.
2 Khand AU, Cleland JG, Deedwania PC. Heart Fail Rev. 2002;7(3):267-83.
3 Fuster V, Ryden LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, *et al.* Eur Heart J. 2001;22(20):1852-923.
4 Maisel WH, Stevenson LW. Am J Cardiol. 2003;91(6A):2D-8D.
5 Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol. 1998;32(3):695-703.
6 Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, *et al.* Circulation. 2003;107(23): 2920-5.
7 Garg R, Yusuf S. JAMA. 1995;273(18):1450-6.
8 Vermes E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M, *et al.* Circulation. 2003;107(23):2926-31.
9 Ceresne L, Upshur RE. BMC Fam Pract. 2002;3(1):11-6.
10 Hart RG, Benavente O, McBride R, Pearce LA. Ann Intern Med. 1999;131(7):492-501.
11 De Lorenzo F, Saba N, Kakkar VV. Drugs. 2003;63(6):565-76.
12 Atrial fibrillation investigators. Arch Intern Med. 1994;154(13):1449-57.
13 Atrial fibrillation investigators. Arch Intern Med. 1998;158(12):1316-20.
14 Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. JAMA. 2001;285(22):2864-70.
15 The SOLVD Investigators. N Engl J Med. 1991;325(5):293-302.
16 The SOLVD Investigators. N Engl J Med. 1992;327(10):685-91.
17 Bentkover JD, Stewart EJ, Ignaszewski A, Lepage S, Liu P, Cooper J. Int J Cardiol. 2003;88(1): 33-41.
18 O'Brien JA, Patrick AR, Caro JJ. BMC Health Serv Res. 2003;3(1):7.
19 Eckman MH, Falk RH, Pauker SG. Arch Intern Med. 1998;158(15):1669-77.
20 Catherwood E, Fitzpatrick WD, Greenberg ML, Holzberger PT, Malenka DJ, Gerling BR, *et al.* Ann Intern Med. 1999;130(8):625-36.
21 Lumer GB, Roy D, Talajic M, Couturier A, Lambert J, Frasure-Smith N, *et al.* Eur Heart J. 2002;23(13):1050-6.