Review Article

Examining Progress in Research: Cost-effectiveness of Cardiovascular Disease Prevention Using the Markov Model

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Abstract

This article reviews three-volume collection of previously published articles on cost-effectiveness in cardiovascular disease prevention. Firstly, cost–effectiveness analysis of genetic screening for the Taq1B polymorphism in the secondary prevention of coronary heart disease is conducted. Secondly, a "polypill" aimed at preventing cardiovascular disease could prove highly cost-effective for use in Latin America, and lastly, the cost-effectiveness of intensive atorvastatin therapy in secondary cardiovascular prevention in the United Kingdom, Spain, and Germany is assessed, based on the Treating to New Targets study. All three articles in this paper demonstrate how the Markov model can control strategy in terms of cost savings and increase the mean of quality-adjusted life-years (QALYs). Moreover, the Markov model can be used to demonstrate how healthcare systems can control the cost-effectiveness of drug use in terms of cardiovascular disease related to health benefits, costs, and quality-adjusted life-years (QALYs). In conclusion, employing the Markov model through other interventions, especially in the case of health benefits, cost savings, and quality-adjusted life-years (QALYs) is the main recommendation of this article.

Keywords: Markov model, cardiovascular disease prevention, cost effectiveness

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(Received: 30/09/24, Revised: 29/12/24, Accepted: 21/01/25)

1. Introduction

The number of articles in healthcare, especially on the Markov model has been growing. The trend has been for articles to become more specialized in terms of the use of decision-analytical modeling to estimate the cost effectiveness of healthcare intervention. Most importantly, healthcare organizations can evaluate the cost-effectiveness of administering a daily drug for chronic diseases. The Markov model is a technique of decision analysis to construct a state-transition of both the costs and outcomes and is a powerful tool for economic evaluation modeling in disease prevention programs.

This article examines research on healthcare organizations. Three articles are reviewed. The first is a cost–effectiveness analysis for genetic screening for the Taq1B polymorphism in the secondary prevention of coronary heart disease (Kemp et al., 2007). The second article is on a "polypill" aimed at preventing cardiovascular disease which could prove highly cost-effective for use in Latin America (Bautista et al., 2013). The third article is on the cost-effectiveness of intensive atorvastatin therapy in secondary cardiovascular prevention in the United Kingdom, Spain, and Germany, based on the Treating to New Targets study (Taylor et al., 2009). In this paper, the progress of research on the Markov model is investigated. When employed the Markov model in healthcare organizations, it can help evaluate patients' health state, especially in terms of well, ill, and dead. Furthermore, healthcare organizations can construct a state-transition of cost management and cost saving by using the technique of decision-analysis in the Markov model to make healthcare providers satisfied with cost management and the cost outcomes.

2. Markov Model

A first-order Markov model assumes that to predict the state of the system at time t+1, one need only know the state of the system at time t (Usher, 1981). A particular type of model is now used frequently in economic evaluation and has a long history of use in healthcare service decision-making. Health economics evaluation studies are also beginning to use the Markov models more widely because the Markov model can simply and intuitively handle both costs and outcomes simultaneously (Briggs & Sculpher, 1998).

Briggs and Sculpher (1998) stated that economic evaluation should ideally be undertaken early in the development of new healthcare technology, and they described four stages of economic evaluation in which decision-analytical modeling has an important role to play in each stage. Stage I economic analysis is the first assessment of the economic characteristics of a new technology and is undertaken when a basic scientific investigation has been completed. The focus of analysis at this stage tends to be on the cost effectiveness of the new intervention by estimating the cost effectiveness of the existing form(s) of management against which new technology will ultimately complete and hence, the costs and/or effectiveness the new technology must attain to supplant the existing intervention(s).

Stage II economic evaluation is required on all technologies which, based on the analysis undertaken in stage I, were considered to offer some scope for being more cost effective than the existing interventions. This stage of analysis is usually undertaken when the intervention is being used on patients in a few specialist centers which produce data in the form of case series and small randomized trials. Again, modeling is crucial to this stage of analysis. One major role of the model is to assist in the design of trial-based economic evaluation that is subsequently undertaken.

Stage III economic evaluation is probably the most prevalent in terms of publications. Although the randomized trial is widely seen as the ideal data collection vehicle for this stage of analysis, the model still has a major role. Often stage III analysis is based on the synthesis of data from various sources.

Stage IV analysis is concerned with evaluating the cost-effectiveness of interventions when they are used in routine clinical practice. Many stage III analyses are based on trials undertaken in artificial clinical contexts involving unrepresentative patients which may generate inappropriate estimates of the cost-effectiveness of interventions when used in clinical practice.

In addition, a second order to obtain a better understanding and greater detail is “the Markov model” in health state and transition probability (see figure I). The Markov model shows that there are three states that are related to each other, which are as follows:

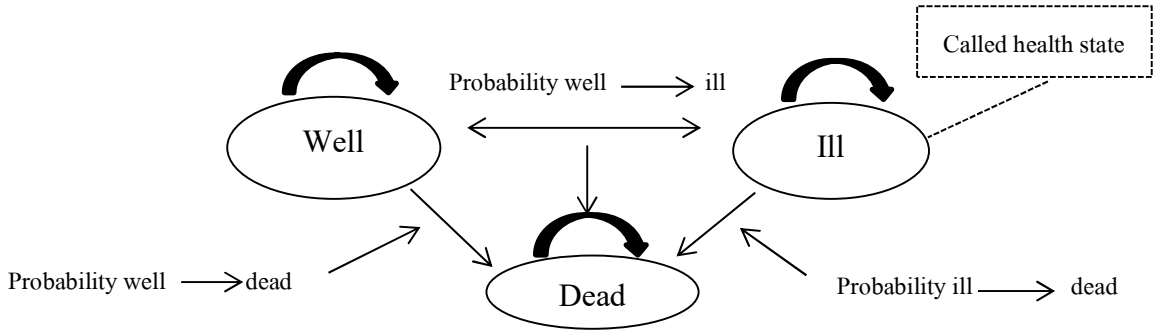

Figure1. The Markov Model

Note. Dirogtornsakul and Chaiyakunapreuk (2016)

Briggs and Sculpher (1998) stated that the Markov model has three stages: 1) well, 2) ill, and 3) dead. When constructing a Markov model for disease progression, the first task is to define the disease in terms of different states.

The Markov model not only has merits of a decision tree, but it also has limitations that are listed below (Wallisch et al., 2014):

- Less suitable for longer-term outcomes, though possible to add branches, but these are not efficient.
- Difficult to handle disease recurrence.
- Need to be able to assess full implications of each possibility of the patient pathway.
- No account is taken of history.
- Assuming uniform populations are equal and constantly risk.
- May overcome these limitations by using a large number of states.
- Alternatively use other methods (individual sampling models, discrete event simulation.

3. Three Examples

From these three example articles are updated and employing the Markov model as its approach, we can predict cardiovascular disease related events by measuring the health benefits and costs associated with the use of the pill. There are three examples from article reviews that reveal the diversity of how drug therapy can be carried out using the Markov model to evaluate cost-effectiveness in preventing cardiovascular disease and that could prove highly cost-effective for use.

Kemp et al. (2007) proposed a cost-effectiveness analysis of genetic screening for the Taq1B polymorphism in the secondary prevention of coronary heart disease. In this paper, the research was conducted in Australia because Coronary Heart Disease (CHD) is a major cause of mortality and morbidity and the leading disease in Australia for both of males and females. Moreover, CHD also has major economic consequences. In total, AUS$5.4 billion was spent on cardiovascular diseases in 2000-2001 (Australian Institute of Health and Welfare, 2004). Accordingly, there is now more evidence suggesting that genetic polymorphism may be associated with the development and progression of CHD and impact on the effectiveness of pharmaceuticals used to treat CHD patients. So, in this study, the purpose is to examine the cost-effectiveness of genetically testing CHD and stroke patients for the Taq1B polymorphism before prescribing statins. The Markov model is applied in this study to estimate the long term economic and health effects. Four of the population of CHD and stroke patients were analyzed and prescribed statins:

- With the B2B2 genotype
- With either the B1B2 or B2B2 genotypes
- Irrespective of genotype
- To prescribe statins to patients with either the B1B2 or B2B2 genotypes and to prescribe ezetimibe to the remainder

The results of this study in terms of costs, effects and cost-effectiveness to support Taq1B were as follows (Kemp et al., 2007):

Table 1. Results in terms of costs, effects and cost-effectiveness.

Parameter	Treat all patients with statins	Treat B2B2 patients with statins	Treat B1B2 and B2B2 patients with statins	Treat B1B2 and B2B2 patients with statins and B1B1 with ezetimibe
Net cost (AUS$ million)	2,008	385	1,416	1,961
(95%CI)	(1,418-2,742)	(276-526)	(1,006-1,932)	(1,390-2,676)
DALY averted	75,922	21,814	68,043	84,302
(95%CI)	(46,456-106,659)	(10,169-32,252)	(54,618-93,033)	(56,215-114,688)
Percentage of time Cost effective		1%*	89%**	98%*

Note. * Treat all patients with statins is the comparator

** Treat B1B2 and B2B2 patients with statins is the comparator

CI: Confidence Interval

From the above table, the study revealed that there is a probability of 89% that genetically testing all CHD and stroke patients, but prescribing statins to only those with the B1B2 or B2B2 genotypes, are more cost-effective than the current regime of not genetically testing anyone but treating them all. However, this study showed that there were potentially large cost savings and health benefits to be gained within the healthcare sector by genetically testing CHD and stroke patients.

Bautista et al. (2013) also employed the Markov model in a case study in Latin America aiming to determine cost-effective strategies for the prevention of cardiovascular disease. In Latin America cardiovascular disease accounts for 35 percent of deaths and as many years of life lost as all communicable diseases combined. In this paper, administering a daily “polypill” consisting of three antihypertensive drugs, a statin, and aspirin to prevent cardiovascular disease among high-risk patients in Latin America was tested and three study results were mentioned in this paper to support polypill used as follows:

The lifetime risk of cardiovascular events in women was 29.1 percent but it could be reduced by 15 percent if the polypill were given to those in the high-risk group (those with ten-year risk of cardiovascular disease greater than or equal to 15 percent) or to those age fifty-five or older. The life-time risk of cardiovascular events for men was 36.5 percent, which could be reduced by 21 percent if the polypill were given to those in the high-risk group (see table 2) (Bautista et al., 2013).

Table 2. Lifetime risk of fatal and nonfatal cardiovascular events if the polypill were used in different risk groups.

Group	Percent of group	Fatal event Risk of death	RR	Nonfatal event Risk of CVE	RR
Women					
No polypill	100.0	28.3	1.00	29.1	1.00
Group receiving polypill					
≥ 55 years old	24.8	24.0	0.85	24.7	0.85
High Risk	25.1	23.9	0.84	24.6	0.85
Men					
No polypill	100.0	36.2	1.00	36.5	1.00
Group receiving polypill					
≥ 55 years old	23.0	33.1	0.95	33.4	0.95
High Risk	26.1	29.5	0.81	29.8	0.79

Note. RR is relative risk, or the ratio of the lifetime risk with use of the polypill to the lifetime risk with Non-use of the polypill in a target group.

CVE is a cardiovascular event.

- Gaining one Quality-Adjusted Life-Year (QALY) for women would require spending between $25 (if the polypill were not used, reflecting the costs of diagnosis and treatment) and $49 (if the polypill were given to every woman who met the World Health Organization criterion for abdominal obesity). Giving the polypill to women in the high-risk group would be the best intervention, since it would result in the lowest increase in cost per additional

QALY gained-an incremental cost-effectiveness ratio of $268 per QALY. Among men, gaining one QALY would cost $21 under the null option and $38 if the polypill were given to those who met the Lain American criterion for abdominal obesity. Giving the polypill to men aged fifty-five or older would be the best approach, with an incremental cost-effectiveness ratio of $499 per QALY (see table 3) (Bautista et al., 2013).

Table 3. Cost-effectiveness of the polypill if it were used in different risk groups.

Group	Cost ($)	Effectiveness	Cost-effectiveness ($)	ICER ($)
Women				
No polypill	576	23.076	25	Not Applicable
High risk	742	23.696	31	268
Abdominal				
- Obesity (WHO)	1,163	23.849	49	2,770
Men				
No polypill	444	21.660	21	Not Applicable
≥ 55 years old	617	22.046	28	449
High risk	743	22.166	34	1,041
Abdominal				
- Obesity (LASO)	854	22.198	38	3,533

Note. Cost is cost of diagnosis and treatment of cardiovascular diseases.

Effectiveness is quality-adjusted life-years (QALYs) gained.

Cost-effectiveness and incremental cost-effectiveness ratio (ICER) are per QALY gained.

Figures were obtained options were not included for women ≥55 years old.

- Abdominal obesity defined by the Latin Consortium of Studies on Obesity (LASO).

Figures were obtained options were not included for women ≥55 years old

- Abdominal obesity defined by the World Health Organization (WHO).

Not Applicable means ten-year risk of coronary heart disease ≥ 15 percent calculated with the Framingham risk score.

- The sensitivity analysis that can be shown by the incremental cost-effectiveness ratio among women ranged from $158 per QALY in the best scenario (average adherence and

high baseline risk of cardiovascular disease in the population) to $804 per QALY in the worst scenario (very low adherence and low baseline risk of cardiovascular disease in the population). Corresponding figures for men were $365 per QALY in the best scenario and $933 per QALY in the worst (see table 4) (Bautista et al., 2013).

Table 4. Best risk groups to target with polypill, by adherence and baseline risk, according to sensitivity analyses.

	Best group	Cost ($)	Cost-effectiveness ($)	ICER ($)
Women				
Average adherence				
Low baseline risk	≥ 55 years old	595	24	494
Average baseline risk	High risk	742	31	268
High baseline risk	High risk	834	36	158
Very low adherence				
Low baseline risk	≥ 55 years old	624	25	804
Average baseline risk	High risk	774	33	440
High baseline risk	High risk	873	38	281
Men				
Average adherence				
Low baseline risk	≥ 55 years old	488	21	629
Average baseline risk	≥ 55 years old	617	28	449
High baseline risk	High risk	810	37	365
Very low adherence				
Low baseline risk	≥ 55 years old	507	22	933
Average baseline risk	≥ 55 years old	637	29	677
High baseline risk	High risk	835	39	524

Note. The best risk groups to target are those with the lowest incremental cost-effectiveness ratio (ICER).

Cost is of diagnosis and treatment of cardiovascular diseases.

Cost-effectiveness and ICER is estimated at average cost.

Adherence means the percentage of the group taking the polypill.

Average adherence (85 percent) corresponds the adherence observed in the Indian Polycap Study (Indian Polycap Study (TIPS et al., 2009).

Low adherence is 50 percent

Very low adherence is 30 percent

Average baseline risk is the risk of cardiovascular disease in people with average levels of Cardiovascular risk factors in the population.

Low baseline risk is 50 percent of average baseline risk

High baseline risk is 150 percent of average baseline risk.

High risk is a ten-year risk of coronary heart disease ≥ 15 percent, calculated with the Framingham risk score (D' Agostino et al., 2008).

A third example of a study on Markov model is provided by Taylor et al, who were interested in the cost-effectiveness of intensive atorvastatin therapy for secondary cardiovascular prevention in the United Kingdom, Spain, and Germany, based on the Treating to New Targets study. For this reason, a development by using the Markov model to predict a lifetime of cardiovascular disease-related events, costs, survival, and quality-adjusted life-years (QALYs) has emerged. In this article, the Markov model was employed as a decision analysis to construct a state-transition model of the management, outcomes, and costs of secondary cardiovascular prevention, predicting the likelihood of major cardiovascular events such as Myocardial Infraction (MI), Stroke, Congestive Heart Failure (CHF), Revascularization, Resuscitated Cardiac Arrest (RCA), Minor Cardiovascular Events (Peripheral Artery Disease: PAD), Transient Ischemic Attack (TIA), Documented Angina, and Death. In addition, there were several distinct health states that are shown in the figure as follows:

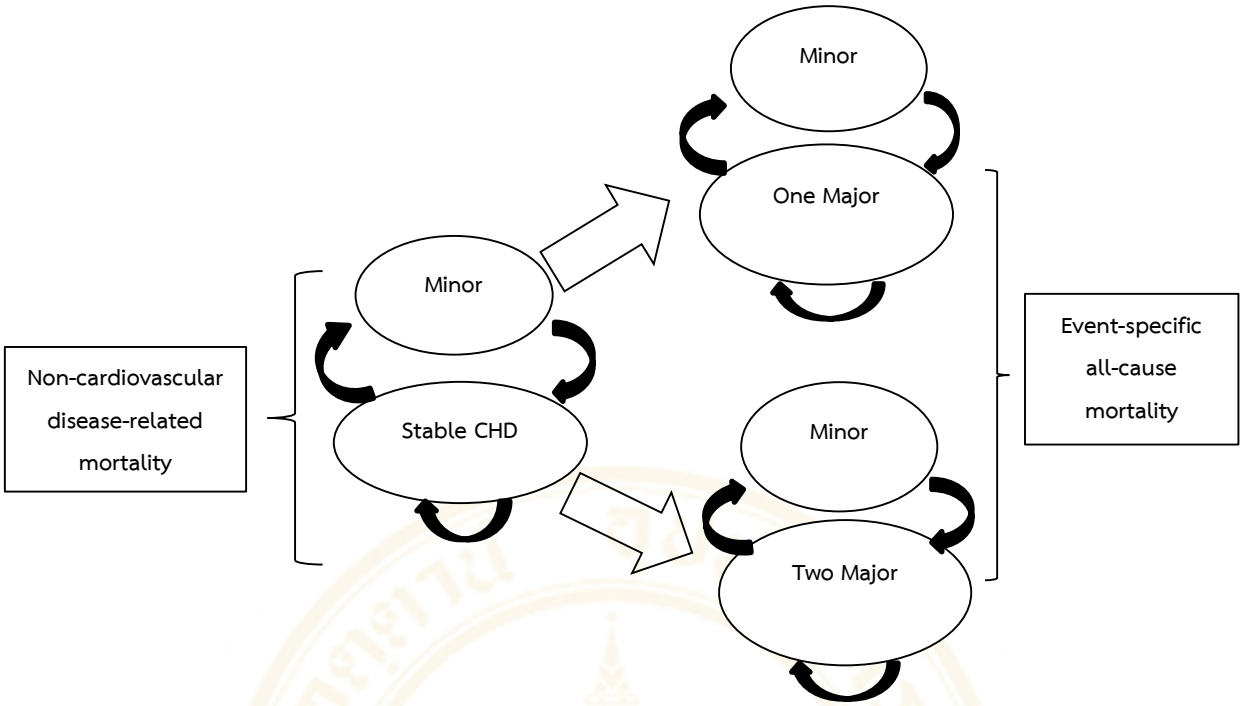

Figure 2. Markov model states and possible transitions.

Note. Taylor et al. (2009)

Figure 2. Single asterisk: separate major event states for myocardial infraction, stroke, congestive heart failure, revascularization, and resuscitated cardiac arrest. Double asterisk: separate major event states for all possible combinations of two major events (excluding resuscitated cardiac arrest). Triple asterisk: minor events include peripheral artery disease, transient ischemic attack, and documented angina and shows that health states involving two major events allow for all possible combinations of events (excluding RCA). A summary measure of quality of life on a zero-to-one scale and economic cost are assigned to each health state. Patients in major event states are subjected to the long-term utility and mortality consequences of their specific cardiovascular event(s). Minor events result only in short-term cost and utility consequences, reflecting the transient nature of these conditions.

One result of this article is interesting, the base-case scenario. Treatment with 80 mg atorvastatin is estimated to yield increased life-years and QALYs vs atorvastatin 10 mg in each setting (see table 5). The total discounted costs of secondary cardiovascular prevention are

estimated to be € 1,791, € 3,880, and € 2,896 higher per-patient for those receiving atorvastatin 80 mg in the UK, Spain, and Germany, respectively, reflecting higher lifetime costs for atorvastatin 80 mg therapy (€ 6,139 vs € 3,851, € 8,451 vs € 4,153, and € 7,533 vs € 4,204). These therapy costs are offset in part by lower costs of treating cardiovascular events (€ 3,857 vs € 4,353), € 3,730 vs € 4,148, and € 3,518 vs € 3,951). The incremental cost per QALY gained for atorvastatin 80 mg compared to 10 mg is estimated to be € 9,500, € 21,000, and € 15,000 in the UK, Spain, and Germany (see table 5) (Taylor et al., 2009):

Table 5. Cost-effectiveness of atorvastatin 80 mg vs atorvastatin 10 mg in the management of secondary cardiovascular prevention.

Atorvastatin therapy	Total cost	LY*	QALYs**	ICER*** (cost per LY)	ICER*** (cost per QALY)
UK base-case analysis					
Atorvastatin 10 mg	€ 8,205	11.18	8.51	---	---
Atorvastatin 80 mg	€ 9,996	11.39	8.69	€ 8,600	€ 9,500
Spanish base-case analysis					
Atorvastatin 10 mg	€ 8,301	11.44	8.70	---	---
Atorvastatin 80 mg	€12,181	11.64	8.89	€ 19,000	€ 21,000
German base-case analysis					
Atorvastatin 10 mg	€ 8,155	11.18	8.50	---	---
Atorvastatin 80 mg	€ 11,051	11.39	8.70	€ 13,000	€ 15,000

Notes: *LY: Life-years, ** QALY: Quality-adjusted life-years, *** ICER: Incremental cost-effectiveness ratio

4. Discussion: Relationship of the three strands of research in the Markov model

The three strands of research are related to each other. In the first article, it identified various degrees of effectiveness for statins. The Taq1B polymorphism is an example of a genetic polymorphism that is thought to influence the effectiveness of statins. The Markov model was applied to estimate the long term economic and health effects in this paper. The second article

referred to the use of a polypill which consist of three antihypertensive drugs, a statin, and aspirin to prevent cardiovascular disease among high-risk patients in Latin America. In this article, the Markov model also revealed that it could handle costs and outcomes. In the third article, the Markov model also revealed that it could lead to cost-effective, outcomes and a lifetime Markov model was developed to predict cardiovascular disease-related events, costs and outcomes (survival and quality-adjusted life-years (QALYs)) to prevent cardiovascular disease by using intensive atorvastatin in Treating to New Targets (TNT) in the United Kingdom, Spain, and Germany.

The employment of the Markov model can yield cost savings and an increase in the mean for quality-adjusted life-years (QALYs). In a healthcare context, Markov models are particularly suited to modeling chronic disease. The first advantage of using the Markov model is the economic evaluation of healthcare intervention.

5. Conclusion

What these three strands of research offer is an idiosyncratic collection of recent articles on an extremely important subject. The central message is that the Markov model is a decision-analytical model used to estimate the cost effectiveness of healthcare interventions, and it is very widely-used, especially for economic evaluation. The Markov model can handle not only costs but also outcomes. Consequently, it is a powerful tool for economic evaluation modeling. Healthcare professionals should employ this method to enhance the prevention of cardio-prevention of cardio-vascular disease. This method could also be applied to assess the costs and outcomes in the treatment of other chronic diseases, which could be investigated in future research.

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