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ORIGINAL RESEARCH



Long-term cost-effectiveness of a disease management program for patients with atrial fibrillation compared to standard care – a multi-state survival model based on a randomized controlled trial

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ABSTRACT

Aim: To assess the long-term cost-effectiveness of an atrial fibrillation disease management program (i.e. the SAFETY program) from the Australian healthcare system perspective.

Methods: A multistate Markov model was developed based on patient-level data from the SAFETY randomized controlled trial. Predicted long-term survival, dependent on hospital admission history, was estimated by extrapolating parametric survival models. Quality-adjusted life years (QALY) and life years (LY) were the primary and secondary outcome measures used to estimate the incremental cost-utility/effectiveness ratio (ICUR/ICER). Both deterministic and probabilistic sensitivity analyses (PSA) were undertaken.

Results: The SAFETY program was associated with both higher costs (\$94,953 vs. \$78,433) and benefits [QALY (3.99 vs 3.60); LY (5.86 vs 5.24)], with an ICUR of \$42,513/QALY or ICER of \$26,356/LY, compared to standard care. Due to the extended survival, the SAFETY was associated with a greater number of hospitalizations (14.85 vs 11.65) and higher costs for medications (\$25,084 vs \$22,402) and outpatient care (\$12,904 vs \$11,524). The cost per hospitalization for an average length of stay, analytical time horizon, and cost of medication are key determinants of ICUR. The PSA showed that the intervention has a 70.4% probability of being cost-effective at a threshold of \$50,000/QALY.

Conclusions: The SAFETY program has a high probability of being cost-effective for patients with atrial fibrillation. It is associated with uncertainty that further research could potentially eliminate; implementation with further evidence collection is recommended.

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Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia observed in medical practice¹ and is associated with detrimental consequences, including heart failure (HF), ischemic stroke, and mortality. It also imposes a great economic burden on society. For example, in Australia, it affects approximately 400,000 people, with aging as a prominent risk factor. In 2014–2015, there were 58,608 hospitalizations for AF as a principal diagnosis (National Hospital Morbidity database), and ~ 20–25% of patients with AF are admitted to hospital annually. Caring for AF costs the Australian economy over AU\$1.25 billion per year through medical costs, long-term care costs for those with a stroke-related disability, and lost productivity output^{2,3}. Internationally, the Global Burden of Disease study⁴ estimated that, in 2010, there were 33.5 million patients with AF in the world, constituting ~ 0.5% of the total world population⁵. The projected

worldwide population ageing, combined with an accumulation of cardiovascular diseases and lifestyle risk factors, ensures a likely and dramatic increase in the number of patients with AF (primarily the non-valvular AF, NVAF) in the coming years. Given its prevalence and the severe complications associated with it, AF is considered one of the major threats to cardiovascular health⁶.

Management of NVAF includes five components that target different sections of the heart: acute stabilization of patients who present with NVAF complications or hemodynamic compromise; detection and treatment of underlying and accompanying cardiovascular conditions; stroke risk assessment and oral anticoagulation for stroke prevention; rate control; and rhythm control therapy. However, adherence to treatment is generally considered suboptimal. For example, an Australian study found that nearly half of the patients with NVAF did not adhere to the prescribed

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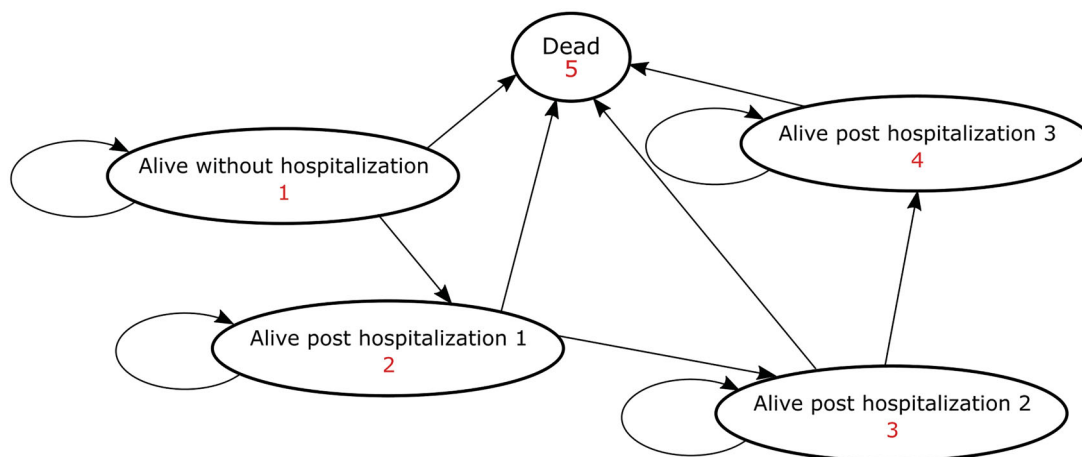


Figure 1. Illustration of multi-state Markov model.

treatment^{7–9}, rendering them at higher risk of developing cardiovascular complications, including stroke.

A nurse-coordinated multidisciplinary program has significant potential to promote the management of patients with NVAF, with the role of a NVAF nurse outlined in the most recent European guidelines¹⁰. It could involve a home-based, NVAF-specific management strategy (including greater clinical surveillance and longer-term support) with an aim to optimize antiplatelet/thrombotic treatment, preserve cardiac function, and improve clinical stability¹¹. A randomized controlled trial (RCT) of a multidisciplinary disease management program aiming to improve NVAF patients' adherence to treatment reported that this multicomponent service was associated with proportionately more days alive and out of hospital but observed no impact on all-cause mortality relative to standard management, and a potential to improve poor health outcomes in patients admitted with chronic NVAF¹². A within-trial economic analysis was undertaken to assess the short-term cost-effectiveness of this disease management program and showed that, compared with standard management, this intervention is a potentially dominant strategy for NVAF patients (i.e. $-\$4,375$ and 0.02 quality-adjusted life year gains per patient)¹³. Given that lifetime management is foreseeable for patients with NVAF, ascertaining the long-term cost-effectiveness of this service program would complement its economic credentials and provide a more comprehensive examination of the long-term costs and benefits, which is required if it is to be scaled up to the national level and seek public subsidy.

This study aimed to undertake a modelled economic evaluation for the disease management program that targeted patients with NVAF to assess its long-term cost-effectiveness by extrapolating the patient-level data collected from the SAFETY RCT¹².

Methods

SAFETY program

The details of the SAFETY program were reported elsewhere¹². Briefly, the SAFETY program was a structured post-discharge intervention delivered by a senior specialist nurse

consisting of a home visit 7–14 days after discharge ensued by a series of repeated home visits, scheduled clinical reviews, and telephone follow-up. The aim of the program was to optimize both drug treatment and non-pharmacological management.

Model structure

A multi-state Markov model, consisting of five Markov health states, was developed to simulate the long-term health outcome and costs associated with the NVAF disease management program (i.e. the SAFETY program). The five health states were: alive without hospitalization, alive post first hospitalization, alive post second hospitalization, alive post third hospitalization, and dead.

All patients entered the model in the alive without hospitalization state and could then (i) remain event-free; (ii) be hospitalized, or (iii) die due to all causes in quarterly (3-month) cycles. Patients experiencing more than three hospitalizations were aggregated into the “alive post-third hospitalization” health state.

Given that patients requiring frequent hospital care are indicative of persistent and refractory NVAF that can predict the long-term prognosis¹⁴, the alive post n number of hospitalizations states (i.e. one, two, or three) were modelled separately to account for this difference. A half-cycle correction was applied to adjust for both costs and benefits (i.e. all transitions were assumed to occur in the middle of the cycle; if patients died during a cycle, only half of the costs and benefits would be accrued). Costs and benefits were discounted at a rate of 5% according to the Australian guideline for preparing submission (including economic evaluation) to the Pharmaceutical Benefits Advisory Committee (the national agency for pharmaceutical reimbursement)¹⁵. The model structure is illustrated in Figure 1. TreeAge software was utilized for the modelling analysis (TreeAge Pro 2019, TreeAge Software, Williamstown, MA).

Modelled population

The modelled population were Australian patients diagnosed with chronic NVAF but not chronic heart failure, according to

international guidelines¹⁶. The population characteristics were the same as of those recruited in the RCT: equal proportions of male and female participants with a mean age of 72 years and 90% experiencing persistent NVAF, 64% being managed by a rate-control strategy, and 33% having a comorbid coronary heart disease¹². The time horizon was set at 10 years, given the average age of the population modelled. The comparator was the standard care (i.e. current clinical practice in Australia, including routine medical care, hospital care, and pharmacotherapy) for patients with NVAF, which is consistent with the pivotal RCT¹². For the standard care arm, patients were managed predominantly by a General Practitioner (GP) in consultation with a specialist doctor and received medications including warfarin, antiplatelet agents, antiarrhythmic drugs¹². More recent oral anticoagulants (e.g. apixaban) were not available in Australia during the study period (2010–2012).

Model inputs

Transition probabilities

All the transition probabilities – including probabilities of first hospitalization, recurrent hospitalization, and death due to all causes dependent on number of re-hospitalizations (i.e. overall survival) – were generated from time-to-event analyses using individual patient data (IPD) from the pivotal RCT. For the derivation of transition probabilities over the trial duration (i.e. the minimum follow-up of 2 years), the Kaplan-Meier survival analysis was adopted to estimate the survival function for the first 900 days. Finally, parametric survival analysis was undertaken to base extrapolation of transition probabilities beyond the trial follow-up period.

A multi-state time to event modelling approach¹⁷ was adopted to statistically estimate the following transition probabilities:

- i. No further event to first hospitalization;
- ii. No further event to death;
- iii. Post first hospitalization to second hospitalization;
- iv. Post first hospitalization to death;
- v. Post second hospitalization to third hospitalization;
- vi. Post second hospitalization to death;
- vii. Post third hospitalization to death.

A multistate modelling technique was chosen because (1) it is often used to model complex disease profiles by accounting for competing events at each transition (i.e. a single patient faces the risks of rehospitalization and death simultaneously) and (2) it allows the use of patient-level data, offers flexibility to extrapolate each transition by a variety of parametric models, and possibly enables parameter sharing across transitions. Specifically, the STATA code provided by Crowther and Lambert¹⁷ was adapted to derive the aforementioned transition probabilities over the SAFETY trial duration.

For the time to death/hospitalization analysis (i.e. transition probabilities i to vii), exponential, Weibull, loglogistic, lognormal, and Gompertz distributions were fitted to the IPD

with respect to the particular dataset. The best fit distribution was selected based on predefined criteria^{18,19}. To estimate the transition probabilities for the within-trial period, the following formula was employed using estimates from Kaplan-Meier survival functions²⁰:

$$\begin{aligned} \text{transition probability}_{t-1 \sim t} \\ = \frac{(\text{survival function}_{t-1} - \text{survival function}_t)}{\text{survival function}_{t-1}} \end{aligned}$$

After 900 days, the SAFETY program and standard care groups were assumed to have identical transition probabilities (i.e. no treatment). All IPD-level analysis was performed by STATA version 15 (StataCorp. Statistical Software: Release 15, College Station, TX: StataCorp LP).

Costs and utility weights

Costs and utility weights were sourced from the trial data, from the perspective of costs to the Australian healthcare system. Correspondingly, those incorporated in the model included costs relating to hospitalization, medications, outpatient care (i.e. visits to primary care physician/specialist, examinations, etc.), and disease management services. The cost due to hospitalization was adjusted by the probability of prolonged/average length of stay (LoS). Since there is no significant between-group difference in the hospitalization cost, the same cost per hospitalization (based on hospitalization presentation diagnostic related group) was applied. Particularly, the average LoS and cost of hospitalization thereof were calculated across the entire sample regardless of randomization status. Then, the probability of prolonged LoS (i.e. proportion of individuals with LoS longer than the average LoS) was derived from the IPD by randomized groups (given that this is significantly different between the groups), whereas the average cost of hospitalization for a prolonged LoS was computed across all individuals with prolonged LoS irrespective of their group status. All costs were valued in the year 2018 and corresponding consumer price indices (CPI) from the health sector were used to inflate the costs not derived from 2018.

Disutility associated with hospitalization was derived from the trial data. In order to derive the utility decrement associated with repeated rehospitalizations, a regression analysis of utility at 24 months was undertaken with number of rehospitalizations as the predictor (i.e. entered as dummy variable) regardless of randomized groups. The quality-adjusted life years (QALY) were then estimated based on the utility weights attached to the health states multiplied by the time spent in each health state. The life years (LY) gained were also calculated. Since no adverse effects associated with this management program intervention were reported, no costs in relation to adverse effects were included in the model. The unit costs and utility weights are summarized in Table 1.

Cost-utility and cost-effectiveness analysis

Cost utility analysis was undertaken by calculating the incremental cost-utility ratio (ICUR) from the difference in costs

Table 1. Costs and utility weight used in the model.

Cost	Cost per cycle/event	Range	Source
Cost of SAFETY program	\$738	0–\$1,476	SAFETY RCT
Cost of hospitalization with ALoS	\$4,053.05	0–\$8,106	SAFETY RCT
Cost of hospitalization with PLoS	\$6,834.74	0–\$13,669	SAFETY RCT
Cost of medications	\$1,070	0–\$4,279	SAFETY RCT
Cost of outpatient care	\$550	0–\$3,001	SAFETY RCT
Utility of NVAF	0.7381	0.60–1.00	SAFETY RCT
Disutility of first rehospitalization	–0.03715	0–0.06512	SAFETY RCT
Disutility of second rehospitalization	–0.01821	0–0.06512	SAFETY RCT
Disutility of third rehospitalization	–0.02769	0–0.06512	SAFETY RCT
Proportion of prolonged LoS*			
SAFETY program	0.1883	0–0.3766	SAFETY RCT
Standard of care	0.2187	0–0.4374	SAFETY RCT

Abbreviations. ALoS, average length of stay; PLoS, prolonged length of stay; NVAF, atrial fibrillation.

*After 900 days, the proportion of prolonged LoS was the same across the two groups.

divided by the difference in QALY for the SAFETY program vs the standard care. Similarly, the incremental cost-effectiveness ratio (ICER) was also estimated using LY gain as the outcome measure. The often-quoted willingness-to-pay per QALY/LY of \$50,000 in Australia was utilized to assess the cost-effectiveness of the intervention²¹.

Sensitivity analysis

Deterministic (DSA) and probabilistic sensitivity analyses (PSA) were performed to test the robustness of base case results. For DSA, a series of one-way sensitivity analyses were undertaken by varying key model parameters within a range (based on the best available evidence or assumptions). The results from the one-way sensitivity analyses are shown as Tornado diagrams, sequentially graphing the variable with the largest impact on the cost-utility results. PSA was performed to assess the overall impact of uncertainty in the model by defining distributions for the key parameters (i.e. variables regarding transition probabilities, utilities, and costs). The uncertainty around parameters (i.e. lambda for an exponential distribution; lambda and gamma for a Gompertz distribution) defining the parametric survival functions was also examined by incorporating the distribution for these parameters. Finally, 5,000 iterations (i.e. second-order Monte Carlo simulation) were run to construct a mean and 95% credible interval (CI) for the corresponding cost and benefit, and the results were plotted on a cost-effectiveness plane and cost-effectiveness acceptability curve.

Value of perfect information

The uncertainty in the results was further examined using the value of information technique to quantify the expected value of perfect information (EVPI). The EVPI denotes a theoretical monetary value from future research that would remove all measured uncertainty included in the analysis (e.g. parameter uncertainty around transition probability, cost, and utility weights)²². The EVPI per person is calculated as the difference between the net monetary benefit (NMB, which represents the value of an intervention in monetary terms with a positive value indicating the intervention being cost-effective) of the proposed intervention across all iterations (i.e. all sampled iterations from PSA) and the NMB of

each individual iteration (i.e. one sampled iteration). For example, if 5,000 iterations (i.e. 5,000 sampled estimates per parameter from a single distribution) are run for the PSA and the NMB from one single iteration is the same as the overall average NMB (i.e. mean of all iterations), its EVPI value is zero. However, when these two NMBs are not identical, there is some value to eliminating the uncertainties being simulated (i.e. the difference between the iteration NMB and the mean NMB). The total EVPI is then estimated by multiplying the per-person EVPI by the estimated number of incident NVAF hospital admissions (i.e. 35,000 in Australia per annum^{3,23}) and the useful life of the new technology (in this case, the assumed minimum number of years the NVAF disease management program is likely to be standard practice, 4 years) with the value that accrues in future years discounted at 5%²¹.

Results

Transition probabilities and costs

The transition probability over the trial duration was directly calculated from the corresponding Kaplan-Meier curve (Supplementary Figures S1–S3). As to the long-term extrapolation, except for transition probability ii (where the Gompertz distribution was selected), the exponential distribution was chosen to extrapolate the long-term transition probabilities. Details on the parametric survival analysis and model selection for extrapolation are provided in Tables 2 and 3 and Supplementary Figures S4–S7. Intervention membership-specific transition probabilities were employed regardless of significance in between-group differences. The transition probabilities for the trial duration are detailed in Supplementary Table S1.

Cost-utility and cost-effectiveness analysis

The base case result showed that the SAFETY program was associated with both higher costs (\$16,520) and greater benefits (0.39 QALY and 0.62 LY gains, respectively), compared to the standard care group. The total cost of care for patients with NVAF was \$94,953 in the SAFETY program vs \$78,433 in standard care groups, which included total cost of hospitalizations (\$56,377 vs \$44,506), medications (\$25,084 vs

\$22,402), and outpatient care (\$12,904 vs \$11,524). With regard to the outcome measure, subjects from the SAFETY program arm achieved both greater QALY (3.99 vs 3.60) and LY (5.86 vs 5.24) gains. However, due to the marginally longer quality-adjusted survival (i.e. 0.63 LY \approx 7.6 months), patients assigned to the SAFETY program are likely to have more hospitalizations (\approx 3 hospitalizations). Finally, the ICUR and ICER are \$42,513/QALY and \$26,356/LY, respectively,

which suggests the SAFETY program is cost-effective for patients with NVAF from an Australian healthcare perspective over a life-time horizon (Table 4).

Sensitivity analysis

The DSA showed that the ICUR was sensitive to the cost of hospitalization due to average LoS, time horizon, cost of medication, and outpatient care. Utility of NVAF, utility decrement of hospitalization, and discount rate also contributed to the variation in ICUR to a lesser extent (Figure 2). The DSA for the effectiveness outcome (i.e. LY) suggested that the ICER was most sensitive to the cost of hospitalization due to average LoS and the time horizon (Supplementary Figure S8).

Generally, the results from the PSA were comparable to the base case analysis (Table 4). The incremental cost-effectiveness plane (Figure 3) showed that the SAFETY program has a probability of 70.4% of being cost-effective compared to the standard care at a WTP/QALY threshold of \$50,000. The cost-effective acceptability curve (Figure 4) suggested that if the WTP/QALY threshold is greater than \$75,000 the intervention has a high likelihood (>90.7%) of being a cost-effective intervention for patients with NVAF.

Value of perfect information

By incorporating all parameter uncertainty in terms of transition probabilities, costs and utility weights, the total value of perfect information for the SAFETY program amounted to \$217 million and, in contrast, the NMB was \$14 billion over the same period. Where the cost of further research is likely to be less than \$217 million, it is suggestive that further research is warranted. However, given the positive and large NMB (including the opportunity cost associated with delaying implementation of a service that provides patient survival gain), implementation with further evidence collection is the recommended strategy²⁴.

Discussion

The results from this modelled economic evaluation show that the SAFETY program has a high probability (>70.4%) of being cost-effective in patients with NVAF from the Australian healthcare system perspective. Its implementation

Table 2. Results of model fitness for the parametric survival analyses.

Distribution	AIC	BIC
No event to death		
Loglogistic	135.82	146.78
Weibull	134.97	145.93
Lognormal	140.38	151.34
Gompertz	131.71	142.67
Exponential	133.32	140.62
Hosp1 to death		
Loglogistic	74.04	84.13
Weibull	74.16	84.25
Lognormal	73.54	83.63
Gompertz	73.25	83.34
Exponential	72.28	79.00
Hosp2 to death		
Loglogistic	58.58	68.04
Weibull	58.78	68.24
Lognormal	58.35	67.81
Gompertz	57.82	67.28
Exponential	57.78	64.09
Hosp3 to death		
Loglogistic	120.31	129.59
Weibull	120.41	129.69
Lognormal	120.26	129.54
Gompertz	120.32	129.60
Exponential	118.79	124.98
No event to Hosp1		
Loglogistic	1,048.45	1,066.71
Weibull	1,023.78	1,042.05
Lognormal	1,040.11	1,058.37
Gompertz	1,040.19	1,058.45
Exponential	1,050.07	1,064.68
Hosp1 to Hosp2		
Loglogistic	372.52	389.33
Weibull	341.97	358.67
Lognormal	353.54	370.35
Gompertz	352.84	369.65
Exponential	356.85	370.30
Hosp2 to Hosp3		
Loglogistic	84.99	100.76
Weibull	56.51	72.27
Lognormal	65.12	80.89
Gompertz	57.61	73.38
Exponential	55.85	68.46

Abbreviations. Hosp, hospitalization; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 3. Parameters for the parametric survival models applied for the long-term extrapolation.

	Parametric survival distribution	Parameters	
		Mean	SD
No event to death	Exponential	lambda -8.255915	0.3333
First hospitalization to death	Exponential	lambda -8.058327	0.4472
Second hospitalization to death	Exponential	lambda -7.77073	0.4472
Third hospitalization to death	Exponential	lambda -8.257998	0.3015
No event to first hospitalization	Weibull	Cons -0.2410344	0.0480
		p 0.7858146	0.0377
First hospitalization to second hospitalization	Weibull	Cons -2.844625	0.7110
		p 0.7024144	0.0692
Second hospitalization to third hospitalization	Exponential	lambda -4.218297	0.5705

*Lambda is the exponential form of the value presented here, for example, lambda = exp(-8.826905). For Weibull distribution, p is the shape parameter; exp(cons) is the scale parameter. Abbreviation. SD, standard deviation.

Table 4. Results of base case and probabilistic sensitivity analyses.

	Costs	QALYs	ICUR	LYs	ICER	No. hospitalizations
Base case results						
SAFETY program	\$94,953	3.99		5.86		14.85
Standard of care	\$78,433	3.60	\$42,513	5.24	\$26,356	11.65
PSA						
SAFETY program	\$94,697 (72,074–12,1012)	3.96 (1.19–5.57)		5.87 (5.51–6.30)		14.88 (13.90–16.03)
Standard of care	\$78,580 (60,302–99,249)	3.58 (1.09–4.99)	\$42,791	5.24 (4.97–5.57)	\$25,594	11.67 (10.92–12.54)

Abbreviation. QALYs, quality-adjusted life years; ICUR, incremental cost utility ratio; ICER, incremental cost effectiveness ratio.

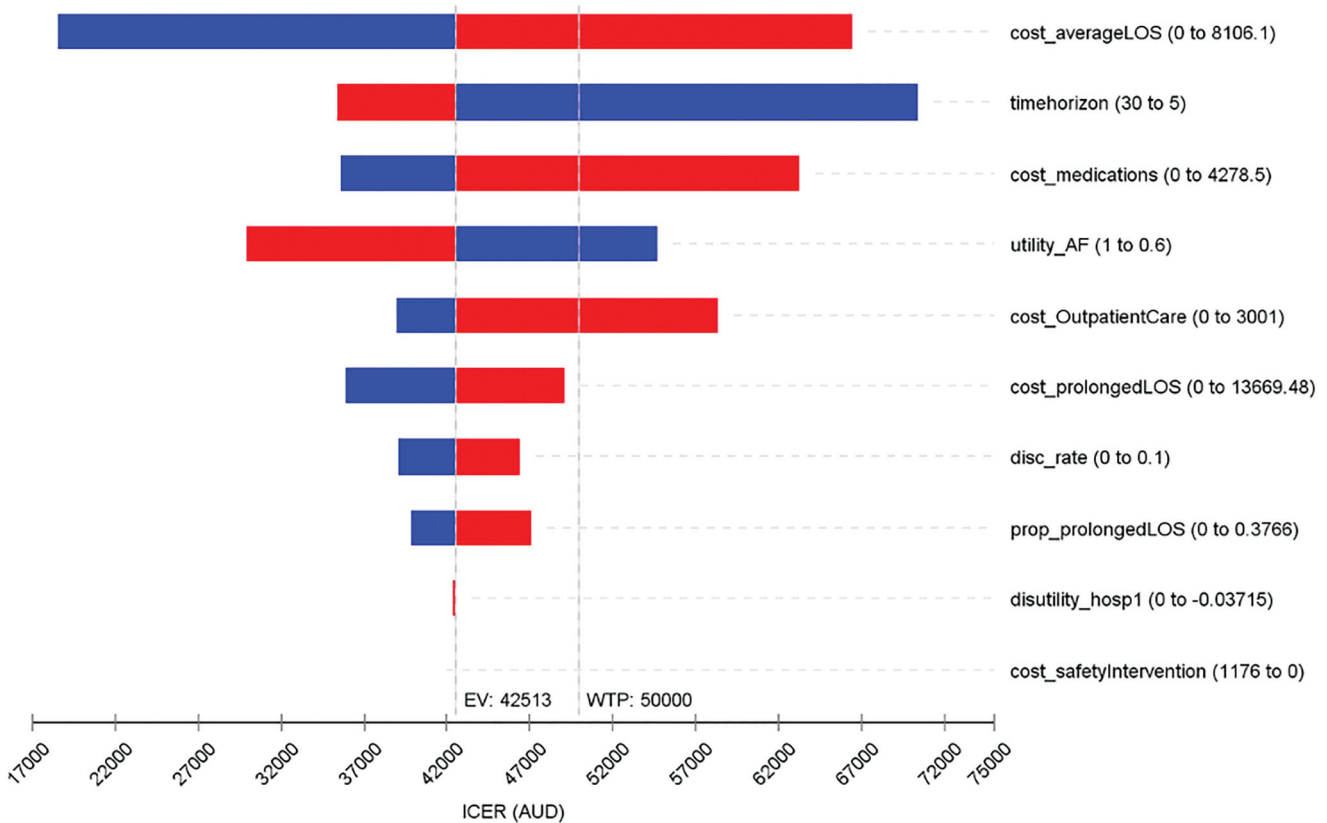


Figure 2. Tornado diagram for a series of one-way deterministic sensitivity analysis (QALY as the outcome measure).

is associated with both higher cost and greater benefits. Due to the increased life expectancy, which may be attributed to better management of NVAf via improved prescription of evidence-based treatment and compliance to the treatment plan (similarly to a disease management program that benefited patients with HF²⁵) patients who received the SAFETY program are likely to incur greater costs in terms of hospitalization, medication, and outpatient care. The total estimated NMB is \$14 billion through monetizing the increased health benefits (i.e. QALY), which shows the significant potential gains for society via implementation of this health service in Australia. Meanwhile, the estimated value of perfect information is \$217 million, which indicates the potential gain from further research to reduce the uncertainty in the current results. Although there is value in undertaking further research to eliminate this uncertainty, delaying access to the favorable intervention might also undermine the health benefits of potential patients. In this regard, even though the uncertainty of the estimates is not negligible and warrants

future research, the opportunity cost of delaying or, indeed, not actioning these measures (i.e. loss of extended survival) could justify their immediate implementation.

For a modelled economic analysis, an intervention’s effect and the extrapolation of that effect beyond the trial duration (which underpins the transition probability across modelled health states) is a key determinant of the modelled outcome. Conventionally, the transition probability is derived from the aggregated outcome of the trial and then extrapolated or assumed to be constant beyond the trial duration¹⁹. The transition probabilities among health states presented in this study were based on the individual patient-level information and made the maximum use of trial data. The unobserved and unknown covariance between variables are inherently captured in such data; thus, the derived transition probability has taken competing risks into consideration (i.e. the patient faces the risk of rehospitalizations and death simultaneously). In addition, patients can have a time-varying mortality after each hospitalization event. For example, if the patient

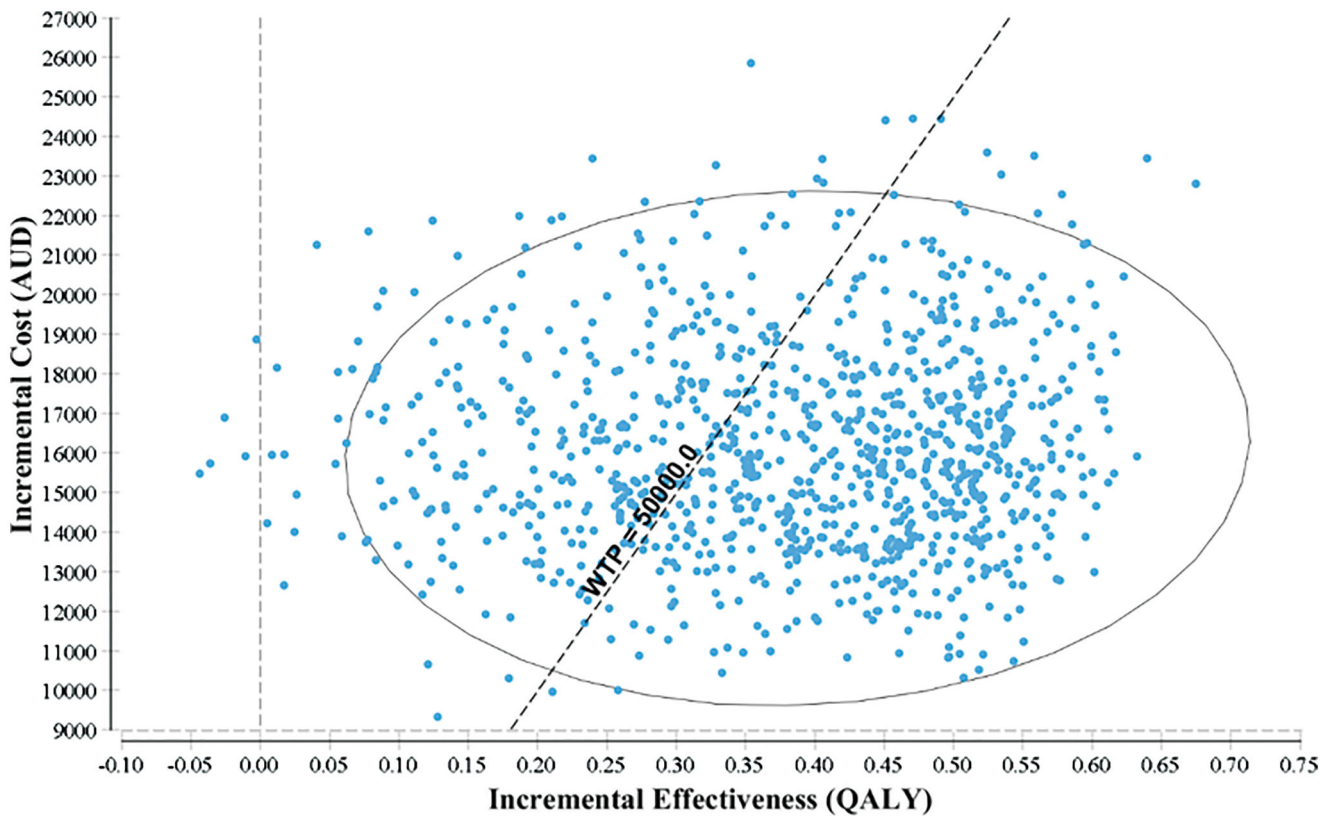


Figure 3. Incremental cost-effectiveness plane for QALY as the outcome measure.

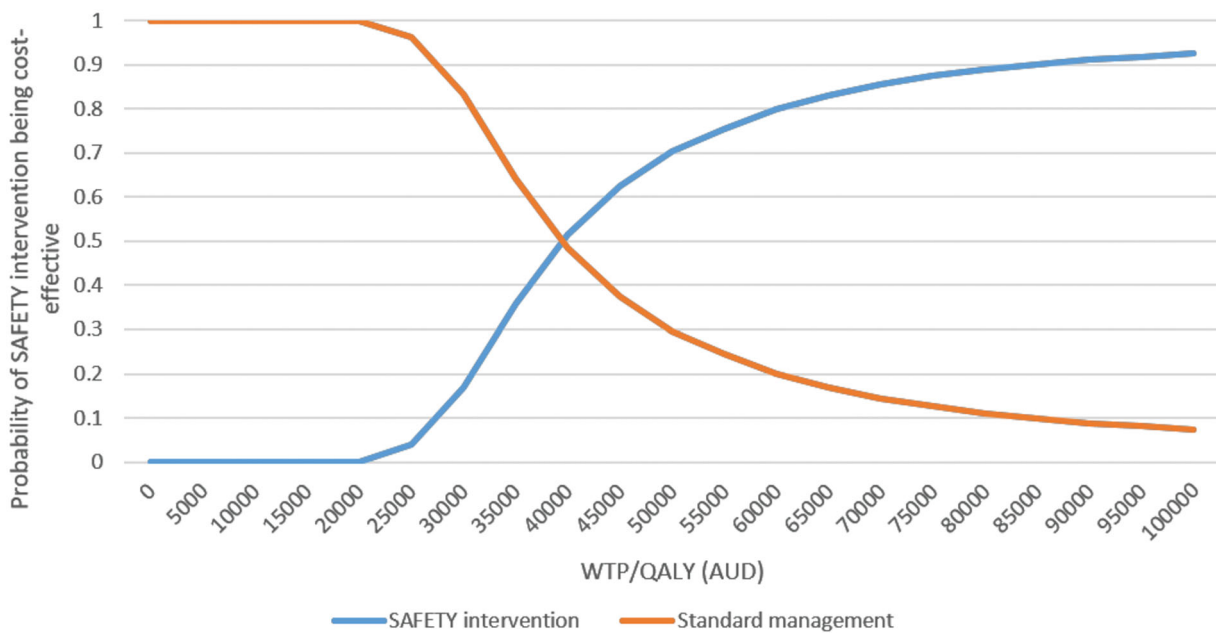


Figure 4. Cost-effectiveness acceptability curve (QALY as the outcome measure). Abbreviations. AUD, Australian dollar; QALY, quality adjusted life year; WTP, willingness to pay.

remains hospitalization-free, the mortality of that health state should vary with time (decreasing with time initially and then eventually increasing with time and age). Use of the trial-based individual patient-level data confers the advantage of taking this into account. For the first 900 days, all the transition probabilities were derived from the trial by counting the number of patients that had transitted to a certain

health status at various time points. Survival beyond those 900 days was estimated with the parametric survival analysis method. Likewise, the model parameters for cost and utility weights were also generated from the SAFETY trial data. This achieved the best outcome in terms of internal validity.

Given the ageing population worldwide, the prevalence of NVAF is expected to escalate over time. Multidisciplinary

management programs that promote the prescription of and adherence to evidence-based treatment are needed, as the management of NVAF is complex and multilayered²⁶. Whilst the SAFETY program was only delivered after the index hospitalization, the intervention's effect was measured at a minimum follow-up time of 24 months. If such an intervention is implemented in the real world, it is highly likely that the patients discharged from another hospitalization will receive the SAFETY program again, which, in theory, could further improve the cost-effectiveness of this intervention. The main benefit from the SAFETY program is the extended survival but not avoided hospitalizations, and such a trend was observed during the trial period (supplementary figures A1 and A2 of Stewart et al.¹²) An interesting finding from the DSA is that the more the cost of prolonged hospitalization decreased, the higher the resultant ICUR would be. This is because the SAFETY program was associated with a lower probability of extended hospital stay (see table 1 of Stewart et al.¹²) Medicare Australia has dedicated items (item numbers 721 and 723) for chronic disease management to enable a GP to plan and coordinate multidisciplinary, team-based healthcare. However, this is not specifically designed for the management of patients with atrial fibrillation and there are still gaps in the care provision to improve the outcome of people with NVAF.

We believe this is the first modelled economic evaluation assessing the long-term cost-effectiveness of a multidisciplinary management program for patients with NVAF. An Australian study reported cost saving of weight and risk-factor management programs in patients with NVAF where the focus was not to improve adherence to NVAF-related treatment²⁷. In contrast, economic evaluations of services for patients with HF are plentiful. These services include remote monitoring programs involving a HF nurse, HF nurse-led clinics, and HF disease management programs. In terms of the cost-effectiveness of these services, Gohler et al.²⁸ found that HF disease management programs increased quality-adjusted life expectancy by an average of 0.19 years and increased the lifetime costs by €1,700, with a corresponding ICER of €8,900/LY. Another study reported that HF programs extended the average life expectancy by 0.55 years with an additional cost of US\$5,300 per patient (ICER of US\$9,700/LY) and the PSA calculated the mean ICER as US\$12,882/LY²⁹. The service components incorporated into these programs targeted for HF and NVAF are highly similar. For example, they unanimously included promotion of pharmacological treatment as per guidelines and non-pharmacological management, provision of post-discharge care, prescription of repeat examinations, and review management plans⁵. Although these results are not directly comparable (since the applied populations are different), they indeed suggest that disease management programs could be a cost-effective approach to patients with chronic heart conditions and ongoing care needs.

There are other integrated care models for NVAF like the Atrial fibrillation Better Care (ABC) pathway program that included stroke avoidance, symptom management, and cardiovascular and other comorbidities management^{30–33}. On the other hand, the SAFETY program which aimed to optimize the pharmacological treatment and management post-hospital

discharge with a transitional care focus differs to the ABC pathway that provides an integrated care model for ongoing management. However, these two care models can potentially be synchronized to provide continuity in the care of patients with NVAF post-discharge and for ongoing management.

This study is not without limitations. First, the trial only followed patients for a median of 905 days (interquartile range = 773–1050). Extrapolation is necessary for post-intervention survival for different health states. However, the recommended approaches were adopted to undertake this analysis and the comparable results between the modelled and observed overall survival can ease this concern to some extent. Second, the utility weight of NVAF was derived from the SAFETY trial and may not be the true utility weight due to an insufficient sample size. Sensitivity analysis was performed to examine this uncertainty. Third, perhaps most importantly, the transition probability for the fourth and subsequent rehospitalization was not estimated and was assumed to be the same for the remaining time horizon. This is due to the insufficient number of patients experiencing more than four hospitalizations during the observation period, which did not permit a reliable estimation of these transitions. However, since the non-group-specific transition probabilities were applied beyond the fourth rehospitalization, this is considered conservative and not to favor the SAFETY program. Last, the almost-3-year trial did find a trend in survival gain between SAFETY and standard care; the longer-term modelled results projected that patients who received the SAFETY program were likely to have better survival than those managed by the standard care. However, the projected survival benefit warrants confirmation via longer-term study. Given the clinical need for better management of patients with AF, the SAFETY program can be implemented in real-world practice, but the key area of uncertainty (i.e. what is identified from sensitivity analyses) requires continuous monitoring and evaluation.

Conclusions

The SAFETY program has a high probability of being a cost-effective program to manage patients with NVAF in the Australian healthcare system. Although it is associated with uncertainty that further research could potentially eliminate, the current clinical needs warrant its implementation with further evidence collected, particularly as it has the potential to extend a patients days alive and out of hospital.

Transparency

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Declaration of financial/other interests

All authors confirm that there is nothing to declare.

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