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ORIGINAL ARTICLE

Cost-Effectiveness of Ivabradine in the Treatment of Chronic Heart Failure

Michael A. Adena, PhD [a*], Gary Hamann, BPharm [b], Andrew P. Sindone, BMed, MD [c]

[a]Datalytics Pty Ltd, Kingston, ACT, Australia
[b]Servier Laboratories (Aust) Pty Ltd, Melbourne, Vic, Australia
[c]Director Heart Failure Unit and Department of Cardiac Rehabilitation, Concord Hospital, Sydney, NSW, Australia

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Background In the Systolic Heart failure treatment with the I_f inhibitor Trial (SHIFT) randomised placebo-controlled trial, ivabradine was shown to reduce hospital admissions for worsening heart failure (HF) and deaths due to HF in patients with symptomatic systolic HF and an elevated resting heart rate (HR). This analysis evaluates the cost effectiveness of adding ivabradine to optimal standard HF treatment in patients with a HR $\geq$ 77 bpm.

Methods A Markov model was developed to assess the impact of ivabradine on mean survival and quality of life over a patient's lifetime (10 years). The hospitalisation and death rates were calculated using patient-level data from SHIFT. The reduction in quality of life due to HF hospitalisations was estimated directly from EQ-5D data collected in SHIFT. Australian costs were applied to the resource use from SHIFT.

Results The modelled mean increase in survival with ivabradine was 0.115 years. The mean increase in quality-adjusted survival was 0.108 years. The average cost of ivabradine was A$2,957 and the cost savings associated with a reduction in HF hospitalisations was A$1,344. The cost per quality adjusted life year gained (QALYG) was A$14,905. The conservative approach to the modelled evaluation, as well as results of the sensitivity analysis, demonstrates that ivabradine is likely to be cost-effective in this indication.

Conclusions The conservative approach to the modelled evaluation, as well as results of the sensitivity analysis, demonstrates that ivabradine is a cost-effective treatment in the Australian setting for HF patients with a HR $\geq$ 77 bpm on optimal standard therapy with a cost per QALYG similar or lower than that for other publicly funded treatments.

Keywords Ivabradine • Heart failure • Cost effectiveness • Economic evaluation • Australia • Quality-Adjusted Life Years

Introduction

Chronic heart failure (CHF) is a disabling and often fatal condition. Approximately 440,000 Australians have CHF and 30,000 new cases are diagnosed each year [1,2]. CHF occurs in 1.5% to 2.0% of Australians, and its incidence and prevalence rise markedly with age [3]. The point prevalence of CHF is approximately 1% in people between the ages of 50 and 59 years, 10% in people aged 65 to 84 years, and over 50% in people aged 85 years and older.

Regardless of patients' clinical status, an estimated one-third of CHF patients are hospitalised each year, adding a significant cost to the health care system [3]. Elevated heart rate (HR) is an important risk factor for mortality and

*Corresponding author at: Datalytics Pty Ltd, 19/12 Trevillian Quay, Kingston, ACT 2604, Australia. Tel.: +61 2 6113 1503., Email: michael.adena@datalytics.com.au

morbidity amongst CHF patients and HR reduction is associated with improved outcomes [4].

Chronic heart failure treatment recommendations among various international guidelines (the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, the National Institute for Health and Clinical Excellence, and the European Society of Cardiology) are broadly similar [3,5,6]. The Guidelines recommend that all patients with CHF should be treated with an angiotensin–converting enzyme inhibitor or angiotensin receptor blocker and a beta blocker as these have been demonstrated to reduce mortality. However, as HR remains increased in many patients despite treatment with beta blockers, new therapeutic strategies to reduce HR are needed [4].

Ivabradine is the first-in-class selective sinus node I_f channel inhibitor, defined as a cardiotonic agent that lowers HR by selective inhibition of the cardiac pacemaker I_f current that controls the sinus node and regulates HR [7]. Ivabradine is guideline-recommended for CHF [3]. The approved use of ivabradine in Australia [8] is for the treatment of symptomatic CHF which is New York Heart Association (NYHA) class II or III with documented left ventricular ejection fraction (LVEF) $\leq$ 35% in adult patients in sinus rhythm and with HR $\geq$ 77 beats per minute (bpm) in combination with optimal standard CHF treatment. Regulatory approval was based on the Systolic Heart failure treatment with the I_f inhibitor Trial (SHIFT), which included 6,505 adult patients with moderate to severe symptoms of CHF and a baseline resting HR $\geq$ 70 bpm [4]. For the primary composite endpoint of cardiovascular (CV) death or hospitalisation for worsening HF, baseline HR was found to be a treatment effect modifier with ivabradine being significantly more effective in patients with a HR $\geq$ 77 bpm compared with <77 bpm (hazard ratios of 0.75 and 0.93, respectively; p for interaction = 0.029) [4]. In a pre-specified high HR subgroup (baseline HR $\geq$ 77 bpm; n = 3357), treatment with ivabradine reduced the rates of death from HF (0.022/year, as compared with 0.036/year in the placebo group; hazard ratio, 0.61; p = 0.0017), death from CV causes (0.085/year vs 0.105/year; hazard ratio, 0.81; p = 0.0137), death from any cause (0.095/year vs 0.117/year; hazard ratio, 0.81; p = 0.0074) and hospitalisations due to worsening HF (0.110/year vs 0.161/year; hazard ratio, 0.69; p < 0.0001) [9].

The cost-effectiveness of ivabradine in patients with a HR $\geq$ 75 bpm has been assessed for the United Kingdom (UK) health care system [10–12], and the UK economic model has been adapted to assess cost-effectiveness for Greece and Italy [13,14]. This study describes a new economic model that incorporates more conservative modelling assumptions than the UK model. The assumptions include using the intention to treat (ITT) estimate of efficacy instead of that in the high HR subgroup and assuming that efficacy waned after the end of follow-up of SHIFT. This approach was necessary to evaluate cost-effectiveness from the Australian health care perspective in a way that was consistent with the guidelines for preparing Pharmaceutical Benefits Advisory Committee (PBAC) submissions [15].

Methods

Overview

Cost-effectiveness of adding ivabradine to standard therapy for CHF in patients with a baseline HR $\geq$ 77 bpm was assessed in a trial-based evaluation and a modelled evaluation. The trial-based evaluation compared the resource use and outcomes observed between the treatment groups in SHIFT over its 3-year follow-up period and are summarised as the incremental cost per life year gained (LYG). The modelled evaluation extrapolated the resource use and outcomes beyond the SHIFT follow-up period to estimate the cost-effectiveness of ivabradine over the patients' lifetimes. The results for the modelled evaluation are presented as the incremental cost per LYG and the incremental cost per quality-adjusted life-year gained (QALYG). Consistent with recommendations in the PBAC guidelines for economic evaluations, costs and benefits were discounted annually at 5% [15].

Model Structure

Previous economic models assessing treatments for HF have usually included health states based on hospitalisations, New York Heart Association (NYHA) classification and/or death [11,16,17]. The health states for this model are based on HF hospitalisations and death, consistent with the primary endpoint in SHIFT. There are five mutually exclusive health states: (1) ''Stable HF''; (2) ''HF Hosp''; (3) ''HF Death''; (4) ''Non-HF CV Death'' (cardiovascular [CV] death other than HF); and (5) ''Non-CV Death'' (Figure 1). All patients start in the ''Stable HF'' state. Patients who have a hospitalisation due to worsening HF move to the ''HF Hosp'' state and remain in this health state until death (i.e. they cannot move back to the ''Stable HF'' state). In the ''HF Hosp'' state, patients may experience additional HF hospitalisations. Patients in the two alive health states (''Stable HF'' and ''HF Hosp'') may die due to HF, a non-HF CV cause or a non-CV cause. In SHIFT, an endpoint validation committee was masked to study treatment adjudicated HF hospitalisations and cause of death (HF, CV or non-CV) using pre-specified definitions. Cause of death was disaggregated in the model to enable the specific effect of ivabradine on HF deaths to be modelled. Patients could move between the health states once every 6 months for 10 years. The cycle length of 6 months was chosen based on the frequency of hospitalisation and death events observed in SHIFT. Life-table half-cycle correction was applied to the cost of ivabradine, LYs and the non-hospitalisation component of QALYs. Hospitalisations are counts of events and therefore were not half-cycle corrected. The time horizon of 10 years is consistent with the life expectancy for patients with HF (in the model, approximately 20% are alive at 10 years).

Model Parameters and Inputs

Transition Rates

Survival analysis methods were used to estimate the rate at which patients in the high HR subgroup of SHIFT moved

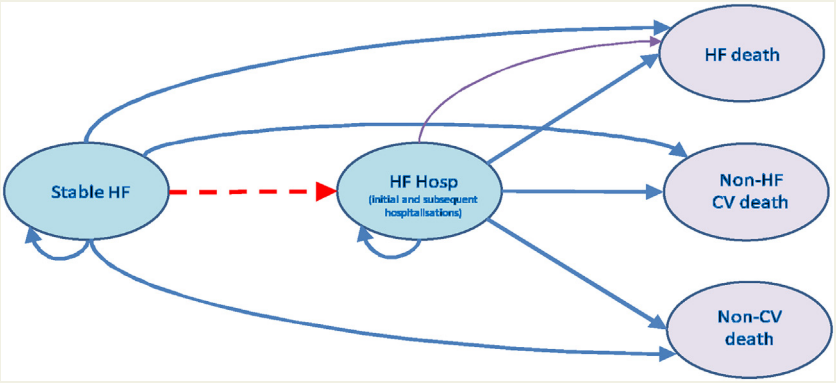

Figure 1 Markov model diagram.
Notes: Possible transitions shown with arrows. The transition that differs between treatments (ivabradine or placebo) is shown with a red dashed arrow.
Transitions that are the same for both treatments are shown with solid blue arrows.
The purple transition from the ''HF Hosp'' to the ''HF death'' state denotes when patients enter this state a proportion die within 1 week and hence transition immediately to the ''HF death'' state. This proportion is the same for both treatment groups.
Transitions are time-dependent.

between health states or had subsequent hospitalisations due to worsening HF (Table 1).

Death Rates

Non-CV and non-HF CV death rates were approximately constant over the 3-year follow-up period of SHIFT and were similar for patients in the two treatment groups. Accordingly, these death rates were modelled as being the same for all patients, regardless of treatment group. In the general Australian population the annual age-related increase in the death rate is 10% [18] and the base case assumed a 10% annual increase in non-CV and non-HF CV death rates over the 10-year time horizon of the model.

The rate of HF deaths was substantially higher for patients in the ''HF Hosp'' state compared with the ''Stable HF'' state. This reflects that most patients who die of HF die after hospitalisation due to worsening HF. Regardless of treatment group, the rate for patients in the ''Stable HF'' health state in SHIFT was 0.40 deaths per 100 person-years, and this was increased in the model by 10% annually (as described for the non-HF CV and non-CV death rates). In SHIFT, the rate of HF death for patients in the ''HF Hosp'' state varied with time since hospitalisation, but not treatment group. In the two treatment arms combined, 5.4% of patients died of HF within a week of the HF admission (280 deaths per 100 person-years). The rate declined to 23.2 deaths per 100 person-years during the following 6 months, after which the rate approximately halved to 13.5 deaths per 100 person-years. In the model, the rate of HF deaths from the ''HF Hosp'' health state was not increased over time because this rate was high in SHIFT compared with the death rate for the general Australian population (and may not vary with age); this ensures that the impact of ivabradine on reducing HF deaths is not overstated.

HF Hospitalisation Rates

The HF hospitalisation rate (transition from ''Stable HF'' to ''HF Hosp'') in SHIFT was significantly lower for patients randomised to ivabradine compared with placebo ($p < 0.0001$) [4]. As the efficacy of ivabradine in reducing HF hospitalisations in the high HR versus low HR subgroup was not statistically significantly different (test for interaction, $p = 0.15$), the efficacy estimates for the ITT population were used for the base case (0.70 and 0.78, Table 1).

The benefit of ivabradine in reducing HF hospitalisations was assumed to diminish over time. Specifically, the efficacy difference between ivabradine and placebo observed in SHIFT was assumed for the first 3 years (the follow-up period for SHIFT) and reduced linearly over the following 3 years so that there was no difference from year 6 onwards.

The rate of a subsequent hospitalisation for worsening HF was approximately constant over time and similar for both treatment groups.

Resource Use and Costs

Resource use associated with ivabradine and HF hospitalisations was costed in the trial-based and modelled evaluations (Table 2). Ivabradine was costed based on the steady state doses received in SHIFT. In the modelled evaluation, patients are treated with ivabradine on average for 90% of the time while they are alive. Each hospital admission for worsening HF was costed using the relevant Australian public hospital cost weights [19]. Ivabradine would be added to standard therapy, which would remain unchanged, and resource use associated with standard therapy has not been explicitly modelled.

Quality of Life/Utilities

In the modelled evaluation LYs were transformed to QALYs by weighting the time spent in each alive health state by an appropriate utility value, for which 1 corresponds to perfect

Table 1 Transition rates for the model.

Transition	Estimate from SHIFT*
Death rates	
Stable HF or HF Hosp → Non-CV Death	1.14 events/100 person-years
Stable HF or HF Hosp → Non-HF CV Death	6.58 events/100 person-years
Stable HF → HF Death	0.40 events/100 person-years
HF Hosp → HF Deaths	
First week	5.4% of patients
0–6 months	23.2 events/100 person-years
>6 months	13.5 events/100 person-years
Annual increase in death rates (except HF Hosp → HF Deaths)	10%
Hospitalisation rates	
Stable HF → HF Hosp, placebo	
0–6 months	24.1 events/100 person-years
>6 months	12.7 events/100 person-years
Stable HF → HF Hosp, ivabradine, relative rate vs. placebo	
0–6 months	0.70
6–36 months	0.78
Period over which relative rate is increased to 1	Between 3 and 6 years
HF Hosp, readmission for worsening HF	86 events/100 person-years

Abbreviations: CV, cardiovascular; HF, heart failure; Hosp, hospitalisation.
*Transition rates have been estimated in the High HR subgroup of SHIFT, except for the relative rate for "Stable HF" → "HF Hosp" which has been estimated in the ITT population.

Table 2 Cost and utility inputs.

Variable	Input	Source
Costs		
Ivabradine, annual cost	A$704	Pack price provided by Servier; Steady-state doses in SHIFT ITT population
Ivabradine, proportion of time on treatment	0.9	SHIFT ITT population
HF hospital admission, per admission	A$6,699	Public Sector, Round 13 (2008–2009) cost for AR-DRG F62A (HF and shock with CCC) and F62B (HF and shock without CCC), weighted by number of separations
Utility values		EQ-5D™ data for SHIFT ITT population
Stable HF	0.75	
HF Hosp	0.65	
Disutility for hospitalisation	0.016	

Abbreviations: AR-DRG, Australian refined diagnosis-related groups; CCC, catastrophic complications or comorbidities; CV, cardiovascular; HF, heart failure; Hosp, hospitalisation; ITT, intention to treat.

health and 0 corresponds to death. Quality of life was measured in SHIFT using the EQ-5D instrument, from which utility values were inferred using the standard Dolan UK algorithm [20]. The utility for the "Stable HF" health state (0.75) was the average utility for patients before their first hospitalisation for worsening HF. A transient reduction in patient quality of life (QoL) was observed in the period between 28 days before and 28 days after an HF hospital admission. Using a regression model, the overall reduction in QoL (or the disutility) for each hospital admission was estimated to be 0.016 life-years. The utility for the "HF Hosp" state (0.65) was the average utility between 28 and 168 days after a HF hospitalisation. Mean utility values were estimated in the ITT population for both treatment groups combined because the impact of an HF hospitalisation on QoL should not depend on baseline HR or prior treatment.

Results

Base Case

Trial Based Evaluation

At the end of the SHIFT follow-up period, there were an additional 3.4% of patients alive with ivabradine compared with placebo. The deaths avoided were associated with a mean increase in survival (or life years gained) of 0.0841 years. The life-years gained within the trial period undervalues the benefit of avoiding deaths because it excludes the value of survival after the end of the trial. The mean duration of ivabradine treatment was 1.63 years, for which the associated cost was A$1,148. Ivabradine treatment resulted in 0.13 fewer HF hospital admissions per patient for which the cost saving was A$872. Thus, the additional cost with ivabradine treatment was A$276. The cost per death avoided was A$8118 and the cost per LYG was A$3,282 (Table 3).

Modelled Evaluation

With ivabradine treatment fewer patients transition to the ''HF Hosp'' state, and hence a higher proportion remained in the ''Stable HF'' state where the risk of HF death is lower. Thus patients treated with ivabradine have fewer HF hospitalisations and fewer HF deaths than patients on placebo. Over the 10-year time horizon, the mean increase in survival with ivabradine was 0.115 years. Applying quality (utility) weights to the life years gained resulted in 0.108 QALYG. The average cost of ivabradine was A$2,957 and the cost savings associated with a reduction in HF hospitalisations was A$1,344. Thus, the additional cost with ivabradine treatment was A$1,613, and the cost per LYG and cost per QALYG was A$14,087 and A$14,905, respectively (Table 4).

Sensitivity Analysis

For the modelled evaluation the impact of varying each of the individual parameters was tested in sensitivity analyses. The results for the 15 parameters with the greatest impact on the cost per QALYG are summarised in Figure 2. The cost per QALYG was less than A$32,000 for all scenarios. The results are most sensitive to changes in the rates for the first HF hospitalisation as this is the only transition for which the rates differ between the two treatment groups.

Halving the rate of re-admission for worsening HF resulted in a cost per QALYG of A$19,539. Similarly, halving the rate of HF death following a first HF hospitalisation resulted in a cost per QALYG of A$18,389. These parameters quantify the adverse sequelae of moving to the ''HF Hosp'' state. The only other parameter with a substantial impact on the cost per QALYG was the utility for the ''Stable HF'' state. When this was decreased from 0.75 to 0.65, the same as for the ''HF Hosp'' state, the cost per QALYG increased to A$20,776. Extreme variation in the non-HF CV and non-CV death rates, and their age-related increases, affected the cost per QALYG by less than 15%.

Scenario analyses were undertaken to assess specific model assumptions. For the base case, ITT efficacy results were used, and efficacy was assumed to wane after 3 years. Use of efficacy for the high HR subgroup (0.63 in the first 6 months and 0.74 thereafter) reduced the cost per QALYG to A$10,187. When efficacy was stopped at 3 years, the cost per QALYG was A$17,862 and when efficacy did not wane at all, the cost per QALYG was A$11,123.

Prior to a hospital admission for worsening HF, no utility difference was assumed for patients treated with ivabradine and placebo. However, in SHIFT, the observed utility for patients before they had a HF hospitalisation was significantly

Table 3 Base-Case Results of Trial-Based Economic Evaluation for Patients With a Baseline Heart Rate of ≥ 77 bpm (High HR subgroup).

	Ivabradine	Placebo	Difference
Ivabradine cost			
Annual cost (A)	A$704	NA	
Mean treatment duration, years (B)	1.63	NA	
Mean cost per patient for study duration (C = A × B)	A$1,148	NA	A$1,148
HF Hospitalisation costs			
Cost per hospitalisation (D)	A$6,699	A$6,699	
Mean number of hospitalisations per patient (E)	0.319	0.449	−0.130
Mean cost per patient for study duration (F = D × E)	A$2,135	A$3,007	−A$872
Total cost per patient (G = C + F)	**A$3,283**	**$3007**	**$276**
Incremental cost-effectiveness ratios			
Deaths, percentage of patients (H)	17.2%	20.6%	−3.4%
Incremental cost per death avoided (G ÷ H)			**A$8,118**
Mean survival, years (I)	2.6121	2.5280	0.0841
Incremental cost per life year gained (G ÷ I)			**A$3,282**

Abbreviations: A$, Australian dollars; bpm, beats per minute; HF, heart failure; HR, heart rate; N, number of patients; NA, not applicable.

Table 4 Base-Case ICERs Calculated by Modelled Economic Evaluation for Patients With a Baseline Heart Rate of ≥ 77 bpm (High HR subgroup).

	Ivabradine	Placebo	Difference
Cost			
Ivabradine	A$ 2,957	NA	A$ 2,957
Hospitalisation due to worsening HF	A$ 7,958	A$ 9,302	−A$ 1,344
Total	A$10,916	A$ 9,302	A$ 1613
Life years	4.668	4.553	0.115
Quality adjusted life years	3.374	3.266	0.108
Cost per life year gained			A$14,087
Cost per quality adjusted life year gained			A$14,905

Costs and outcomes discounted at 5%.

Abbreviations: A$, Australian dollars; HF, heart failure; HR, heart rate; NA, not applicable.

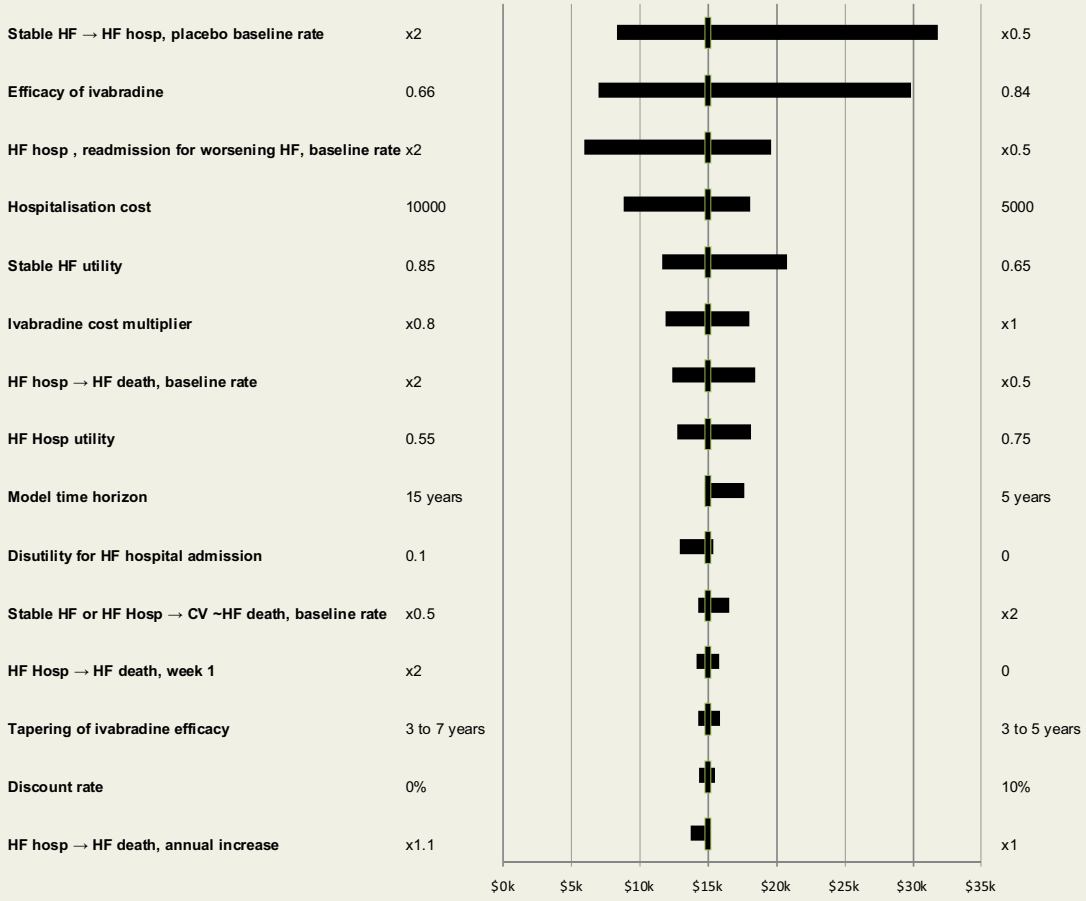

Figure 2 Results of one-way sensitivity analysis of base case scenario.

higher when treated with ivabradine instead of placebo (difference = 0.011, p = 0.024) and this change to the model resulted in the cost per QALYG being A$10,922.

When event rates were estimated in the ITT population of SHIFT (baseline HR ≥ 70 bpm), the cost per LYG was A $19,105 and the cost per QALYG was A$19,764 (Table 5). Ivabradine is more cost-effective in the high HR subgroup because of the higher event rates, and hence larger reductions in the absolute number of HF hospitalisations and HF deaths with ivabradine treatment.

Table 5 Results of Modelled Economic Evaluation for ITT Population (Baseline Heart Rate of ≥70 bpm).

	Ivabradine	Placebo	Difference
Cost			
Ivabradine	A$ 3,197	NA	A$ 3,197
Hospitalisation due to worsening HF	A$ 7,422	A$ 8,700	−A$ 1,278
Total	A$10,619	A$ 8,700	A$ 1919
Life Years	5.046	4.945	0.100
Quality Adjusted Life Years	3.664	3.566	0.097
Cost per Life Year Gained			A$19,105
Cost per Quality Adjusted Life Year Gained			A$19,764

Costs and outcomes discounted at 5%.

Abbreviations: HF, heart failure; HR, heart rate; ITT, intention to treat, NA, not applicable.

Discussion

This analysis suggests that ivabradine plus standard therapy versus standard therapy is likely to be acceptably cost-effective for patients with HF in an Australian setting. The discounted incremental cost per QALYG of A$14,905 (A$14,087 per LYG) for patients with a baseline HR ≥ 77 bpm is below the threshold typically considered to provide value [21,22]. Ivabradine was recommended for public reimbursement for these patients by the PBAC at their March 2013 meeting [23]. The cost-effectiveness ratio for ivabradine is similar or lower than that for other publicly funded HF treatments in Australia (<A$15,000 per LYG for eplerenone where treatment starts within 3 to 14 days of an acute myocardial infarction [24]; A$25,362–A$45,706 per QAYLG for cardiac resynchronisation therapy (CRT) [25]; A$18,681–A$44,479 per LYG for implantable cardioverter defibrillators (ICD) [26]; A$13,786–A$34,870 per LYG for CRT with ICD (CRT-D) in patients with NYHA class III or IV HF [26]; A$27,737 per QALYG for CRT-D in patients with NYHA class II HF [27]).

The cost per LYG in the modelled evaluation is substantially higher than for the trial-based analysis (A$14,087 vs A$3282). This reflects in part the intentionally conservative assumptions implemented in the model biasing the analysis against ivabradine. Firstly, the efficacy of ivabradine as observed in the ITT population of SHIFT was used in the model for the high HR subgroup. A significant difference in efficacy was observed between the high and low HR subgroups for the primary outcome of CV death or hospitalisation for worsening HF, and use of the efficacy estimates for the high HR subgroup reduces the cost per LYG to A$9,625. Secondly, the efficacy of ivabradine is assumed to wane after 3 years. If the efficacy as observed during SHIFT was assumed to be maintained for the model duration, the cost per LYG reduces to A$10,686. Using the efficacy for the high HR subgroup and assuming it does not wane reduces the cost per LYG to A$6,593. Overall, with a longer timeframe, the cost-effectiveness of ivabradine is expected to be reduced due to the impact of competing comorbidities on the patient's life expectancy. This was incorporated into the model by increasing the non-HF death rates over time in line with those observed in the general Australian population.

Both the UK and Australian ivabradine economic models were populated using SHIFT data; however, there were differences in the model structure and assumptions, and each model used local cost data. Overall for the base case analyses, the UK model estimated larger increases in LYG and QALYG with ivabradine treatment compared with the Australian model (LYG: 0.25 vs 0.115; QALYG 0.28 vs 0.108). The larger gains with the UK model are due to less conservative assumptions regarding the efficacy of ivabradine for the trial follow-up period (use of the efficacy estimates for the subgroup of patients with a HR ≥ 75 bpm compared with the ITT efficacy estimates) and for the extrapolated period (constant efficacy compared with the efficacy waning after the third year), inclusion of an increase in QoL due to ivabradine treatment, and a lower annual discount rate for benefits (3.5% vs 5.0%).

The economic model does not allow patients who have an HF hospitalisation to return to the Stable HF health state (Figure 1). After HF hospitalisation, patients have poorer utility, a higher rate of HF hospitalisation and a higher HF death rate than before HF hospitalisation. Each of these differences contributes to the cost-effectiveness of ivabradine (see sensitivity analyses in Figure 2). A model that allows patients to return to the Stable HF health state after HF hospitalisation would estimate poorer cost-effectiveness for ivabradine than the current model.

The HF hospitalisation and death rates were sourced directly from SHIFT. Therefore, the results of the economic evaluation will be directly applicable to Australian clinical practice only if the event rates in SHIFT are similar to Australian event rates. A literature review identified five Australian studies that recruited HF patients and reported either hospitalisation or death rates. One of the identified studies, the National Benchmarking and Evidence-Based National Clinical Guidelines for Heart Failure Management Programs (BENCH) study [28], like SHIFT, recruited community patients with at least one prior HF hospitalisation. The

remaining four studies recruited patients hospitalised due to HF [29–32]. The Australian studies did not select patients on the basis of HR and therefore data from these studies have been compared with data for the ITT population in the placebo arm of SHIFT. During the 6-month follow-up period for the BENCH study, the rate of hospitalisation was slightly higher than observed over the same period in SHIFT (42–68 vs 30 per 100 person years). Conversely, the rate of a subsequent hospital admission in Stewart et al. 2012 [30] and Barker et al. 2011 [29] was marginally lower than in SHIFT (51 and 45–79 vs 84 per 100 person years). The all-cause death rate was similar in the BENCH and SHIFT studies (4–19 vs 9 per 100 person years). The all-cause death rate during the first 12 months following a HF hospitalisation was similar in SHIFT and the Australian studies (28 vs 19 [30], 33 [31] and 29 [32] per 100 person years). Overall, the hospitalisation and death rates in SHIFT were consistent with those reported for Australian HF patients. This supports the use of the event rates from SHIFT in the model.

Beta blockers, like ivabradine, reduce HR and for inclusion in SHIFT patients were required to be on optimum and stable beta blocker doses for at least 4 weeks. In SHIFT 89% of patients were treated with a beta blocker at baseline, of which 26% were treated with target doses as defined by European Society of Cardiology guidelines, and 56% were treated with at least 50% of the target doses. The proportion of patients treated with beta blockers in the identified Australian studies [28,30,31] was lower than in SHIFT although higher estimates of use in more recent cohorts suggests that use of beta blockers is increasing in Australian clinical practice. Most Australian patients using beta blockers are supplied through the Pharmaceutical Benefits Scheme. For patients who had at least six beta blocker prescriptions filled, and hence were likely to be on steady-state doses, their last prescription was at the target dose for 26% of patients and was more than 50% of the target dose for 58% (analysis of PBS data for a 10% sample of patients; data supplied by Department of Human Services and analysed by the authors). That is, the doses used by patients in Australian clinical practice are similar to those reported for SHIFT. This further supports the applicability of the results from SHIFT to Australian clinical practice.

Conclusion

Overall, for HF patients with a HR $\geq$ 77 bpm on optimal standard therapy, ivabradine is a cost-effective treatment in the Australian setting. The conservative approach to the modelled evaluation, as well as results of the sensitivity analysis, means that the true ICER is likely to be less than A$14,095/QALYG.

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