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Cost-Effectiveness of Switching Patients With Heart Failure and Reduced Ejection Fraction to Sacubitril/Valsartan: The Australian Perspective

Q2 Ken Lee Chin, PhD^{a,b}, Ella Zomer, PhD^a, Bing H. Wang, PhD^a,
Danny Liew, PhD^{a*}

^aCCRE Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Vic, Australia

^bMelbourne Medical School, The University of Melbourne, Melbourne, Vic, Australia

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Background

The cost-effectiveness, from the Australian health care perspective, of switching patients with heart failure and reduced ejection fraction (HFREF) stable on angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs) to sacubitril/valsartan is unclear. We sought to assess the cost-effectiveness of sacubitril/valsartan versus enalapril in patients with HFREF in the contemporary Australian setting.

Methods

We developed a Markov model with two health states ('Alive' and 'Dead') to assess the cost-effectiveness of sacubitril/valsartan versus enalapril in patients with HFREF. Model subjects were 63 years of age at entry and had simulated follow-up over 20 years. Transition probabilities were derived from the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) study. Costs and utility data were derived from published sources. All costs and effects were discounted at an annual rate of 5% and are presented in Australian dollars. Sensitivity analyses were undertaken to test variability in key data inputs.

Results

In the base-case analysis, sacubitril/valsartan was found to reduce non-fatal heart failure hospitalisations and cardiovascular deaths, with numbers-needed-to-treat over a 20-year period of 40 and 27, respectively. The use of sacubitril/valsartan led to an additional 6 months of life gained per patient, translating to A\$27,954 per years of life saved (YoLS) and A\$40,513 per quality-adjusted-life-years (QALY) gained. The results of the sensitivity analyses indicated that the results were robust.

Conclusions

Our analysis supports switching HFREF patients on ACE inhibitor or ARB to sacubitril/valsartan.

Keywords

Heart failure • Cost-effectiveness • Sacubitril-valsartan • Enalapril

Introduction

Q3 Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNi) which concurrently inhibits the

renin angiotensin aldosterone system and neprilysin. The clinical benefit of sacubitril/valsartan in patients with heart failure with reduced ejection fraction (HFREF) was demonstrated in the 'Prospective comparison of ARNI with ACEI to

*Corresponding author at: Centre of Cardiovascular Research & Education (CCRE) in Therapeutics, Department of Epidemiology & Preventive Medicine, Monash University/Alfred Hospital, Commercial Road, Melbourne, Vic, 3004, Australia. Tel.: +61 3 9903 0759, Fax: +61 3 9903 0556., Email: danny.liew@monash.edu

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Determine Impact on Global Mortality and morbidity in Heart Failure' (PARADIGM-HF) study. In this study, patients with left ventricular ejection fraction $\leq 40\%$ and New York Heart Association (NYHA) functional class II to IV symptoms were randomly assigned to receive either 200 mg sacubitril/valsartan twice daily or 10 mg enalapril twice daily. Background usual therapy other than with angiotensin converting enzyme (ACE) inhibitors was maintained. A total of 8,399 patients were enrolled in PARADIGM-HF, and the median duration of follow-up was 27 months. The results indicated that sacubitril/valsartan 200 mg twice daily was superior to enalapril 10 mg twice daily in reducing the composite of death from cardiovascular (CV) causes or first hospitalisation for worsening heart failure (HF) (hazard ratio [HR]: 0.80; 95% confidence interval (CI): 0.73–0.87), death from CV causes (HR: 0.80; 95% CI: 0.71–0.89), all-cause death (HR: 0.84; 95% CI: 0.76–0.93) and first hospitalisation for worsening HF (HR: 0.79; 95% CI: 0.71–0.89) [1].

The Australian government subsidised A\$8 billion of prescribed medications via the Pharmaceutical Benefits Scheme (PBS) in 2015–16, and this has grown substantially in recent years [2]. Economic evaluations to define the value of new therapeutic agents in the local context are important to ensure that government subsidy is spent only on medications that are cost-effective. A further unanswered question is whether or not HFREF patients with NYHA class II to III symptoms who are stable on angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) should be considered for switching to an ARNi in the Australian setting. In this study, we sought to determine the cost-effectiveness of sacubitril/valsartan compared with enalapril in patients with HFREF, from the perspective of the (publicly-funded) Australian health care system.

Methods

Model and Modelled Population

A decision analytic transition Markov model [3] with yearly cycles was developed to compare the health and economic effects of sacubitril/valsartan (200 mg twice daily) versus enalapril (10 mg twice daily) in patients with HFREF. Decision analytic Markov modelling is a common method used in economic evaluations of health care interventions. It informs choices in health care by estimating the long-term costs and outcomes of disease, and comparing these to costs and outcomes from scenarios in which interventions are assumed. The modelling accounts for variability and uncertainty associated with decisions [4]. The model developed for the present study is illustrated in Figure 1. The model population comprised 1,000 subjects profiled on participants in the PARADIGM-HF trial, the pivotal efficacy study for sacubitril/valsartan in patients with HREF [1]. Because other smaller trials of sacubitril/valsartan were dose-ranging studies that recruited patients with hypertension or heart failure with preserved ejection fraction, data from these studies were not

pooled for the current evaluation [5–7]. Enalapril 10 mg twice daily, which has been widely studied in previous trials and observational studies in HFREF, is commonly regarded as the reference standard, and was therefore selected as the comparator [8]. Clinical data and treatment effect sizes were also sourced from the PARADIGM-HF study. The model had two health states: 'Alive (with HFREF)' and 'Dead'. All patients entered the model in the 'Alive' health state and could progress through four possible transition states in any cycle: (i) 'No HF hospitalisation, stay alive'; (ii) 'Non-fatal hospitalisation for HF'; (iii) 'CV death'; and (iv) 'Non-CV death'. The transition state non-fatal hospitalisation for HF was defined by one or more HF hospitalisations and survival (no death) until the end of the cycle.

At baseline, subjects were assumed to be aged 63 years, as this was the mean age of PARADIGM-HF subjects at baseline in the trial. Other than sacubitril/valsartan, treatment with other pharmacological agents and devices was assumed to be similar in both groups over the model time horizon. The time horizon of the model was 20 years and the costs were calculated based on 2018 Australian dollars (A\$). A discount rate of 5% per annum was applied to all costs, years of life lived and quality-adjusted-life-years (QALY) lived, as per Australian guidelines [9]. The outcome of interest was the incremental cost-effectiveness ratio (ICER) in terms of Australian dollars per years of life saved (YoLS) and Australian dollars per QALY gained.

Transition Probabilities

Key data inputs for the model are summarised in Table 1.

Transition probabilities underpinning transitions in the first model cycle were derived by applying annualised incidence measures from the PARADIGM-HF trial [1]. In all subsequent cycles, we applied expected age-related trends to the first-cycle probabilities. These trends were extracted from life tabling of 2014 CV and non-CV mortality data provided in the Australian Institute of Health and Welfare's (AIHW) General Record of Incidence of Mortality (GRIM) [10]. Non-CV mortality was calculated as all-cause mortality minus CV mortality. Due to lack of data on the age-related trends in non-fatal hospitalisation for HF, the trend was assumed to be the same as that for CV mortality.

Costs

The costs of a HF hospitalisations (AR-DRG item code, F62B), were derived from the latest available data from Australian Refined Diagnosis Related Groups (AR-DRGs)(2014–15) [11,12]. The cost of CV death was calculated as the weighted average cost due to acute myocardial infarction (B70D) and stroke (F60B). The cost of non-CV death was assumed to be equal to the cost of CV death. The costs of a HF hospitalisations, CV deaths and non-CV deaths were A\$5,955, \$1,932 and \$1,932, respectively.

The costs of sacubitril/valsartan and enalapril were those currently met by the Australian PBS, which already funds

Figure 1 Decision analytic Markov model.

Abbreviations: CV, cardiovascular; HF, heart failure; PARADIGM-HF, Determine Impact on Global Mortality and morbidity in Heart Failure.

Table 1 Key model inputs.

Variables	Base case values		Ranges	Distribution in PSA	References
Baseline event rates, %/yr	Sacubitril/valsartan Enalapril				
HF hospitalisation	5.7%	6.9%	±10%	Triangular	[1]
CV deaths	5.9%	7.3%			
Non-CV deaths	1.6%	1.5%			
Utility weight					
Baseline utility	0.69		0.64 to 0.73	Beta	[11]
Annual background costs					
Total weighted cost for background HF treatment costs	A\$191		±50%	Lognormal	[9]
HF hospitalisation	A\$6,069				[29]
CV deaths	A\$1,969				
Non-CV deaths	A\$1,969				
Fixed costs					
Sacubitril/valsartan costs per year	A\$2,638		N/A	N/A	[30]
Enalapril costs per year	A\$354		N/A	N/A	[31]

Abbreviation: PSA, probabilistic sensitivity analyses; CV, cardiovascular; HF, heart failure.

both drugs for patients with HF [13]. The cost of sacubitril/valsartan per day was A\$7.22, equating to an annual cost of A\$2,638. The cost of enalapril 10 mg twice daily was A\$0.97, equating to an annual cost of A\$354. NYHA class-specific HF-related background treatment costs were obtained from Ford *et al.* [14].

All costs were updated using the Australian Institute for Health and Welfare Health price index to 2018 values [15]. These are summarised in Table 1.

Utilities

Utility values according to NYHA functional class were obtained from King *et al.* [16] and are summarised in Table 1. A weighted average utility of 0.69 was calculated based on the proportional distribution of patients according to NYHA classes in PARADIGM-HF at baseline. We made a conservative assumption that patients did not transition from one NYHA class to another throughout the model time horizon.

Sensitivity Analyses

We quantified uncertainty in the model outputs by performing one-way sensitivity analyses varying key data inputs one at a time. The values of the key data inputs that were varied deterministically are specified in Table 1.

Probabilistic sensitivity analyses (PSA) were also performed allowing utilities, transition probabilities and event costs to be varied simultaneously. Costs of drug treatment were not varied because these are fixed in the PBS. A Monte Carlo simulation [17] with 10,000 iterations was performed.

Table 1 summarises the uncertainty distributions used for the key model inputs.

Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and @Risk version 7.5 (Palisade Corporation, New York, NY, USA) were used to create and analyse the model.

Results

Key results are summarised in Table 2. The base case analysis predicted that over the 20-year time horizon, the 1,000 subjects in the sacubitril/valsartan group would experience 786 non-fatal HF hospitalisations, 814 CV deaths and 184 non-CV deaths (Table 2). The 1,000 subjects in the enalapril group would experience 811 non-fatal HF hospitalisations, 850 CV deaths, and 148 non-CV deaths. The differences resulted in numbers needed to treat (NNT) over a 20-year period of 40, 27 and -28, respectively. Less than 5% of the patients remained alive in each group at the end of the 20 years of simulation.

Over the 20-year time horizon, subjects in the sacubitril/valsartan group were projected to live an average of 5.36 years (discounted) and 3.70 QALYs (discounted), while patients in the enalapril group were projected to live 4.92 years (discounted) and 3.39 QALYs (discounted). Total treatment and disease-related costs (all discounted) were AU \$14,128,566 and A\$6,150,973, respectively, in the sacubitril/valsartan group and A\$1,741,735 and A\$6,334,631, respectively, in the enalapril group. These amounted to total

Table 2 Results of base-case analysis comparing enalapril with sacubitril/valsartan, using sample size of 1,000 subjects (A\$ used).

		Enalapril	Sacubitril/ valsartan	Difference	NNT
Events	Non-fatal hospitalisation for HF	811	786	-25	40
	CV deaths	850	814	-36	27
	Non-CV deaths	148	184	36	-28
Years of life lived	Total	5,812	6,425	613	
	Discounted at 5% annually	4,919	5,356	437	
QALYs lived	Total	4,011	4,433	423	
	Discounted at 5% annually	3,394	3,696	301	
Costs	Non-fatal hospitalisation for HF	\$4,923,728	\$4,770,711	-\$153,017	
	CV deaths	\$1,674,082	\$1,602,376	-\$71,706	
	Non-CV deaths	\$291,985	\$362,499	\$70,513	
	Background costs	\$1,109,305	\$1,226,214	\$116,908	
	Study drug	\$2,057,851	\$16,948,139	\$14,890,287	
	Total	\$10,056,952	\$24,909,938	\$14,852,986	
	Discounted at 5% annually	\$8,076,366	\$20,279,538	\$12,203,172	
ICERs	Cost per YoLS			\$27,954	
	Cost per QALY			\$40,513	

Abbreviation: NNT, numbers needed to treat; HF, heart failure; CV, cardiovascular; ICERs, incremental cost-effectiveness ratios; YoLS, years of life saved; QALY, quality-adjusted-life-years.

costs of A\$20,279,538 in the sacubitril/valsartan group and A\$8,076,366 in the enalapril group, a difference of A\$12,203,172. These figures equated to ICERs of A\$27,954 per year of life saved (YoLS) and A\$40,513 per QALY gained.

Our sensitivity analyses demonstrated the ICER did not exceed A\$50,000 per QALY saved with reasonable variations to event costs and utilities (Table 3). As illustrated in the tornado diagram in Figure 2, the ICER was most sensitive to the incidence of CV deaths, followed by the incidence of non-CV deaths and utilities. The results of the PSA showed that sacubitril/valsartan was cost-effective in 74% of 10,000 iterations, when a threshold of A\$50,000 per QALY gained was

applied (Figure 3). At a willingness-to-pay threshold of A\$85,000 per QALY gained, there was a 96% probability that sacubitril/valsartan would be cost-effective.

Discussion

Our analyses suggest that sacubitril/valsartan is cost-effective compared to enalapril among patients with HFREF with NYHA class II to IV in the Australian setting. The ICER of A\$40,513 per QALY gained is comparable to other guideline-directed medical therapies in HF [18,19]. Of note, a previous analysis has shown that the Australian Pharmaceutical

Table 3 Deterministic sensitivity analysis varying key model inputs one at a time and the subsequent ICER per YoLS and QALY (A\$ used).

Variables	Input values	ICER (Cost per YoLS)	ICER (Cost per QALY)
Base case		\$27,954	\$40,513
Background costs [reduced by 50%]	\$95	\$27,859	\$40,375
Background costs [increased by 50%]	\$286	\$27,954	\$40,513
Non-fatal hospitalisation for HF [reduced by 50%]	\$3,034	\$28,211	\$40,886
Non-fatal hospitalisation for HF [increased by 50%]	\$9,103	\$27,697	\$40,141
CV deaths [reduced by 50%]	\$984	\$28,060	\$40,666
CV deaths [increased by 50%]	\$2,953	\$27,849	\$40,361
Non-CV deaths [reduced by 50%]	\$984	\$27,898	\$40,431
Non-CV deaths [increased by 50%]	\$2,953	\$28,011	\$40,596
Utility [reduced by 50%]	0.345	\$27,954	\$8,870
Utility [increased by 50%]	1.035	\$27,954	-\$15,780

Abbreviations: HF, heart failure; CV, cardiovascular; ICER, incremental cost-effectiveness ratio; YoLS, years of life saved; QALY, quality-adjusted-life-years.

Figure 2 Tornado diagram (A\$).

Abbreviations: CV, cardiovascular; HF, heart failure.

Figure 3 Cost-effectiveness acceptability curve (A\$).

Benefits Advisory Committee is likely to recommend a product for reimbursement if the ICER per QALY gained falls under threshold range of A\$42,000 to A\$76,000 [20]. The results of sensitivity analyses showed that the ICER was most sensitive to CV deaths at cost difference of A\$71,706 and the NNT to prevent one CV death was 27, assuming treatment effect continued through-out the model time horizon.

Sacubitril/valsartan is currently reimbursed under PBS in Australia but restricted to symptomatic HFREF patients already taking an ACE inhibitor or ARB, with use *in addition* to optimal standard chronic HF treatment, which must include the maximum tolerated dose of a beta blocker [21]. The most recent American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America guidelines recommended that HFREF patients with NYHA class II to III symptoms stable on ACE inhibitors/ARB should be considered for *switching* to an ARNi to further reduce mortality and morbidity [22,23]. Based on our analysis, relaxing the eligibility criteria of sacubitril/valsartan has the potential to improve patient outcomes in a cost-effective manner. Heart failure imposes a large burden in Australia, where the prevalence of cardiomyopathy in 2015 was estimated at 87 per 100,000 persons, and annual patient care costs were A\$2.7 billion [24,25].

Our results concur with findings from other published reports [16,26–29]. Gaziano *et al.* estimated that over a 30-year time horizon, sacubitril/valsartan was cost-effective compared with enalapril, with an ICER of US\$45,017 per QALY gained and was projected to reduce the cost of HF readmissions by more than US\$27 million [26]. King *et al.* found that the cost-effectiveness of sacubitril/valsartan was highly dependent on the duration of treatment, ranging from US\$249,411 per QALY gained at 3 years to US\$50,959 per QALY gained over a lifetime, and the value may be greater in patients with higher risk [16]. When sacubitril/valsartan was compared with lisinopril, the cost per QALY gained over a

lifetime in HF patients with NYHA class II was US\$44,531 compared with US\$58,194 in HF patients with NYHA class III or IV, suggesting that its use is of greater value in HF patients with NYHA class II than class III or IV [27]. A Dutch study showed that the ICER obtained was €26,491 when indirect medical costs of life-years gained was incorporated. The probability of sacubitril/valsartan being cost-effective at a €50,000 threshold was 99.8%, and this was mainly driven by reductions in CV mortality and hospitalisation as well as improvements in health-related quality of life [30].

Subsequent analyses from PARADIGM-HF showed that the benefit of sacubitril/valsartan relative to enalapril was maintained across various subgroups [31–33]. Actuarial estimates of age-specific event rates and expected survival times using data regarding the age at randomisation and the age at the time of an outcome event from PARADIGM-HF suggested that treatment with sacubitril/valsartan would result in a projected benefit of 1 to 2 years of increased life expectancy and survival free from heart failure [34]. Further analysis using the PARADIGM-HF dataset indicated that patients with HFREF who are unable to tolerate target doses of sacubitril/valsartan or enalapril still benefit from lower doses of sacubitril/valsartan compared with lower doses of enalapril [35]. Similarly, Ramos *et al.* provided further evidence that the ICERs had little variation across subgroups [30].

Our analysis adds to the body of literature demonstrating that sacubitril/valsartan is cost-effective among HFREF patients. The results support the relaxing of eligibility criteria for reimbursement for this drug via the PBS to include switching from ACE inhibitor or ARB to sacubitril/valsartan.

Limitations

Our analysis has several limitations that warrant mention. First, our modelled analysis adopted the perspective of the

Australian health care system and therefore the results may not be directly applicable to other settings. Secondly, treatment effects were derived from a single trial which enrolled only patients who could tolerate sacubitril/valsartan and enalapril during a run-in phase. Hence, the benefits observed in real-world clinical practice may be over-estimated. Furthermore, we assumed the benefits observed in PARADIGM-HF were maintained beyond the trial duration 20 years, while in real-life, long-term benefits may not be sustained. Also, it was assumed that HF hospitalisation only occurred once per cycle and that 50% of deaths occurred in hospital to simplify calculations and due to lack of data. Such assumptions may not hold true in real life settings, and hence we would have over-estimated the cost-effectiveness, of sacubitril/valsartan relative to enalapril. Finally, we did not model changes in disease severity (left ventricular ejection fraction or NYHA classes), adverse events and adherence over time, each of which may have affected our results in an unpredictable fashion depending on the extent and differences between the sacubitril/valsartan and enalapril groups.

Conclusions

Compared with enalapril, sacubitril-valsartan represents a cost-effective means of managing patients with HFREF in the Australian setting. Our analysis supports switching HFREF patients on ACE inhibitor or ARB to sacubitril/valsartan.

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Conflict of Interest

DL has received honoraria or study grants from Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Pfizer, Sanofi and Shire.

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