Journal of the American Heart Association

ORIGINAL RESEARCH

Cost-Effectiveness of Combination Therapy for Patients With Systemic Sclerosis–Related Pulmonary Arterial Hypertension

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BACKGROUND: To evaluate the cost-effectiveness of combination pulmonary arterial hypertension specific therapy in systemic sclerosis–related PAH.

METHODS AND RESULTS: Health outcomes and costs were captured through data linkage. Health utility was derived from Medical Outcomes Study Short Form-36 scores. A probabilistic discrete-time model was developed to simulate lifetime changes in costs and health utility. Mortality was predicted using a Gompertz parametric survival model. For both treatment arms, the simulations were started using the same cohort of 10 000 patients. Probabilistic sensitivity analysis was performed using the Monte Carlo simulation with 1000 sets of sampled parameter values. Of 143 patients with systemic sclerosis–related pulmonary arterial hypertension, 89 were on monotherapy and 54 on combination therapy. Mean simulated costs per patient per year in monotherapy and combination therapy groups were AU$23 411 (US$16 080) and AU$29 129 (US$19 982), respectively. Mean life years and quality-adjusted life years from pulmonary arterial hypertension diagnosis to death of patients receiving monotherapy were 7.1 and 3.0, respectively, and of those receiving combination therapy were 9.2 and 3.9, respectively. Incremental costs per life year and quality-adjusted life year gained of combination therapy compared with monotherapy were AU$47 989 (US$32 920) and AU$113 823 (US$78 082), respectively. At a willingness-to-pay threshold of AU$102 000 (US$69 972) per life year gained, and of AU$177 222 (US$121 574) per quality-adjusted life year gained, the probability of combination therapy being cost-effective was 0.95.

CONCLUSIONS: The incremental cost per quality-adjusted life year gained of combination therapy compared with monotherapy was substantial in the base case analysis. Given the fatal prognosis of systemic sclerosis–related pulmonary arterial hypertension and the incremental cost per life year of AU$47 989 (US$32 920), combination therapy could be considered cost-effective in systemic sclerosis–related pulmonary arterial hypertension.

Key Words: cost-effectiveness analysis ■ pulmonary arterial hypertension ■ pulmonary vasodilator therapy ■ scleroderma ■ systemic sclerosis

Systemic sclerosis (SSc) is a chronic multisystem autoimmune disease characterized by vasculopathy and fibrosis[1] that is associated with significant morbidity, mortality, and reduced health-related quality of life (HRQoL).[2] Pulmonary arterial hypertension (PAH), which occurs at a prevalence of 8%–12% in patients with SSc,[3] is the leading cause of SSc-related death,[4] with a standardized mortality ratio of 5.8 (95%

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015816.

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For Sources of Funding and Disclosures, see page 13.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- We have shown that dual combination therapy in systemic sclerosis–related pulmonary arterial hypertension compared with monotherapy can significantly improve patient survival and health-related quality of life, in terms of life years and quality-adjusted life years gained.

What Are the Clinical Implications?

- We have shown that dual combination therapy in the treatment of systemic sclerosis–related pulmonary arterial hypertension is potentially cost-effective depending on drug pricing and given the imminent expiry of drug patents and subsequent availability of lower-priced generic agents.

Nonstandard Abbreviations and Acronyms

ASCS	Australian Scleroderma Cohort Study
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ILD	interstitial lung disease
LY	life year
PAH	pulmonary arterial hypertension
PBS	Pharmaceutical Benefit Scheme
QALY	quality-adjusted life year
SSc	systemic sclerosis
SSc-PAH	systemic sclerosis–related pulmonary arterial hypertension
WHO	World Health Organization
WTP	willingness to pay

CI, 4.3–7.8) and 15.2 years of life lost,[5] and is a significant determinant of healthcare usage, unemployment, and ensuing economic burden.[6–8]

The exact etiology and pathogenesis of systemic sclerosis–related pulmonary arterial hypertension (SSc-PAH) is incompletely understood. PAH is characterized by abnormal proliferation, vasoconstriction, and in-situ thrombosis of the pulmonary vasculature, leading to elevated pulmonary vascular resistance, resulting ultimately in right heart failure and death.[9] Historically, treatment options for patients with SSc-PAH were limited,[9] with an average life expectancy without treatment of 2 to 3 years.[6] However, in the past decade, with the introduction of new advanced pulmonary vasodilator therapies used as monotherapy or combination therapy (using ≥2 drugs with different modes of action), improvement in symptoms, function, and survival has been demonstrated.[8–10] Furthermore, there is evolving evidence to suggest that the treatment of PAH with up-front combination therapy, compared with monotherapy, is associated with improved survival and reduced hospitalizations for worsening PAH and disease progression.[8,11] This survival benefit has also been shown in small randomized trials and observational studies with combination therapy as an "add-on" therapy to monotherapy.[12,13]

In Australia, there are 7 PAH-specific therapeutic agents with regulatory approval available for use. These agents target the prostacyclin pathway (iloprost and epoprostenol), nitric oxide pathway (sildenafil and tadalafil), or endothelin pathway (ambrisentan, macitentan, and bosentan). Currently, the Australian Pharmaceutical Benefit Scheme (PBS), which operates uniformly across all Australian States and Territories, subsidizes monotherapy with one of these agents only if prescribed by a physician in a government-designated PAH treatment center. Combination therapy can only be prescribed by compassionate access through hospital pharmacies or the manufacturers, or at patients' own expense.

Connective tissue disease–related PAH accounts for over a third (33.9%) of all World Health Organization (WHO) Group 1 PAH, with SSc-PAH accounting for the majority of these (62.3%).[14] Despite only an estimated 615 Australians having SSc-PAH, the total cost to the government for PAH-specific therapies for SSc-PAH between 2011 and 2015 was AU$7 238 823.76 (US$5 327 774.29).[6] Efficient usage of healthcare budgets is critical for maintenance of a sustainable healthcare system, and as such, decisions to list new therapeutic agents on the PBS are guided by the agent's clinical efficacy and cost-effectiveness relative to its comparator. Therefore, we sought to evaluate, from a healthcare perspective, the cost-effectiveness of dual combination therapy compared with monotherapy in SSc-PAH, taking into account effects on survival, HRQoL, healthcare usage, and cost of drugs.

METHODS

Patients

Patients with SSc from 4 Australian states (Victoria, South Australia, Western Australia, and Tasmania) prospectively enrolled in the ASCS (Australian Scleroderma Cohort Study), a multicenter study of risk and prognostic factors for cardiopulmonary and other clinically important outcomes in SSc, were included. The ASCS contains comprehensive demographic, disease-related, and medication use data that are collected annually and entered into a custom-made database. Written consent was obtained from all patients at recruitment, and ethical approval was obtained from all of the participating hospitals in Victoria, Tasmania,

South Australia and Western Australia. These states were chosen as they comprise the majority of patients enrolled in the ASCS and have the most complete and up-to-date clinical data entered in the database. The authors of the study will make data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results or replicating the procedure, on request.

Inclusion and Exclusion Criteria

We included all adult (>18 years) patients with SSc recruited between June 2008 and June 2015 who were diagnosed with WHO Group 1 PAH on right heart catheterization (mean pulmonary arterial pressure of at least 25 mm Hg and a pulmonary arterial wedge pressure of <15 mm Hg) according to international criteria.[15,16] Patients were excluded if they had WHO Group 2 or 3 pulmonary hypertension or Group 1 PAH but with coexisting interstitial lung disease (ILD) with a forced vital capacity <60% and an abnormal high-resolution computed tomography of the chest. All patients fulfilled either the American College of Rheumatology or Leroy and Medsger criteria for SSc.[17–19]

Healthcare Usage

Healthcare resource usage was captured by means of data linkage. Through the Australian Institute of Health and Welfare, the ASCS database of demographic information, disease-related data, medication, and HRQoL data of deidentified patients with SSc-PAH were merged with the respective state-based hospital admission database, emergency department presentation database, and the Medical Benefit Schedule, thereby capturing all hospital admissions, emergency department presentations, and ambulatory care use, respectively. All deidentified data were stored and analyzed within the Secure Unified Research Environment, which is a remote-access secure computing environment that allows researchers to analyze linked data. Annual healthcare costs from PAH diagnosis for each patient were included.

Costing Methodology

In Australia, every hospital admission and emergency department presentation is assigned a diagnosis-related group and an urgency-related group, respectively. Each diagnosis-related group or urgency-related group is associated with a weighted cost unit, which incorporates the cost of investigations and medications administered for that group in a hospital setting. In this study, hospital cost was calculated on the basis of financial year of admission and the corresponding weighted value. Ambulatory care cost was calculated using the total Medical Benefit Schedule "benefit payable fee," as this is what the government contributes to each service. Medication cost was determined from the Pharmaceutical Benefit Scheme (PBS) Dispensed Price for Maximum Quantity paid for the standard dose of each medication, which is the cost the government contributes to each medication dispensed. Costs are also presented in US dollars based on currency conversion performed on September 17, 2019.

Health Economic Outcomes and Follow-Up Procedures

Patients were assessed at PAH diagnosis (within 1 month of the first right heart catheterization and before starting pulmonary vasodilator therapy) and every 12 months thereafter during the follow-up period. Clinical variables included disease duration at PAH diagnosis (disease onset based on first non-Raynaud manifestation), ILD (defined on the basis of characteristic changes on high-resolution computed tomography lung), disease subtype (diffuse and limited), digital ulceration, WHO Functional Class, and gastrointestinal involvement (the presence of any of the following: reflux esophagitis or esophageal stricture on endoscopy, intestinal dysmotility defined on barium and nuclear medicine studies, and fecal incontinence). Patient-reported outcome measures included SSc-specific health assessment questionnaire and the Medical Outcomes Study Short Form-36 . Health utility was estimated by converting Medical Outcomes Study Short Form-36 to Short Form-6D using the algorithm developed by Brazier et al.[20] If a patient died during the follow-up period, the date of death was recorded.

Model Structure and Statistical Analysis

A probabilistic discrete-time simulation model with annual cycles was developed to estimate the total annual healthcare cost incurred by, and changes in health utility of, a patient with specific baseline characteristics and under a specific treatment for PAH. In this way, the incremental cost of combination therapy per quality-adjusted life year (QALY) gained compared with monotherapy could be adjusted for the differences in patient baseline characteristics. Within each cycle, nondrug healthcare costs, health utility, and probability of mortality were estimated on the basis of a set of statistical models, and drug costs were estimated using the cost distribution of different drugs in the population. A 2-part model was used to model nondrug healthcare cost, of which the first part was a logistic model used to determine whether cost was

positive, and the second part was a log-transformed model used to estimate nonzero cost. A linear model was used to estimate health utility, and a Gompertz parametric survival model was used to estimate the probability of mortality. Multiple imputation was used to replace missing values with the estimates. Twenty imputed data sets were generated, and the statistical regression models were fitted to the observed data within each imputed set. Rubin's rule was used to combine values of the coefficients and variance-covariance matrices obtained from the 20 imputed data sets. Rheumatologists' opinions and backward stepwise procedures were used to select predictors in each of the above-mentioned statistical models.

At the beginning of the simulation, a patient was created with characteristics sampled from the probability distributions of the SSc-PAH cohort, which were used to update total cost and health utility at the end of each cycle. Within each cycle, the probability of mortality was calculated and compared with a random number drawn from the standard uniform distribution. We assumed death occurred in the middle of the cycle if the mortality probability was larger than the random number. The model was run until death, and QALYs were calculated as the area under the health utility curve.

Cost-Effectiveness Analysis

For each treatment arm, the simulation was run for 10 000 patients. To minimize the first order uncertainty, that is, patients with identical characteristics may have different outcomes attributable to chance, we performed the Monte Carlo simulation with increasing number of replications for each patient until the mean costs and QALYs were stable. Variance reduction technique was applied so that the differences in healthcare costs, health utility, and incidence of mortality between the 2 treatment strategies reflect the true effect of the treatment rather than the external differences in the random numbers used for estimating the outcomes. In the base case analysis, mean lifetime cost, life years (LYs) and QALYs per patient were estimated, on the basis of which the costs per LY or QALY gain were calculated. In the bivariate sensitivity analysis, the incremental cost-effectiveness ratios (ICERs) were computed for the 4 scenarios where the least and most expensive combination therapies were compared with the least and most expensive monotherapies. To examine the impact of changes in drug price after patent expiration on the ICER, we ran the simulation with prices of all drugs reduced by 5%, 10%, …, 90% and 95%.

In both base case and sensitivity analyses, we estimated 95% CIs of costs, LYs, QALYs, and ICERs by bootstrapping (ie, sampling with replacement) 10 000 patients in the simulated data sets. The lower and upper bounds of the 95% CIs of each variable were calculated as the 2.5th and 97.5th percentiles of the means obtained from 2000 bootstrap replications.

In the probabilistic sensitivity analysis, 1000 sets of fully correlated coefficients in the statistical models used to estimate costs, utility, and mortality risk were sampled from the multivariate normal distributions estimated on the basis of the variance-covariance matrices obtained from model fitting. A net-benefit framework was used to construct the cost-acceptability curves from the Monte Carlo simulation results. In all the analyses, costs and utility were discounted at an annual rate of 5%.

The simulation model was developed using C++, and statistical modeling was performed using R (R Foundation for Statistical Computing, Vienna, Austria).[21]

RESULTS

Patient Characteristics

Of the 1128 patients with SSc enrolled within the ASCS between June 2008 and June 2015, 143 (12.7%) developed WHO Group 1 PAH. Patient characteristics and hemodynamic measurements are summarized in Table 1. Our PAH cohort compromised predominantly White (93.0%) women (87.4%) with limited scleroderma (75.5%). The majority of patients with SSc-PAH experienced gastrointestinal involvement (68.5%), with half experiencing digital ulceration (59.6%) and mild ILD (44.8%). At PAH diagnosis, the mean age was 63.2 (±10.2) years with a median SSc disease duration of 12.7 (4.6–20.7) years, and the majority of patients were in either WHO functional Class III (37.8%) or Class IV (20.9%). Despite treatment, the median survival in SSc-PAH was 4.2 (2.3–6.4) years.

PAH-Specific Therapy Distribution and Associated Cost

Of the 143 patients with SSc-PAH, 89 (62.2%) were treated with monotherapy and 54 (37.8%) received combination therapy. Patients treated with combination therapy compared with monotherapy had more severe PAH reflected by hemodynamic parameters (Table 2). Bosentan (52.3%) was the most commonly prescribed monotherapy with an annual per person cost to the government of AU$32 791.80, while bosentan and sildenafil (61.8%) were the most commonly prescribed combination therapy, with an annual per-person cost to the government of AU$36 628.44.

Table 1. Characteristics of Patients With SSc-PAH

Characteristic	Mean (±SD or %)
Total number of patients	143
Female	125 (87.4)
Limited disease subtype	108 (75.5)
Age at PAH diagnosis, years	63.2 (±10.2)
Disease duration* at PAH diagnosis, y, median (IQR)	12.7 (4.6–20.7)
Alive at censorship	65 (45.8)
Survival time from PAH diagnosis of dead patients, y, median (IQR)	4.2 (2.3–6.4)
Clinical manifestations§	
Digital ulceration	85 (59.4)
Synovitis	34 (23.8
Joint contracture	76 (53.2)
GIT involvement	98 (68.5)
Mild ILD	64 (44.8)
WHO Functional Class at time of PAH diagnosis	
Class I	6 (4.2)
Class II	29 (20.3)
Class III	54 (37.8)
Class IV	30 (20.9)
Hemodynamic parameters	
Baseline 6MWD, m	324.0 (±105.6)
Baseline mRAP, mm Hg	8.3 (±3.9)
Baseline mPAP, mm Hg	35.2 (±10.0)
Baseline PAWP, mm Hg	11.1 (±4.0)
Baseline mCI, L/min per m^2	2.9 (±1.4)
Baseline PVR, Wood units	4.9 (±2.9)
Presence of a pericardial effusion at PAH diagnosis	14 (9.9)
Mean DLCO, % predicted mL/min per mm Hg	48.7 (±14.9)
Mean DLCO/VA, % predicted mL/min per mm Hg	58.5 (±19.7)
Pulmonary vasodilator therapy‡	
Monotherapy†	89 (62.2)
Combination therapy	54 (37.8)
Baseline HAQ at PAH diagnosis	3.2 (1.6)
Mean HAQ during follow-up	2.9 (2.1)

Mild ILD (forced vital capacity >70% and <20% ILD high-resolution computed tomography), no patients with moderate or severe ILD.

6MWD indicates 6-minute walk distance; DLCO, diffusing capacity of the lung for carbon monoxide; DLCO/VA, DLCO adjusted for alveolar volume; GIT, gastrointestinal; HAQ, Health Assessment Questionnaire; ILD, interstitial lung disease; mCI, mean cardiac index; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, peripheral vascular resistance; and WHO, World Health Organization.

*Disease duration from first non-Raynaud manifestation; follow-up duration was defined as years from study enrollment.

†Monotherapy is treatment with a single PAH-specific therapy. Combination therapy is treatment with >1 specific PAH agent from different classes at one time.

‡Treatment ever following the diagnosis of PAH.

§Manifestations defined as present if present from systemic sclerosis diagnosis.

Table 3 outlines the drug distribution and associated pharmaceutical cost of our SSc-PAH cohort.

Survival, Healthcare Usage, and Associated Cost

Despite patients with SSc-PAH on combination therapy having more severe PAH, the mean survival time from PAH diagnosis of those who died during the follow-up was higher for patients receiving combination therapy compared with monotherapy (5.6 versus 4.1 years; P=0.003; Table 2). Predictors in the parametric survival model for time to death included the use of combination therapy, mean pulmonary arterial pressure, WHO functional class, coexistent ILD, and time from PAH diagnosis (see Table 4 for coefficient estimates). The mean simulated life expectancy since PAH diagnosis

Table 2. Patient Characteristics by PAH Therapy†

Variables	Monotherapy	Combination Therapy	*P* Value
Patient number, n (%)	89 (62.2)	54 (37.8)	
Female, n (%)	80 (89.9)	45 (83.3)	0.25
Age at PAH diagnosis	63.9±10.4	62.0±9.9	0.22
Disease duration‡ at PAH diagnosis	13.7±10.8	15.2±13.0	0.45
White race, n (%)	82 (92.1)	51 (94.4)	0.60
Limited, n (%)	68 (76.4)	40 (74.1)	0.75
Follow-up from PAH diagnosis	4.3±2.7	5.0±2.5	0.10
Survival from PAH diagnosis*, y	4.1±2.8	5.6±3.2	0.003
Clinical manifestations,§ n (%)			
Digital ulceration	52 (58.4)	33 (61.1)	0.72
Synovitis	23 (25.8)	11 (20.4)	0.46
Joint contractures	40 (44.9)	36 (66.7)	0.01
GIT manifestations	63 (70.8)	35 (64.8)	0.46
Mild ILD¶	34 (38.2)	30 (55.6)	0.04
WHO Functional Class at PAH diagnosis, n (%)			
Class I	5 (5.6)	1 (1.9)	0.002
Class II	23 (25.8)	6 (11.1)	
Class III	37 (68.5)	17 (31.5)	
Class IV	10 (11.2)	20 (37.0)	
Hemodynamic parameters			
Baseline 6MWD, m	325.7±107.2	322.4±103.9	0.87
Baseline mRAP, mm Hg	8.3±3.7	8.2±4.1	0.88
Baseline mPAP, mm Hg	33.9±10.4	37.3±9.1	0.05
Baseline PAWP, mm Hg	11.8±3.8	10.1±4.2	0.01
Baseline mCI, L/min per m^2	3.1±1.9	2.8±0.8	0.53
Baseline PVR, Wood Units	4.1±2.6	6.4±3.2	<0.001
Presence of a pericardial effusion at diagnosis, n (%)	6 (6.8)	8 (14.8)	0.27
DLCO, mL/min per mm Hg	52.5±15.2	43.1±12.8	0.002
DLCO/VA, mL/min per mm Hg	66.8±17.5	60.9±15.8	0.43
Baseline HAQ at PAH diagnosis	3.4±1.7	3.1±1.3	0.34
Mean HAQ	3.3±2.3	2.3±2.1	0.07

6MWD indicates 6- minute walk distance; DLCO, diffusing capacity of the lung for carbon monoxide; DLCO/VA, DLCO adjusted for alveolar volume; GIT, gastrointestinal; HAQ, Health Assessment Questionnaire; ILD, interstitial lung disease; mCI, mean cardiac index; mPAP, mean pulmonary arterial pressure; mRAP mean right atrial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, peripheral vascular resistance; and WHO, World Health Organization.

*Survival time from PAH diagnosis in those that died.

†Monotherapy is treatment with a single PAH specific therapy. Combination therapy is treatment with 2 specific PAH agents from different classes at one time. Treatment ever following the diagnosis of PAH.

‡Disease duration from first non-Raynaud manifestation.

§Manifestations defined as present if present from systemic sclerosis diagnosis.

¶Mild ILD (forced vital capacity >70% and <20% ILD high-resolution computed tomography), no patients with moderate or severe ILD.

per patient on combination therapy and monotherapy were 9.19 and 7.11 years, respectively (Table 5).

Although patients on combination therapy had more severe PAH, they did not use more healthcare services than those on monotherapy. In fact, the mean cost of healthcare services per patient on combination therapy was AU$1408 less than the mean per patient on monotherapy (Table 5). Predictors in the two-part model for healthcare cost included combination therapy, worsening WHO Functional Class and the presence of gastrointestinal manifestations (coefficient estimates are summarized in Table 4).

Mean health utility declined each year following PAH diagnosis in both the monotherapy and combination therapy groups, with a slower decline in the combination group. The incremental mean QALY per patient in the combination group compared with the monotherapy group was 0.87 (Table 5). Predictors in the linear model for health utility included the use of combination therapy, WHO Functional Class, the presence of ILD,

Table 3. Distribution of Medication Usage and Associated Costs

Medication	Patient Number	Proportion	Annual Cost to the Government per Person (AU$)	Beta Distribution of the Proportion§	
				Alpha	Beta
Monotherapy*					
Bosentan or ambrisentan or sitaxsentan‡	68	0.77	32 791.80	68	20
Sildenafil	13	0.14	3836.64	13	76
Macitentan	4	0.05	35 081.88	4	84
Tadalafil	4	0.05	10 025.76	4	84
Total	89	1			
Combination therapy†					
Sildenafil+bosentan/ sildenafil+ambrisentan	41	0.76	36 628.44	41	13
Sildenafil+macitentan	8	0.15	38 918.52	8	47
Tadalafil+ambrisentan	4	0.07	42 817.56	4	51
Epoprostentol+sildenafil+bosentan	2	0.02	37 427.04	1	54
Total	54	1			

*Monotherapy is treatment with a single pulmonary arterial hypertension (PAH)-specific therapy.
†Combination therapy is treatment with 2 specific PAH agents from different classes at one time.
‡Sitaxsentan was withdrawn from the market in 2010 because of adverse events.
§Parameters in the beta distributions used to sample the proportions of patients on different drugs.

and time from PAH diagnosis (coefficient estimates are summarized in Table 4).

Incremental Cost-Effectiveness and Probabilistic Sensitivity Analysis

Over a lifetime, an average patient on combination therapy would cost an additional AU$1378 (US$945) to the healthcare system, but would gain 2.07 LYs and 0.87 QALYs compared with a patient on monotherapy. The mean incremental cost per LY gained associated with combination therapy compared with monotherapy was AU$47 989 (US$32 920), while the mean incremental cost per QALY gained was AU$113 823 (US$78 082).

Results of the sensitivity analysis comparing costs, health outcomes, and ICERs of four different drug models are shown in Table 6. Compared with the most expensive monotherapy (macitentan), the cheapest combination therapy (bosentan or ambrisentan with sildenafil) was associated with the lowest incremental costs per LY, and QALY gained (AU$26 228 [US$17 992] and AU$62 209 [US$42 675], respectively). During the study time period, all PAH-specific therapies were on patent. Our analyses of the impact of drug patent expiration on ICERs showed that every 5% reduction in on-patent drug prices was associated with a reduction of AU$2433 per LY gained and AU$5770 per QALY gained (see Figure 1). A breakdown of total cost and health outcomes associated with the current 25% reduction in drug prices for each therapy is presented in Table 7. When the on-patent drug prices are reduced by 55%, the incremental cost per QALY gained associated with combination therapy compared with monotherapy was AU$50 352, which represents value for money of the combination therapy given the currently suggested willingness-to-pay (WTP) thresholds in Australia[22–24] and the United States.[25]

The scatterplots of the joint uncertainty in the incremental cost against incremental LYs (Figure 2) and against incremental QALYs (Figure 3) of combination therapy compared with monotherapy showed all data points lying in the northeast quadrant of the cost-effectiveness. At WTP of AU$48 455 (US$32 240) per LY gained, and of AU$114 583 (US$78 603) per QALY gained, the probabilities of combination therapy and monotherapy, respectively, being cost-effective were equal. At a WTP of AU$102 000 (US$69 972) per LY gained, and of AU$177 222 (US$121 574) per QALY gained, the probability of combination therapy being cost-effective was 0.95 (Figures 4 and 5).

DISCUSSION

Our study showed that in SSc-PAH, dual combination therapy compared with monotherapy significantly improved patient survival represented by LYs gained, but at a considerable financial cost to the healthcare system. The total cost was largely driven by the use of specific drugs as outlined in our 4 drug scenarios in Table 6. Using the drug distribution prescribed in our cohort while all drugs were on patent, the ICER per LY gained was AU$47 989 (US$32 920) and per QALY

Table 4. Parameters in the Statistical Models Used to Estimate the Probability of Mortality, Annual Healthcare Cost, and Health Utility in Patients With SSc-PAH

Dependent Variable	Mortality Rate	Annual Total Healthcare Cost		Health Utility
Number of Patients	n=143	n=143		n=143
Model	Gompertz Proportional Hazards Survival Model	Logistic Model	Log-Normal Regression Model	Linear Model
Parameters	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Intercept		−1.094 (−1.435 to −0.752)	7.679 (7.505 to 7.853)	0.583 (0.564 to 0.602)
Combination therapy	−0.589 (−1.076 to −0.101)	−0.545 (−0.901 to −0.189)		0.030 (0.015 to 0.045)
WHO functional class at PAH diagnosis	1.112 (0.315 to 1.909)	0.421 (0.013 to 0.829)		−0.024 (−0.041 to −0.008)
mPAP at PAH diagnosis	0.041 (0.016 to 0.064)			
ILD	0.606 (0.140 to 1.072)			−0.015 (−0.028 to −0.001)
Gastrointestinal manifestations			0.287 (−0.054 to 0.628)	
Time from PAH diagnosis, years				−0.006 (−0.009 to −0.001)
Rate	−5.278 (−6.418, −4.137)			
Shape	0.189 (0.106, 0.274)			

ILD indicates interstitial lung disease; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; and WHO, World Health Organization.

gained was AU$113 823 (US$78 082). These ICER thresholds reduce further when comparing the most expensive monotherapy (macitentan) to the cheapest combination therapy (bosentan or ambrisentan and sildenafil) (AU$26 228 [US$17 992] per LY and AU$62 209 [US$42 675] per QALY gained).

To determine whether a particular ICER represents value for money requires comparing this with a WTP threshold that varies in different countries and settings. Research suggests an acceptable cost-effectiveness threshold in Australia lies in the range of AU$45 000 to AU$60 000 per QALY gained.[22–24] This WTP threshold is similar to other thresholds across the world including the National Institute for Health and Care Excellence in the United Kingdom with a threshold of £20 000 to £30 000 per QALY gained,[26] the United States of between US$50 000 and US$100 000[25] per QALY,[27] Japan of US$60 000 to US$75 000,[28] and the Netherlands of €20 000 to €73 000.[29]

Some authors argued that there should be higher WTP thresholds for diseases with a higher burden of illness, defined by the condition severity and level of unmet need,[28] both of which epitomize SSc-PAH. The healthcare systems of the United Kingdom and the Netherlands have acknowledged this important factor, and threshold adjustments are made depending on disease severity, disease burden, and end-of-life treatment.[28,30] Such threshold adjustments can be seen with the approval of immunotherapy in oncology patients, with certain immunotherapies compared with standard therapy being cost-effective at a WTP of US$146 000.[31] Furthermore, the up-front treatment of patients with SSc-PAH with combination therapy may help to reduce its associated direct healthcare costs and indirect costs resulting from unemployment and lost workforce productivity.[6,7,32]

Despite the ICER being a convenient tool for economic evaluations, allowing comparisons to be made

Table 5. Base Case Analysis (Sampling Drugs Based on Distributions)

	Combination Therapy*	Monotherapy†	Incremental
Drug cost (95% CI), AU$	255 983 (252 354 to 259 679)	155 179 (152 596 to 157 816)	100 804 (99 750 to 101 863)
Nondrug cost (95% CI), AU$	6556 (6477 to 6635)	7934 (7824 to 8045.45)	−1378 (−1419 to −1339)
Total cost (95% CI), AU$	262 539 (258 865 to 266 300)	163 113 (160 462 to 165 819)	99 426 (98 394 to 100 441)
Life years	9.19 (3.84 to 3.96)	7.11 (2.97 to 3.08)	2.07 (0.87 to 0.88)
QALYs	3.90 (9.02 to 9.36)	3.02 (6.97 to 7.26)	0.87 (2.05 to 2.09)
ICER, AU$ per life year gained			47 989 (47 897 to 48 084)
ICER, AU$ per QALY gained			113 823 (113 302 to 114 364)

ICER indicates incremental cost-effectiveness ratio; and QALY, quality-adjusted life year.
*Combination therapy is treatment with two specific PAH agent from different classes at one time.
†Monotherapy is treatment with a single PAH-specific therapy.

Table 6. Costs, Health Outcomes and Incremental Cost-Effectiveness Ratios Resulting From Sensitivity Analyses Using Different Combinations of Drug Classes

	Combination Therapy	Monotherapy	Incremental
Cheapest monotherapy (sildenafil), cheapest combination therapy (sildenafil+bosentan or sildenafil+ambrisentan)			
Drug cost (95% CI), AU$	250,555 (247 000 to 254 179)	21,308 (20 953 to 21 667)	229 247 (226 052 to 232 513)
Nondrug cost (95% CI), AU$	6556.39 (6477 to 6635)	7934.64 (7824 to 8045)	–1378.25 (–1419.63 to –1339)
Total cost (95% CI), AU$	257 111 (253 515 to 260 792)	29 242 (28 801 to 29 692)	227 869 (224 704 to 231 102)
Life years	9.19 (3.84 to 3.96)	7.18 (2.97 to 3.08)	2.07 (0.87 to 0.88)
QALYs	3.90 (9.02 to 9.36)	3.02 (6.97 to 7.26)	0.87 (2.05 to 2.09)
ICER, AU$ per life year gained			109 985 (109 478 to 110 526)
ICER, AU$ per QALY gained			260 867 (258 644 to 263 144)
Most expensive monotherapy (macitentan), cheapest combination therapy (sildenafil+bosentan or sildenafil+ambrisentan)			
Drug cost (95% CI), AU$	250 555 (247 000 to 254 179)	194 836 (191 595 to 198 121.82)	55 718.63 (55 354 to 56 071)
Nondrug cost (95% CI), AU$	6556 (6477 to 6636)	7934.64 (7825 to 8045)	–1378 (–1420 to –1339)
Total cost (95% CI), AU$	257 112 (253 515 to 260 792)	202 772 (199 468 to 206 151)	54 340 (53 999 to 54 669)
Life years	9.19 (3.84 to 3.96)	7.11 (2.97 to 3.08)	2.07 (0.87 to 0.88)
QALYs	3.90 (9.02 to 9.36)	3.02 (6.97 to 7.26)	0.87 (2.05 to 2.09)
ICER, AU$ per life year gained			26 228 (26 084 to 26 373)
ICER, AU$ per QALY gained			62 209 (62 125 to 62 288)
Cheapest monotherapy (sildenafil), most expensive combination therapy (tadalafil+ambrisentan)			
Drug cost (95% CI), AU$	292 892 (288 736 to 297 128)	21 308 (20 953 to 21 667)	271 584 (267 789 to 275 463)
Nondrug cost (95% CI), AU$	6556 (6477 to 6636)	7 936 (7825 to 8046)	–1378 (–1420 to –1339)
Total cost (95% CI), AU$	299 448 (295 247 to 303 748)	29 242 (28 802 to 29 693)	270 206 (266 440 to 274 051)
Life years	9.19 (3.84 to 3.96)	7.11 (2.97 to 3.08)	2.07 (0.87 to 0.88)
QALYs	3.90 (9.02 to 9.36)	3.02 (6.97 to 7.26)	0.87 (2.05 to 2.09)
ICER, AU$ per life year gained			130 420 (129 813 to 131 067)
ICER, AU$ per QALY gained			309 334 (306 683 to 312 051)
Most expensive monotherapy (macitentan), most expensive combination therapy (tadalafil+ambrisentan)			
Drug cost (95% CI), AU$	292 892 (288 736 to 297 128)	194 837 (191 595 to 198 121)	98 055 (97 138 to 98 979)
Nondrug cost (95% CI), AU$	6556 (6477 to 6636)	7936 (7824 to 8045)	–1378 (–1420 to –1339)
Total cost (95% CI), AU$	299 448 (295 247 to 303 748)	202 771 (199 468 to 206 151)	96 677 (95 778 to 97 565)
Life years	9.19 (3.84 to 3.96)	7.11 (2.97 to 3.08)	2.07 (0.87 to 0.88)
QALYs	3.90 (9.02 to 9.36)	3.02 (6.97 to 7.26)	0.87 (2.05 to 2.09)
ICER, AU$ per life year gained			46 663 (46 572 to 46 754)
ICER, AU$ per QALY gained			110 677 (110 306 to 111 055)

ICER indicates incremental cost effectiveness ratio; and QALY, quality-adjusted life year.
*Combination therapy is treatment with 2 specific PAH agents from different classes at one time.
†Monotherapy is treatment with a single PAH-specific therapy.

between drugs and therapeutic interventions, the validity of the threshold is increasingly being challenged[27] and most research suggests that $50 000 per QALY is too low.[27] Economists and researchers alike are continuing to determine what constitutes a reasonable cost-effectiveness threshold on the basis of economic theory or empirical estimates, as more expensive drugs become available. For example, the WHO suggests that a therapeutic agent is cost-effective if the ICER falls within a range between 1 and 3 times the gross domestic produce per capita.[33] Using this criterion, the Australian ICER threshold would range between AU$44 648.71 and AU$133 946.13 on the basis of 2017 Australian gross domestic product per capita of AU$44 648.71.[34] This would increase the likelihood of our dual combination therapy scenarios in Table 6 being considered cost-effective by the Pharmaceutical Benefits Advisory Committee for public listing on the PBS.

Furthermore, all PAH therapies, with the exception of sildenafil, were on patent during our study, and costs are reflective of this. As drug patents expire and as generics become available, PBS costs will reduce with an initial up-front 25% price cut. The expiration of the patent for Tracleer (bosentan) was in 2017, while that for Volibris (ambrisentan) and Adcirca (tadalafil) were in 2020. Despite our cost-effectiveness threshold being above the insinuated acceptable threshold in Australia

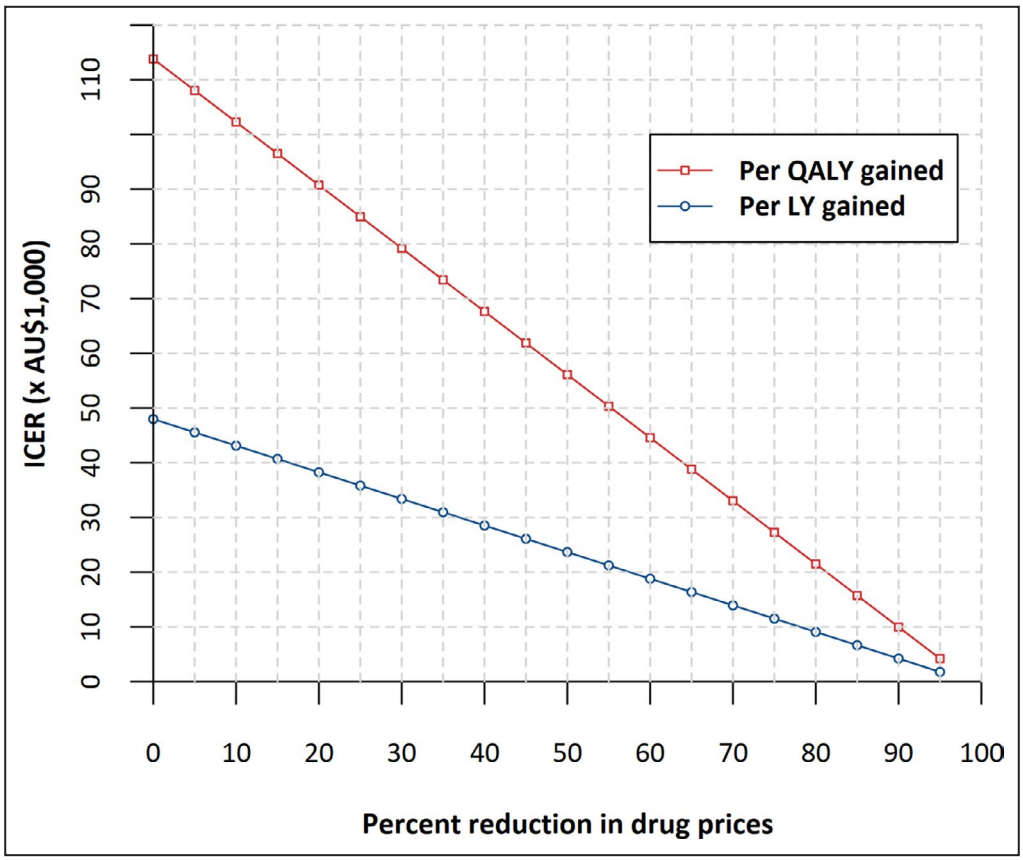

Figure 1. Relationship between percent reduction in drugs prices and incremental cost-effectiveness ratio.
ICER indicates incremental cost effectiveness ratio; LY, life year; and QALY, quality-adjusted life year.

for common conditions, there are many valid reasons as outlined above that make us optimistic about the future public listing of dual combination therapy on the PBS for the treatment of SSc-PAH.

Strengths of our study include the large, well-defined multicenter cohort of patients with SSc-PAH and the detailed patient related data recorded electronically using well-validated tools and methods. Furthermore, our data linkage methodology ensures a high degree of accuracy and reliability of healthcare usage and associated cost. Our study has some limitations. First, at the 6th World Congress in 2019, the definition of PAH was updated from a mean pulmonary arterial pressure of >25 mm Hg (as used in this study) to a mean pulmonary arterial pressure >20 mm Hg. On reanalyzing our data, this definition would include an additional 3.2% of patients with PAH without any change in treatment. Consequently, we do not feel

Table 7. Costs, Health Outcomes and Incremental Cost-Effectiveness Ratios Resulting From the Simulation in Which the Drug Prices of All Drugs Were Reduced by 25%

	Combination Therapy*	Monotherapy†	Incremental
Drug cost (95% CI), AU$	191 987 (189 266 to 194 759)	116 384 (114 447 to 118 363)	75 603 (74 813 to 76 397)
Nondrug cost (95% CI), AU$	6556 (6477 to 6636)	7935 (7825 to 8045)	–1378 (–1420 to –1339)
Total cost (95% CI), AU$	198 544 (195 777 to 201 378)	124 319 (122 320 to 126 364)	74 224.98 (73 456 to 74 978)
Life years	9.19 (3.84 to 3.96)	7.11 (2.97 to 3.08)	2.07 (0.87 to 0.88)
QALYs	3.90 (9.02 to 9.36)	3.02 (6.97 to 7.26)	0.87 (2.05 to 2.09)
ICER, AU$ per life year gained			35 826 (35 758 to 35 896)
ICER, AU$ per QALY gained			84 973 (84 588 to 85 371)

ICER indicates incremental cost effectiveness ratio; and QALY, quality-adjusted life year.
*Combination therapy is treatment with 2 specific PAH agents from different classes at one time.
†Monotherapy is treatment with a single PAH-specific therapy.

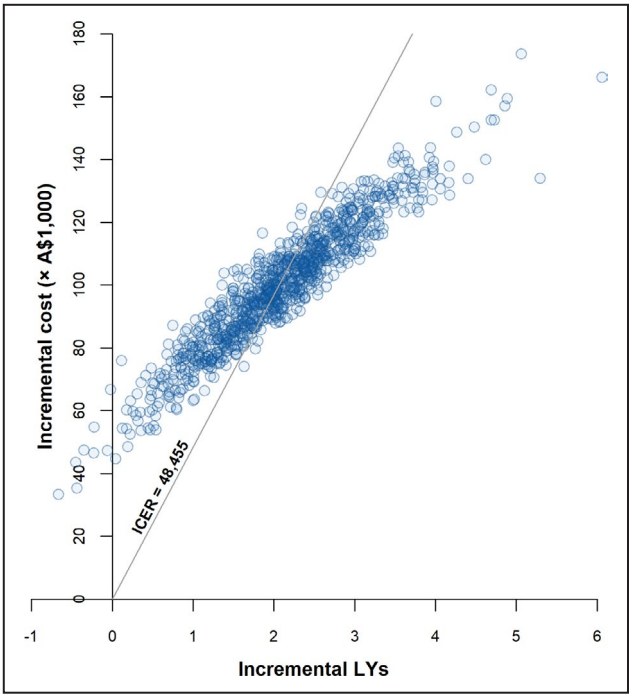

Figure 2. Cost-effectiveness plane showing incremental costs (in AU$) against incremental life years of combination therapy compared with monotherapy in probabilistic sensitivity analysis.
Each of 1000 data point was obtained from one simulation for 10 000 patients with a set of fully correlated random parameters in the statistical models used for estimating costs and health utility. ICER indicates incremental cost effectiveness ratio; and LYs, life years.

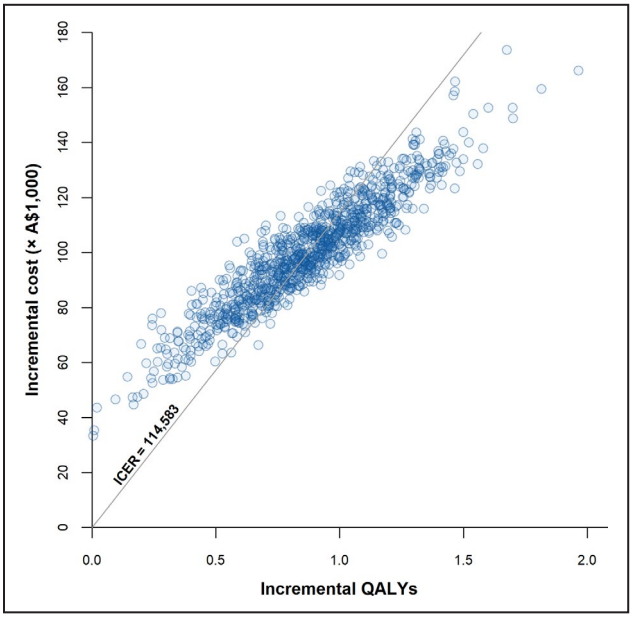

Figure 3. Cost-effectiveness plane showing incremental costs (in AU$) against incremental QALYs of combination therapy compared with monotherapy in probabilistic sensitivity analysis.
Each of 1000 data point was obtained from one simulation for 10 000 patients with a set of fully correlated random parameters in the statistical models used for estimating costs and health utility. ICER indicates incremental cost effectiveness ratio; and QALYs, quality-adjusted life years.

that this new definition would have a substantial impact on our results. Healthcare usage in each of the treatment arms might be underestimated as public hospital outpatient clinic costs are not recorded in the Medical Benefit Schedule and the cost of privately run allied health services and private hospital admissions are not covered by the Medical Benefit Schedule. However, it is not clear if this underestimation affects the difference in total cost between the combination and monotherapy. In the ASCS, patient characteristics that potentially affect costs and health utility were measured only at the baseline, and therefore the covariates in the models for predicting future costs and health utility were selected only from the baseline covariates. The lack of simulation of changes over time in time-varying characteristics such as WHO functional class and incorporation of these changes into the model to predict annual health utility and costs might increase the uncertainty in the estimated ICER. If combination therapy had reduced the rates of manifestation and deterioration of functional status compared with monotherapy, the ICER could have been overestimated because the differences in health outcomes between patients on combination therapy and those on monotherapy should have been increasing over time, potentially leading to smaller incremental cost and larger incremental health utility. Although we have adjusted the effect of combination therapy relative to monotherapy on mortality rate, healthcare cost, and health utility for a range of patient characteristics, including variables known to impact PAH outcomes such as PAH severity, there might be unknown confounding factors that we did not account for in our statistical models. However, we note that in our additional sensitivity analyses, varying the treatment effect by ±20% did not change our conclusions regarding the cost-effectiveness of combination therapy (Figures S1 and S2). To quantify the impact of changes in the treatment effect (see Table 4) on the ICERs, we (1) increased and decreased the hazard ratio (0.56) of mortality for combination therapy compared with monotherapy by 20%, (2) increased and decreased the odds ratio (0.580) of nonzero cost for combination therapy compared with monotherapy by 20%, and (3) increased and decreased the marginal effect (0.030) of combination therapy on health utility. We found that the change in the treatment effect on mortality resulted in moderate changes (~8%–25%) in ICERs, and the changes in the treatment effect on cost and health utility resulted in only small changes

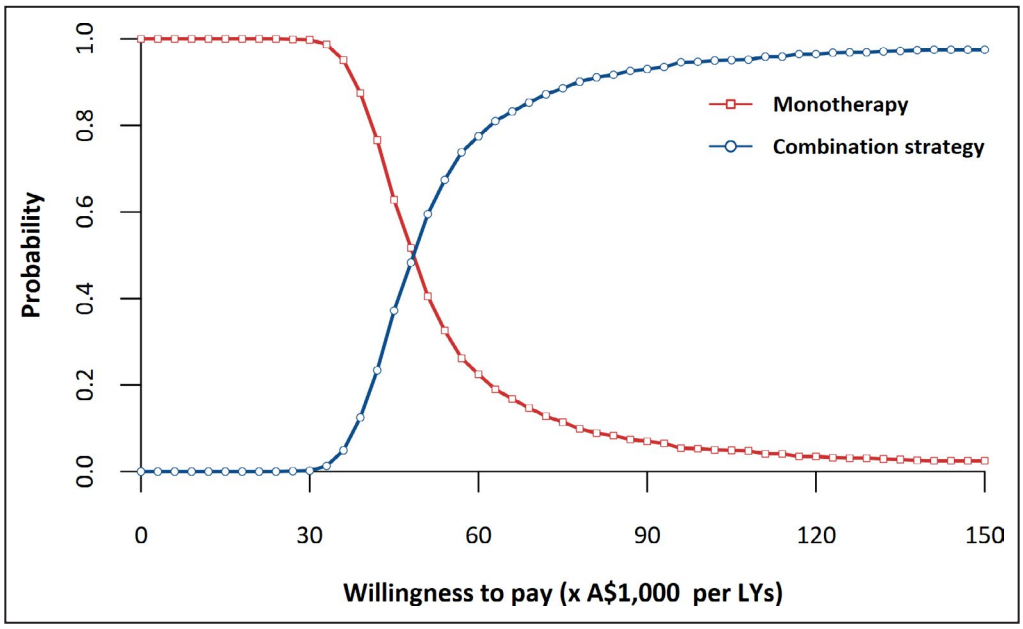

Figure 4. Cost-effectiveness acceptability curves for monotherapy and combination therapy with life years as effectiveness.

(~1%–5%) in ICERs (see Figures S1 and S2). These sensitivity analyses indicate that the ICERs were relatively sensitive to the effect of combination therapy on mortality. To reduce the uncertainty in the ICERs, priority should be given to conducting large studies on survival of patients receiving combination therapy versus monotherapy in which the treatment effect could be adjusted for a larger number of potential confounding factors. Furthermore, we were unable to evaluate the cost-effectiveness of triple combination therapy inclusive of prostacyclin agonists such as selexipag. As this class of drugs becomes increasingly available for use in PAH throughout the world, availability of long-term survival and HRQoL data will enable evaluation of cost-effectiveness analysis of "triple" combination therapy.

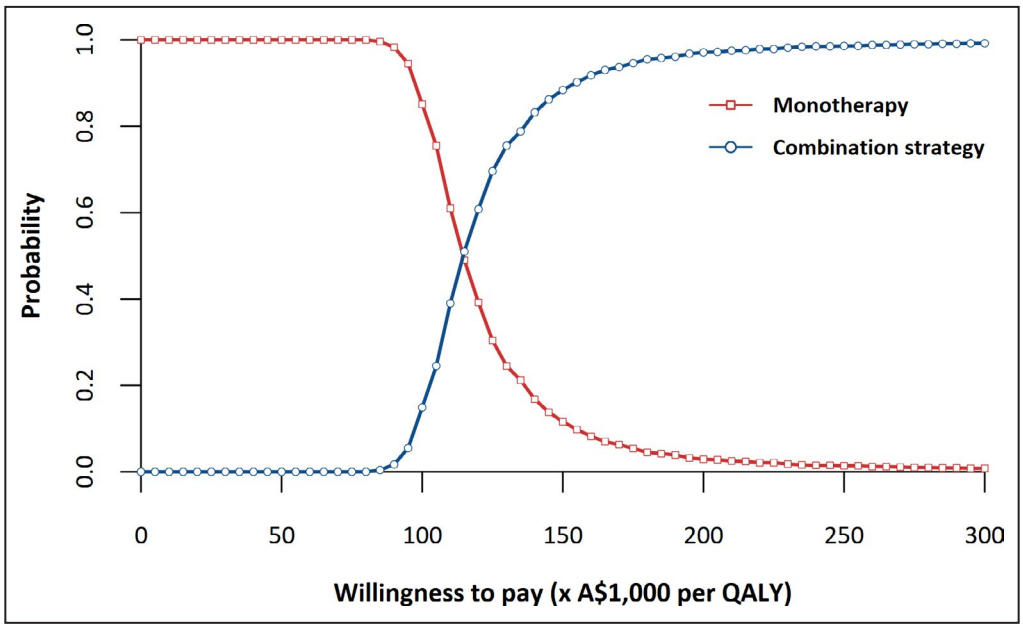

Figure 5. Cost-effectiveness acceptability curves for monotherapy and combination therapy with QALYs as effectiveness.
QALY indicates quality-adjusted life year.

CONCLUSIONS

Dual combination therapy in SSc-PAH compared with monotherapy can significantly improve patient survival and HRQoL, in terms of LYs and QALYs gained, but at a considerable direct cost to society. The ICER for dual combination therapy depends on the price of PAH drugs and the imminent expiration of patents and subsequent availability of lower-priced generics will likely improve the cost-effectiveness of dual combination therapy in SSc-PAH.

APPENDIX

Members of the Australian Scleroderma Interest Group Who Contributed Data

Mandana Nikpour (Melbourne, Victoria), Susanna Proudman (Adelaide, South Australia), Wendy Stevens (Melbourne, Victoria), Joanne Sahhar (Melbourne, Victoria), Lucy Croyle (Melbourne, Victoria), Nava Ferdowsi (Melbourne, Victoria), Kathleen Morrisroe (Melbourne, Victoria), Gene-Siew Ngian (Melbourne, Victoria), Gemma Strickland (Geelong, Victoria), Jennifer Walker (Adelaide, South Australia).

ARTICLE INFORMATION

Received December 31, 2019; accepted December 31, 2020.

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Acknowledgments

Author contributions: AT-D: study design, data analysis, simulation model development and execution, uncertainty and sensitivity analyses, interpretation of results, preparation of manuscript, and critical revision of the manuscript for important intellectual content. KM: study design, data collection, data analysis, interpretation of results, and preparation of manuscript. PC: study design, data analysis, interpretation of results, preparation of manuscript. WS: data collection, interpretation of results, and preparation of manuscript. SP: data collection, interpretation of results, and preparation of manuscript. JS: data collection, interpretation of results, and preparation of manuscript. MN: study design, data collection, data analysis, interpretation of results, and preparation of manuscript.

Sources of Funding

This work was supported by Scleroderma Australia, Arthritis Australia, Actelion Australia, Bayer, CSL Biotherapies, GlaxoSmithKline Australia, and Pfizer. MN holds a National Health and Medical Research Council of Australia Investigator Grant (GNT1176538). KM holds a Royal Australasian College of Physicians (RACP), Australian Rheumatology Association (ARA), and DEV Starr Research Establishment Fellowship. AT-D is partly supported by Australian Research Council Centre of Excellence in Population Ageing Research.

Disclosures

None.

Supplementary Material

Figures S1–S2

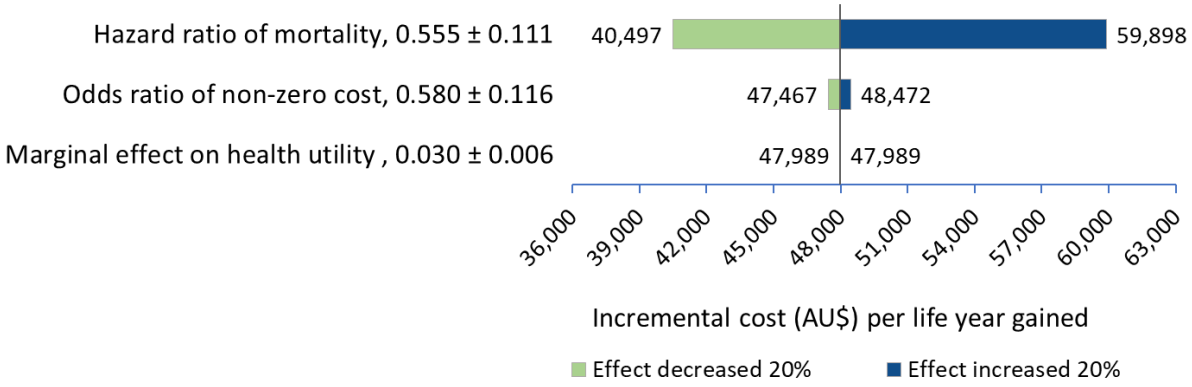
REFERENCES

1. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum*. 2008;37:223–235. DOI: 10.1016/j.semarthrit.2007.05.003.
2. Thombs BD, Taillefer SS, Hudson M, Baron M. Depression in patients with systemic sclerosis: a systematic review of the evidence. *Arthritis Rheum*. 2007;57:1089–1097. DOI: 10.1002/art.22910.
3. Hao Y, Thakkar V, Stevens W, Morrisroe K, Prior D, Rabusa C, Youssef P, Gabbay E, Roddy J, Walker J, et al. A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis. *Arthritis Res Ther*. 2015;17:7. DOI: 10.1186/s13075-015-0517-5.
4. Hao Y, Hudson M, Baron M, Carreira P, Stevens W, Rabusa C, Tatibouet S, Carmona L, Joven BE, Huq M, et al. Early mortality in a multinational systemic sclerosis inception cohort. *Arthritis Rheumatol*. 2017;69:1067–1077. DOI: 10.1002/art.40027.
5. Morrisroe K, Stevens W, Huq M, Prior D, Sahhar J, Ngian GS, Celermajer D, Zochling J, Proudman S, Nikpour M. Survival and quality of life in incident systemic sclerosis-related pulmonary arterial hypertension. *Arthritis Res Ther*. 2017;19:122. DOI: 10.1186/s13075-017-1341-x.
6. Morrisroe K, Stevens W, Sahhar J, Ngian GS, Rabusa C, Ferdowsi N, Hill C, Proudman S, Nikpour M. Quantifying the direct public health care cost of systemic sclerosis: a comprehensive data linkage study. *Medicine (Baltimore)*. 2017;96:e8503. DOI: 10.1097/MD.0000000000008503.
7. Morrisroe K, Huq M, Stevens W, Rabusa C, Proudman SM, Nikpour M. Determinants of unemployment amongst Australian systemic sclerosis patients: results from a Multicentre Cohort Study. *Clin Exp Rheumatol*. 2016;34(Suppl 100):79–84.
8. Anand V, Roy SS, Archer SL, Weir EK, Garg SK, Duval S, Thenappan T. Trends and outcomes of pulmonary arterial hypertension-related hospitalizations in the United States: analysis of the nationwide inpatient sample database from 2001 through 2012. *JAMA Cardiol*. 2016;1:1021–1029. DOI: 10.1001/jamacardio.2016.3591.
9. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. 1991;115:343–349. DOI: 10.7326/0003-4819-115-5-343.
10. Chen YF, Jowett S, Barton P, Malottki K, Hyde C, Gibbs JS, Pepke-Zaba J, Fry-Smith A, Roberts J, Moore D. Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation. *Health Technol Assess*. 2009;13:1–320. DOI: 10.3310/hta13490.
11. Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grunig E, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373:834–844. DOI: 10.1056/NEJMoa1413687.
12. Ngian GS, Stevens W, Prior D, Gabbay E, Roddy J, Tran A, Minson R, Hill C, Chow K, Sahhar J, et al. Predictors of mortality in connective tissue disease-associated pulmonary arterial hypertension: a Cohort Study. *Arthritis Res Ther*. 2012;14:R213. DOI: 10.1186/ar4051.
13. Simonneau G, Rubin LJ, Galie N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med*. 2008;149:521–530. DOI: 10.7326/0003-4819-149-8-200810210-00004.
14. Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, Miller DP, Nicolls MR, Zamanian RT. Characterization of connective tissue disease-associated pulmonary arterial hypertension from reveal: identifying systemic sclerosis as a unique phenotype. *Chest*. 2010;138:1383–1394. DOI: 10.1378/chest.10-0260.

15. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Kumar RK, Landzberg M, Machado RF, et al. Updated clinical classification of pulmonary hypertension. *Turk Kardiyol Dern Ars*. 2014;42(Suppl 1):45–54.
16. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Kardiol Pol*. 2015;73:1127–1206. 10.5603/KP.2015.0242.
17. Masi AT. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum*. 1980;23:581–590. DOI: 10.1002/art.1780230510.
18. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. *J Rheumatol*. 2001;28:1573–1576.
19. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA Jr, Carreira PE, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2013;72:1747–1755. DOI: 10.1136/annrheumdis-2013-204424.
20. Ara R, Brazier J. Predicting the short form-6d preference-based index using the eight mean short form-36 health dimension scores: estimating preference-based health-related utilities when patient level data are not available. *Value Health*. 2009;12:346–353. DOI: 10.1111/j.1524-4733.2008.00428.x.
21. Reference: R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2017. Available at: https://www.R-project.org/. Accessed January 4, 2021.
22. Roche products pty ltd. Access to oncology medicines in Australia, Roche response to medicines Australia oncology industry taskforce report. Available at: Medicinesaustralia.Com.Au/files/2013/07/131021_oit_roche_response_final_.Pdf.
23. Lowe ADS.New therapies for advanced cancers: can our society afford them? Is it ethical to deny patients access to them? Actuaries Institute 2013 actuaries summit. Sydney, Australia.
24. Wang S, Gum D, Merlin T. Comparing the ICERs in medicine reimbursement submissions to NICE and PBAC-does the presence of an explicit threshold affect the ICER proposed? *Value Health*. 2018;21:938–943. DOI: 10.1016/j.jval.2018.01.017.
25. Cameron D, Ubels J, Norstrom F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Glob Health Action*. 2018;11:1447828. DOI: 10.1080/16549716.2018.1447828.
26. McCabe C, Claxton K, Culyer AJ. The nice cost-effectiveness threshold: what it is and what that means. *Pharmacoeconomics*. 2008;26:733–744. DOI: 10.2165/00019053-200826090-00004.
27. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med*. 2014;371:796–797. DOI: 10.1056/NEJMp1405158.
28. Shiroiwa T, Igarashi A, Fukuda T, Ikeda S. WTP for a QALY and health states: more money for severer health states? *Cost Eff Resour Alloc*. 2013;11:22. DOI: 10.1186/1478-7547-11-22.
29. Raad voor de volksgezondheig en zorg. Zicht op zinnige enduurzame zorg. Quantes, rijswijk. Available at: http://rvz.Net. Accessed January 4, 2021.
30. Collins M, Latimer N. Nice's end of life decision making scheme: impact on population health. *BMJ (Clinical research ed.)*. 2013;346:f1363.
31. Verma V, Sprave T, Haque W, Simone CB II, Chang JY, Welsh JW, Thomas CR Jr. A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. *J Immunother Cancer*. 2018;6:128. DOI: 10.1186/s40425-018-0442-7.
32. Morrisroe K, Sudararajan V, Stevens W, Sahhar J, Zochling J, Roddy J, Proudman S, Nikpour M. Work productivity in systemic sclerosis, its economic burden and association with health-related quality of life. *Rheumatology (Oxford, England)*. 2018;57:73–83. DOI: 10.1093/rheumatology/kex362.
33. Hutubessy R, Chisholm D, Edejer TT. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. *Cost Eff Resour Alloc*. 2003;1:8. DOI: 10.1186/1478-7547-1-8.
34. Trading economics: Available at: https://tradingeconomics.Com/australia/gdp-per-capita-ppp. Accessed January 4, 2021.

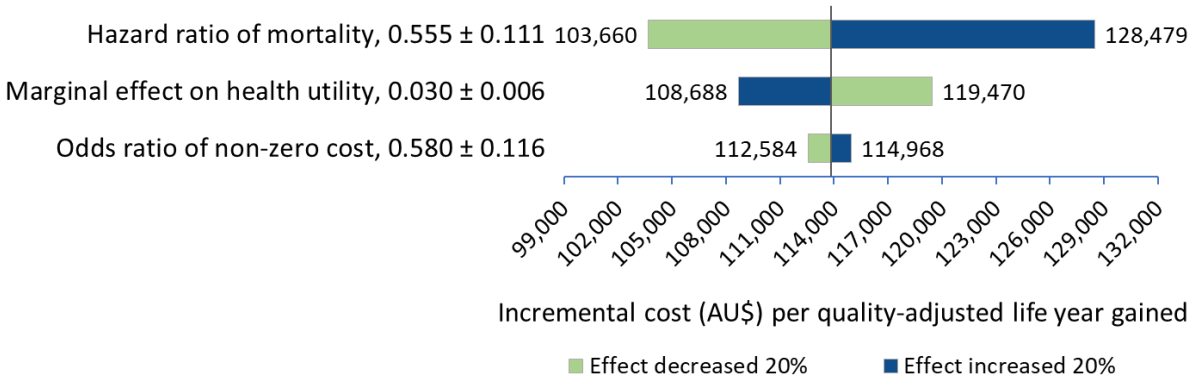
Supplemental Material

Figure S1. Tornado plot of the impact of changes in the treatment effect on the incremental cost-effectiveness ratio (ICER; AU$ per life year gained).



The tail of each bar represents the absolute value of ICERs corresponding to the new value of the treatment effect. In the base case analysis, the incremental cost (AU$) per life year gained was 47,989, which is the x-coordinate of the vertical line.

Figure S2. Tornado plot of the impact of changes in the treatment effect on the incremental cost-effectiveness ratio (ICER; AU$ per quality-adjusted life year (QALY)) gained.



The tail of each bar represents the absolute value of ICERs corresponding to the new value of the treatment effect. In the base case analysis, the incremental cost (AU$) per QALY gained was 113,823, which is the x-coordinate of the vertical line.