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The cost-effectiveness of canakinumab for secondary prevention of cardiovascular disease: The Australian healthcare perspective

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ABSTRACT

Background: Canakinumab is a fully human monoclonal antibody targeting interleukin-1β. It is currently indicated for use in those with rheumatologic disorders due to its anti-inflammatory properties, and was recently shown to be beneficial for the secondary prevention of cardiovascular disease (CVD). However, the cost-effectiveness of canakinumab used to treat CVD is unknown.

Methods: A Markov state transition model was developed and populated with a hypothetical sample of 1000 individuals profiled on the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS); with a history of myocardial infarction (MI) and blood concentrations of high-sensitivity C-reactive protein (hsCRP) of >2 mg/L. With each annual cycle, individuals could have a recurrent non-fatal CVD event (MI or stroke), or die from a CVD event or die from other causes based on data from CANTOS. Individuals continued to cycle through the model for 20 years or until death. Cost and utility data was applied. Outcomes were discounted (5% annually).

Results: Over a 20-year time horizon, canakinumab is predicted to prevent 40 recurrent cardiovascular events and save 287 (discounted) years of life and 239 (discounted) quality-adjusted life years (QALYs) in 1000 individuals. At an annual cost of AUD36,049 (USD25,590, GBP19,662) per person, canakinumab would not be considered cost-effective within the Australian healthcare system, with an incremental cost-effectiveness ratio (ICER) of AUD1,221,170 per QALY gained.

Conclusions: Canakinumab is an attractive treatment option to reduce recurrent CVD among patients with high hsCRP. It would be considered cost-effective in this treatment setting within the perspective of the Australian public healthcare system if its annual costs do not exceed AUD1500 (USD1065, GBP818) per person.

1. Introduction

Inflammatory markers, such as high-sensitivity C-reactive protein (hsCRP) and interleukin-6, have been shown to be associated with an increased risk of cardiovascular disease (CVD) [1,2]. Subsequently, studies have suggested that reducing inflammation may reduce the risk of CVD [3]. However, until recently, this has only been demonstrated with statin therapy, which reduces both inflammation and cholesterol levels concurrently [3].

Canakinumab is a fully human monoclonal antibody targeting interleukin-1β, a pro-inflammatory cytokine which plays a central role in driving the interleukin-6 signalling pathway. Canakinumab is currently approved for clinical use in the treatment of rheumatologic disorders due to its anti-inflammatory properties [4,5]. More recently, canakinumab has demonstrated positive results in cancer [6] and vascular disease trials [7].

The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) was a randomised, placebo-controlled trial which showed that treatment with canakinumab significantly reduced the recurrence of cardiovascular events compared to placebo in patients with a history of myocardial infarction and hsCRP levels of >2 mg/L [7]. Both canakinumab and placebo were administered against a background of recommended secondary prevention therapies. At a median follow-up of 3.7 years, 150 mg and 300 mg of canakinumab administered every 3 months significantly reduced the primary composite endpoint of non-fatal myocardial infarction (MI), stroke and cardiovascular death (15% and 14%, respectively), compared to placebo [7]. Secondary analysis of CANTOS according to on-treatment hsCRP level demonstrated that with any dose of canakinumab, those with a hsCRP concentration <2 mg/L had a larger (25%) reduction in the primary endpoint [8].

The cost-effectiveness of canakinumab for the prevention of cardiovascular disease is unknown. We aimed to determine the effectiveness and cost-effectiveness of canakinumab for the secondary prevention of CVD, from the perspective of the Australian public healthcare system.

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2. Methods

2.1. Model structure

A Markov state transition model [9] was developed to simulate the experiences of a hypothetical cohort of 1000 individuals with established CVD over a 20-year time horizon. With each annual cycle, individuals could remain in their current health state (healthy but with previous CVD, have a recurrent non-fatal CVD event or die, Fig. 1). The health state entered was determined by transition probabilities that underpinned their movement in any cycle (see below). Individuals continued to cycle through the model for 20 years or until death. All events were assumed to occur half-way through a cycle [10].

The model estimated the number of recurrent CVD events, quality-adjusted life years (QALYs), years of life lived and total costs. Decision analysis [9] was used to compare the downstream health and economic outcomes incurred by subjects treated with 150 mg of canakinumab compared to subjects treated with placebo. The primary outcome was the incremental cost-effectiveness ratio (ICER) in terms of cost per QALY and cost per year of life saved, where cost-effectiveness was determined assuming a threshold of AUD50,000 per QALY saved [11].

2.2. Population

The model population comprised an arbitrary sample of 1000 individuals profiled on the CANTOS population [7]. CANTOS was conducted in 39 countries drawn particularly from developed countries, including Australia. The trial population included adults with a history of myocardial infarction and a blood hsCRP concentration of >2 mg/L despite treatment with aggressive secondary prevention strategies. Baseline characteristics of CANTOS subjects are detailed elsewhere [7]. The model population was assumed to be aged 61 years at baseline, in line with the mean age of the CANTOS population at baseline.

2.3. Transition probabilities

Transition probabilities are summarised in Table 1. In Cycle 1, the probability of developing an event (non-fatal CVD, fatal CVD or death from other causes) was determined from incidence rates observed in CANTOS [7]. The probability of a non-fatal CVD event included non-fatal MI and non-fatal stroke and was derived by subtracting the risk of cardiovascular death from the primary outcome in CANTOS, which comprised cardiovascular death, non-fatal MI and non-fatal stroke. The probability of death from other causes was derived by subtracting cardiovascular death from all-cause death.

With each subsequent cycle (Cycle 2 and beyond), the probability of an event was adjusted as per age-related changes. Age-related changes for risk of fatal CVD and death from other causes were derived from age-specific differences in Australian mortality rates. Death from other causes was calculated as death from all causes minus death from circulatory causes. Five-year mortality rates reported by the Australian Institute of Health and Welfare for the last available year (2014) [12] for death from all causes and death from circulatory causes were extrapolated to single years using exponential functions (see Appendix 1). That is, the mid-point of each age-group and corresponding incidence for each cause of death were plotted and exponential functions were fitted to determine single age-related changes. For example, the derived risk of death from circulatory disease was 0.102% for a 61 year old and 0.117% for a 62 year old [12]. Therefore, the probability of a fatal CVD event was increased by a factor of 1.15 in moving from age 61 to 62 years. The age-related changes in risk of non-fatal CVD events were assumed to be equivalent to fatal CVD, in line with results from a recent Australian study which reported that age-specific trends of non-fatal and fatal recurrent coronary heart disease (CHD) are well matched [13].

After an individual experienced a recurrent non-fatal CVD event, he/she could either remain alive or die. The risk of death (from CVD or non-CVD causes) was derived from incidence rates observed in CANTOS, and was adjusted for the increased mortality risk conferred by recurrent MI and stroke by 1.56 [14] and 2.3 [15], respectively. Taking into account the proportion of non-fatal MI and stroke events, weighted average values of 1.73 and 1.77 were applied to the placebo and canakinumab arm, respectively. As mentioned above, age-related changes in risk were applied.

2.4. Costs

Acute event costs for non-fatal and fatal CVD were assumed to be those incurred in hospital. We conservatively assumed that only 50% of fatal CVD events occurred in hospital. These were derived from hospitalization admission data for Australian Refined Diagnosis Related Groups (AR-DRGs) reported for the most recent financial year 2013–2014 for which financial data is available [16]. The cost of non-fatal MI was derived as the weighted average cost for AR-DRG codes F41A and F60A (AUD10,217), the cost of non-fatal stroke was derived as the weighted average cost for AR-DRG codes B70A, B70B and B70C (AUD12,469), and the cost of CVD death was derived as the weighted average cost of AR-DRG F41B, F60B and B70D (AUD5,292).

Chronic disease costs for non-fatal CVD were derived from 2008 reported costs in a study by Cobiac et al. [17].

The cost of CVD was calculated prior to and following recurrent CVD events. The cost following events were determined as weighted average values based on the proportion of the population with MI and stroke in each treatment arm as observed in CANTOS [7]. These were 76.7% and 23.3% for the placebo arm and 72.0% and 28.0% for the canakinumab arm, respectively.

The cost of death from other causes was equivalent to the cost of fatal CVD, assuming 50% of these occurred in hospital.

The acquisition cost of canakinumab in Australia is currently unknown. The Australian Pharmaceutical Benefits Scheme (PBS), which subsidises medicines for Australian residents, does not currently subsidise canakinumab [18]. In the US, the cost of canakinumab is USD16,000 per dose [19], totalling USD64,000 per annum. As per expert opinion, we adjusted this price according to the pricing ratio of pharmaceuticals in the US and Australia using PCSK9 inhibitors as a reference drug. That is, in the US current prices of PCSK9 inhibitors are USD14,523 [20], while in Australia they are AUD8180 [21]. Thus, the pricing ratio is 1:0.563 and PCSK9 inhibitors are therefore 43.7% less expensive in Australia compared to the US. Assuming this pricing ratio, the cost of canakinumab in Australia was assumed to be AUD36,049 (USD25,590, GBP19,662).

In addition, the cost of canakinumab was adapted from US to Australian dollars using a recently published method which comprised a three-step process: correction for varying levels of resource utilisation, modification for varying prices of healthcare services, and adjustment for changes in level of resource utilisation over time [22]. As mentioned above, the current cost of canakinumab per person per year in the US is USD64,000 (in 2013 values). For adaptation to Australian-equivalent prices, this value was multiplied by 0.4849 [23] for resource utilisation, then by 1.44 [24] for differences in healthcare prices as per the purchase parity power, and by 1.09 [25] for changes in costs over time, resulting in an annual cost of AUD49,304 (2016 values). Finally, a range of values were tested to determine the annual cost per person at which canakinumab would be considered cost-

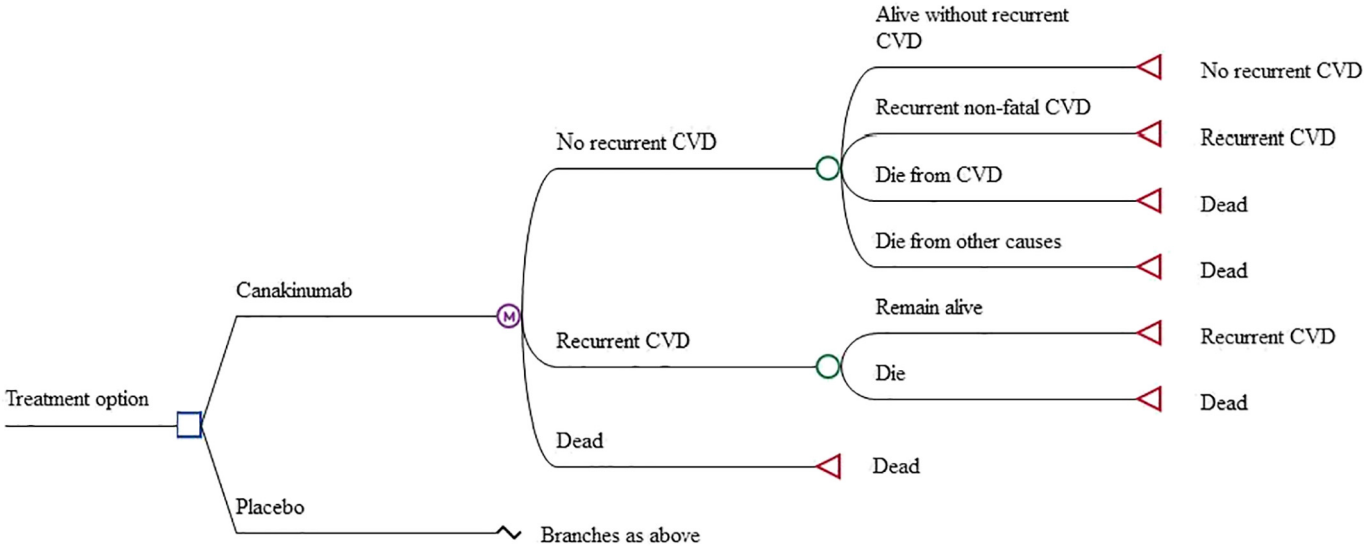

Fig. 1. Tree diagram of the Markov state transition model and possible health states. *Non-fatal and fatal cardiovascular disease (CVD) is limited to myocardial infarction (MI) and stroke events only.

Table 1
Model inputs for the base-case analysis.

Parameter	Point estimate		95% CI		Distribution	Reference
	Canakinumab	Placebo	Canakinumab	Placebo		
Transition probabilities for cycle 1 (per 100 person-year)						
Non-fatal MI/stroke	2.60	3.06	1.99 to 3.29	2.50 to 3.67	Beta	[7]
CVD death	1.26	1.44	0.84 to 1.76	1.06 to 1.87	Beta	[7]
Non-CVD death	1.47	1.53	1.02 to 2.00	1.14 to 1.97	Beta	[7]
Costs (AUD)						
Annual no recurrent CVD	5524		140 to 20,376		Gamma	[17]
Acute non-fatal CVD	19,360	18,752	490 to 71,417	475 to 69,175	Gamma	[16]
Annual recurrent CVD	5067	5144	128 to 18,692	130 to 18,974	Gamma	[17]
CVD death	2646		67 to 9761		Gamma	[16]
Non-CVD death	2646		67 to 9761		Gamma	[16]
Utilities						
No recurrent CVD	0.80		0.79 to 0.81		Beta	[26]
Recurrent CVD	0.70		0.68 to 0.72		Beta	[26]

AUD = Australian dollars, CI = confidence interval, CVD = cardiovascular disease, MI = myocardial infarction; all costs are reported in 2018 values; the acute and annual costs of recurrent non-fatal CVD were derived from the reference costs as weighted values based on the proportional distribution of MI and stroke.

effective: AUD5000 (USD3549, GBP2727), AUD4000 (USD2839, GBP2182), AUD3000 (USD2130, GBP1636), AUD2000 (USD1420, GBP1091), AUD1500 (USD1065, GBP818) and AUD1000 (USD710, GBP545).

All included costs were inflated to 2018 prices to reflect current prices, using the total health price index (TPI) [25].

The 2018 values included in the model are reported in Table 1 and are expressed in Australian dollars (AUD). The costs of acute non-fatal CVD and following a recurrent event represent the weighted average values as described above and differ for each treatment arm due to differences in the proportional distribution of MI and stroke.

2.5. Utilities

All individuals entered the model with a utility of 0.80 (standard deviation [SD] 0.23), derived from the Valsartan in Acute Myocardial Infarction (VALIANT) trial [26], to reflect that the included population had an existing history of MI. The utility ascribed to subjects who suffered a subsequent cardiovascular event was assumed to fall to 0.70 (SD 0.29) [26].

2.6. Discounting

All future outcomes (QALYs, years of life lived and costs) were discounted by 5% annually as per current Australian guidelines [27].

2.7. Sub-group and sensitivity analyses

A series of deterministic sensitivity analyses (DSA) were performed to assess the impact of uncertainty surrounding key input parameters, when assuming a base case cost of canakinumab of AUD36,049 (USD25,590, GBP19,662) per year. The ICERs resulting from each DSA were recorded for the upper and lower value and are presented in a Tornado diagram. To account for joint parameter uncertainty, probabilistic sensitivity analyses (PSA) with Monte Carlo sampling were undertaken using 10,000 iterations. The input parameters, variations and corresponding distributions are presented in Table 1. As variance in transition probabilities and costs were not available, methodology employed by Briggs was applied [9]. Transition probabilities and utilities were assumed to be beta distributions, while costs assumed gamma distributions.

We performed a secondary analysis, stratifying the model population by on-treatment hsCRP level at 3 months. Data on the risk of events according to hsCRP level (<2 mg/L), and compared to placebo, were informed by updated data from CANTOS [8] and analysed separately.

3. Results

Sixteen non-fatal CVD events and 24 fatal CVD events were prevented in 1000 individuals treated with canakinumab compared to placebo over 20 years, equating to numbers needed to treat of 61 and 41, respectively. In total, 287 (discounted) years of life and 239 (discounted) QALYs were saved among 1000 individuals over 20 years. Table 2 summarises the ICERs (mean values and 95% confidence intervals [95%CI]) with varying annual treatment costs of canakinumab. At an annual treatment cost of AUD36,059 (USD25,590, GBP19,662), the total (discounted) costs were AUD51,203,493 in the placebo arm and AUD342,479,762 in the canakinumab arm. The ICERs were AUD1,013,338 (USD719,338, GBP552,692) per year of life saved and AUD1,221,170 (USD866,871, GBP666,047) per QALY gained. Using the recently published measure to adapt costs of canakinumab to Australian dollars (AUD49,304), the ICERs increased to AUD1,384,319 (USD982,686, GBP755,031) per year of life saved and AUD1,668,237 (USD1,184,230, GBP909,885) per QALY gained. Reducing the annual treatment cost of canakinumab to AUD1500 (USD1065, GBP818) per person, the total costs (discounted) were reduced to 64,535,926 in the canakinumab arm and the ICERs were AUD46,383 (USD32,926, GBP25,298) per year of life saved and AUD55,896 (USD39,679, GBP30,487) per QALY gained.

Our PSA results are shown in Fig. 2, highlighting that with 100% of iterations, canakinumab at an acquisition cost of AUD36,049 (USD25,590, GBP19,662) does not meet Australia's cost-effectiveness threshold of AUD50,000 (USD35,494, GBP27,271). In fact, 25% of iterations demonstrated canakinumab was more costly and produced poorer outcomes (as measured by QALYs). Results from the one way deterministic sensitivity analyses are depicted in the Tornado diagram in Appendix 2. The red bars represent the ICER produced by the lower bound of the interval and the blue bars represent the ICER produced by the upper bound of the interval. These results demonstrated that the utilities and costs of recurrent CVD (for both placebo and canakinumab) were the key drivers of cost-effectiveness. Variance in transition probabilities resulted in dominated ICERs, where canakinumab was more costly and less effective. Specifically, this occurred when placebo transition probabilities for mortality were lower than the canakinumab arm and vice versa, and therefore transition probabilities were omitted from the graph. The ICERs produced from the one-way sensitivity analyses are reported in Appendix 3.

Our secondary analysis by on-treatment hsCRP level at 3 months demonstrated that in those with an on-treatment hsCRP level of <2 mg/L, 1018 (discounted) years of life were saved and 803 (discounted) QALYs were saved. Analysis of acquisition costs is included in Appendix 4.

4. Discussion

To the best of our knowledge, this is the first effectiveness and cost-effectiveness analysis of canakinumab for the prevention of recurrent CVD. At current estimated acquistion prices, canakinumab is not considered cost-effective. Our results show that an acquisition annual price of AUD1500 (USD1065, GBP818) per person would meet willingness to pay thresholds of AUD50,000 (USD35,494, GBP27,271) per QALY gained. Cost-effectiveness was improved in those with an on-treatment hsCRP level of <2 mg/L, resulting in higher acquisition prices of up to AUD4000 (USD2840, GBP2182) per person per annum.

Table 2
The incremental cost-effectiveness ratios for canakinumab versus placebo in a cohort of 1000 people with MI and baseline hsCRP >2 mg/L over 20 years, using a range of treatment costs.

Annual treatment cost per person (AUD)	YLL		QALYs		Total costs		ICER	
	Canakinumab	Placebo	Canakinumab	Placebo	Canakinumab	Placebo	$/YoLS	$/QALY
36,049	8045	7757	6268	5030	342,479,762	51,203,493	1,013,338	1,221,170
49,304					449,115,136		1,384,319	1,668,237
5000					92,693,135		144,341	173,945
4000					84,648,218		116,353	140,216
3000					76,603,302		88,365	106,488
2000					68,558,385		60,377	72,760
1500					64,535,926		46,383,	55,896
1000					60,513,468		32,389	39,032

AUD = Australian dollars, CI = confidence intervals, ICER = incremental cost-effectiveness ratio, IQR = interquartile range, QALY = quality-adjusted life year, YLL = years of life lived, YoLS = years of life saved. All outcomes and costs reported are discounted values. YLL, QALYs, and total costs for the placebo arm remain constant.

Canakinumab is currently indicated for use in those with juvenile idiopathic arthritis [4,28] and gouty arthritis [29] and is priced at USD16,000 per dose (AUD22,540) in the US [19] and GBP9927.80 (AUD18,202) in the UK [31]. While direct comparisons cannot be made due to lack of Australia specific costs and cost-effectiveness studies thus far, other new secondary prevention CVD therapies such as proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors have shown similar results. PCSK9 inhibitors have been shown to be effective at reducing lipid levels [32], and in turn cardiovascular events [33], but they are currently only approved for use in those with familial hypercholesterolemia. Studies in the US and UK have shown that in secondary prevention CVD populations, at current acquisition prices (which are 80% less than that of canakinumab per year of treatment), PCSK9 inhibitors would not be considered cost-effective [34–37]. Similar results were seen in Australia, where the current price of PCSK9 inhibitors is just over AUD8000 (USD5679, GBP4363) per person per year [38]. In fact, Australia demonstrated that while cost-effectiveness was improved in higher risk patients as a result of increased cardiovascular benefits, price was the key driver in meeting cost-effectiveness thresholds and acquisition costs would need to be reduced to less than AUD1500 (USD1065, GBP818) per person per year to meet cost-effective thresholds [38].

There are several limitations to our study. First, canakinumab is associated with increased risk of serious acute infections and death from infections. The incidence rates of any serious infective adverse event in CANTOS were 2.86 and 3.13 per 100 person years in the placebo and 150 mg canakinumab arms, respectively ($p = 0.12$) and for fatal infection or sepsis, the respective incidences were 0.18 and 0.28 ($p = 0.09$). Conversely, canakinumab improved cancer outcomes, with incidences for any cancer of 1.88 and 1.69 ($p = 0.31$) per 100 person years in the placebo and 150 mg canakinumab arms, respectively, and 0.64 and 0.50 ($p < 0.001$) for fatal cancer, respectively. The non-fatal harms and potential additional benefits were not included in the model. However, the effects in reducing fatal cancer and increasing fatal sepsis are captured in the modelling of non-vascular deaths using CANTOS mortality data. Secondly, the cardiovascular benefits of canakinumab were based on short term data. In our model, incidence rates observed in CANTOS were applied to the first cycle and thereafter, rates were increased according to age-related changes in both arms equally. Therefore, no additional treatment effect of canakinumab was assumed beyond the first year. This may be a conservative assumption given that the survival curves observed in CANTOS continued to diverge over the entire duration of the trial. Third, CANTOS did not see a statistically significant reduction in all-cause mortality or cardiovascular

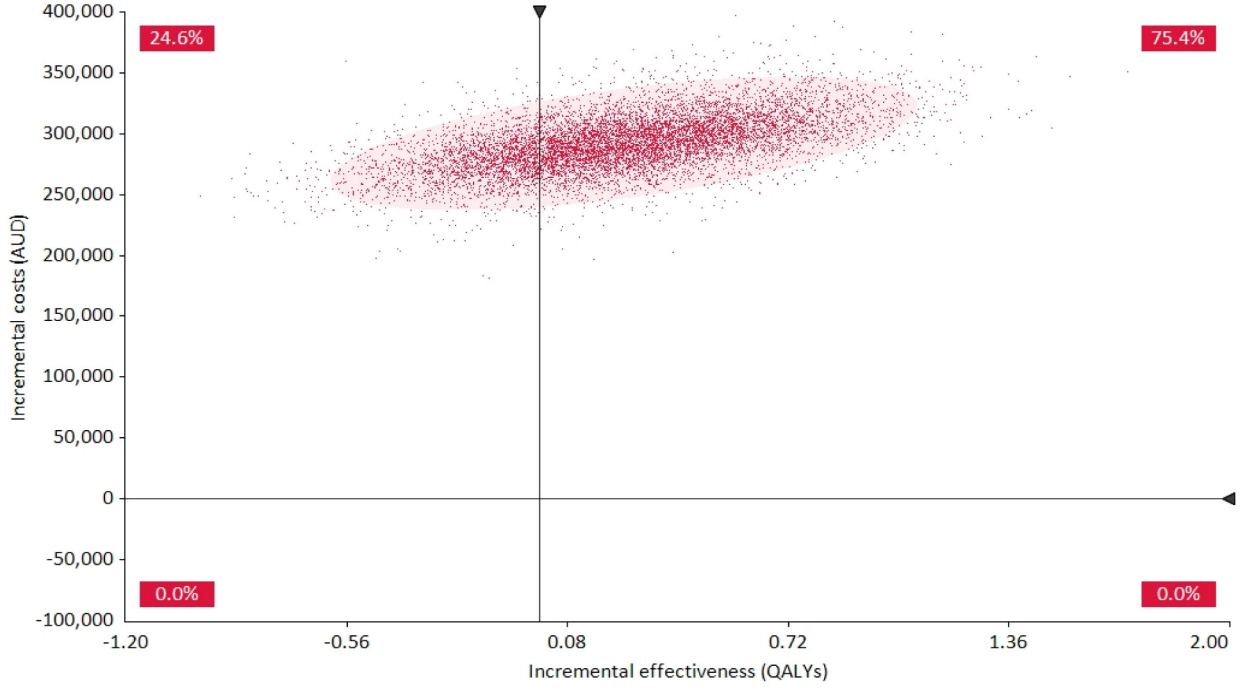

Fig. 2. Cost-effectiveness plane of 10,000 iterations assuming an annual cost of canakinumab of AUD36,049 per person. AUD = Australian dollars, QALYs = quality-adjusted life years.

death and therefore the transition probabilities for death (from cardiovascular or from other causes) may be an over- or under-estimate. Our PSA analysis, which incorporates variability in transition probabilities, demonstrates that canakinumab is not cost-effective to the healthcare system, with 25% of iterations demonstrating higher costs and poorer health (as measured by QALYs) and 75% of iterations demonstrating greater costs and better health. These negative results are driven by the variability surrounding mortality estimates. Fourth, transition probabilities in our model were directly based on the risk of events observed in CANTOS, and hence the results may not be applicable to patient populations not represented by the inclusion and exclusion criteria of CANTOS.

5. Conclusions

The cardiovascular benefits of canakinumab have been demonstrated in a secondary prevention setting, but its cost-effectiveness remains unknown. Canakinumab would be considered cost-effective within the perspective of Australian public healthcare system at an annual per person cost of AUD1500 (USD1065, GBP818) or less.

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Contributions

- DL conceived and designed the study.
- DL and EZ developed the model.
- EZ and ZA performed the analysis and interpretation of the data.
- All authors provided intellectual input, critically revised the manuscript and approved the final version.
- EZ is the guarantor.
- The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Disclosures

EZ has received study grants from AstraZeneca, Pfizer and Shire. DL has served on advisory boards for Amgen regarding evolucumab. DL has received honoraria or study grants from Abbvie, Astellas, AstraZeneca, Bohringer Ingelheim, Bristol Myers Squibb, Novartis, Pfizer, Sanofi and Shire. AT has received research funding from Bayer and honoraria or travel expenses from Amgen, Bayer, Merck and Pfizer. JMT is a recipient of an Early Career Fellowship from the National Health and Medical Research Council (Australia). ZA has no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.037.

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