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# The cost-effectiveness of PCSK9 inhibitors - The Australian healthcare perspective

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ABSTRACT

*Background:* For patients in whom statins are not tolerated or effective as monotherapy, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) represent a new class of lipid lowering therapies that may reduce low-density lipoprotein cholesterol (LDL-C) levels by up to 50% and lower cardiovascular events. While an important treatment option, the cost-effectiveness of PCSK9i in Australia remains unknown. This study aimed to determine the cost-effectiveness of PCSK9i compared to placebo in the prevention of atherosclerotic cardiovascular disease (CVD).

*Methods and results:* A Markov cohort state-transition model was developed in Microsoft Excel. A hypothetical sample of 1000 individuals based on subjects in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial populated the model. With each five-year cycle, model subjects could have non-fatal CVD events (myocardial infarction and/or stroke), or die from CVD or other causes. Follow-up was simulated for 25 years. CVD risk reduction, cost and utility data were gathered from published sources. At current acquisition prices (AU$8174 per person per year), the incremental cost effectiveness ratio (ICER) was AU$308,558 per quality-adjusted life year (QALY) saved. Acquisition prices would need to be reduced to approximately AU$1500 per person per annum for PCSK9i to reach the arbitrary cost-effectiveness threshold of AU$50,000 per QALY saved.

*Conclusion(s):* PCSK9i are an effective alternative for those with existing CVD or at high risk of CVD in whom statin therapy alone is ineffective, but are not cost-effective to the Australian healthcare system based on current prices.



## 1. Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are highly efficacious at reducing low density lipoprotein cholesterol (LDL-C) levels and lowering CVD risk [1] and currently comprise first line therapy in the treatment of hyperlipidaemia and prevention of CVD [2]. Previous research has demonstrated that a decrease of 1 mmol/L of LDL-C results in an approximate 20% decrease in risk of CVD major vascular events [1,3].

However, statins are unsuitable for approximately 5 to 10% of individuals, predominantly due to intolerance or ineffectiveness as monotherapy [4]. For such people, the new class of lipid lowering agents, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), represents an alternative treatment option. Randomised controlled trials of PCSK9i thus far have demonstrated reductions in LDL-C levels by >50% compared to placebo [5]. More recently, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial reported that on a background of statin therapy, the PCSK9i evolocumab reduced the risk of CVD outcomes [6]. Hence PCSK9i represent an important treatment option for patients with statin intolerance and/or ineffectiveness, but their cost-effectiveness is currently unknown.

This study sought to determine the long-term effectiveness and cost-effectiveness of PCSK9i from the Australian healthcare perspective.

## 2. Methods

### 2.1. Model structure

A Markov state-transition model was developed in Microsoft Excel to assess the cost-effectiveness of PCSK9i versus placebo in the prevention of CVD. The model structure is conceptualized in Fig. 1.

With each 5-year cycle, model subjects could develop non-fatal CVD events (myocardial infarction [MI] and/or stroke), fatal CVD or die from other causes. All events were assumed to occur half-way through the cycle. Individuals continued to cycle through the model for 25 years or until death.

The model estimated the number of CVD events, quality-adjusted life years (QALYs), years of life lived and total costs for the treatment (PCSK9i) and no treatment (placebo)

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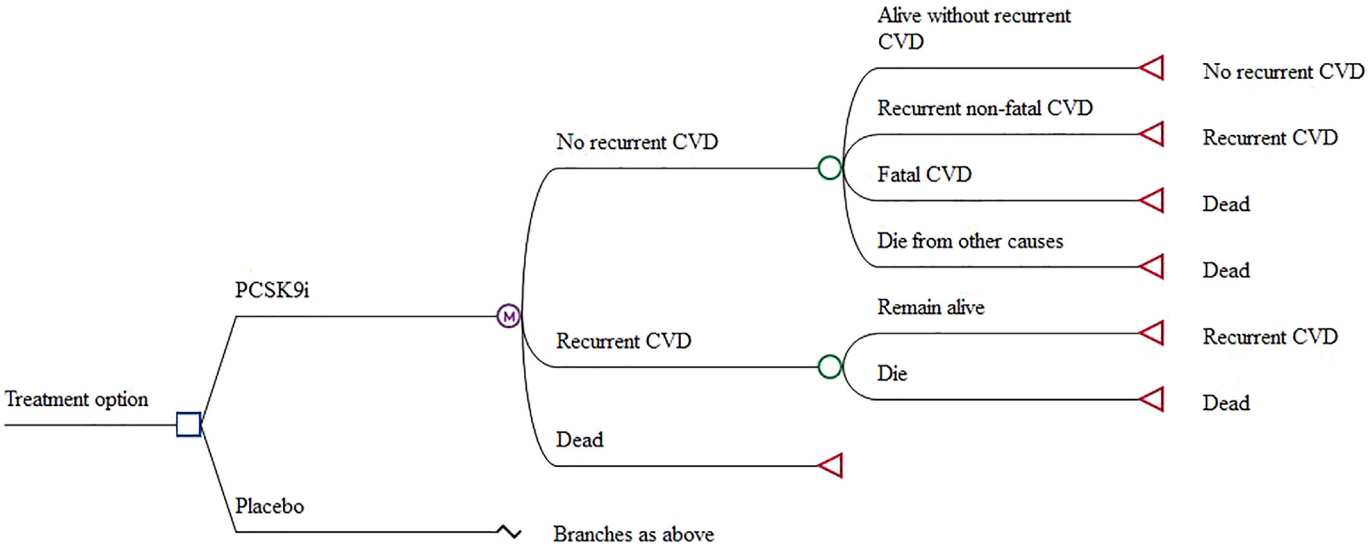


**Fig. 1.** Decision tree of the cardiovascular disease model. CVD: cardiovascular disease.

group. The primary outcome was the incremental cost-effectiveness ratio (ICER) in terms of cost per QALY and cost per year of life saved over the 25-year time horizon.

Cost-effectiveness was determined assuming a threshold of AU$50,000 per QALY saved [7].

### 2.2. Population

The model population comprised a hypothetical sample of 1000 subjects profiled on participants of the FOURIER [6] trial. These were patients aged 40 to 85 years with clinically evident atherosclerotic CVD or at high risk of CVD, with elevated LDL-C and/or non-high density lipoprotein cholesterol (HDL-C) despite being on an optimized regimen of lipid-lowering therapy. The mean age of the FOURIER population was 62.5 years, 24.6% of whom were female. Eighty one percent had had a previous myocardial infarction (MI), 19% had a previous non-hemorrhagic stroke and 13% had symptomatic peripheral artery disease. Baseline characteristics are summarized in Table 1 of the Supplementary Appendices. In line with the FOURIER population, it was assumed that patients entering the model were 62 years at baseline.

### 2.3. Transition probabilities

Transition probabilities for initial and subsequent events are summarized in Table 2 of the Supplementary Appendices.

#### 2.3.1. Initial CVD

The probability of having a CVD event was determined from incidence rates for the composite endpoint of CVD death, MI or stroke, as observed in FOURIER [6]. Incidences of the composite outcome for each arm (evolocumab and placebo) at 1080 days reported in FOURIER were used to determine 5-year probabilities using the formula

$$[(365.25 * 5)/1080] * \text{event rate}.$$

As per outcomes in FOURIER [6], 76.3% of CVD events were considered to be non-fatal and 23.7% fatal in the placebo arm, while in the PCSK9i (evolocumab) arm, the corresponding proportions were 69.2% and 30.8%, respectively.

For non-fatal events, as per FOURIER [6], 70.9% were considered to be MI and 29.1% stroke in the placebo arm and 69.3% and 30.7% in the PCSK9i arm, respectively. For fatal events, the corresponding proportions were 12.5% and 13.8% in the placebo arm and 10.0% and 12.4% in the PCSK9i arm, respectively.

#### 2.3.2. Death from other causes

The probability of dying from other causes was determined using death rates observed in FOURIER [6], where death from other causes was equal to 'death from any cause' minus 'CVD death'.

#### 2.3.3. Events following a CVD event

After an individual was deemed to have a non-fatal CVD event, he/she could either stay alive or die (Fig. 1). The subsequent risk of dying (from any cause) among those who experienced a CVD event was derived from multiplying the risk of death from any causes observed in FOURIER for each arm by a factor of 1.79, this being the relative risk of death from any causes among those with established CVD. This was calculated as the weighted average relative risk determined by the proportion of people who had a non-fatal MI or stroke in FOURIER [6] and the respective relative risk of all-cause mortality of 1.56 [8] and 2.3 [9], respectively.

All transition probabilities described above were applied to the first cycle, and inflated with each subsequent cycle according to age-related changes in death rates observed in Australian specific mortality data [10]. For example, Australian Institute of Health and Welfare (AIHW) mortality data from 2014 (the latest available) indicated that circulatory death rates were 0.125% in 60–64 year olds, 0.197% in 65–69 year olds and 0.342% in 70–74 year olds. Thus with each age-group increment, death rates increased by a factor of 1.58 and 1.74, respectively. These factors were applied to transition probabilities for CVD (both non-fatal and fatal) in Cycles 2 and 3, respectively, to reflect these changes. Likewise, age-specific changes in death from other causes, as well as death from any causes were applied to the relevant transition probabilities.

### 2.4. Costs

As the model considered a secondary prevention population, the average weighted annual cost of CVD was applied. This was determined by the proportion of the baseline cohort with a previous MI or stroke, and the long-term (subsequent) costs associated with the event (Table 1).

The total costs of a subsequent CVD event comprised those with both non-fatal and fatal events [7,11], and are summarized in Table 1. Non-fatal event costs included the cost for the first year of the event as well as subsequent years (long-term costs). Fatal event costs were derived from relevant diagnosis-related groups (DRG) hospitalization data. Conservatively, 50% of fatal events were assumed to occur in hospital.

At present in Australia, evolocumab is reimbursed under the Pharmaceutical Benefits Schedule [12] (PBS) for homozygous familial hypercholesterolemia. The acquisition cost is AU$943.15 per three units of 140 mg/mL injection. The same costs were assumed for the present evaluation. Assuming that one dose of evolocumab (140 mg/mL) is injected fortnightly, in line with FOURIER [6], the cost of evolocumab per person per year was estimated to be AU$8174.

**Table 1**
Cost and utility model inputs.

| Utility | Value | Reference |
|---|---|---|
| Alive without CVD | 0.85 | |
| Alive following MI | −0.12 | 7 |
| Alive following stroke | −0.24 | 7 |
| Cost[a] | | |
| Pre-event | $5150 | |
| Post-event | | |
| Non-fatal MI | | |
| *First year* | $15,535 | 7 |
| *Subsequent year* | $5457 | 7 |
| Non-fatal stroke | | |
| *First year* | $28,352 | 7 |
| *Subsequent year* | $3849 | 7 |
| Fatal CVD[b] | | |
| *MI* | $5585 | 11 |
| *Stroke* | $4091 | 11 |

CVD: cardiovascular disease; MI: myocardial infarction.

[a] All costs are presented in 2017 AU$.

[b] Fatal CVD costs comprised fatal MI, the weighted average cost for diagnosis-related group (DRG) F41B and F60B, and fatal stroke, equal to DRG B70D.

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