Supplementary Online Content

Arrieto A, Hong JC, Khera R, Virani SS, Krumholz HM, Nasir K. Updated Cost-effectiveness Assessments of PCSK9 Inhibitors From the Perspectives of the Health System and Private Payers: Insights Derived From the FOURIER Trial. *JAMA Cardiology*. Published online October 18, 2017. doi:10.1001/jamacardio.2017.3655

This supplementary material has been provided by the authors to give readers additional information about their work.

Technical Appendix for Reviewers

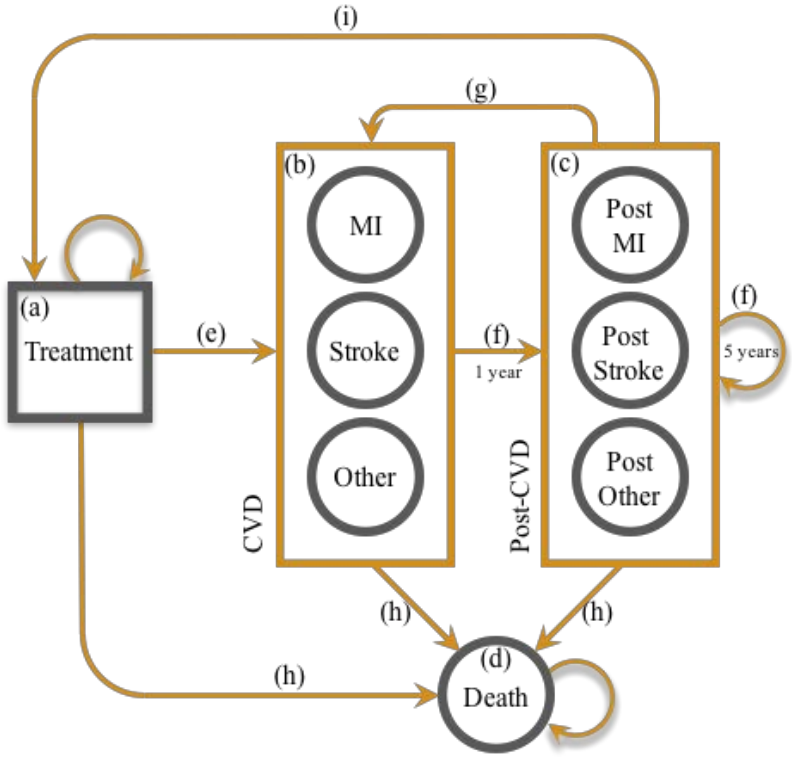
Model

The annotated figure S1 describes our primary Markov decision analysis model. A hypothetical cohort of individuals resembling the FOURIER population start either PCSK9i treatment (PCSK9i plus statin) or usual care (statin only treatment). We use an annual cycle. Each year, individuals transit from treatment to cardiovascular (CVD) events, and then to a post-cardiovascular state where they may i) have a sub-sequent cardiovascular event, ii) die as a result of a cardiovascular event, or iii) remain in the post-cardiovascular event for up to 5 years before they transit again to their regular treatment. Individuals may die at any state for non-cardiovascular disease factors. In the private payer perspective model, individuals can also leave the insurance plan at any state. Both, death or leaving the plan are absorbing states, meaning that individuals in those states leave the model permanently.

Input

The transition probabilities of our Markov model were age-dependent. Costs (in 2016 US dollars), health utilities and probabilities were obtained from the literature and adjusted to the model as follows (letters correspond to Figure S1). All costs and health utilities were discounted at a 3% annual discount rate.

Figure S1. Annotated Markov Decision Analysis Model



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(a) Treatments were PCSK9i (cost $14,300/year) plus statin therapy (cost $267/year)[1], or statin only therapy (usual care). We considered a baseline treatment cost of $13,515/year[2]; baseline health utility: 0.79[3].
For the private payer perspective, we considered that at the treatment, CV and post-CVD states, individuals pay an insurance premium equivalent to the average premium of the private individual health insurance plans when members were 57–64 years old. When they turned 65, they were assumed to be in a Medicare Advantage plan. We assumed a monthly premium of $520 for age 57–64 years old[4], and $835 for 65 or older[5]. We also assumed a cost-sharing component. Statins were assumed as tier 1 drugs and PCSK9 inhibitors as tier 2 drugs. No copayments/coinsurance for visits to providers were assumed. We considered average insurance drug copayment and deductible from private individual health insurance plans when individuals were 57–64 years. Drug monthly copayments were assumed at $11 for statins and $31 for PCSK9, and an annual deductible of $3,731 was assumed for this age group[6]. For individuals 65 years old or older, we considered average Medicare Advantage plan cost-sharing. We assumed a drug monthly copayment of $5 for statins and $11 for PCSK9, and an annual deductible of $2,158 for this age group[5].

(b) The CVD event states in the primary model were myocardial Infarction (MI), stroke and other CVD disease events (Other) including unstable angina and transient ischemic attack. An alternative model included coronary revascularization as a forth CVD event. The first-year costs were: MI at $46,099/year, stroke at $35,142/year, and other CVD at $16,442/year[2]. First year health utilities were 0.58 for MI, 0.46 for stroke and 0.62 for other CVD[3]. When coronary revascularization was included, we considered it with a first-year cost of $57,705/year and health utility of 0.78[2,3].

(c) For the post-CVD states, we considered second-year cost of $10,531/year, $13,510/year and $5,311/year for MI, stroke and other CVD, respectively[2]. Costs converged to baseline cost at fifth year. Post-CVD health utility for MI: 0.73; stroke: 0.65; other CVD: 0.75[2]. Health utilities converge to baseline at fifth year. When coronary revascularization was included, we considered it with a second-year cost of $7,379/year and health utility of 0.79[3].

(d) Death (absorbent state). We considered an incremental cost of fatal CVD events of $13,145/year[2]. Health utility for death was equal to 0. For the private payer perspective, we considered that leaving the insurance plan meant an elimination of the premium revenue stream.

(e) We used the 1-to-3-year relative risk reduction of CVD events reported in the FOURIER study, including unstable angina and transient ischemic attack for other CVD events[7]. To project annual probabilities of CVD events beyond the third year, we used the baseline survival function from the 10-year Framingham study, under the assumption that the Framingham survival function is proportional to the unobserved evolocumab survival function[8]. One-year probabilities of CVD events were obtained separately for males and females for each CVD event (MI, stroke and other CVD) based on FOURIER CVD event distribution. Probabilities were then combined based on female-male FOURIER distribution. Annual risk of incident cardiovascular disease events for MI, stroke and other CVD were 3.1-

11.9% for PCSK9i intervention (age-dependent), and 3.7-14.7% for statin only intervention (age-dependent).

(f) Survival of incident cardiovascular disease event was calculated (tunnel states). The transition to post-CVD event occur after one cycle (one year) with probability 1. Progression within post-CVD event (tunnel state) assumes that individuals remain in the post-CVD event for 5 years, implying that it takes 5 years to recuperate from the CVD event. At any time during that 5-year period, they can transit to a subsequent CVD event (b) or they can die (d).

(g) One-year probability of subsequent CVD events were obtained from 4-year follow-up Framingham study on subsequent CVD events[9]. 1-year probabilities of CVD events were obtained separately for males and females for each CVD event (MI, stroke and other CVD) based on the 2008-2010 average of CVD distribution by age[10]. Probabilities were then combined based on FOURIER female-male distribution. Annual risk of subsequent cardiovascular disease events for MI, stroke and other CVD were 3.4-11.9% for the PCSK9i intervention (age- and time-dependent), and 4.0-14.7% for the statin only intervention (age- and time-dependent).

(h) Transition to death (absorbing state) assumes a non-CVD mortality rate of 0.5-18.3% (age-dependent). These were obtained from the 2010 U.S. life tables[10]. CVD mortality rates at first year (after MI, stroke or other CVD) were 6.3-100% (age-dependent)[11,12]. CVD mortality at second-to-fifth year were 2.9-67.3% (age- and time-dependent)[11,12]. For the private payer perspective, we considered an annual insurance turnover rate of 12.2%[13].

(i) Return to baseline risk after 5 years of cardiovascular disease (calculated).

Output

For the health system perspective, we report 3 outputs (see Table 2 in main document): i) the treatment cost or incremental cost of treating hyperlipidemia with PCSK9i plus statin compared to statin only. ii) the savings or avoided cost of CVD events. Avoided CVD events translate into savings in the long-run. iii) Quality-Adjusted Life Years (QALY) were obtained by multiplying the number of individuals in each health state by its correspondent health utility. Gains in QALYs and life years were obtained by comparing outcomes of treating hyperlipidemia with PCSK9i plus statin compared to statin only All outputs were discounted over lifetime at a 3% discount rate.

The incremental cost-effectiveness ratio (ICER) is equivalent to treatment costs net of gains for avoided costs, divided by QALYs. For example, for the baseline case (see table 2):

ICER = $136,101 (treatment cost) - $15,740 (avoided costs) / 0.36 (QALYs) = $337,729

For the private payer perspective, we report 3 outputs (see Table 2 in main document): i) the investment in PCSK9i (treatment cost) that excludes patient cost-sharing. ii) the avoided costs excluding the fraction of savings that private payers do not accrue because of members who shift out of the plan every year. iii) incremental gain in premium revenues that resulted from living longer and staying more time contributing to the private payer's premium revenue stream.

The NPV is equivalent to net gains minus investment. For example, for the baseline case (see table 2):

NPV= 516 (premium revenue gains) + 5,423 (avoided costs or savings to the payer) – 41,846 (treatment cost) = -35,907

While the ROI is defined as (net gains minus investment)/investment:

ROI= (516 + 5,423 – 41,846) / 41,846 = -85.81%

Validation

Validation to judge the accuracy of the Markov model predictions are limited in this type of simulation models. However, we used the key findings over the 3 years of data reported by the FOURIER study[7] to compare with the implicit hazard ratios predicted by our model at year 3. The table below shows end points reported in Table 2 of Sabatine et al. 2017 paper and the corresponding values from our model. Our results are reassuring as the 3-year predicted hazard ratio values fall within the FOURIER confidence intervals, suggesting that the simulated cohort is similar to FOURIER. The only outcome where our model under predicts FOURIER is cardiovascular death, which was not statistically significant in FOURIER. Our model predicts cardiovascular mortality after an MI and Stroke event using evidence from previous RCTs [11,12]. while the result from FOURIER are affected by i) including other cardiovascular deaths with hazard ratio of 1.10 (0.90–1.35) and ii) being still underpowered for mortality outcomes given the short period of time.

Health outcomes	**Hazard ratio and 95% CI (Sabatine et al. 2017)**	**Implicit hazard ratio (model prediction)**
Myocardial infarction	0.73 (0.65–0.82)	0.72
Stroke	0.79 (0.66–0.95)	0.79
Ischemic stroke or transient ischemic attack	0.77 (0.65–0.92)	1.08
Hospitalization for unstable angina	0.99 (0.82–1.18)	
Cardiovascular death	1.05 (0.88–1.25)	0.81
Non-cardiovascular death	1.04 (0.91–1.19)	1.01

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