Cost-effectiveness Analysis of Evolocumab in Patients With Recent Acute Coronary Syndrome in China

Xiaoyu Xi
China Pharmaceutical University

Xin Wang
Hangzhou Medical College

Wenwen Xie (✉ 1832712679@qq.com)
China Pharmaceutical University

Yu Jia
Amgen Inc

Santiago Zuluaga Sanchez
Amgen Inc

Laura Martinez
Amgen Inc

Quanming Zhao
Beijing An Zhen Hospital: Capital Medical University Affiliated Anzhen Hospital  https://orcid.org/0000-0003-3457-4953

Research Article

**Keywords:** Cost-effectiveness, Evolocumab, PCSK9 inhibitors, Acute Coronary Syndrome, Low-density lipoprotein cholesterol, Markov Model

**DOI:** https://doi.org/10.21203/rs.3.rs-464160/v1

**License:** ☛ This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Cost-effectiveness Analysis of Evolocumab in Patients With Recent Acute Coronary Syndrome in China

Xiaoyu Xi, Xin Wang, Wenwen Xie, Yu Jia, Santiago Zuluaga Sanchez, Laura Martinez, Quanming Zhao*

1. National Drug Policy and Economic Research Center of Pharmaceutical Industry, China Pharmaceutical University
2. School of Pharmacy, Hangzhou Medical College
3. Amgen, Inc
4. Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

*Correspondence

Abstract

Purpose: To assess the cost-effectiveness of evolocumab, a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor, added to background statins therapy in patients with a recent acute coronary syndrome (ACS) event (in the past 12 months) and low-density lipoprotein cholesterol (LDL-C) levels ≥100 mg/dL in China.

Methods: A health economic evaluation was performed from a Chinese healthcare perspective, using a Markov model over a lifetime horizon based on baseline CV event rate from claims database data and efficacy from the FOURIER trial. The health benefit was reflected in the decrease of LDL-C level, which led to the decrease of cardiovascular events. The cost of cardiovascular events and the utility value of each health state were derived from published literature. Sensitivity analysis were conducted to evaluate the effects of uncertainty in parameters and the robustness of the model. The cost-effectiveness of evolocumab was also explored in patients with recent MI, very high-risk (VHR) ASCVD and homozygous familiar hypercholesterolemia (HoFH).

Results: In recent ACS patients, evolocumab was associated with incremental quality adjusted life years (QALYs) of 1.41 and incremental costs of 120,966 yuan vs. ezetimibe, both with background statins therapy, resulting in an ICER of 85,964 yuan per QALY gained. The probability that evolocumab is cost-effective at a threshold of 217,341 yuan (3 times per capita GDP, 2020) was 100% in patients with recent ACS, recent MI, VHR ASCVD and HoFH.

Conclusion: Compared with ezetimibe, evolocumab was considered to be cost-effective in patients with a recent ACS event in China.

Keywords

Cost-effectiveness • Evolocumab • PCSK9 inhibitors • Acute Coronary Syndrome • Low-density lipoprotein cholesterol • Markov Model
Introduction

Acute Coronary Syndrome (ACS) has become one of the most serious diseases threatening people's health in China. China cholesterol education program (CCEP) expert advice for the management of dyslipidaemias to reduce cardiovascular risk (2019) have suggested that patients with recent ACS events should be classified as ultra-high risk groups of atherosclerosis cardiovascular disease (ASCVD). After discharge from hospital, there is a high risk of recurrence of cardiovascular (CV) events, which increases hospitalization expenses and brings tremendous economic burden to patients and their families[1].

Low-density lipoprotein cholesterol (LDL-C) level is a major risk factor of ASCVD, including ACS[2]. Lowering LDL-C levels has been consistently shown to reduce the rate of CV events in several interventional and epidemiologic studies[3-5]. The meta-analysis conducted by the Cholesterol Treatment Trialists’ Collaboration shows a relationship (i.e., the CTTC relationship) between LDL-C and risk, results of the analysis show that for every 1 mmol/L of LDL-C reduction, there is a 22% reduction in the risk of any major vascular event (defined as CHD death, non-fatal MI and stroke)[2]. Among recent ACS patients in China who had received statins lipid-lowering treatment (LLT), the proportion of patients achieving LDL-C target levels below 70mg/dL, according to American College of Cardiology (ACC) and American Heart Association (AHA) guidelines, is only 36.1%[6]. Even when ezetimibe was added, the proportion of patients reaching target LDL-C levels only increased to 50.6%[7]. According to the 2019 European Society of Cardiology (ESC), European Atherosclerosis Society (EAS) guidelines, and the China Cholesterol Education Program (CCEP) Expert Advice for the management of dyslipidaemias to reduce cardiovascular risk (2020), for recent ACS (ultra-high risk ASCVD patients), the treatment goal for LDL-C is <55mg/dL (less than~ 1.4 mmol/L) and a ≥50% reduction from baseline LDL-C, which will result in a lower proportion of patients achieving this LDL-C target goal with only statins and ezetimibe treatment.

In recent years, the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) have become available for the management of patients with ASCVD and patients with familial hypercholesterolemia (FH), whose LDL-C levels are still high despite the treatment of background LLT[8]. Evolocumab is the first PCSK9 inhibitor approved in China to reduce the risk of MI, stroke and coronary revascularization in patients with ASCVD. In FOURIER study (NCT01764633), the mean percentage reduction in LDL-C levels with evolocumab vs. placebo was 59% (95% CI: 58% to 60%; p<0.001)[9]. For the subgroup of Chinese patients in FOURIER, the mean LDL-C difference vs placebo at 48 weeks was 68.08% (95%CI: 65.2% to 70.9%; p<0.001). In addition, the favorable safety profile and good tolerance to long-term evolocumab therapy were also confirmed by the results of the Open-label Study of Long-term Evaluation Against LDL-C Trial (OSLER-1), which, to date, had the longest exposure to a PCSK9 inhibitor (up to 5 years in follow-up)[10,11]. Some commentators have opined on the cost-effectiveness of evolocumab[12-14].
In October 2018, the price of evolocumab was reduced to $5,850 per year (a decrease of 60%) in the United States. According to this pricing, Fonarow et al. [15] (2019) evaluated the cost-effectiveness of evolocumab added to the background treatment (statins with or without ezetimibe) vs. background treatment in ultra-high-risk ASCVD patients. Results showed that the addition of evolocumab on top of background treatment was cost-effective. Other studies in various European countries have supported this conclusion [16,17].

At present, the only other CE study of evolocumab in Chinese setting targets high risk Myocardial infarction (MI) groups [18], and there is no economic evaluation of evolocumab for Chinese patients with recent ACS events. Therefore, we will assess whether evolocumab after statins is cost-effective in Chinese patients with recent ACS events. Scenario analysis were conducted to explore the cost-effectiveness of evolocumab after statins in patients with a recent MI, and after statins and ezetimibe in patients with recent ACS, in patients with HoFH, and in patients with very high-risk ASCVD. The cost-effectiveness results were also presented from a payer’s perspective including reimbursement limits to drug and hospitalization costs.
Methods

Model structure

Figure 1 Evolocumab Economic Model Structure CV, cardiovascular disease; ACS, acute coronary syndrome; IS, ischemic stroke

A Markov cohort-state transition model was used for the analyses, as used in previous cost-effectiveness models for PCSK9i[19,20][15][17]. The model comprises 11 main health states: Starting health state, acute coronary syndrome (ACS), ischemic stroke (IS), post-ACS, post-IS, ACS2+, IS2+, Post-ACS2+, Post-IS2+, CV death, and non-CV death. The states for ACS and IS cover the first-year period after the event; Patients would transition to ACS2+ and IS2+ states after experiencing two or more consecutive ACS or IS; Post-event health states cover the subsequent years after an event. This separation is made to take account of differences in risks, utilities and costs between the first and subsequent years. Figure 1 shows a simplified representation of the model (composite health states not presented).

Additionally, the model includes composite health states that are a combination of two
post-event health states. They were created to retain memory of previous CVD events: Post-IS+post-ACS, a combination of two post-event health states. Neglecting CV event history would underestimate the increase in CVE risk and long-term consequences in terms of quality of life and costs associated with a history of multiple CV events. The following assumptions are made regarding composite health states: The utility of a composite health state is defined by the lowest of the utilities for the individual health states, and the highest of the costs for the individual health states is used as the cost for a composite health state. The CV event rate at baseline is adjusted by the CV event history as embodied by the respective composite health state (see Section Baseline Cardiovascular Event Rate for details). The assumptions on costs and utility are generally conservative as treatment with evolocumab makes patients stay longer in the post-event health states by avoiding (fatal) CV events. Clinical and economic experts concur that these assumptions are valid and if anything would result in underestimating cost-effectiveness results for evolocumab.

Patients with recent ACS enter the model in the ‘Starting health state’. Patients remain in that health state unless they have a fatal CV event, non-fatal CV event (ACS or IS), or die from other causes. The model considers an annual cycle length, which is in line with the cycle length most often reported in economic evaluations of statins/LLTs[21]. Being a standard limitation of Markov models, a patient in a given state can make only one single state transition during each cycle, and so cannot experience more than one CV event per year. There is, however, no limit to the number of events which can be experienced over a lifetime. The Markov trace is half-cycle corrected[22]: CV events that occur in any annual cycle on average are assumed to take place halfway through the year.

During any cycle following a CV event, patients transit to the corresponding post-event health state unless they experience the same or a different CV event. Transition to CV death and non-CV death is possible from each health state.

Revascularization (RV), either urgent or elective, is included as a procedure (ie, cost), not as a separate health state because the baseline cardiovascular event rate has considered the impact of revascularization on subsequent events. In the model, urgent RV is linked to an ACS event by applying the cost of elective RVs to a certain proportion of patients entering the ACS health state (100%) or residing in the post-ACS health state (10%). The rates of urgent RV are indirectly impacted by the treatment effect applied on ACS events; elective RV are assumed not to affect the CV event risk or patients’ HRQoL.

Population

While evolocumab is highly effective in all patients included in its approved indication, this study aims to assess the cost-effectiveness of evolocumab as second line treatment in the subset of patients with a recent acute coronary syndrome (ACS) event (in the last 12 months) and whose LDL-C levels still ≥ 100 mg/dL in spite of statins therapy.
Patients’ baseline characteristics came from SuValue®, a standardized Chinese hospital-based health-information-system electronic database which includes over 90 million patients in 168 hospitals in China with up to 10-year longitudinal data, representing 6.5% of total population in China (1.39 billion in 2017). A total of 17,966 ASCVD patients treated with statins and with LDL-C ≥ 100 mg/dL (2.6 mmol/L) were identified in the database. For these patients, the mean age was 69 years (12.98), of which 53% are women, and the average LDL-C was 141.0 mg/dL. All patients received high-intensity statins treatment.

Transition Probabilities

Baseline Cardiovascular Event Rate

The baseline CV event rate is the number of CV events per year patients are expected to suffer while on background LLT. The recent ACS second line (base-case) baseline rate used in the model of 9.09 per 100 patient-years is constructed using US claims database data, adjusted to account for the different risk factors in the population to be modeled, as described in this section.

First, the model takes the real-world CV event rate (6.4 per 100 patient-years, a composite rate including non-fatal MI, non-fatal IS and CV death) gained from the US Truven Market Scan claims database in an ASCVD population[23] with a mean LDL-C level of 114.5 mg/dL and an average age of 57 years.

For alignment with the definition of the target population, patients with recent ACS, the rate from the US Truven Market Scan database is adjusted to also include unstable angina (UA) events based on a Chinese study looking at in-hospital mortality in patients with ACS, where it was estimated that 40.9% of all ACS events are UA with the remainder 59.1% being MIs[24]. This adjustment results in a composite rate including non-fatal ACS, non-fatal IS and CV death.

In view of the different characteristics of Asian and North American populations, the adjusted composite US rate was further increased using a HR of 1.04 to reflect the higher risk of CV events in Asian patients, as reported by Abtan et al.[25]. The final adjusted composite baseline rate (including non-fatal ACS, non-fatal IS and CV death) used in the model was 9.09 per 100 patient-years.

The model also accounted for the differences in population characteristics between the US Truven Market Scan database and the Chinese SuValue database by adjusting the baseline rate by age and LDL-C level using the following formula:

\[
r_a = r_0 \times HR_{age}^{(\Delta age)} \times RR^{(\Delta LDL-C)}
\]

Where
- \(r_a\) = adjusted baseline rate
- \(r_0\) = baseline rate at mean age
- \(HR_{age}\) = hazard ratio for age as estimated using data from CPRD (See Table 1)
- \(RR\) = hazard ratio for LDL-C (See Table 1)
- \(\Delta age\) = age difference between the age of Chinese
patients in each cycle and the mean age of the cohort from which the baseline rate was obtained from

RR = rate ratio per 1 mmol/L of LDL-C reduction, equal to CTTC's RR for any major vascular event (0.78; 95% CI: 0.76 to 0.80)

$$\Delta \text{LDLc} = \text{LDL-C difference in mmol/L after subtracting the mean LDL-C of the Chinese population from the cohort LDL-C from which the baseline rate was obtained}$$

Given that the target population refers to patients with a recent ACS, that is that patients had an event in the last 12 months, the final adjusted baseline rate (9.09 per 100 patients per year) is increased during the first two years of the model to account for the significantly higher risk observed in patients during the first two years after an event. This rate increase during the first two years is achieved by leveraging hazard ratios obtained from a Swedish register-based study in patients with a recent MI (see table 1)[26].

The CV event rate is then further adjusted throughout the model to account for the increased risk once patients experience subsequent CV events. Based on the previous data[27][16], this study re-estimated the REACH[28] covariates and measured event rates in sub-populations with other ASCVD, MI, IS and combinations of these states to obtain a HR corresponding to the increased event rate associated with that event history. Results from this study indicate that there is an increasing risk gradient from single to multiple events. As the baseline rate was already adjusted during the first two years of the model, the event-specific hazard ratios are not applied during this period to avoid over-estimating the risk. See table 1.

The adjusted composite CV event rates at baseline are disaggregated to CV event-specific annual rates for ACS, IS, and CV death, based on the event distribution from the FOURIER trial.

**Mortality**

Mortality from non-CVD causes was estimated calculating first the proportion of CV deaths based on mortality data of cerebrovascular disease and acute MI, as shown in the report by the national center for cardiovascular diseases in China (2018)[29], and then excluding the proportion of CV deaths from the total mortality of the general population. The mortality rate of the general population of different ages and genders is derived from the national bureau of statistics of China. Mortality due to CVD is modeled separately as a consequence of incident CV events predicted by the model.

**Treatment Effects**

In the FOURIER trial, the mean percentage reduction in LDL-C levels with evolocumab vs. placebo is 59% (95% CI: 58% to 60%; p<0.001) (intention-to-treat analysis)[9]. For Chinese patients in FOURIER, the mean LDL-C reduction vs placebo at 48 weeks was 68.08% (95%CI: 65.2% to 70.9%; p<0.001)[30]. A constant reduction over a lifetime
treatment duration, consistent with long-term follow-up data, was assumed[31].

For ezetimibe, the model used the 18.3% (95% CI: 17.5% to 19.1%) LDL-C reduction reported in IMPROVE-IT trial[7]. Cardiovascular event rates after treatment were calculated using the following formula:

\[ r_{tx} = r_0 \times RR^{\Delta LDL-C} \]

where \( r_{tx} \), rate after treatment; \( r_0 \), rate before treatment; \( RR \), rate ratio per 1 mmol/L of LDL-C reduction; and \( \Delta LDL-C \), absolute LDL-C reduction.

The rate ratio (RR) for any major vascular event (ACS, IS and CV death) per 1 mmol/L of LDL-C reduction was 0.78 (95% CI: 0.76 to 0.80) based on the CTTC meta-analysis[2].

**Costs**

From the perspective of Chinese healthcare system, only medication and other direct health-care costs associated with the modeled CVD health states were considered following the local guidelines. Total costs were calculated by multiplying the state-specific costs by the probabilities of residing in each health state.

The price of one dose of evolocumab (140mg) was the current wholesale acquisition price 1,298 CNY in China. Based on the dosage of evolocumab (140 mg) injected every 2 weeks, the annual cost of evolocumab was calculated to be 31,152 CNY/person. The cost of ezetimibe and statins were the average of the bidding prices available in different provinces in the past three years. Statins price was based on the average prices of atorvastatin and rosvuastatin. A summary of the calculated drug costs were included in Table 1.

Direct CVD event costs, including long-term follow-up costs, had been estimated from the SuValue database and a study in ACS patients in China[28]. These costs were applied every time the corresponding event occurs (Table 1).

Therapy persistence for evolocumab and ezetimibe, as observed in the FOURIER and IMPROVE-IT study respectively, was included in the model to adjust the treatment cost over the modelled time horizon. All costs are expressed in 2020 Chinese Yuan (CNY).

**Utility**

The baseline utility in the Starting health state was derived from a Health Survey in Beijing in a cohort of patients with chronic disease. Once patients have an event, the model uses CVD health state utilities previously used in CV economic evaluations, derived from a utility study based on a general population sample in the UK[32] (Table 1)[33]. Total QALYs were calculated by applying the state-specific utilities to the probabilities of residing in each state over the modeled lifetime horizon.

The utility of patients in the year of CV events occur was different from that in the subsequent years. The distinction of acute versus post-event impact was important as time since CV event is a statistically significant factor in determining HRQoL[16].
Economic Analyses

In line with local recommendations, both costs and outcomes were discounted at an annual rate of 5.0%. The analysis assumed a lifetime horizon, appropriate for evaluating the impact of an intervention on a chronic condition. The primary measure of health benefit was the quality-adjusted life year (QALY), with the incremental cost-effectiveness ratio (ICER) calculated as the incremental cost per QALY gained.

Sensitivity analyses

Systematic sensitivity analyses were conducted to evaluate the effects of uncertainty in the model parameters and the robustness of the model. In one-way deterministic sensitivity analyses, the RR for any major vascular event (ACS, IS and CV death) per 1 mmol/L of LDL-C reduction was varied separately through 97.5% confidence interval. Costs of CV events, health state utility values, baseline rates and their adjustment factors were also varied based on their distributions included in Table 1. The results were shown in tornado diagrams.

In probabilistic sensitivity analyses, probability distributions were assigned to model parameters based on their respective means and standard errors, and values for parameters were sampled by Monte-Carlo simulation with 1,000 iterations in each loop. Cost-effectiveness acceptability curves (CEAC) were plotted to reflect the probability of evolocumab being an optimal treatment strategy at various willingness-to-pay (WTP) thresholds.

| Table 1 Key inputs in the model |
|---------------------------------|
| Parameters | Base value | Range | Distribution | Source |
| Patient Characteristics | | | | |
| Age, years | 69 | NA | NA | SuValue database |
| LDL-C level, mg/dL | 141.0 | NA | NA | SuValue database |
| CV event rate per 100 patient-years | 9.09 | 8.56-9.61 | Normal | Calculated |
| Hazard Ratios used to adjust baseline CV rate | | | | |
| Year 1 and MACE in last year | 3.8300 | 3.3577-4.3687 | Lognormal | 26 |
| Year 2a | 1.5600 | | | |
| 1 previous ACS | 1.1300 | 1.0400-1.2200 | Lognormal | 16,27,28 |
| 1 previous IS | 1.1300 | 0.9900-1.3000 | Lognormal | 16,27,28 |
| 2+ previous ACS | 1.1900 | 1.0500-1.3400 | Lognormal | 16,27,28 |
| 2+ previous IS | 1.3600 | 1.0300-1.8000 | Lognormal | 16,27,28 |
| History of ACS and IS | 1.9400 | 1.2300-3.0400 | Lognormal | 16,27,28 |
| Age | 1.0600 | 1.0599-1.0601 | Lognormal | 16,27,28 |
| LDL-C reduction | | | | |
### Treatment effect per 1 mmol/L LDL-C reduction, RR

| Event                  | RR Value       | 95% CI          | Distribution | Study               |
|------------------------|----------------|-----------------|--------------|---------------------|
| ACS, IS, and CV death  | 0.7800         | 0.7600-0.8000   | Lognormal    | CTTC meta-analysis  |

### Annual cost of drugs, CNY

| Drug       | Cost (CNY) | NA   | NA   | Notes                        |
|------------|------------|------|------|------------------------------|
| Evolocumab | 31,152     | NA   | NA   | Based on the price per 140mg of CNY 1,298 |
| Ezetimibe  | 2,661      | NA   | NA   | Calculated                   |
| Statins    | 4,329      | NA   | NA   | Calculated                   |

### Cost of CV events, CNY

| Event      | Cost (CNY) | 95% CI          | Distribution | Database                  |
|------------|------------|-----------------|--------------|---------------------------|
| ACS        | 53,266     | 42,826-63,705   | Gamma        | SuValue database,28       |
| IS         | 47,993     | 38,586-57,399   | Gamma        | SuValue database,28       |
| CV death   | 15,086     | 12,129-18,043   | Gamma        | SuValue database,28       |
| RV         | 65,179     | 52,404-77,954   | Gamma        | SuValue database,28       |

### Utility

| Health state | Value | 95% CI           | Distribution | Notes |
|--------------|-------|------------------|--------------|-------|
| Starting     | 0.9230| 0.8989-0.9471    | Beta         | 33    |
| ACS          | 0.6720| 0.6249-0.7191    | Beta         | 32    |
| IS           | 0.3270| 0.2638-0.3902    | Beta         | 32    |
| Post-ACS     | 0.8240| 0.7999-0.8481    | Beta         | 32    |
| Post-IS      | 0.5240| 0.4718-0.5762    | Beta         | 32    |

---

**LDL-C, low-density lipoprotein cholesterol; CV, cardiovascular; MACE, major cardiovascular event; ACS, acute coronary syndrome; IS, ischemic stroke; CNY, Chinese yuan; RV, revascularization; NA, not applicable**

*a Uncertainty captured within the uncertainty of the baseline CV event rate

### Scenario Analyses

In scenario analyses we modeled the cost-effectiveness of evolocumab in different populations. These included the use of evolocumab as a second-line therapy (background therapy of statins) in patients with recent MI events (in the past 12 months) and the use of evolocumab as a third-line therapy (background therapy of statins and ezetimibe) both in patients with very high-risk ASCVD events and in patients with recent ACS events (in the past 12 months). The modeling inputs and assumptions were aligned with the recent ACS second line (base-case).

In addition, we also modeled the use of evolocumab as a second-line therapy
(background therapy of statins) in a high-risk population of homozygous familial hypercholesterolaemia (HoFH), with patients with an average LDL-C level of 582 mg/dL, which is 5-7 fold-higher than those without HoFH. A summary of the key model inputs which differ from the recent ACS second line (base-case) population were included as Supplementary material.

Cost-effectiveness results were also presented from a payer’s perspective by applying a 44.60% and 64.60% reimbursement limit to drug and hospitalization costs, respectively (calculated based on the proportion of outpatient and hospitalization reimbursement rates in different regions of China).

Results

Recent ACS second line (base-case) analyses

Evolocumab added to statins was associated with QALY gains and increased costs compared with ezetimibe added to statins therapy (Table 2). The ICER of CNY 85,964 was below CNY217,341 per QALY gained, the generally accepted willingness-to-pay threshold in China[34].

Table 2 Recent ACS second line (base-case) results

| Health outcomes (full life cycle) | Evolocumab + Statins | Ezetimibe + Statins | Increment (Δ) |
|----------------------------------|----------------------|---------------------|---------------|
| Total QALYs, discounted          | 4.45                 | 3.04                | 1.41          |
| Total LYs, discounted            | 5.25                 | 3.71                | 1.54          |
| CV event rates                   | 1.61                 | 1.87                | -0.26         |
| ACS                              | 0.67                 | 0.75                | -0.08         |
| IS                               | 0.15                 | 0.18                | -0.03         |
| CV death                         | 0.78                 | 0.84                | -0.06         |
| 5-year event risk                | 56%                  | 71%                 | -15%          |
| 10-year event risk               | 71%                  | 81%                 | -10%          |
| life-year event risk             | 80%                  | 85%                 | -5%           |

Costs, CNY (full life cycle)

| Total cost, CNY | 244,984 | 124,018 | 120,966 |
|-----------------|---------|---------|---------|
| Medication      | 164,704 | 25,267  | 139,437 |
| ACS             | 26,693  | 34,416  | -7,723  |
|                | Evolocumab + Statins | Ezetimibe + Statins | Increment (Δ) |
|----------------|----------------------|---------------------|--------------|
| IS             | 5,473                | 7,271               | -1,798       |
| CV death       | 8,426                | 10,319              | -1,893       |

**ICER (CNY per QALY)** 85,964

ACS, acute coronary syndrome; CV, cardiovascular; ICER, incremental cost-effectiveness ratio; IS, ischemic stroke; LY, life year; QALY, quality-adjusted life-year; MACE, major cardiovascular event; CNY, Chinese yuan

**Sensitivity analyses**

One-way sensitivity analyses demonstrated that recent ACS second line (base-case) results were robust to changes in model input parameters. A tornado diagram (Figure 2) shows the parameters that affect the recent ACS second line (base-case) ICER (CNY85,964) by more than 1% when varied. Three parameters affected the recent ACS second line (base-case) ICER most when varied are: evolocumab reduction (%) in LDL-C (CNY82,449 to CNY89,908); effect of evolocumab LDL-C lowering on CV death rates (year 1+) (CNY82,747 to 89,865) and effect of evolocumab LDL-C lowering on ACS rates (year 1+) (CNY83,027 to 89,095).

For the probabilistic sensitivity analysis, Figure 3 shows that evolocumab added to statins is both more costly and more effective than ezetimibe with statins therapy. One thousand of the 1,000 iterations of the PSA fell below the WTP threshold of CNY217,341 per QALY gained (3 times per capita GDP, 2020), represented by the dashed line in Figure 3, meaning that evolocumab added to statins is estimated to have a 100% chance of being cost-effective compared with ezetimibe added to statins. Figure 4 shows the CEAC for evolocumab vs ezetimibe on top of statins in patients with a recent ACS event and LDL-C levels ≥100 mg/dL. The curves illustrate the probability of evolocumab and ezetimibe to be cost-effective over a range of WTP thresholds. From the figure, we can know that since threshold CNY104,324, the use of evolocumab as an add-on treatment has a 100% probability of being cost-effective, which further strengthens the confidence that evolocumab provide economic value in patients with recent ACS events and elevated LDL-C levels.
**Figure 2** Tornado diagrams in one-way deterministic sensitivity analyses
ASCVD, Atherosclerotic cardiovascular disease; LDL-C, Low Density Lipoprotein Cholesterol; CV, cardiovascular; ACS, acute coronary syndrome; IS, ischemic stroke
Figure 3 Monte Carlo simulation scatter plot in probabilistic sensitivity analyses. The dotted line shows the willingness-to-pay threshold, with a slope of CNY72,447 per quality-adjusted life-year gained.

CNY, Chinese yuan; QALY, quality-adjusted life-year; WTP, willingness-to-pay

Figure 4 Cost-effectiveness acceptability curves in probabilistic sensitivity analyses. The graph shows the probability of each therapy being cost-effective in various willingness-to-pay thresholds.

CNY, Chinese yuan; QALY, quality-adjusted life-year
Scenario analyses

We explored the cost-effectiveness of evolocumab in different populations and alternative scenarios for the comparator (Table 3). In recent MI patients, the ICER for evolocumab versus ezetimibe, both added to statins therapy, was CNY100,056 per year.

When evolocumab were used as a third-line therapy (background therapy of ezetimibe and statins therapy) in patients with recent ACS events and with very high-risk (VHR) ASCVD, the incremental cost of evolocumab therapy compared with background therapy were CNY131,612 and CNY174,340, and the incremental QALYs were 1.92 and 1.63, respectively. As a result, the ICERs for evolocumab versus background therapy in two scenarios were CNY68,715 and CNY106,950 per QALY gained accordingly.

For HoFH population, the ICER for evolocumab added to background therapy versus background therapy alone was 78,356 CNY per QALY gained.

Table 3 Scenario analyses results

| Treatment alternative       | Cost, CNY | QALY | ICER, CNY |
|----------------------------|-----------|------|-----------|
|                            | Total     | Incremental | Total | Incremental |
| Recent MI (second line)     |           |           |         |             |
| ezetimibe+statins          | 119,681   | -        | 3.82   | -           |
| evolocumab+statins         | 260,175   | 140,493  | 5.22   | 1.40        | 100,056     |
| Recent ACS (third line)     |           |           |         |             |
| ezetimibe+statins          | 127,350   | -        | 2.53   | -           |
| evolocumab+ezetimibe+statins | 258,962 | 131,612  | 4.45   | 1.92        | 68,715      |
| VHR ASCVD (third line)      |           |           |         |             |
| ezetimibe+statins          | 115,558   | -        | 4.35   | -           |
| evolocumab+ezetimibe+statins | 289,898  | 174,340  | 5.98   | 1.63        | 106,950     |
| HoFH Population (third line)|           |           |         |             |
| ezetimibe+statins          | 357,815   | -        | 4.03   | -           |
| evolocumab+ezetimibe+statins | 672,463  | 314,468  | 8.04   | 4.02        | 78,356      |

Table 4 presents a summary of the cost-effectiveness results from the payer’s perspective for the target population included in the base-case as well as the additional populations considered as part of the scenario analyses. From a payer’s perspective, a reimbursement limit of 44.6% and 64.6% is applied to drug costs and hospital costs respectively, referring to the maximum cost that would be incurred by the payer. Consequently, cost-effectiveness results of evolocumab significantly improved with ICERs well below the WTP for all populations.
considered.

| Drug                          | Reimbursement rates, % | Cost, CNY | QALY | ICER, CNY |
|-------------------------------|------------------------|-----------|------|-----------|
|                              | drug hospitalisation   | Total     | Incremental | Total | Incremental |
| Recent ACS (second line)      |                        |           |      |           |
| ezetimibe+statins            |                        | 75,062    | -    | 3.04      | -         | -         |
| evolocumab+statins           | 44.60 64.60            | 125,319   | 50,257 | 4.45      | 1.41      | 35,715    |
| Recent MI (second line)       |                        |           |      |           |
| ezetimibe+statins            |                        | 71,106    | -    | 3.82      | -         | -         |
| evolocumab+statins           | 44.60 64.60            | 130,038   | 58,932 | 5.22      | 1.40      | 41,970    |
| Recent ACS (third line)       |                        |           |      |           |
| ezetimibe+statins            |                        | 77,869    | -    | 2.53      | -         | -         |
| evolocumab+ezetimibe+statins | 44.60 64.60            | 131,553   | 53,685 | 4.45      | 1.92      | 28,029    |
| VHR ASCVD (third line)        |                        |           |      |           |
| ezetimibe+statins            |                        | 67,577    | -    | 4.35      | -         | -         |
| evolocumab+ezetimibe+statins | 44.60 64.60            | 140,997   | 73,420 | 5.98      | 1.63      | 45,040    |
| HoFH Population (third line)  |                        |           |      |           |
| ezetimibe+statins            |                        | 223,331   | -    | 4.03      | -         | -         |
| evolocumab+ezetimibe+statins | 44.60 64.60            | 339,729   | 116,398 | 8.04      | 4.02      | 28,986    |

CNY, Chinese yuan; VHR, Very high-risk; MI, myocardial infarction; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; HoFH, homozygous familial hypercholesterolaemia; Statins, high-intensity statins therapy.
Discussion

Evolocumab is a PCSK9 inhibitor and can significantly reduce CV events and slow or halt coronary atheroma progression or reduce atheroma volume through consistent, maximized, and durable LDL-C lowering. The present study indicate that when used in patients with a recent ACS event and LDL-C levels ≥100 mg/dL, evolocumab on top of statins is a cost-effective treatment option, compared with ezetimibe plus a statin. The estimated ICER fall below the threshold of CNY217,341 (3 times per capita GDP, 2020), which is conventionally applied to new technologies in determining whether or not they represent value for money.

The sensitivity analysis show that the model is robust to changes in the model input parameters and evolocumab remain cost-effective in recent ACS patients. The probability that evolocumab is cost-effective as add-on therapy in patients with recent ACS in China is high. The results from the scenario analyses suggest that evolocumab is also cost-effective as a second-line treatment in patients with a recent MI, and as a third-line treatment in patients with recent ACS and in the VHR ASCVD population. Besides, when used in the HoFH population with high LDL-C levels (mean 582 mg/dL), evolocumab also showed its cost-effectiveness.

Our results were also consistent with recent cost-effectiveness analyses in the US and Swedish context. In the US context, Fonarow et al.[15] modeled that PCSK9 inhibition with evolocumab may be cost-effective in very high-risk patients with ASCVD. Ladmesser et al.[19] showed evolocumab was cost-effective in three different Swedish populations: patients with recent MI and LDL-C levels from 89 mg/dL (2.3 mmol/L), patients with an MI and a risk factor and LDL-C levels from 89 mg/dL (2.3 mmol/L) and patients with MI with a second event and LDL-C levels from 66 mg/dL (1.7 mmol/L). In other European countries, Toth et al.’s[17] study shows that although the price before reduction is used, evolocumab is still cost-effective in high-risk ASCVD population. The research of Villa et al.[16] also confirms the cost-effectiveness of evolocumab in FH patients in Spain and patients with a history of CV events. Other previously published European cost-effectiveness analyses in Germany[14], the Netherlands[13], and Norway[12] considered higher PCSK9i prices that are no longer relevant.

The only other CEA study in Chinese setting concluded that evolocumab is not cost-effective in the high risk Myocardial infarction (MI) groups[18]. We compared their study with ours and found some differences in their model. First, the other study’s model structure does not capture increased risk after subsequent events, thus underestimating the long-term implication of the condition. Furthermore, the model does not use the established relationship between LDL-C lowering and reduction in CV outcomes, underestimating the efficacy of PCSK9i. Taken the above into consideration, our research may more completely reflect the treatment effect of evolocumab, and can better show the differences in risks, utilities and costs between the first and subsequent years, thus make our results more reliable.

The results of this study should be interpreted in the context of the data and modelling assumptions used. First, efficacy data used in this model are from the FOURIER trial based
on a short follow-up of 2.2 year, while the health benefits estimated are life-time long. If the clinical benefit differs from that modeled in the study or significant adverse events emerge, the cost-effectiveness results would be affected[35,36]. Furthermore, if levels of persistence with, and adherence to evolocumab therapy differed from those modelled based on the FOURIER trial, outcomes, and costs might be affected. Thus, real-world study in patients with recent ACS events are expected to provide applicable data for further study. Based on these, it is important to note that extrapolating the cost-effectiveness results directly to other countries may be not appropriate, but relevant parameters can be modified depending on specific health-care systems, or other patients with similar, or even higher risk profiles to get their own conclusions.

It should also be noted that the analyses were conducted using the list price of evolocumab in China. In practice, however, a reimbursement agreement often involves a payment of a confidential net price that is lower than the list price. Using such a net price in the model would have further improved the cost-effectiveness of treatment.

In addition, a scenario taking the payer’s perspective was also explored, where a payer reimbursement limit is applied to drug (44.60%) and hospitalization (64.60%) costs. Consequently, evolocumab is even more cost-effective from the payer’s perspective, with ICERs well below the WTP, namely CNY35,715 in recent ACS patients (second line), CNY41,970 in recent MI patients (second line), CNY28,986 in HoFH patients (third line), CNY45,040 in VHR ASCVD patients (third line), and CNY28,029 in recent ACS patients (third line).

Based on the above study, we conclude that there is strong evidence of evolocumab to be cost-effective in patients with recent ACS compared with ezetimibe in the Chinese health-care setting. This finding will support the inclusion of evolocumab as an efficient treatment in Ultra-high-risk ASCVD patients.

Declarations

Authors’ Contributions Model construction, data collection and analysis were performed by Xiaoyu Xi, Yu Jia, Santiago Zuluaga Sanchez, and Laura Martinez. Xiaoyu Xi, Wenwen Xie, Xin Wang and Yu Jia drafted and wrote the manuscript. Xiaoyu Xi, Yu Jia, Santiago Zuluaga Sanchez, and Laura Martinez had actively participated in the subsequent critical revision. Professional clinical advice on disease development and model path were provided by Quanming Zhao. All authors contributed to this article and approved the last version to be published, and have agreed to be accountable for all aspects of the work.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate Not applicable.

Consent for publication All authors read and approved the final manuscript.

Availability of data and materials All data generated or analyzed during this study are included in the article.
Funding  This study was sponsored by Amgen Inc.

Compliance with Ethical Standards

Conflicts of Interest  The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals  This research did not involve human participants or animals.

Informed consent  This study did not involve individual participants, so informed consent was exempted.
Reference

[1] HUO Y, HAN Y, GE J, et al. TWO-YEAR OUTCOMES POST DISCHARGE IN CHINESE PATIENTS WITH ACUTE CORONARY SYNDROME: FINDINGS FROM THE EPICOR ASIA STUDY [J]. Journal of the American College of Cardiology, 2016, 67(13): 505.

[2] CHOLESTEROL, TREATMENT, TRIALISTS', et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials [J]. Lancet, 2010,

[3] HOWARD W J. Efficacy and safety of cholesterol-lowering treatment: prospective metaanalysis of data from 90 056 participants in 14 randomised trials of statins [J]. Yearbook of Medicine, 2007, 2007(515-6.

[4] LAW M R, WALD N J, THOMPSON S G. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? [J]. Bmj Clinical Research, 1994, 308(6925): 367-72.

[5] LAROSA J, GRUNDY S, WATERS D D, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease [J]. The New England journal of medicine, 2005, 352 14(1425-35.

[6] XING Y, LIU J, HAO Y, et al. Prehospital statin use and low-density lipoprotein cholesterol levels at admission in acute coronary syndrome patients with history of myocardial infarction or revascularization: Findings from the Improving Care for Cardiovascular Disease in China (CCC) project [J]. American heart journal, 2019, 212(120-8.

[7] CANNON C P, BLAZING M A, GIUGLIANO R P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes [J]. New England Journal of Medicine, 2015, 372(25): 2387-97.

[8] SMITH L, MOSLEY J, YATES J, et al. The New Face of Hyperlipidemia Management: Proprotein Convertase Subtilisin/Kexin Inhibitors (PCSK-9) and Their Emergent Role As An Alternative To Statin Therapy [J]. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Société canadienne des sciences pharmaceutiques, 2016, 19(1):

[9] SABATINE M S, GIUGLIANO R P, KEECH A C, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease [J]. New England Journal of Medicine, 2017, 1713.

[10] KOREN M J, SABATINE M S, GIUGLIANO R P, et al. Long-term Low-Density Lipoprotein Cholesterol-Lowering Efficacy, Persistence, and Safety of Evolocumab in Treatment of Hypercholesterolemia: Results Up to 4 Years From the Open-Label OSLER-1 Extension Study [J]. JAMA cardiology, 2017,

[11] KOREN M, SABATINE M, GIUGLIANO R, et al. Final Report of the OSLER-1 Study: Long-Term Evolocumab for the Treatment of Hypercholesterolemia [J]. Journal of clinical lipidology, 2019, 13(3): e53-e4.

[12] MAX K, TORBJRN W. Modelling the cost-effectiveness of PCSK9 inhibitors vs. ezetimibe through LDL-C reductions in a Norwegian setting [J]. European Heart Journal Cardiovascular Pharmacotherapy, 2017, 1): 1.

[13] STAM-SLOB M C, YOLANDA V D G, DE BOER A, et al. Cost-effectiveness of PCSK9 inhibition in addition to standard lipid-lowering therapy in patients at high risk for vascular disease [J]. International journal of cardiology, 2018, 253(148-54.

[14] ALEXANDER, DRESSEL, BURKHARD, et al. Cost effectiveness of lifelong therapy with PCSK9 inhibitors for lowering cardiovascular events in patients with stable coronary artery disease: Insights from the Ludwigshafen Risk and Cardiovascular Health cohort [J]. Vascular Pharmacology, 2019,
[15] FONAROW G, HOUT B V, VILLA G, et al. Updated Cost-effectiveness Analysis of Evolocumab in Patients With Very High-risk Atherosclerotic Cardiovascular Disease [J]. JAMA cardiology, 2019.

[16] VILLA G, CATTERICK D, PEMBERTON-ROSS P, et al. PCV36 - ESTIMATION OF THE INCREASED RISK ASSOCIATED WITH RECURRENT EVENTS OR POLY-VASCULAR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN THE UNITED KINGDOM FOR USE IN ECONOMIC EVALUATIONS [J]. Value in Health, 2018.

[17] TOTH P P, DANENE M, VILLA G, et al. Estimated burden of cardiovascular disease and value-based price range for evolocumab in a high-risk, secondary-prevention population in the US payer context [J]. J Med Econ, 2017, 1-10.

[18] LIANG Z, CHEN Q, YANG F, et al. Cost-Effectiveness of Evolocumab Therapy for Myocardial Infarction: The Chinese Healthcare Perspective [J]. Cardiovascular drugs and therapy, 2020, 10065): 1-11.

[19] ULF L, PETER L, EMIL H, et al. Cost-effectiveness of PCSK9 inhibition with evolocumab in patients with a history of myocardial infarction in Sweden [J]. European Heart Journal - Quality of Care and Clinical Outcomes, 2020.

[20] GANDRA S R, VILLA G, FONAROW G C, et al. Cost-Effectiveness of LDL-C Lowering With Evolocumab in Patients With High Cardiovascular Risk in the United States [J]. Clinical cardiology, 2016, 39(6): 313-20.

[21] CHING-YUNWEI, QUEK R W, GUILLERMOVILLA, et al. A Systematic Review of Cardiovascular Outcomes-Based Cost-Effectiveness Analyses of Lipid-Lowering Therapies [J]. PharmacoEconomics, 2017, 35(3): 297–318.

[22] GRAY A C, CLARKE P, WOLSTENHOLME J, et al. Comprar Applied Methods of Cost-effectiveness Analysis in Healthcare | Alastair M. Gray | 9780199227280 | Oxford University Press, F, 2010 [C].

[23] JENA A B, BLUMENTHAL D M, STEVENS W, et al. Value of Improved Lipid Control in Patients at High Risk for Adverse Cardiac Events [J]. American Journal of Managed Care, 2016, 22(6): e199-e207.

[24] PENG Y, DU X, ROGERS K D, et al. Predicting In-Hospital Mortality in Patients With Acute Coronary Syndrome in China [J]. American Journal of Cardiology, 2017, 1077.

[25] ABTAN J, STEG P G, STONE G W, et al. Efficacy and Safety of Cangrelor in Preventing Periprocedural Complications in Patients With Stable Angina and Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: The CHAMPION PHOENIX Trial [J]. Jacc Cardiovascular Interventions, 2016, 9(18): 1905-13.

[26] HAGSTRM E, VILELA F S, SVENSSON M E, et al. Rates of major cardiovascular events in patients with a history of myocardial infarction and additional risk factors: Evidence from a Swedish nationwide register-based study [J]. Atherosclerosis, 2020, 315(e179.

[27] An international model to predict recurrent cardiovascular disease [J]. American Journal of Medicine, 2012, 125(7): 695-703.e1.

[28] TAYLOR B, LOTHGREN M, VILLA G, et al. Abstract 18114: Differences Between Observed and Predicted Cardiovascular Event Rates Using the Framingham and REACH Equations: The Case of High-intensity Statin Users in the United Kingdom [J]. Circulation, 2015.

[29] 胡盛寿, 高润霖, 刘力生, et al. 《中国心血管病报告 2018》概要 [J]. 中国循环杂志, 2019, 34(03): 209-20.

[30] Instructions for Repatha.

[31] A M J K, B M S S, B R P G, SM, et al. Long-Term Efficacy and Safety of Evolocumab in Patients With Hypercholesterolemia [J]. Journal of the American College of Cardiology, 2019, 74(17): 2132-46.
[32] MATZA L S, STEWART K D, GANDRA S R, et al. Acute and chronic impact of cardiovascular events on health state utilities Utilization, expenditure, economics and financing systems [J]. BMC health services research, 2015, 15(1): 173.

[33] YANG C, XUN T, Li Y, et al. [Influence of chronic diseases on health related quality of life in middle-aged and elderly people from rural communities: application of EQ-5D scale on a Health Survey in Fangshan, Beijing] [J]. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi, 2012, 33(1):

[34] https://data.stats.gov.cn/search.htm?s=2020%E5%B9%B4%E4%BA%BA%E5%9D%87GDP

[35] SHAH P, GLUECK C J, JETTY V, et al. Pharmacoeconomics of PCSK9 inhibitors in 103 hypercholesterolemic patients referred for diagnosis and treatment to a cholesterol treatment center [J]. Lipids in Health & Disease, 2016, 15(1): 132.

[36] GANDRA S R, VILLA G, FONAROW G C, et al. Cost-Effectiveness of LDL-C Lowering With Evolocumab in Patients With High Cardiovascular Risk in the United States [J]. Clinical cardiology, 2016, 39(6): 313-20.

[37] BUJO H, TAKAHASHI K, SAITO Y, et al. Clinical features of familial hypercholesterolemia in Japan in a database from 1996-1998 by the research committee of the ministry of health, labour and welfare of Japan [J]. J Atheroscler Tromb, 2004, 11(3): 146.

[38] ROBINSON J G, HUIJGEN R, RAY K, et al. Determining When to Add Nonstatin Therapy: A Quantitative Approach [J]. Journal of the American College of Cardiology, 2016.

[39] RAAL F J, HONARPOUR N, BLOM D J, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial [J]. Lancet, 2015, 385(9965):

[40] YANG Z, BUSSCHBACH J, LIU G, et al. EQ-5D-5L norms for the urban Chinese population in China [J]. Health and Quality of Life Outcomes, 2018, 16(1):
## Supplementary figures and tables

### Table S1 Key model inputs in the HoFH population

| Parameters                                                                 | Base value | Range       | Distribution | Source           |
|---------------------------------------------------------------------------|------------|-------------|--------------|-----------------|
| **Patient Characteristics**                                               |            |             |              |                 |
| Age, years                                                                | 26         | NA          | NA           | Bujo[37]        |
| LDL-C level, mg/dL                                                        | 582        | NA          | NA           | Bujo[37]        |
| Primary prevention CV event rate (per 100 patient-years)                  | 4.26       | 4.05 – 4.47 | Normal       | Robinson[38]    |
| Secondary prevention CV event rate† (per 100 patient-years)               | 9.34       | 8.89 – 9.80 | Normal       | Jena[23], Wilson[27] |
| **LDL-C reduction**                                                       |            |             |              |                 |
| Evolocumab                                                                | 31%        | 30.4% - 31.6%| Normal       | TESLA[39]       |
| **Annual cost of drugs, CNY**                                             |            |             |              |                 |
| Evolocumab                                                                | 46,728     | NA          | NA           | Based on the price per 140mg of CNY 1,298 and 3 dosages per month |
| **Utility**                                                               |            |             |              |                 |
| Starting health state for primary prevention patients                      | General population utility based on EQ-5D study | NA         | NA           | Yang[40]        |

* CV event rate for HoFH patients with a previous CV event was estimated based on the US real-world CV event rate of 6.4 per 100 patient-years (Jena) increased by the diabetes hazard ratio of 1.46 (Wilson) to account for the increased risk in HoFH patients
Figures

Figure 1
Enclosed grating ruler structure diagram

Figure 2
Schematic diagram of equivalent conversion of Weibull distribution

Figure 3
The process of the case analysis

Figure 4
Accelerated life test device for grating ruler
Figure 5

Relationship between characteristic life and temperature and humidity stress

$t=14023\text{h}$,

$F^{(\text{MS})}(t)=F^{(\text{OS})}(t)=0.5609$

$t=15357\text{h}$,

$F^{(\text{OS})}(t)=F^{(\text{ES})}(t)=0.5941$

Figure 6
Figure 7
Probability density function based on competing risk model