Cost-effectiveness of statin vs ezetimibe vs PCSK9 inhibitor for secondary prevention of cardiovascular

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Introduction

◇ Although rates of cardiovascular disease (CVD) have decreased over the last 30 years, it remains the leading cause of mortality worldwide. In 2017, CVD death has been accounted for 30% of all global deaths[1]. Dyslipidemia, especially high-density lipoprotein(HDL) and low-density lipoprotein(LDL) is the primary risk factor and main prevention target of cardiovascular diseases[2].
In recent years, the inhibitor of proprotein convertase subtilisin/kexin type 9(PCSK9) and the cholesterol absorption inhibitor represented by ezetimibe have become the clinical optional lipid reducing drugs, which makes the patients with low blood lipid treatment with medium dose statin have more choices.
◇ With the publication of large-scale clinical trials related to PCSK9 inhibitors in recent years, previous studies have shown that PCSK9 inhibitors can significantly reduce major cardiovascular events (MACE), stroke, non-fatal myocardial infarction and other cardiovascular events in primary and secondary prevention (medium-level evidence)[3].
◇ However, the global price of evolocumab is relatively high. According to the evaluation of health economics in Europe and North America, although this drug can effectively reduce cardiovascular events, its price is far higher than the social and patient's economic affordability[4-7]. A Chinese based study has also shown that PCSK9 has no economic benefit compared with statins in secondary prevention.
◇ However, based on the perspective of China, there is no economic comparison of the four secondary prevention treatment strategies (PCSK9 + Statin, Ezetimibe + Statin, Statin, and PCSK9+ Ezetimibe + Statin) currently.

Objective

◇To assess the value of different strategy of secondary prevention of CVD and provide pharmacoeconomics evidence for decision making in China, we evaluate the long-term cost-effectiveness of statin, ezetimibe and PCSK9 inhibitors, separately or their combinations for very high-risk patients.

Methods

➢Population: Secondary prevention of cardiovascular disease patients with very high risk.
➢Model Structure: We figure out 4 treatment strategy for evaluation. A 6 states Markov model, including secondary prevention of CVD, non-fatal stroke recurrence, non-fatal myocardial infarction (MI) recurrence, MI maintenance therapy, stroke maintenance therapy, and death, is developed to estimate the incremental cost- effectiveness ratio (ICER) to simulate for 25 years.
➢Therapy: High dose statin group: atorvastatin 40mg, once a day;
PCSK9+ Statin group: atorvastatin 40mg once a day, plus evolocumab 420mg once a month.
Ezetimibe+ Statin group: atorvastatin 40mg once a day, plus ezetimibe 10mg once a day;
PCSK9+Ezetimibe+Statin group: atorvastatin 40mg once a day, plus ezetimibe 10mg once a day , plus evolocumab 420mg once a month.

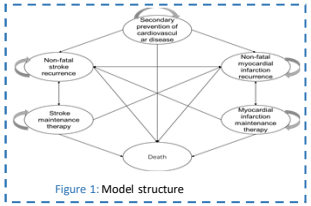

Figure 1: Model structure

Model assumptions

In order to fully evaluate the three therapy strategies, we constructed a long-term Markov model with the following assumptions.
➢ The event risk ratio will not change between different ages.
➢ The quality of life of patients in secondary prevention of cardiovascular disease stage is consistent with that of patients in maintenance treatment of myocardial infarction.

Model Parameters

Transition probability

➢ CVD risk reduction is gathered from a network-meta-analysis (NMA).

Table 1: CVD risk rate of patients with very high risk

Rate	Statin	PCSK9+Statin	Ezetimibe+Statin	PCSK9+Ezetimibe+Statin
All cause mortality	0.032	0.03	0.032	0.03
Cardiovascular mortality	0.019	0.018	0.018	0.017
Nonfatal myocardial infarction	0.084	0.068	0.073	0.059
Nonfatal stroke	0.08	0.059	0.066	0.048

Cost

➢ From the perspective of the healthcare system, this study considers direct medical cost. The average drug consumption of the two groups is selected as the drug dosage.
➢ The unit price was selected from the bid-winning price in China in 2020[8]. The costs of cardiovascular events were from published research and were corrected using consumer price index (CPI)[9].
➢ We convert CNY to US$, divide by 6.8974 (average exchange rate in 2020)[10].
➢ In this study, 5% is used as the discount rate and 0-8% as the upper and lower limit in sensitivity analysis.

Table 2: Base case and plausible ranges of model cost (USD)

Parameter	Value	Range	Reference
Utility reduction due to the event			
Stroke	37.1%		[14]
Myocardial infarction	24%		[14]
Utility value			
Secondary prevention of cardiovascular disease	0.80	0.72-0.88	
The first year after stroke recurrence	0.36	0.35-0.40	[14, 15]
Maintenance therapy after stroke recurrence	0.58	0.52-0.64	[14]
The first year after MI recurrence	0.61	0.55-0.67	[14, 15]
Maintenance therapy after MI recurrence	0.80	0.72-0.88	[14]
Death	0	0	

Table 2: Base case and plausible ranges of model utility

Parameter	Costs (2020)	Range	Reference
Annual cost of drugs, USD			
High dose statin group	325	292-357	[8]
Ezetimibe group	536	482-589	[8]
Evolocumab group	6937	6243-7631	[8]
Cost of cardiovascular events, USD			
Secondary prevention of cardiovascular disease	1240	930-1550	[11]
The first year after stroke recurrence	3979	3581-4377	[12]
Maintenance therapy after stroke recurrence	1157	1041-1273	[12]
The first year after MI recurrence	9916	8924-10907	[12]
Maintenance therapy after MI recurrence	1141	1026-1255	[12]
Cardiovascular death	11563	10407-12720	[13]
Non-cardiovascular death	0	0	

Utility

➢In this model, health output is utility, which is measured by quality adjusted life years (QALYs).
➢ Since there is no utility research about the patients in the secondary prevention of cardiovascular disease in China, the utility of the model was used by a utility research from South Korea[14]. The utility values of the state in the first year after myocardial infarction and stroke recurrence were expressed by the utility values of the population when the disease was in the acute state, and the calculation formula was: recurrence state of the disease = maintenance therapy state of the disease * (1-percentage of utility reduction). The reduction of the utility was from previous study[15]
➢ The discount rate of the utility is equal to that of the cost..

Threshold

➢In this study, three times per capita GDP of China in 2020 is used as the willing-to-pay (WTP) threshold. According to the website of the National Bureau of statistics, per capita GDP of China in 2020 is CNY72000 (US$10439)[9].
➢The threshold value set in this study is CNY216,000 (US$31316) per QALY gained.

Sensitivity analyses

➢One-way sensitivity analyses are conducted in the models to test alternative modeling assumptions and alternative values for key model parameters. Depending on data availability, the ranges considered in the one-way sensitivity analyses include 95% confidence intervals, or ±10% of the base case values. The main indicators of one-way sensitivity analysis are the price of two drugs, the clinical outcome, the probability of each transfer and the utility value of the two drugs after treatment. The results from the one-way sensitivity analyses are presented in a Tornado diagram, showing sequentially the variables with the largest impact on the cost-effectiveness results.
➢ The overall impact of uncertainty in the model is assessed with probabilistic sensitivity analyses by defining distributions for key parameters in the model. The key parameters included in the PSA are clinical outcome, unit cost, and utility variables. An overall summary of the variables included in the PSA, and the distributions applied to these variables, is provided in Table 7. The PSA is run for 1000 iterations (simulations), and the results are plotted on the cost-effectiveness plane (CAP) as scatterplots and cost-effectiveness acceptability curves (CEACs) to evaluate the pharmacoeconomic value of the two treatments.

Results

Base case result

➢PCSK9+Ezetimibe+Statin group had higher cost, but also higher utility gained compared to other 2 groups.
➢Compared to statin group, the ICER for PCSK9+Statin therapy is $43321; the ICER for Ezetimibe + Statin therapy is $19642 per QALY; the ICER for PCSK9+Ezetimibe+Statin therapy is $37747 per QALY.

Table 3: Cost-effectiveness results for statin, ezetimibe, and evolocumab

Group	Cost	Effectiveness	incrCost	incrEffectiveness	ICER
Statin group	23123.87	6.92	0	0	0
Ezetimibe + Statin group	25403.23	7.04	2279.36	0.12	19642.33
PCSK9 + Statin group	35686.84	7.21	10283.6	0.17	60237.48
Evolocumab + Ezetimibe + Statin group	38223.22	7.32	2536.38	0.11	23238.64

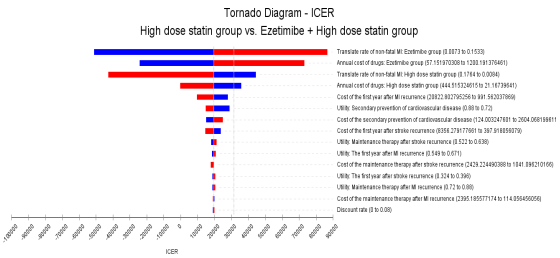

Figure 2: The one-way analysis result of Ezetimibe VS Statin

One-way sensitivity analyses

➢One-way sensitivity analyses are conducted in the models to test alternative modeling assumptions and alternative values for key model parameters. Depending on data availability, the ranges considered in the one-way sensitivity analyses include 95% confidence intervals, or ±10% of the base case values.
➢ Ezetimibe group is the most cost-effective based on the current price in China. The main indicators of one-way sensitivity analysis in Ezetimibe VS statin are the translate rate of none-fatal MI in Ezetimibe group, annal cost of ezetimibe drug cost, and the translate rate of none-fatal MI in statin group.
➢ The main indicators of one-way sensitivity analysis in PCSK9(evolocumab) VS statin are annal cost of evolocumab drug cost, the translate rate of none-fatal MI in statin group, and the translate rate of none-fatal MI in Evolocumab group.

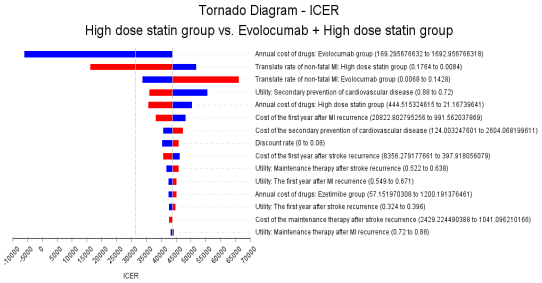

Figure 3: The one-way analysis result of PCSK9 (Evolocumab) VS Statin

Probabilistic sensitivity analyses

➢The probability sensitivity analysis of incremental cost-effectiveness ratio (ICER) is carried out, and Monte Carlo simulation is conducted 1000 times to reflect the influence of each parameter on the model.
➢ With WTP threshold, the probability of cost-effectiveness of evolocumab versus other therapy is 1.5%.
➢ The probability of cost-effectiveness of ezetimibe is 56%.
➢ The probability of cost-effectiveness of ezetimibe plus evolocumab is 9.7%.
➢ A reduction in acquisition price of evolocumab by approximately 21.3% is needed to be cost-effective.

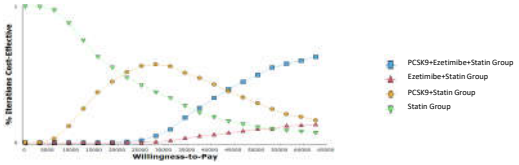

Figure 4: The Acceptability Curve of 4 strategies

Table 3: The Acceptability rate of 4 strategies in the threshold

WTP($)	STRATEGYNAME	ACCEPTABILITY
31316	High dose statin group	32.80%
31316	Ezetimibe + High dose statin group	56.00%
31316	Evolocumab + High dose statin group	1.50%
31316	Evolocumab + Ezetimibe + High dose statin group	9.70%

Limitation

◇In the research, we didn't consider the adverse reactions. This could under-estimate the impact of AEs in the model as evolocumab has a more favorable safety profile than statin.
◇What's more, the utility of patients of prevention of cardiovascular diseases in China was not reported and these were, therefore, sourced from the published literature and were only available for a Korea population

Conclusion

◇Among the current secondary prevention strategies of CVD in very high-risk patients in China, ezetimibe is the most economic advantage. Although the price of evolocumab has been greatly reduced, it still needs to be cut if it wants to be cost-effectiveness

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