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ORIGINAL RESEARCH

Comprehensive Assessment of PCSK9 Inhibitors for Lipid Management: Scientific Guidance Based on Drug Selection Recommendations for Chinese Medical Institutions

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Objective: This study aims to support the selection of PCSK9 inhibitors for patients requiring lipid management within medical institutions. By quantitatively evaluating four PCSK9 inhibitors, we provide evidence-based guidance for optimal selection in this patient population.

Methods: According to the Rapid Guide for Drug Evaluation and Selection in Chinese Medical Institutions (Second Edition) released in 2023, relevant databases such as PubMed, Cochrane, Embase, drug labels, and clinical guidelines were searched for drug information. Using a percentage scoring method, we systematically evaluated 4 PCSK9 inhibitors marketed in China for safety, efficacy, economy, pharmacological properties, and other attributes.

Results: The final assessment result scores from highest to lowest were evolocumab (78.00 points), alirocumab (77.24 points), inclisiran (72.89 points), and tafolecimab (65.33 points). Evolocumab was the best in the economy, alirocumab scored the highest in terms of efficacy and other attributes, and inclisiran had the strongest performance in terms of pharmacological properties.

Conclusion: For lipid management in medical institutions, evolocumab, alirocumab, inclisiran, and tafolecimab may be prioritized accordingly based on evaluation results.

Keywords: PCSK9 inhibitor, Health technology assessment, Antihyperlipidemic, Inclisiran, Drug evaluation

Introduction

Cardiovascular disease (CVD) has been one of the major health challenges globally, posing a serious threat to human health. Atherosclerotic cardiovascular disease (ASCVD)-dominated CVDs (eg, ischemic heart disease and ischemic stroke, etc.) are the first cause of death for both urban and rural residents in China, accounting for more than 40% of the cause-of-death composition. [1] While high cholesterol levels are closely associated with the risk of cardiovascular events, Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors have become a drug class of interest in CVD management due to their excellent cholesterol-regulating function.

Globally, PCSK9 inhibitors are recognized as an important class of drugs for managing hypercholesterolemia and reducing the risk of cardiovascular disease. The four major PCSK9 inhibitors—evolocumab, alirocumab, inclisiran, and tafolecimab—each have distinct market positions and usage backgrounds. Evolocumab and alirocumab, both approved by the FDA in 2015, were the first to enter the market and have seen widespread use across North America and Europe, with numerous clinical trials confirming their effectiveness in significantly lowering cholesterol and reducing cardiovascular events. Inclisiran, a later addition with an innovative dosing regimen of twice per year, has rapidly gained traction, particularly in Europe and North America, for its ability to improve patient adherence. Tafolecimab, a newer PCSK9 inhibitor approved in China in 2023, is still in the early stages of global market expansion but is steadily gaining attention

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in the Asian market. These four drugs demonstrate unique advantages in terms of safety, efficacy, and ease of use, collectively advancing the global market for PCSK9 inhibitors and offering additional therapeutic options for patients requiring substantial LDL-C reduction.

However, when faced with different PCSK9 inhibitors, healthcare decision-makers must carefully weigh various factors to ensure patients receive the best treatment outcomes. Hospital-based health technology assessment (HB-HTA), refers to the comprehensive and systematic evaluation of relevant health technologies based on the actual needs of hospitals and the application of the principles and methods of evidence-based medicine and health technology assessment to make rapid decisions on the selection, acquisition, and use of new technologies to improve health equity, is a commonly used policy analysis tool in the international arena.[2,3] Based on the Rapid Guide for Drug Evaluation and Selection in Chinese Medical Institutions (Second Edition),[4] this study evaluated four PCSK9 inhibitors (including evolocumab, alirocumab, inclisiran, and tafolecimab) marketed in China by using a percentage-based quantitative evaluation method, which provides a reference for the introduction and rational use of PCSK9 inhibitors in other low- and middle-income countries, and in medical institutions with lower medical care or those who are unable to carry out their own drug evaluation work.

Information and Methods

Evaluation of Drugs

All four PCSK9 inhibitors have only one manufacturing unit and are all original drugs. Therefore, the selection of drugs to be evaluated is shown in Table 1.

Evaluation Basis

The health technology assessment of the four PCSK9 inhibitors was conducted by the "Rapid Guide for Drug Evaluation and Selection in Chinese Medical Institutions (Second Edition) "[4] using a quantitative percentage-based assessment. With reference to the results of evidence-based research and in the light of China's national conditions, the Guide adopts the Mini-HTA assessment combined with the SOJA method, and applies a multi-attribute scoring tool to establish a drug evaluation system comprising five major aspects, namely, pharmacological properties, efficacy, safety, economy and other attributes, and the dimensions and weights of the evaluation are determined by the Guideline Steering Group and the Expert Group through the Delphi Method. The evaluation included five aspects: pharmacological properties (28%), efficacy (27%), safety (25%), economy (10%) and other attributes (10%). In terms of pharmacological properties, it mainly evaluates the drug's pharmacological effects, in vivo processes, whether the pharmacology and methods of use are clear, the length of the drug's validity period, and storage requirements. In terms of drug effectiveness, it mainly evaluates the clinical efficacy of the drug and the degree of recommendation of relevant authoritative professional information such as clinical guidelines or expert consensus. In terms of safety, it mainly evaluates adverse events, the use of drugs in special populations, drug interactions, etc. In terms of economy, the average daily therapeutic cost of the drug was evaluated. In addition, the supply information of the drug is also evaluated.

Data Source

The sources of information include drug manuals, drug registration information, DrugWise.com DrugWise data on drug winning prices,[5] the National Health Insurance Information Database,[6] the Drug Evaluation Centre of the State Food and Drug Administration[7] and other authoritative medical institutions information query platform. English databases PubMed, Embase, Update databases and Cochrane Library, as well as Chinese databases Chinese Biomedical

Table 1 Drugs Included in the Evaluation

Generic Name	Evolocumab injection	Alirocumab injection	Inclisiran injection	Tafolecimab injection
Production units	AmgenManufacturingLimited	Sanofi Winthrop Industrie	Sandoz GmbH	Innovent Biologics (Suzhou) Co. Ltd.
Dosage forms and strengths	1mL:140mg	1mL:75mg	1.5mL:284mg	1mL:150mg

Sciences, China Knowledge Network (CNKI), Wanfang Database, Medication Assistant and Medical Pulse Database,[8] to search for 5 years' worth of information published by authoritative institutions within 5 years.

Analysis and Evaluation

Drugs included in the assessment were scored according to the drug assessment guidelines, based on evidence gathered by searching relevant databases. If scoring breakdown rules were not available, experts in the field were invited to refine them. Evaluations were conducted independently by two clinical pharmacists. If there were conflicting results, experts in the relevant field were invited to discuss the evaluation results. The results of the evaluation are ultimately used for decision-making on drug selection and clinical medication planning in healthcare organizations.

Results

Pharmacological Properties (28%)

The information was obtained from drug manuals, drug registration information, guidelines, Chinese and English literature databases, etc. The objective was to compare the differences in details and confirm whether the drugs were substitutable with each other by scoring the selected drugs in five aspects, pharmacological effect, in vivo processes, pharmacy and the use of drugs, storage conditions, and expiration date of the drugs. In particular, the scoring criteria for the frequency of administration in the pharmacy and the use of drugs were adjusted to consider the actual situation.

Pharmacological Effects and in vivo Processes

4 PCSK9 inhibitors with obvious clinical efficacy, clear and innovative mechanism of action, all scoring 5 points; simultaneously, the in vivo process and pharmacokinetic parameters are complete, scoring 5 points.

Pharmacy and the Use of Drugs

The ingredients and excipients of the 4 PCSK9 inhibitors are clearly defined; the dosage forms are all subcutaneous injections. In terms of specifications and packaging, all 4 PCSK9 inhibitors are compatible with clinical use and dosage can be adjusted. In terms of administration frequency, evolocumab, alirocumab, and tafolecimab are all administered every 2 weeks, whereas inclisiran is administered every 6 months. In addition, in terms of ease of use, all patients treated with PCSK9 inhibitors need to be trained by a healthcare provider.

Storage Conditions

Evolocumab, alirocumab, and tafolecimab need to be stored at 2–8°C, which is refrigerated/frozen storage and needs to be protected from light, while inclisiran can be stored at 20–25°C and does not need to be shaded/protected from light.

Expiration Dates

The expiry dates for evolocumab, alirocumab, inclisiran, and tafolecimab are 36, 30, 24, and 18 months, respectively. Table 2 displays the results of the pharmacologic properties evaluations for the 4 PCSK9 inhibitors.

Efficacy (27%)

Indications

The range of approved indications for different PCSK9 inhibitors in China is slightly different, as shown in Table 3. PCSK9 inhibitors are a new class of lipid-lowering drugs, often used in combination with statins, or with statins and other lipid-lowering therapies, or alone or in combination with other lipid-lowering therapies, in patients who are intolerant of or contraindicated for the use of statin drugs alone or in combination with other lipid-lowering therapies in patients in whom statins are intolerant or contraindicated. Therefore, all four PCSK9 inhibitors are classified as having a high number of drug choices, and all score 1.

Guideline Recommendations

Several guidelines have recommended PCSK9 inhibitors for lipid-lowering therapy or cardiovascular risk reduction, including three guidelines with a recommendation grade of IA, namely, the 2023 China Guidelines for Lipid Management,[9] the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice"[10] and "2019 ESC/

Table 2 Pharmacological Properties Score Results

Pharmacological Properties (28points)		Grade	Evolocumab	Alirocumab	Inclisiran	Tafolecimab
Pharmacological effect (5 points)	Clinical efficacy obvious, action mechanism is clear, mechanism or target is innovative	5	5	5	5	5
	Clinical efficacy obvious, mechanism is clear	4				
	Clinical efficacy general, mechanism is unclear	2				
	Clinical efficacy poor, mechanism is unclear	1				
In vivo processes (5 points)	In vivo process clear, pharmacokinetic parameters complete	5	5	5	5	5
	In vivo process clear, pharmacokinetic parameters not complete	3				
	In vivo process not clear, pharmacokinetic parameters not complete	1				
Pharmacy and the use of drugs (12 points)	Main ingredients and excipients	2	2	2	2	2
	Specification and Packaging	2	2	2	2	2
	Dosage form (oral/inhalation/topical preparations (2 pts), subcutaneous/intramuscular injections (1.5 pts), intravenous drip/injection (1 pt))	2	1.5	1.5	1.5	1.5
	Dose of administered (fixed dosage (2 pts), dosage adjustment required during use (1.5 pts), dosage based on body mass or body surface area (1 pt))	2	2	2	2	2
	Administration frequency (>1x/months, (2 pts); 1x/months (1 point);	2	1	1	2	1
	Convenient use (self-administered without assistance (2 pts), self-administered without assistance, with help or training (1.5 pts), administered by medical personnel (1 pt))	2	1.5	1.5	1.5	1.5
Storage conditions (4 points)	Room temperature storage	3			3	
	Cool storage	2				
	Refrigerated/frozen storage	1	1	1		1
	No need for shading/sheltering	1			1	
Expiration dates (2 points)	>60 months	2				
	≥36 months, <60 months	1.5	1.5			
	≥24 months, <36 months	1		1	1	
	≥12 person-months, <24 months	0.5				0.5
	<12 months	0.25				
The results of the pharmacological properties		28	22.5	22	26	21.5

Table 3 Indications for the Four PCSK9 Inhibitors

Evaluation of drugs	Indications
Evolocumab, Alirocumab, Inclisiran	In adults with established CVD to reduce the risk of myocardial infarction, stroke, and coronary revascularization
Evolocumab, Alirocumab, Inclisiran, Tafolecimab	Primary hyperlipidemia, including HeFH and mixed dyslipidaemia
Evolocumab, Alirocumab	HoFH

Abbreviations: HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia.

EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk",[11] with the first 2 guidelines mentioning evolocumab, alirocumab, and inclisiran. Therefore, all three drugs scored 12 points in this category. While tafolecimab has not yet been recommended by clinical guidelines or expert consensus, three randomized,

double-blind, placebo-controlled Phase 3 trials[12–14] have demonstrated that tafolecimab was safe and showed robust lipid-lowering efficacy in Chinese patients at high or very high cardiovascular risk with hypercholesterolemia. Two of the clinical trials had sample sizes greater than 300 cases, and the level of evidence was classified as Class A evidence. Therefore, tafolecimab scored 9 out of 10 for this item, which is a guideline recommendation of grade II and below (level A evidence). The recommendations of the guidelines and expert consensus are shown in Table 4.

Table 4 Recommendations in Domestic and Foreign Guides and Consensus

Guide Name	Guideline Makers and Sources	Recommended Medications	Recommended Content	Evidence level
2021 ESC Guidelines on cardiovascular disease prevention in clinical practice	ESC; EAPC	Evolocumab, Alirocumab, Inclisiran	For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended.	I A
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk	ESC; EAS	Evolocumab, Alirocumab	In patients with PAD, lipid-lowering therapy, including a maximum tolerated dose of statin, plus ezetimibe or a combination with a PCSK9 inhibitor if needed, is recommended to reduce the risk of ASCVD events.For secondary prevention in patients at very-high risk not achieving their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I A
The 2023 China Guidelines for Lipid Management	Joint Committee on the 2023 China Guidelines for Lipid Management; National Center for Cardiovascular Diseases	Evolocumab, Alirocumab, inclisiran	1) Moderate-intensity statins combined with cholesterol absorption inhibitors LDL-C still cannot achieve the target, combined with PCSK9 inhibitors. (2) Single or combination LDL-C-lowering drugs, including statins, cholesterol absorption inhibitors, PCSK9 inhibitors, etc., are selected according to LDL-C compliance needs and individual tolerances.	I A
Tafolecimab in Chinese Patients With Hypercholesterolemia (CREDIT-4)	Litong Qi, Dexue Liu, Yanling Qu,	Tafolecimab	Tafolecimab was safe and showed robust lipid-lowering efficacy in Chinese patients at high or very high cardiovascular risk with hypercholesterolemia.	A
Tafolecimab in Chinese patients with non-familial hypercholesterolemia (CREDIT-1): a 48-week randomized, double-blind, placebo-controlled phase 3 trial	Yong Huo, Beijian Chen, Qiufang Lian	Tafolecimab	Tafolecimab dosed at 450 mg Q4W and 600 mg Q6W was safe and showed superior lipid-lowering efficacy versus placebo, providing a novel treatment option for Chinese hypercholesterolemia patients.	A

Abbreviations: EAPC, European Association of Preventive Cardiology. EAS, European Atherosclerosis Society. ESC, European Society of Cardiology. LDL-C, low-density lipoprotein cholesterol.

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Clinical Efficacy

Primary Efficacy Endpoints

PCSK9 inhibitors are effective in reducing the risk of cardiovascular events as a novel lipid-lowering drug, with the core mechanism being the reduction of LDL-C levels.

Cross-sectional and longitudinal comparisons were performed for four PCSK9 inhibitors with different indications. For the longitudinal comparison, tafolecimab showed the largest LDL-C reduction of 63%.[14] For cross-sectional comparisons: in terms of cardiovascular event risk reduction, the LDL-C reductions were, in descending order, alirocumab, evolocumab, and inclisiran,[15–17] and tafolecimab was not supported by relevant clinical trial data for the time being; in terms of hypercholesterolemia, the LDL-C reductions were, in descending order, tafolecimab, evolocumab, alirocumab, and inclisiran.[14,18–20] When hypercholesterolemia was further subdivided for comparison, the LDL-C reductions in HeFH were, in descending order, tafolecimab, alirocumab, evolocumab, and inclisiran,[13,21–23] and in HoFH the LDL-C reductions in descending order, to evolocumab and alirocumab,[24,25] with no statistical significance for inclisiran. The data for Inclsiran were not statistically significant,[26] and tafolecimab is not supported by data from relevant clinical trials at this time.

Although each of the four PCSK9 inhibitors had strengths in different indications, alirocumab was found to be the best overall performer, with the greatest reduction in risk of cardiovascular events and a top ranking in hypercholesterolemia and its 2 subtypes, resulting in a score of 6 for alirocumab in the primary efficacy endpoint score. In contrast, evolocumab ranked second in reducing the risk of cardiovascular events and hypercholesterolemia and received a score of 5.5 for the primary efficacy endpoint score.

For inclisiran and tafolecimab, two recently marketed new drugs, although there are no data to support tafolecimab in reducing the risk of cardiovascular events, it ranked first in hypercholesterolemia and its 2 subtypes, and had the largest reduction in LDL-C in the longitudinal comparisons, and thus was awarded a score of 6 for the primary efficacy endpoint score. Comparatively, inclisiran was ranked last in reduction across indications. Therefore, inclisiran was awarded a score of 5 in the primary efficacy endpoint indicator score.

Secondary Efficacy Endpoints

The selection of non-high-density lipoprotein cholesterol (Non-HDL-C), apoprotein B(ApoB), and lipoprotein(a) [Lp(a)] as secondary efficacy endpoints was based on their important role in the development of atherosclerosis and the need for a comprehensive assessment of the efficacy of treatment. These three indicators play an integral role in the development of atherosclerosis.

Therefore, for the secondary efficacy endpoints Non-HDL-C, ApoB, and Lp(a), we performed a cross-sectional comparison and a longitudinal comparison. For the longitudinal comparison, tafolecimab showed the greatest reduction in all 3 metrics of Non-HDL-C, ApoB, and Lp(a), with 63.9%, 59%, and 34.1%, respectively. For cross-sectional comparisons, the overall results and the ordering of the primary efficacy endpoints were generally consistent, except for the lack of data for some of the metrics in hypercholesterolemia. Therefore, the secondary efficacy endpoint indicator scores for alirocumab, tafolecimab, evolocumab, and inclisiran were 4, 4, 3.5, and 3, respectively. Specific clinical efficacy comparisons are shown in Figure 1, and the efficacy scores results are shown in Table 5.

Safety (25%)

In terms of safety, the evaluation mainly focuses on adverse events, drug use in special populations, and drug interactions.

Adverse Events

The adverse events of the four PCSK9 inhibitors are shown in Table 6.

Special Populations

Specific scores for special populations based on drug inserts, combined with evidence-based medicine such as clinical trial studies are shown in Table 7.

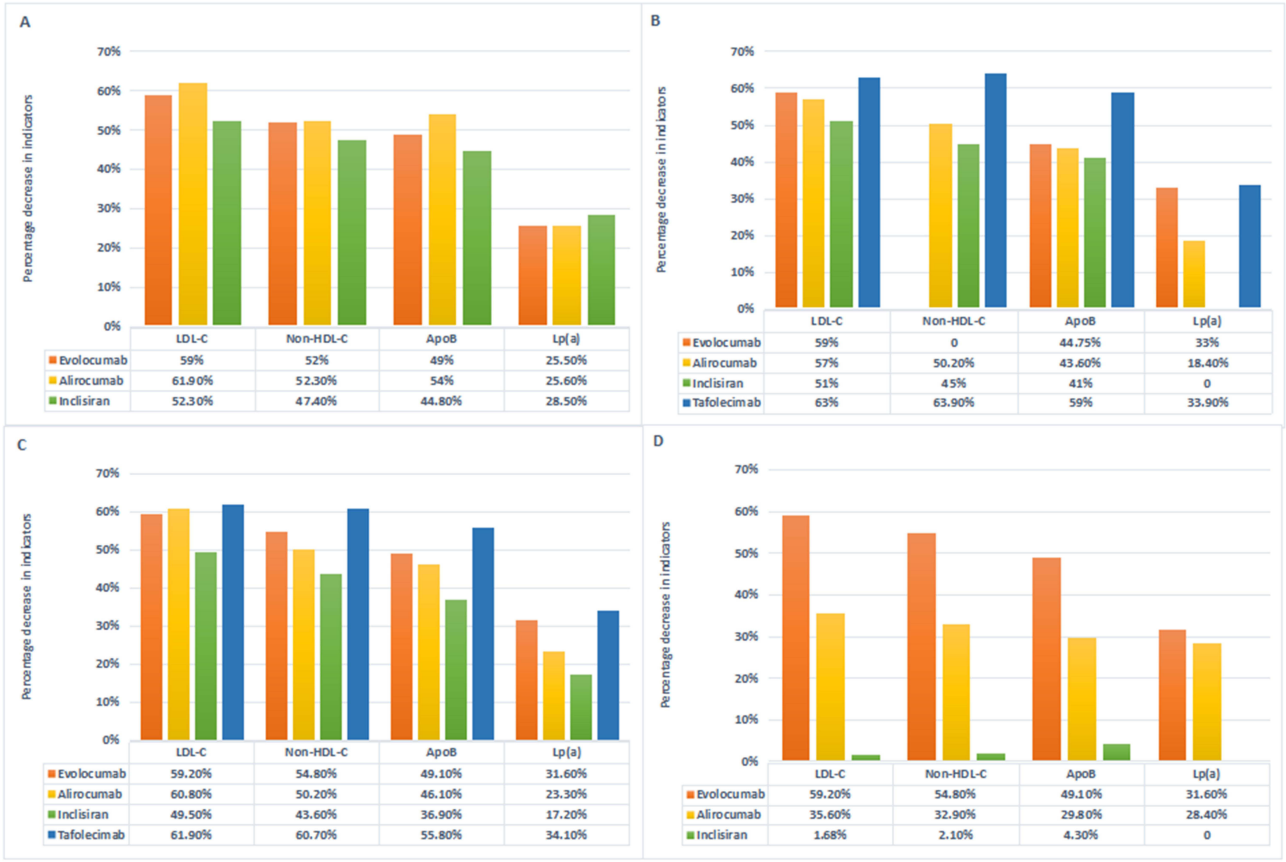

Figure 1 Comparison of clinical efficacy.
Abbreviation: (**A**) is a comparison of clinical efficacy in reducing the risk of cardiovascular events chart; (**B**) is a comparison of clinical efficacy of hypercholesterolemia chart; (**C**) is a comparison of clinical efficacy of HeFH chart; (**D**) is a comparison of clinical efficacy of HoFH chart.

Drug Interactions

No formal drug interaction studies have been conducted with any of the four PCSK9 inhibitors. An approximately 20% increase in clearance was observed with evolocumab in patients who were coadministered with statins. This elevated effect was caused by statins elevating PCSK9 concentrations without the need for dose adjustment. The pharmacokinetics of alirocumab may be affected when it is used in combination with statins, but a biweekly dosing regimen may reduce the effects of the interaction while maintaining efficacy without the need for dose adjustment. Inclisiran is not a common drug transporter protein substrate and is not metabolized by the CYP450 enzyme system, which theoretically poses a low risk of drug-drug interactions with other drugs. Tafolecimab is based on population pharmacokinetic analysis, statins, and ezetimibe may have no significant effect on the pharmacokinetics of this product. In conclusion, all four PCSK9 inhibitors did not require any dosage adjustment and scored 3.

Other

The four PCSK9 inhibitors scored 3 points for meeting the three points that all adverse effects were reversible, no teratogenicity or carcinogenicity, and no special dosing warnings. The safety results are shown in Table 8.

Economy

The economy evaluation was conducted by examining the difference in average daily treatment costs between the four PCSK9 inhibitors and drugs with the same generic name and substitutable drugs for the main indications. The average daily treatment cost was calculated based on the unit price and dosage of different PCSK9 inhibitors, as shown in

Table 5 Efficacy Score Results

Efficacy (27 points)		Grade	Evolocumab	Alirocumab	Inclisiran	Tafolecimab
Indications (5 points)	Clinically necessary and preferred	5				
	Clinical need, second choice	3				
	More drugs available	1	1	1	1	1
Guideline recommendations (12 points)	Diagnostic and treatment protocols/clinical pathways, consensus/management approaches issued by national health administrative agencies, etc., and guideline Level I recommendations (12 points for Level A evidence, 11 points for Level B evidence, and 10 points for Level C evidence and others).	12	12	12	12	
	Guideline Level II and below recommendations (9 points for Level A evidence, 8 points for Level B evidence, and 7 points for Level C evidence and others).	9				9
	Expert Consensus Recommendations (6 points for consensus issued by a Society organization based on systematic evaluation, 5 points for consensus issued by a Society organization, and 4 points for others).	6				
	Systematic Evaluation/Meta-Analysis (3 points for large sample, high quality systematic evaluation/ meta-analysis, 2 points for small sample, low quality systematic evaluation/meta-analysis, and 1 point for systematic evaluation/meta-analysis of non-RCT studies).	3				
Clinical efficacy (10 points)	Primary efficacy endpoints	6	5.5	6	5	6
	Secondary efficacy endpoints	4	3.5	4	3	4
The results of the efficacy		27	22	23	21	20

Table 9. The price information was obtained from the latest one-year (January 2023-January 2024) drug price information published in the database of Pharmaceutical Intelligence Network, Sunshine Purchasing Platform, information on the websites of enterprises, the National Medical Protection Bureau, local drug trading centers and other government

Table 6 Adverse Events of the Four PCSK9 Inhibitors

Adverse events	Concrete content
Evolocumab	The most common adverse events included nasopharyngitis, upper respiratory tract infection, influenza, and back pain. The overall incidence of adverse events was similar to that of the placebo group, with no significant differences observed, but injection site reactions were more prevalent with evolocumab (2.1% versus 1.6%).[27] The majority of adverse events were categorized as mild to moderate in severity and had relatively little impact on treatment. In terms of serious adverse events, the incidence in the evolocumab group was 5.5%.[27]
Alirocumab	Common adverse reactions include local injection site reactions, general allergic reactions, and upper respiratory signs and symptoms with an incidence of 1%-10%. Among them, the incidence of local injection site reactions and general allergic reactions in the treatment group was 6.1% and 7.9%, respectively,[28] which were moderate adverse reactions. In terms of serious adverse events, the incidence of cardiovascular events occurring in the alirocumab-treated and control groups was 3.5% and 3.0%, respectively, mainly including CHD death, myocardial infarction, ischaemic stroke, etc. All-cause mortality was 0.6% and 0.9% in the treatment and control groups, respectively, with most of the causes of death associated with cardiovascular events.[28]

(*Continued*)

Table 6 (Continued).

Adverse events	Concrete content
Inclisiran	Data from the ORION-9, 10, and 11 trials[17,23,29] showed that adverse reactions with a high incidence in the inclisiran-treated group were injection-site pain (8.2%), arthralgia (5.0%), urinary tract infection (4.4%), diarrhea (3.9%), bronchitis (4.3%), pain in the extremities (3.3%), and dyspnoea (3.2%). The majority of these reactions were mild to moderate, with no severe or persistent adverse reactions occurring at an incidence of 1–10%. According to data from the ORION-1, 11, and 18 trials,[29,30] the incidence of serious adverse events in the inclisiran-treated groups was greater than 10%. Specifically, the incidence of serious adverse events was 11% in the ORION-1 trial, 20.4% in ORION-11, and 16.5% in ORION-18.
Tafolecimab	The CREDIT-1 study showed[12] that the most reported adverse events with tafolecimab and their incidence were upper respiratory tract infections (11.2%), urinary tract infections (10.9%) and hyperuricemia (10.5%). Most of the adverse events were mild to moderate in severity.The CREDIT-4 study[14] showed that serious adverse events were mainly upper gastrointestinal bleeding and unstable angina with an incidence of 0.5%.

Table 7 Special Populations Scores for the Four PCSK9 Inhibitors

	Pediatric Use	Renal Impairment	Pregnancy	Lactation	Hepatic Impairment	Geriatric Use
Evolocumab	Evolocumab has a proven safety profile in pediatric patients aged 10 years and older, scoring 0.7.[31]	Evolocumab is available in patients with mild, moderate, and severe renal impairment with a score of 3.	Evolocumab, alirocumab and tafolecimab are need to be weighed against the risks and benefits for pregnancy, scoring 0.5.	The four PCSK9 inhibitors need to be weighed against the risks and benefits for lactating women, scoring 0.5.	The four PCSK9 inhibitors were available in patients with mild to moderate hepatic impairment, but no data were available in patients with severe hepatic impairment, scoring 2.	The four PCSK9 inhibitors can be used in geriatric patients and do not require dose adjustments, scoring 1.
Alirocumab	The study showed that alemtuzumab had a safety profile in pediatric patients aged 8–17 years, scoring 0.9.[32]	Alirocumab and tafolecimab are available for patients with mild to moderate renal impairment and limited data for patients with severe renal impairment, scoring 2.				
Tafolecimab Inclisiran	The safety of both Tafolecimab and inclisiran had no relevant research data scoring 0.	Inclisiran can be used in patients with mild, moderate or severe renal impairment, scoring 3.	Inclisiran instructions and expert consensus[33] do not recommend the use of the drug in pregnant women, scoring 0.			

websites. In the item of drugs with the same generic name, all four drugs are original, and there is no drug with the same generic name, so the score of this item is all 3 points. Taken together, evolocumab injection and alirocumab injection are more economical compared to inclisiran sodium injection and tafolecimab injection. The economy score results are shown in Table 10.

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Table 8 Safety Score Results

Safety (25 Points)		Grade	Evolocumab	Alirocumab	Inclisiran	Tafolecimab
Moderate adverse reactions (3 points)	Incidence < 1%	3				
	Incidence 1%~<10%	2	2	2	2	
	Incidence≥10%	1				1
	ADR occurrence data not provided	0				
Serious adverse reactions (5 points)	Incidence<0.01%	5				
	Incidence 0.01%~<0.1%	4				
	Incidence 0.1%~<1%	3				3
	Incidence 1%~<10%	2	2	2		
	Incidence≥10%	1			1	
	ADR occurrence data not provided	0				
Special populations (multiple choice, 11 points)	Available for children (2 points for all, 1.9 points for 3 months and older, 1.8 points for 6 months and older, 1.7 points for 9 months and older, 1.6 points for 1 year and older, 1.5 points for 2 years and older, 1.4 points for 3 years and older, 1.3 points for 4 years and older, 1.2 points for 5 years and older, 1.1 points for 6 years and older, 1.0 points for 7 years and older, 0.9 points for 8 years and older, 0.8 points for 9 years and older, 0.7 points for 10 years and older, 0.6 points for 11 years and older, 0.5 points for 12 years and older).	2	0.7	0.9	0	0
	Available for the elderly (1 point for available, 0.5 point for caution).	1	1	1	1	1
	Available for women during pregnancy (1 point for early pregnancy, 0.8 points for mid-pregnancy, 0.5 points for late pregnancy).	1	1	0.5	0	0.5
	Available for lactating women (1 point for availability, 0.5 points for caution).	1	0.5	0.5	0.5	0.5
	Abnormal liver function available (3 points for severe available, 2 points for moderate available, 1 point for mild available).	3	2	2	2	2
	Abnormal kidney function available (3 points for severe, 2 points for moderate, 1 point for mild).	3	3	2	3	2
Adverse reactions due to drug interactions (3 points)	No dosage adjustment required	3	3	3	3	3
	Dose adjustment required	2				
	Prohibition of use during the same period of time	1				
Other (multiple choice, 3 points)	Adverse effects are reversible	1	1	1	1	1
	No teratogenicity or carcinogenicity	1	1	1	1	1
	No special medication warnings	1	1	1	1	1
The results of safety		25	18.2	16.9	15.5	16

Other Attributes

The information was obtained from the National Basic Drug Catalogue (2018 Edition),[34] the National Drug Catalogue for Basic Medical Insurance, Work Injury Insurance and Maternity Insurance (2023),[35] the National Centralized Purchasing Drug Catalogue; the 2023 Pharm Exec 50 published by the US-based Pharmaceutical Executive magazine,[36] the Ministry of Industry and Information Technology (MIIT)'s Pharmaceutical Industries Top 100 List;[37]

Table 9 Estimated Average Daily Treatment Costs for the Four PCSK9 Inhibitors

Generic Name	Dosage forms and strengths	Therapeutic dose	Unit price (¥)	Average daily treatment cost (¥)
Evolocumab injection	*1mL:140mg*	*Q2W*	*283.8*	*18.66*
Alirocumab injection	1mL:75mg	Q2W	290.7	19.11
Inclisiran injection	1.5mL:284mg	Q6M	9988	54.73
Tafolecimab injection	1mL:150mg	Q2W	1388	91.27

Note: Italics: lowest cost of treatment per day for the same indication.

Table 10 Economy Score Results

Economy (10 points)		Grade	Evolocumab	Alirocumab	Inclisiran	Tafolecimab
Economy of the primary indication (10 points)	Evaluation method: 10 points for the drug with the lowest average daily cost of treatment, evaluation drug score = (lowest average daily cost of treatment / average daily cost of treatment of the evaluated drug) × 10.	10	10	9.84	5.39	4.43
The results of economy		10	10	9.84	5.39	4.43

China Listed Drug Catalogue Collection, NMPA, FDA, EMA, PMDA official website of drug review and approval, listing information.

National Health Insurance (NHI) and National Essential Drug (NED) Characteristics

Evolocumab injection and alirocumab injection are NHI Category B with payment restrictions and inclisiran sodium injection and tafolecimab injection are not on the NHI catalog. None of the four PCSK9 inhibitors are included in the NED Catalog.

National Centralized Drug Procurement and Original Research Drugs

All four PCSK9 inhibitors are originator drugs, all scored 1 point. In addition, none of the four PCSK9 inhibitors are national centralized drug procurement drugs, scoring 0 points.

Market and Business Characteristics

The other three PCSK9 inhibitors are available in the United States, Europe, and Japan, except for tafolecimab, which are currently available only in China. The manufacturers of evolocumab, alirocumab, and inclisiran are among the top 50 pharmaceutical companies in terms of global sales and are ranked 15th, 9th, and 4th, respectively (2023 rankings). Tafolecimab is ranked 69th in the list of the top 100 pharmaceutical industries of the MIIT of China. The other attributes' score results are shown in Table 11.

Table 11 Other Attributes Score Results

Other attributes (10 points)		Grade	Evolocumab	Alirocumab	Inclisiran	Tafolecimab
NHI (3 points)	NHI Category A, no payment restrictions.	3				
	NHI Category A has payment restrictions	2.5				
	NHI Category B, no payment restrictions.	2				
	NHI Category B, with payment restrictions.	1.5	1.5	1.5		
	Not on the NHI catalog	1			1	1

(*Continued*)

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Table 11 (Continued).

Other attributes (10 points)		Grade	Evolocumab	Alirocumab	Inclisiran	Tafolecimab
NED (3 points)	NED, no requirement.	3				
	NED, Requirements	2				
	Not on the NED List	1	1	1	1	1
National centralized procurement of medicines (1 point)	Selected medicines for centralised national procurement	1	0	0	0	0
Original research/ reference/ consistency evaluation (1 point)	Drug of origin/reference	1	1	1	1	1
	Passing the consistency evaluation of generic drugs	0.5				
Status of production enterprises (1 point)	World's top 50 pharmaceutical companies in terms of sales volume / MIIT's top 100 companies in the pharmaceutical industry (Top 50 pharmaceutical companies in world sales 1–10 1, 11–20 0.8, 21–30 0.6, 31–40 0.4, 41–50 0.2; MIIT Pharmaceutical Industry Top 100 list) (enterprises 1–20 1, 21–40 0.8, 41–60 0.6, 61–80 0.4, 81–100 0.2)	1	0.8	1	1	0.4
Global usage (1 point)	Available in China, USA, Europe, Japan	1	1	1	1	
	Domestic and international sales	0.5				0
Other attribute scores		10	5.3	5.5	5	3.4

Abbreviations: NED, National Essential Drug. NHI, National Health Insurance. MIIT, Ministry of Industry and Information Technology.

Final Scoring Results for the Five Dimensions of the Four PCSK9 Inhibitors

The evolocumab, alirocumab, inclisiran, and tafolecimab scores were aggregated to a total score of 78.00, 77.24, 72.89, and 65.33, in that order, and a comparison of the five-dimensional scores is shown in Figure 2.

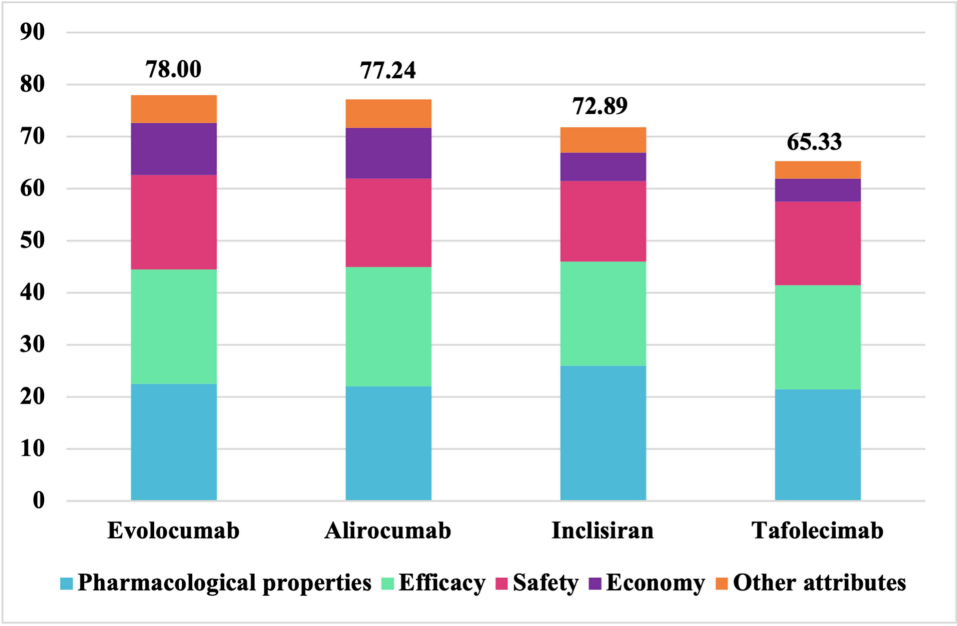

Figure 2 Summary of scores on the five dimensions.

Discussions

Analysis of Results

In terms of pharmacological properties, the evaluation of PCSK9 inhibitors mainly focuses on the frequency of administration, storage conditions, and the duration of the drug. Inclisiran performed well in terms of frequency of administration and storage conditions, and its long-lasting and sustained lipid-lowering effect is its most distinctive feature, reflecting its advantages in formulation and stability. In contrast to the lipid-lowering cornerstone drug statins, which need to be administered daily, inclisiran only needs to be administered twice a year, which greatly improves patients' medication adherence. On the other hand, evolocumab has an advantage in terms of drug expiry date, which may mean that it is more viable for long-term use and storage, and both therefore received relatively high scores in this area.

In terms of efficacy, the differences between the four PCSK9 inhibitors are mainly reflected in clinical efficacy and the degree of recommendation by professional guidelines. Although tafolecimab performed well in terms of clinical efficacy, with the largest reduction in LDL-C, its relatively low score was due to its late introduction to the market and the fact that it is an innovative drug in China, which lacks the support of international guidelines. Alirocumab, on the other hand, performed well in terms of clinical efficacy and scored the highest, which reflects its significant advantage in terms of therapeutic effect.

In terms of safety, the gap between the four PCSK9 inhibitors was relatively small, with each offering some safety advantages in different dimensions and different populations. However, overall, evolocumab performed the best in terms of safety, while inclisiran was relatively poor, and may require a deeper understanding of its potential adverse effects and risks in real-world practice.

In terms of economy, evolocumab and alirocumab are more competitive in terms of relative economic cost due to their entry into the national health insurance drug catalog and greater price reductions. On the other hand, inclisiran and tafolecimab scored lower in terms of economy because they have been on the market for a shorter period and have not yet been included in the health insurance. The difference in this aspect reflects the impact of health insurance policies on drug prices. Combined with the advantage that inclisiran only needs to be administered twice a year, and concerning the price reductions of evolocumab and alirocumab after they enter health insurance, if inclisiran enters into health insurance in the future, it will likely become the best PCSK9 inhibitor in terms of economy after its price is reduced.

In terms of other attributes, the gap between the four PCSK9 inhibitors was relatively small, and tafolecimab, as a newly launched innovative drug in China that has not yet been marketed abroad or entered the national health insurance, scored relatively low.

Overall, among the four PCSK9 inhibitors evaluated, evolocumab achieved the highest composite score, followed closely by alirocumab and inclisiran, with all three exceeding 70 points. These three drugs can be strongly recommended for inclusion in hospital formularies. Tafolecimab, with a composite score ranging between 60 and 70, may be considered for use based on specific clinical needs.

When introducing PCSK9 inhibitors into medical institutions, it is recommended to prioritize evolocumab, followed by alirocumab, inclisiran, and tafolecimab based on the evaluation results. These findings can guide healthcare decision-makers in making informed choices about drug selection and usage, thereby optimizing the range of available pharmaceuticals and hospital formularies. Additionally, the evaluation results can provide clinicians with evidence-based guidance in their practice.

This study provides a comprehensive evaluation of four PCSK9 inhibitors, including the commonly used evolocumab and alirocumab, as well as two newer drugs, inclisiran and tafolecimab. The objective was to assess whether the older drugs maintain their advantages and how the newer drugs compare. The results indicate that evolocumab and alirocumab have strengths in terms of cost-effectiveness and safety. Due to their longer market presence, these drugs have established safety and efficacy profiles supported by extensive clinical trials and real-world data, making them effective in lowering lipid levels and more affordable for patients under current insurance policies.

The newer drugs also demonstrate distinct advantages. Inclisiran stands out for its ability to significantly prolong the duration of LDL-C reduction, which extends the dosing interval, thereby improving patient adherence, reducing injection

frequency, and lowering treatment costs. Tafolecimab, as the first PCSK9 inhibitor developed in China, shows a marked advantage in clinical efficacy, particularly in reducing LDL-C, ApoB, and Lp(a) levels, highlighting its potent lipid-lowering potential. However, the newer drugs face challenges due to their shorter time on the market, limited clinical data, and relatively higher cost burden for patients. As more clinical data emerge over time, these new drugs may reveal further advantages—for instance, the cardiovascular outcomes trial for inclisiran, expected to conclude in 2026, may provide additional insights.

Based on the Chinese guideline, this study conducted a multidimensional comparison of four PCSK9 inhibitors, which provides a valuable reference point for the introduction of PCSK9 inhibitors in healthcare organizations, especially for other low- and middle-income countries, healthcare organizations with low medical standards or those unable to carry out drug evaluation work on their own. Clinicians and patients can make informed decisions based on clinical needs and personal preferences. For other readers, this study also serves as a comprehensive overview of PCSK9 inhibitors.

Limitations

Timeliness of Data

The scores recommended by the guidelines may change with the update of clinical trials or expert consensus; the scores for the economy are time-sensitive and may be constrained by changes in health insurance policies.

Lack of Clinical Trial Data

The lack of clinical trial data for some of the drugs in the secondary efficacy endpoints, in particular the results of the outcome trials for Inclisiran and tafolecimab, have not been published, which may affect the scores for clinical efficacy.

PCSK9 Inhibitor Outlook

PCSK9 inhibitors have shown promise not only in lipid metabolism, but also in other disease areas including atherosclerotic plaque remodelling, acute coronary syndromes, stroke, inflammation and immune response.[38] These findings provide new directions for future indications of PCSK9 inhibitors and further confirm that the application of PCSK9 inhibitors is not limited to cholesterol management, and that they have the potential for development in a wider range of clinical therapies.

Currently, in addition to traditional monoclonal antibody and siRNA therapies, innovative therapeutic strategies for PCSK9, such as oral drugs, vaccines, and gene editing, are rapidly evolving. These new therapies may not only reduce the cost of treatment, but also provide patients with more convenient medication options.[38] For example, the oral PCSK9 inhibitor MK-0616 and antisense oligonucleotide molecules are in clinical trials, and these therapies are expected to improve patient medication adherence and provide longer-lasting therapeutic effects.[39]

This study provides an important reference for the future direction of PCSK9 inhibitor research. First, the ranking and efficacy comparison of different drugs in the study can provide a scientific basis for future clinical trials and patient screening. Second, the safety and efficacy assessment of various types of PCSK9 inhibitors in this paper provides data support for further exploration of the mechanism of novel drugs and their application in the clinic. Finally, as the new generation of PCSK9 inhibitors continues to be introduced, the evaluation system and drug selection criteria established in this study will also provide a reliable tool for future research and help new clinical trials and drug development.

Conclusion

Selecting the right PCSK9 inhibitor just got clearer: evolocumab, alirocumab, inclisiran, and tafolecimab—ranked in that order—offer distinct advantages, paving the way for precision lipid management in China's healthcare landscape.

Abbreviations

ASCVD, Atherosclerotic cardiovascular disease; CVD, Cardiovascular disease; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; HB-HTA, Hospital-based health technology assessment; CNKI, China Knowledge Network; HeFH, Heterozygous familial hypercholesterolemia; HoFH, Homozygous familial hypercholesterolemia; EAPC, European Association of Preventive Cardiology; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, Low-density lipoprotein

cholesterol; Non-HDL-C, Non-high-density lipoprotein cholesterol; ApoB, Apoprotein B; Lp(a), Lipoprotein(a); NED, National Essential Drugs; NHI, National Health Insurance; MIIT, Ministry of Industry and Information Technology of the People's Republic of China.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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