Heart Failure Reviews (2020) 25:1077–1088
https://doi.org/10.1007/s10741-019-09874-2

Cost-effectiveness analysis of PCSK9 inhibitors in cardiovascular diseases: a systematic review

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Published online: 13 December 2019
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Abstract

Aims To assess the cost-effectiveness of pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in cardiovascular disease.

Methods and results We performed a comprehensive search strategy in electronic databases from January 2015 to January 2019. Out of 475 articles, 16 were entered into the study. Quality-adjusted life year, life years gained (LYG), annual cost, and the incremental cost-effectiveness ratio (ICER) regarding the use of PCSK9 inhibitors were considered as the key outcomes. The cost-effectiveness threshold varied from $45,000 in Spain to $150,000 in the USA. The annual cost of PCSK9 inhibitors for studies undertaken in the USA was in the range of $14,000 to $15,000, while it was about $7000 for other developed countries. The results showed that reduction in the price of PCSK9 inhibitors changed from 20 to 88%. The means of QALY were 0.65 and 0.67 in the Markov and Cardiovascular Disease Policy Modeling (CVDPM) models; also, the ICER means were $197,707 and $625,555 for the Markov and CVDPM model, respectively.

Conclusion According to the current study, the effectiveness of PCSK9 inhibitors is well documented, although all studies pointed out a higher cost of these inhibitors.

Trial registration This study was registered within the International Prospective Register of Systematic Reviews (PROSPERO) database of the University of York (CRD42018088472).

Keywords PCSK9 inhibitors · Cardiovascular disease · Cost-effectiveness · Systematic review

Introduction

Cardiovascular diseases (CVDs) impose a serious burden on healthcare systems, both in epidemiological and economic terms, with a mortality rate ranging from 481 to 680 deaths per 100,000 people in Eastern Europe, North Asia, the Middle East, and parts of Africa [1]. CVDs can lead to disability, greatly affect the productivity of active labor force, and result

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in reduced gross domestic product (GDP) and national income [2]. In 2017, CVDs were the main cause of life years lost (LYs) [3, 4]. It is estimated that the global cost generated by CVDs will increase from $863 billion in 2012 to $1044 billion in 2030 (i.e., cost per capita of $125) [2].

In 2015, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issued a license for two molecules, namely alirocumab and evolocumab, which are two injectable drugs belonging to the family of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [5, 6]. FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) trial found that the addition of PCSK9 inhibitors to statins therapy decreased the cholesterol levels to 59% and consequently reduced the risk of cardiovascular diseases, stroke, and MI (myocardial infarction) [7]. PCSK9 is an enzyme encoded by the PCSK9 gene on chromosome 1, has its effect through LDL cholesterol receptors, and regulates blood cholesterol level [8]. These drugs are usually prescribed in case of failure of statins or other anti-hyperlipidemia drugs [9–11]. The inhibition of PCSK9 enzyme is considered as a major therapeutic goal to reduce the risk of atherosclerotic and ischemic heart disease [12].

Although the clinical effectiveness of PCSK9 inhibitors has been studied in a wealth of investigations, their cost-effectiveness is still debated [12–15]. Recently, a number of economic evaluation studies have been conducted on PCSK9 inhibitors [16–18]. However, concerns have been raised whether these inhibitors at this current price are cost-effective for the health care system [18–20].

Given the limited healthcare budget, evidence-based cost-effectiveness studies and economic appraisals need to support healthcare decision and policy-makers. Within this context, the present study aimed to systematically collect and synthesize available economic evaluation studies of PCSK9 inhibitors.

Methods

The objective of the current review was formulated according to the PICO format. In addition, inclusion and exclusion criteria were determined as well (Table 1). The results were reported using the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.

Table 1 PICO questions

P	Defined target group of cardiovascular diseases
I	PCSK9 inhibitors
C	Statins, ezetimibe, and placebo
O	Quality-adjusted life year (QALY), life years gained (LYG), and incremental cost-effectiveness ratio (ICER)

Trial registration

This study was registered within the International Prospective Register of Systematic Reviews (PROSPERO) database of the University of York (CRD42018088472).

Literature search

Published full-economic evaluations and appraisals of PCSK9 inhibitors for CVDs were included in the review. Studies comparing cost-effectiveness of PCSK9 inhibitors (alirocumab and evolocumab) versus standard of care (e.g., statins, ezetimibe, and placebo) were deemed eligible.

Several scholarly databases were searched, including PubMed/MEDLINE, Embase, Web of Science, National Health Service Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database, Scopus, the Cochrane Library, the Tufts Medical Center Cost-Effectiveness Analysis Registry, the Institute for Clinical and Economic Review (ICER), and the National Institute for Health and Care Excellence (NICE). Databases were searched from January 2015 to January 2019. In order to obtain relevant studies, reference list of included studies was also scanned. The adopted search strategy is reported in Table 2.

Main outcomes

Quality-adjusted life year (QALY), life years gained (LYG), and the incremental cost-effectiveness ratio (ICER) regarding the use of PCSK9 inhibitors were the key outcomes of the present review.

Inclusion and exclusion criteria

Studies were included if they (1) focused on CVDs; (2) investigated the use of PCSK9 inhibitors; (3) utilized economic evaluations models (such as the Markov model, decision tree); (4) reported QALY, LYG, or ICER; (5) were published in English; (6) had any type of study design (observational, interventional); and (7) had a follow-up of at least 1 year. Studies were excluded if they (1) were designed as case reports or case series; (2) were not full-text peer-reviewed articles, but conference abstracts; and (3) lacked sufficient details or did not clearly report QALY, LYG, and ICER.

Quality assessment of the studies

Two authors independently evaluated the articles according to the Consolidated Health Economic Evaluation Reporting

Table 2 Complete search strategy for PubMed/MEDLINE

Concept	Search strategy
#1	"PCSK9 Inhibitors" OR "Proprotein convertase subtilisin/kexin type 9" OR "evolocumab" OR "alirocumab"
#2	"Cardiovascular diseases"
#3	"Cost-effectiveness" OR "economic evaluation" OR "cost-utility"
#4	#1 AND #2 AND #3

Complete Search strategy: ("PCSK9 Inhibitors" [Title/Abstract] OR "Proprotein convertase subtilisin/kexin type 9" [Title/Abstract] OR evolocumab [Title/Abstract] OR alirocumab [Title/Abstract]) AND ("Cost-Effectiveness" [Title/Abstract] OR "economic evaluation" [Title/Abstract] OR "cost-utility" [Title/Abstract])

Standards (CHEERS) checklist to assess the methodological quality of the selected studies. Studies that had at least 15 items out of 24 items for the CHEERS checklist were considered acceptable [21]. Any disagreement between the two authors was resolved through the involvement of a third author, who acted as the final referee.

Data extraction

After selecting the studies, two authors independently extracted relevant information, including the surname of the first author, year of publication, country of study, number of patients, mean age of patients, duration of follow-up, reported outcomes, value of QALY, magnitude of LYG, time horizon, type of sensitivity analysis, discount rate, and costs analyzed in each included study.

Results

Search results

The initial search yielded a pool of 475 items, which was reduced to 414 after removing 61 duplicate articles. A total of 370 articles were discarded by reviewing their titles and/or abstracts, and 28 papers were excluded due to not having a minimum of 15 CHEERS checklist items. Finally, 16 articles were retained for the present study (Fig. 1).

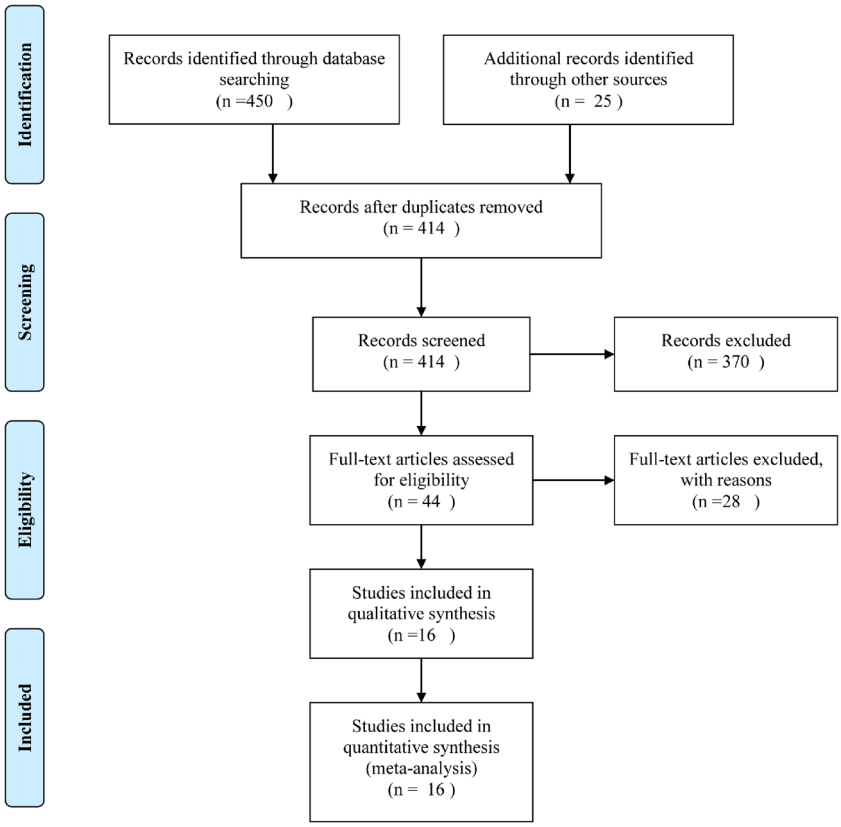

Fig. 1 Process of the systematic literature search, according to the preferred reporting items for systematic review and meta-analyses

Table3 Description of each study analyzed in the review

Study/publication year	Country	Inhibitor type	Health outcomes	Perspective	Time horizon	Number of patients	Update	Research question/ intervention	Mean age	Sensitivity analysis	Discount rate	Cost items
Villa et al. [22] 2017	Spain	Evolocumab	LY, QALY	Health system	Lifetime	196,845 patients for ASCVD and 2752 for HeFH	N	CEA of PCSK9+ STA vs STA	ASCVD (71) HeFH(50)	✓	3%	Direct cost
Fonarow et al. [22] 2017	The USA	Evolocumab	QALY	Payer	Lifetime	FOURIER trial (27,726) patients	N	CEA of PCSK9 vs STA, STA + EZE	66	✓	3%	Direct cost
Gandra [5] 2016	The USA	Evolocumab	LY, QALY	Payer	Lifetime	324 for HF, 351 patients for ASCVD, and 115 patients for ASCVD (statin intolerant)	N	CEA of PCSK9 vs STA	HF (51.2), ASCVD (62.1), and ASCVD (statin intolerant) = 64	✓	3%	Direct cost
Stam-Slob et al. [11] 2017	The Netherlands	-	LY, QALY	Health care	Lifetime	-	N	CEA of PCSK9 vs STA	63	✓	3%	Direct cost
Kodera et al. [18] 2018	Japan	Evolocumab	QALY	Public healthcare payer	30 years	More than 25,000 patients from CREDO-Kyoto	N	CEA of PCSK 9+ STA vs STA	69	✓	2%	Direct medical cost and hospitalization
Arrieta et al. [19] 2016	The USA	Evolocumab	LY, QALY	Health system and private payer	Lifetime	Evolocumab PCSK9 inhibitor trial population (4465)	N	CEA of PCSK9 vs STA	58	✓	3%	Direct cost
Arrieta [20] 2017	The USA	Evolocumab	LY, QALY	Health system and private payer	Lifetime	27,564 FOURIER trial patients between 40 and 85 years	Y	CEA of PCSK9 vs STA	58	✓	3%	Direct cost
Korman and Wisloff [23] 2018	Norway	Evolocumab and Alirocumab	LY, QALY	Health system	Lifetime	-	N	CEA of PCSK9 vs STA, STA + EZE	65	✓	4%	Direct cost
ICER1 [24] 2015	The USA	Evolocumab and Alirocumab	LY, QALY	Health system	Lifetime	Evidence review is based on the 25 clinical trials and two published systematic reviews	N	CEA of PCSK9 vs STA, STA + EZE	-	✓	3%	Direct cost
ICER2 [25] 2016	The USA	Evolocumab and alirocumab	LY, QALY	Health system	Lifetime	Heterozygous FH (n = 1,065,000) History of ASCVD, LDL-C ≥ 70 mg/dL (n = 8,531,000)	Y	CEA of PCSK9 vs STA, STA + EZE	61	✓	3%	Direct cost
ICER3[17] 2017	The USA	Evolocumab and Alirocumab	LY, QALY	Health system	Lifetime	FOURIER Trial	Y	CEA of PCSK9 vs STA, STA + EZE	66	✓	3%	Direct cost
ICER4 [26] 2017	The USA	Evolocumab	QALY	Health system	Lifetime	FOURIER trial	Y	CEA of PCSK9 vs STA	63	✓	3%	Direct cost
ICER5 [27] 2018	The USA	Alirocumab	QALY	Health system	Lifetime	ODYSSEY trial 18,924	Y	CEA of alirocumab versus placebo	58 years	✓	3%	Direct cost
Kumar [28] 2017	Australia	Evolocumab	LY, QALY	Healthcare	25 years	FOURIER trial	N	CEA of PCSK9 vs placebo	62/5	✓	5%	Direct cost
Toth [12] 2017	The USA	Evolocumab	QALY	Payer	5.4 years	Clinical Practice Research Datalink (CPRD) = 2492: atherosclerotic CVD (ASCVD) cohort (n = 1448), acute coronary syndrome (ACS) (n = 602), ischemic stroke (IS) (n = 151), heart failure (HF) (n = 291)	N	Evolocum+ STA vs STA	67	✓	3%	Direct cost

Table3 (continued)

Study/publication year	Country	Inhibitor type	Health outcomes	Perspective	Time horizon	Number of patients	Update	Research question/ intervention	Mean age	Sensitivity analysis	Discount rate	Cost items
Borissov [29] 2017	Bulgaria	Evolocumab	LY, ETPYs	Public health care	Lifetime	HeFH = 329	N	Evolocum+ STA vs STA	51	✓	5%	Direct cost

HeFH, heterozygous familial hypercholesterolemia; *ASCVD*, atherosclerotic cardiovascular disease; *LDL*; low-density lipoprotein; *PCSK9*, pro-protein convertase subtilisin/kexin type 9 inhibitor; *LY*, life year; *QALY*, quality-adjusted life-year, *CEA*, cost-effectiveness analysis; *STA*, statin, *EZE*, ezetimibe; *FOURIER*, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Patients with Elevated Risk) trial; *ICER*, Institute for Clinical and Economic Review; *PSA*, probabilistic sensitivity analysis; *RCT*, randomized controlled trial; *SI*, statin intolerant; *MACE*, major adverse cardiovascular event; *ETPYs*, effectively treated patient years; *Y*, yes; *N*, no

Study characteristics

Main assumptions of the included cost-effectiveness studies are depicted in Table 3.

Table 4 summarizes cost-effectiveness of each study. The included articles reported QALYs, LYs, or both, as well as ICER. Discount rate in majority of studies was 3%. Five studies were based on the ICER Institute for Cardiovascular Disease Policy Modeling (CVDPM), while 11 other studies employed the Markov and decision tree models for measuring the cost-effectiveness of PCSK9 inhibitors. Quality assessment of studies with CHEERS checklist is pictorially reported in Fig. 2.

The results varied according to the models. In the Markov model, cost-effectiveness in secondary prevention and HeFH (Heterozygous familial hypercholesterolemia) was proved; however, CVDPM failed to demonstrate cost-effectiveness of intervention.

The cost-effectiveness threshold varied from $45,000 for the study by Villa et al. in Spain to $150,000 for studies by Fonarow et al., Gandra et al., and Toth et al., in the USA (Table 4).

Table 5 represents cost-effectiveness in diabetes, vascular diseases, and statin-intolerant patients. According to the finding of the studies, the cost-effectiveness of using these inhibitors in HeFH and secondary prevention (SP) may be greater than that in primary prevention (PP) (Table 6).

The results of studies conducted in the USA reported different amounts of cost per QALY (ICER); this value was more than $1,300,000 in the ICER4 study and $75,686 in the Gandra's study. Also, the annual cost of PCSK9 inhibitors for studies undertaken in the USA ranged from $14,000 to $15,000, while it was about $7000 for other developed countries. The results of the studies pointed out that reduction in the price of PCSK9 inhibitors changed from 20% in the study of Toth et al. to up to 88% in the ICER4 study.

Several studies such as ICER studies have also been updated. In their initial study, Arrieta et al. concluded that PCSK9 inhibitors, compared with statins, yielded 0.88 LY and 0.66 QALY, and it required a reduction of 70% in the cost of these inhibitors to be cost-effective. While the recent study by Arrieta et al. highlighted that these inhibitors produced 0.4 LY and 0.3 QALY more

Table 4 Economic evaluation indices of studies

Study/citation	Patient population	Funding/support	Study model	LYs	QALYs	ICER	Threshold	Annual cost	Price reduction	Results
Villa et al. [22]	HeFH, ASCVD	Amgen Inc.	Markov	SP (1/02) HeFH (1.77)	ASCVD (0/93) HeFH (2.12)	ASCVD €45,340 ($51,687) HeFH €30,893 ($35,225)	€45,000 ($51,300)	€4969.6 ($5664)	Cost-effective in current price	Evolocumab plus SoC may provide a cost-effective option for LDL-C lowering in FH and SP.
Fonarow et al. [30] 2017	ASCVD	Amgen Inc.	Markov	-	0/39	$268,637	$150,000	$14,523	33%	Was not cost-effective.
Gandra et al. [5] 2016	HeFH, ASCVD	Amgen Inc.	Markov	HeFH = 2.28 ASCVD = 1.29 ASCVD (statin intolerant) = 1.48	HeFH = 2.02 ASCVD = 1.12 ASCVD (statin intolerant) = 1.36	$75,863 for HeFH $141,699 for ASCVD $100,309 for ASCVD (statin intolerant)	$150,000	$14,139	Cost-effective in current price	Addition of evolocumab to SoC in all three groups was generally cost- effective.
Stam-Slob et al. [11] 2016	HeFH, CVD with MACE risk, CVD with diabetes mellitus	None	Markov	FH = 2.3 0/36 (20% MACE risk) 0/32 (30% MACE risk) 0/40 vascular disease and diabetes	FH = 1.4 0/25 (10-year MACE risk ≥ 20%) 0/22 (10-year MACE risk ≥ 30%) 0/22 vascular disease and diabetes	FH = €78,485 ($89,427) €193,726 ($220,847) with 20% MACE €176,735 ($201,478) 30% MACE €295,543 ($336,919) vascular disease and diabetes	€100,000 ($114,000)	€6000 ($6840)	-	Balance between costs and ICER is most favorable for FH.
Kodera et al. [25] 2018	Coronary artery disease	None	Markov	-	0/48	13,500,000 JPY ($120,150) for PCSK9 + STA	5,000,000 JPY ($44,500)	614,000 JPY ($5280)	70%	Was not cost-effective..
Arrieta et al. [19] 2017	Evolocumab RCT population	None	Decision analytic model	0/88	0/66	$348,807	$100,000	$14,166	70%	Was not cost-effective.
Arrieta et al. [20] 2017	FOURIER trial population	None	Markov	0/44	0/36	$337,729	$100,000	$14,300	Health system = 62%	Was not cost-effective.
Korman and Wislof [23] 2017	HeFH, diabetic, ASCVD	Amgen Inc.	Markov	-	Primary Diabetics = 1.26 Secondary Diabetics = 1.38 HeFH = 1.6 HeFH = 2.16 Statin intolerant = 1.05 Statin intolerant = 1.49	Primary Diabetics = €93,938 ($107,089) Secondary Diabetics = €68,386 ($77,960) HeFH = €101,351($115,540) HeFH = €63 174($72,018) Statin intolerant = €138,943 ($158,359) Statin intolerant = €84,428 ($96,247)	€67,165 ($76,568)	€7800 ($8892)	50%	Was not cost-effective in primary prevention. In SP, they were cost-effective only for older, high-risk patients.
ICER1 [24] 2015	HeFH, ASCVD	Government grants	CVDPM	-	HeFH = 0.69 ASCVD = 0.86	HeFH = $290,000 ASCVD = $302,000	$100,000	$14,500	63%	Was not cost-effective.
ICER2 [25] 2016	HeFH, ASCVD	New England States Consortium Systems Organization	CVDPM	-	HeFH = 0.57 ASCVD = 0/93	HeFH = $503,000 ASCVD = $414,000	$100,000	$14,000	68%	Was not cost-effective in heterozygous FH or ASCVD.

Table 4 (continued)

Study/citation	Patient population	Funding/support	Study model	LYs	QALYs	ICER	Threshold	Annual cost	Price reduction	Results
ICER3 [17] 2017	ASCVD	Ollendorf	CVDPM	-	0/62	$450,000	$100,000	$14,542	71%	Was not Cost- effective.
ICER4 [26] 2017	ASCVD	Government grants	CVDPM	-	0/27	$1,336,221	$100,000	$14,523	88%	Was not Cost- effective.
ICER5 [27] 2018	Patients with a recent acute coronary event	None	CVDPM	-	-	$314,999 for all eligible patients and $164,006 for patients with LDL-C ≥ 100	$100,000	$14,560	77%	Was not cost-effective..
Kumar [28] 2018	ASCVD	None	Decision analytic model	0/21	0/23	AU$308,558 ($215,990)	AU$50,000 ($35,000)	AU$8174 ($5721)	80%	Was not cost-effective
Toth [12] 2017	Cardiovascular disease	Amgen Inc.	Markov	-	0/68	$190,440	$150,000	$14,833	20% ≤	Was not cost-effective.
Borissov [29] 2017	HeFH	None	Markov	0/93	(ETPYs) = 9/30	(BGN/ETPY gained) 12,937 US$7215	-	$7477	-	The use of evolocumab is associated with a relative reduction in the CVD event rate by 38% (18% per 1 mmol/L)

CVDPM, cardiovascular disease policy modeling; *MACE*, major adverse cardiovascular event; *SP*, secondary prevention; *PP*, primary prevention

than statins; hence, a 62% reduction in its cost is needed for them to be cost-effective. Figures 3 and 4 show the average QALY and ICER obtained in the studies by two mentioned models.

Discussion

Interpreting economic evaluations requires judgment. QALYs and ICERs are powerful universal metrics allowing health systems decision makers and politicians to compare diverse interventions [31]. To our knowledge, this is the first economic evaluation of the cost-effectiveness of PCSK9 inhibitors in atherosclerotic cardiovascular disease (ASCVD) based on a standardized framework.

In this article, we aimed to:

1) Compare cost-effectiveness of the PCSK9 in different patient groups.

2) Compare annual cost and threshold difference in selected countries.

3) Calculate and compare the mean of QALYs and ICERs in two models.

Population subgroups

Studies have shown that at current prices, the probability of cost-effectiveness of PCSK9 inhibitors for HeFH is greater than that of the ASCVD [5, 11, 22, 23]. In Villa's study, ICER was $35,225 for HF and $51,687 for ASCVD patients. The reason for such difference in ICER can be due to the difference in the QALY created in these two groups, which is respectively 2.12 and 0.93 for HF and ASCVD. Also, in Gandra's study, ICER was $75,863 for HeFH and $141,699 for ASCVD. Similar to the study of Villa, the difference in ICER is probably due to the different quantities of QALY in these two groups of patients, which are 2.02 and 1.12 for HF and ASCVD, respectively. According to Gandra's study, use of PCSK9 inhibitors was not cost-effective in diabetic and high-risk groups, although it was cost-effective in statin-intolerant patients.

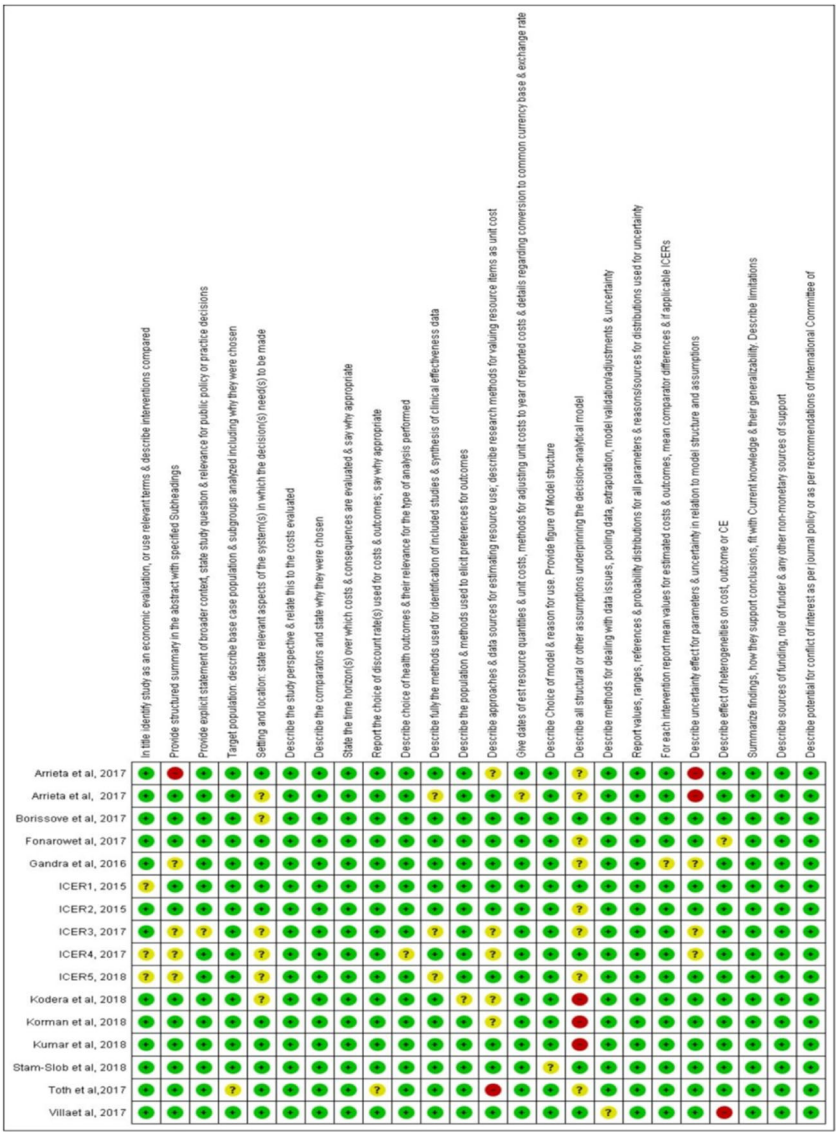

Fig. 2 Quality assessment of studies with CHEERS checklist

Annual cost and threshold difference

Most of the cost-effectiveness studies [5, 13, 19, 20, 30] concerned with these inhibitors have been conducted in the USA, and some have been carried out in other European and developed countries [11, 22, 23, 25]. Therefore, according to the discrepancy in price of these inhibitors between the USA and other countries as well as diversity in health systems, results of research in the area of cost-effectiveness of PCSK9 inhibitors vary on account of using different cost and cost-effectiveness thresholds [16]. The annual cost of evolocumab is $14,100 in the USA, $8700 in Finland, $8110 in Austria, and $6427 in England [24, 26–28]. On the other hand, the cost-effectiveness threshold differs from country to country according to health system characteristics and economic indicators such as gross domestic product (GDP) per capita. Cost-effectiveness threshold was $100,000 in the USA, $35,000 in Australia [28], $45,000 in Spain [22], $44,500 in Japan [20], $76,380 in Norway [23], and $125,400 in the Netherlands [11]. Hence, the difference in the annual price and cost-effectiveness threshold makes it cost-effective in Spain based on Villa's study and not cost-effective in the USA [22]. When considering the price ratio as well as cost-effectiveness threshold ratio, the price ratio of PCSK9 inhibitors in the USA to Spain is 2.58 times and the cost-effectiveness threshold in the USA is 1.9 times more than that in Spain. Comparing price ratio and cost-effectiveness threshold ratio between the USA and other countries, they are 2.11 and 0.77 between the USA and the Netherlands, 2.74 and 2.24 between the USA and

Table 5 Literature summary for diabetics and high risk groups

Study/ citation	Funding/ Support	Study model	Patient	LYs	QALYs	ICER	Threshold	Annual cost	Results
Stam-Slob	None	Markov	Vascular disease and diabetes	0.40	0.22	€295,543 ($336,919)	€100,000 ($114,000)	€6000 ($6840)	Was not cost-effective
			10-year MACE risk ≥ 20%	0.36	0.25	€193,726 ($220,847)	€100,000 ($114,000)	€6000 ($6840)	Was not cost-effective
			10-year MACE risk ≥ 30%	0.32	0.22	€176,735 ($201,478)	€100,000 ($114,000)	€6000 ($6840)	Was not cost-effective
Gandra	Amgen Inc.	Markov	Statin intolerant	1.48	1.36	$100,309	$150,000	$14,139	Was cost-effective
Korman	Amgen Inc.	Markov	Vascular disease and diabetes	-	1.26	€93,938 ($107,089)	€67,165 ($76,568)	€7800 ($8892)	Was not cost-effective

MACE, major adverse cardiovascular event; *LY*, life year; *QALY*, quality-adjusted life-year; *ICER*, incremental cost-effectiveness ratio

Table 6 Incremental effect in primary and secondary prevention

Study	Secondary prevention		Primary prevention	
	QALY	ICER ($)	QALY	ICER ($)
Villa 2017	0.93	51,687	2.12	35,225
Fonarow 2017	0.39	268, 637	-	-
Gandra 2016	1.12	141,699	2.02	75,863
Stam-Slob 2016	0.25	220,847	1.4	89,427
Kodera 2018	0.48	120,150	-	-
Arrieta 2017	0.66	348,807	-	-
Arrieta 2017	0.36	337,729	-	-
Korman 2017	1.6	115,540	1.26	158,359
			2.16*	72,018$*
ICER1 2015	0.69	302,000	0.86	290,000
ICER2 2016	0.93	414,000	0.57	503,000
ICER3 2017	0.62	450,000	-	-
ICER4 2017	0.27	1,336,221	-	-
ICER5 2018	-	164,006	-	314,999
Kumar 2017	0.23	215,990	-	-
Toth 2017	0.68	190,440	-	-

ICER, Institute for Clinical and Economic Review; *QALY*, quality-adjusted life-year

*Quantity for HeFH

Japan, 1.63 and 1.3 between the USA and Norway, and 2.53 and 2.85 between the USA and Australia, respectively. These ratios demonstrate that the price of these inhibitors is higher in the USA than in other countries. A number of studies in the USA have examined the resulting variability based on three hypothetical thresholds including $50,000 to $100,000, and $150,000 [24, 29]. The results showed that the maximum threshold, i.e., $150,000, can increase the chance of PCSK9 inhibitors for being cost-effective.

The updated version of ICER and Arreita studies also demonstrated the same results. In other words, these inhibitors were not cost-effective at annual price and threshold of $14000 and $100,000, respectively.

Analysis of the papers in this review unfolded that all studies had performed sensitivity analysis, and the results were highly sensitive to price variations. Most studies recommended reducing the average price by 50–80% in order to be cost-effective on the threshold of $100,000 in the USA.

Markov and CVDPM models

In total, from 16 final papers, 11 used the Markov model and 5 used the CVDPM model. The CVDPM is a

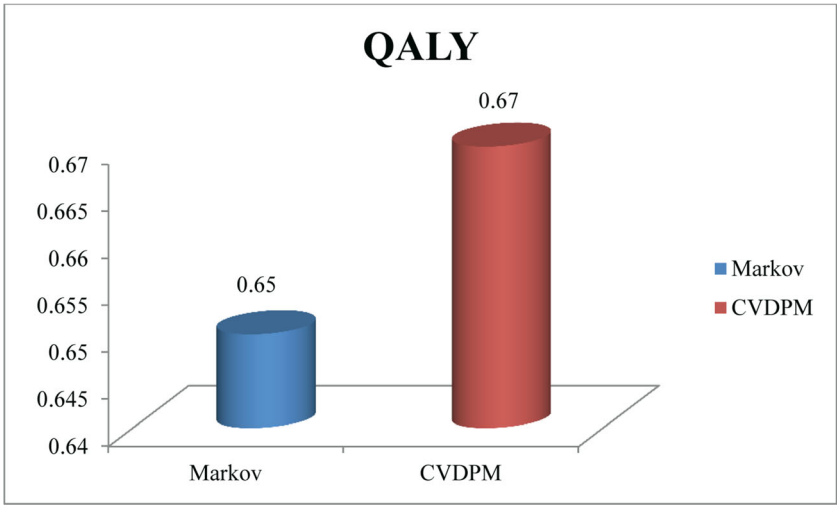

Fig. 3 Mean of QALY in studies based on the model used

computer simulation, discrete-state Markov model exclusively for coronary heart disease and stroke incidence, prevalence, mortality, and costs in the USA population over 35 years [24]. Since all CVDPM model studies have been conducted in the USA by Institute of ICER, the reason for the difference between the two models could possibly be the high price of these inhibitors in the USA compared with other countries.

Although they have significant effect on LDL-C, considering the high cost, their use is limited and there must be a 50 to 80% reduction in their prices [18–20, 26–28]. Due to the resource scarcity in all health systems, the following options would be appropriate in order to provide more utility for general population and health systems: higher price of PCSK9 inhibitors with reducing its use to specific and small groups of patients such as HeFH and statin-intolerant patients or reducing the price and expanding its use for patients with ASCVD.

Limitations

To our knowledge all studies done on economic evaluation of PCSK9 inhibitors had considered only direct medical costs; however, indirect costs could play a significant role in economic evaluation studies.

The lifetime outcomes of these inhibitors especially in young patients are unclear.

Conclusion

The high cost of these inhibitors, which is $7000 in developed countries and $15,000 in the USA, makes them not cost-effective in general population. Rather, the use of these inhibitors in FH and statin intolerants may be more cost-effective.

Due to concerns on the high cost of PCSK9 inhibitors, the price has been cut by Amgen Inc. since October 2018 in the USA. Studies conducted after this price reduction can achieve

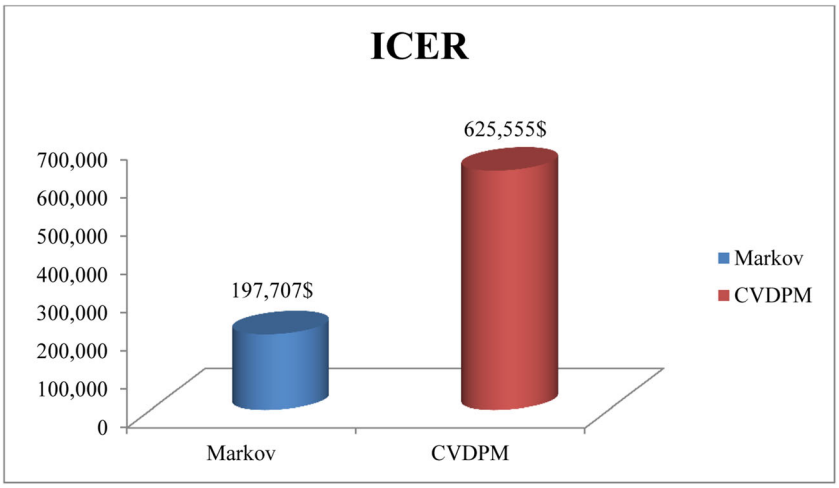

Fig. 4 Mean of ICER in studies based on the model used

different results, and it is highly recommended to have a complementary systematic review to compare results.

Acknowledgments This study is an extract from the research project with the Code of Ethics *IR.IUMS.REC 1396.31176* from Iran University of Medical Sciences, which has been conducted and supported at the Health Management and Economics Research Center, Iran University of Medical Sciences, Tehran, Iran. We would like to thank all who helped us through writing the article.

Authors' contributions All authors contributed to the conceptual background and content of the publication.

Funding information This study was part of research project funded by the health management and economics research center affiliated to Iran University of Medical Sciences (Grant no: 96-03-163-31176 and ethical code: IR.IUMS.REC.1396.31176)

Compliance with ethical standards

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

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