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CKJ Review

CKJ REVIEW

Trimming the fat: is there a health economic case for the use of new lipid-lowering drugs in chronic kidney disease? A scoping review

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ABSTRACT

Background. Individuals with chronic kidney disease (CKD) are at a very high risk for atherosclerotic cardiovascular disease (ASCVD). New lipid-lowering agents offer hope of improved outcomes where traditional agents have been less efficacious, yet the cost of these agents needs consideration in this population before their widespread application.
Objective. We sought to evaluate the cost-effectiveness of novel lipid-lowering therapies for a CKD population.
Methods. We searched four electronic databases, one government registry and the reference lists of included literature to identify cost-effectiveness analyses of novel lipid-lowering agents in CKD. Costs were converted to a single currency to allow cross-country comparisons. Completeness of reporting was analysed using the Consolidated Health Economic Evaluation Reporting Standards checklist. Results were synthesized in narrative form with graphical representation of cost-effectiveness ratios.
Results. Of the 1041 identified studies, 4 met the inclusion criteria. None were specific to a CKD-only population. All examined the impact of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) in the secondary prevention of ASCVD. Incremental cost-effectiveness ratios of new agents compared with standard care were between €7288 and €112 530 per quality-adjusted life year gained. Cost-effectiveness was sensitive to the degree of cardiovascular risk of the underlying populations.
Conclusion. This review found PCSK9is were moderately cost-effective in populations with high cardiovascular risk. People with CKD were included as an undifferentiated subpopulation in the primary studies, but application of these findings to CKD-specific populations should be interpreted with caution. There is insufficient evidence for a health economic case to support novel lipid-lowering therapies for advanced CKD.

Keywords: CKD, cost-effectiveness, novel lipid-lowering therapies, PCSK9 inhibitor, scoping review

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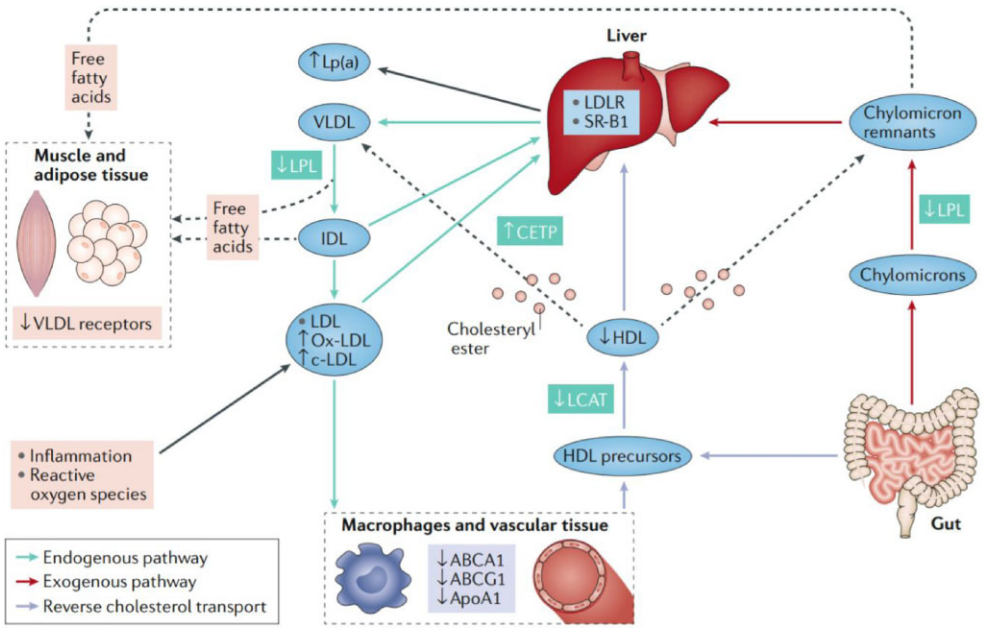

FIGURE 1: Derangements in lipoprotein metabolism in CKD. Reproduced with permission from Ferro et al. [37]. Endogenous pathway: very low-density lipoproteins (VLDL) move triglycerides from the liver into the peripheral circulation. Lipoprotein lipase (LPL) hydrolyses these from intermediate-density lipoproteins (IDL) to LDLs, which are cholesterol-rich dense particles that transport cholesterol peripherally and to the liver. LDL is cleared hepatically by the LDL receptor (LDLR) and by scavenger receptors such as scavenger receptor B1 (SR-B1). Exogenous pathway: chylomicrons transport dietary fats from the gut, which are then metabolized by LDL to free fatty acids for cellular uptake and storage. HDLs transport cholesterol from the periphery to the liver. Renal impairment shifts this balance towards high triglycerides, low HDL and increased oxidized and carbamylated LDL (ox-LDL, c-LDL). There is also increased oxidation of lipoprotein particles in renal disease, making them more atherogenic. ABCA1: ATP-binding cassette transporter A1; ABCG1: ATP-binding cassette transporter G1; CETP: cholesteryl ester transfer protein; LCAT: lecithin–cholesterol acyltransferase.

INTRODUCTION

Chronic kidney disease (CKD) is a potent risk factor for atherosclerotic cardiovascular disease (ASCVD), the major cause of death in this population [1, 2]. Statins have been demonstrated to be cost-effective for prevention of cardiovascular events in the non-dialysis CKD population, most notably in the landmark Study of Heart and Renal Protection (SHARP) trial [3]. However, the benefit of statin therapies decreases as renal function declines, culminating in no significant advantage in end-stage kidney disease (ESKD) [4, 5]. The diminishing utility of statins in advanced CKD may reflect additional pathological processes, such as vascular calcification and uraemic cardiomyopathy, with a potential contribution from a distinct pattern of dyslipidaemia, with low high-density lipoprotein (HDL) cholesterol, normal to low low-density lipoprotein (LDL) cholesterol and high triglycerides, along with important structural and functional alterations to lipoproteins (Figure 1) [6, 7]. Alternatively, increasing non-atherosclerotic cardiovascular deaths in advancing stages of CKD may dilute the risk reductions of statin therapy and seemingly attenuate the protective effects of these agents [8].

The emergence of several new therapies, in particular proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is), presents an attractive alternative to improve cardiovascular outcomes for these high-risk patients with a unique dyslipidaemic phenotype. Pooled data from the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome (ODYSSEY) trials [9] and a secondary analysis of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial have shown preserved efficacy and similar safety of alirocumab and evolocumab, respectively, in stage 2 and to a lesser degree in stage 3 and 4 CKD [10]. Moreover, these agents appear to be clinically effective even in those with baseline LDL cholesterol <2.08 mmol/L (80 mg/L) and they result in a reduction of lipoprotein (a), apolipoprotein B (ApoB) and triglycerides (independent of kidney function), changes which may result in an additional reduction in risk of ASCVD [11]. Given the costly nature of these medications, we sought to systematically evaluate the available literature on the cost-effectiveness of novel lipid-lowering therapies, including (but not limited to) PCSK9is, in a CKD population for the prevention and treatment of ASCVD. A scoping review format was chosen to identify the available body of literature and determine the value of a more detailed systematic review or recommend strategies to bridge knowledge gaps through future research.

METHODS

The protocol for the scoping review was registered and prospectively made available on the Open Science Framework (registration doi 10.17605/OSF.IO/ES6FW; https://archive.org/details/osf-registrations-es6fw-v1). Our review was performed and reported as per recommendations made by the Preferred Reporting Items for Systematic Reviews extension for scoping reviews (PRISMA-ScR) and the Professional Society for Health Economics and Outcomes Research Good Practices Task Force Report for Systematic Reviews with Costs and Cost-Effectiveness Outcomes [12, 13]. The PRISMA-ScR checklist is available in Supplementary data, Table S1.

Inclusion criteria

We conducted an electronic search for any studies on adult patients (age ≥18 years) that presented data on costs and/or

economic benefits of novel lipid-lowering therapies in CKD. Any study with an abstract/executive summary available was included. CKD was defined and categorized by the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of CKD [14]. All subpopulations of CKD were eligible, including CKD stages 1–4 [estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 with albuminuria or eGFR 15–60 mL/min/1.73 m^2 with or without albuminuria], stage 5 or ESKD (eGFR <15 mL/min/1.73 m^2) including those managed with dialysis or conservative care and those with kidney transplantation [14]. Novel lipid-lowering drugs were defined as follows: PCSK9i (alirocumab and evolocumab), PCSK9 short-interfering RNAs (inclisiran), adenosine triphosphate (ATP)-citrate synthase inhibitors (bempedoic acid), ApoB antisense oligonucleotide (mipomersen) and apolipoprotein AI (ApoAI) mimic peptides (CER-001). These agents were chosen because they were in clinical use at the time of the review and product information permits their use in those with at least some degree of renal impairment.

Exclusion criteria

Non-human studies were excluded. Non-primary studies such as review articles, commentaries, letters to the editor and interviews were also excluded. Similarly, we excluded any case studies and publications outside of peer-reviewed or independently validated papers. Studies that only focused on Medicare claims for treatment or that had no demonstrable CKD population were excluded.

Search strategy

Four electronic databases and one government registry were searched from database inception to the end of August 2021: MEDLINE (via Ovid SP), Embase, Tufts Cost-effectiveness Analysis (CEA) Registry, National Health Service Economic Evaluation Database (NHS EED) and the National Institute for Health and Care Excellence (NICE) health technology appraisals. To ensure the most inclusive search strategy, we targeted all cost-effectiveness studies evaluating novel lipid-lowering therapies and then reviewed each study for the proportion of identifiable CKD patients included. A combination of keywords and medical subject headings (MeSH) were used for our MEDLINE and Embase searches that combined terms related to novel lipid-lowering agents and economic evaluations. The Canadian Agency for Drugs and Technologies (CADTH) database search filters were utilized to maximize the sensitivity of our search for economic evaluations [15]. The full search strategies for these databases and their results are provided in Supplementary data, Tables S2 and S3. The search terms 'PCSK9' OR 'Bempedoic acid' OR 'Inclisiran' were used for the Tufts CEA Registry and the NHS EED databases. The NICE registry (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation) was searched for single-technology appraisals for all of the novel lipid-lowering agents.

Study selection

Results from each database search were compiled and duplicate records were manually removed. Two authors (A.G. and B.A.) independently screened the titles and abstracts of all remaining records using Cochrane's Covidence software (Cochrane, London, UK), removing any that did not meet the inclusion criteria or any missed duplicate records. The same two authors then screened all articles selected for full-text review independently. It was during the full-text review that an assessment for the proportion of participants with CKD was made. Any disagreement regarding inclusion at both stages was resolved via discussion with co-authors B.S. and R.L.M. until consensus was reached. An additional review was made of the reference lists of included articles.

Data extraction and synthesis

The following information was extracted from each included study: author, year of publication, country of origin, study type, type of economic evaluation, currency and reference year for costs, sources of funding, conflicts of interest, discount rate, perspective, time horizon, study population, evidence of CKD, treatment type, comparator, outcome, length of follow-up, total quality-adjusted life years (QALYs), costs, incremental cost-effectiveness ratios (ICERs), sensitivity analyses performed, sources of data for modelled evaluations, utilities used to calculate QALYs, how utilities were measured and version and tariffs used to value health status.

If identified studies were homogeneous in their outcomes, we pooled results, and if heterogeneous, we planned a narrative synthesis. Subgroup analysis by CKD stage/dialysis status was planned if sufficient data were available.

A common currency was used to facilitate the comparison of cost-effectiveness results. Of the included studies, the currency with the highest frequency across the studies was used. Purchasing power parity was not used unless multiple studies from one country were identified. It was expected most studies would be published in recent years, with a similar year for costs and therefore a base-case year was not used to adjust costs. If the reported year of costs across the identified studies had a greater range than 5 years, costs were adjusted to a common year. Incremental costs and benefits were then plotted on a chart to represent the incremental cost utility ratio (ICUR) for studies reporting cost per QALY gained. This allows a visualization of cost-effectiveness results and shows whether the primary studies reported lipid-lowering therapy to be a good value for the money.

Appraisal

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) tool was applied to determine the completeness of economic evidence in each study and was performed independently by two authors (B.A. and B.S.). Any disagreement in scoring was reconciled through discussion.

RESULTS

Our preliminary search identified a total of 1041 records from four databases and one registry (see Figure 2). One study identified via the NHS EED database was excluded prior to screening, as it was not available in the public domain [16]. Of the 133 records sought for full-text retrieval, 4 studies met the inclusion criteria (see Tables 1 and 2).

General study characteristics

The four included studies comprised three cost-utility analyses and one CEA (Table 1). All studies included participants with

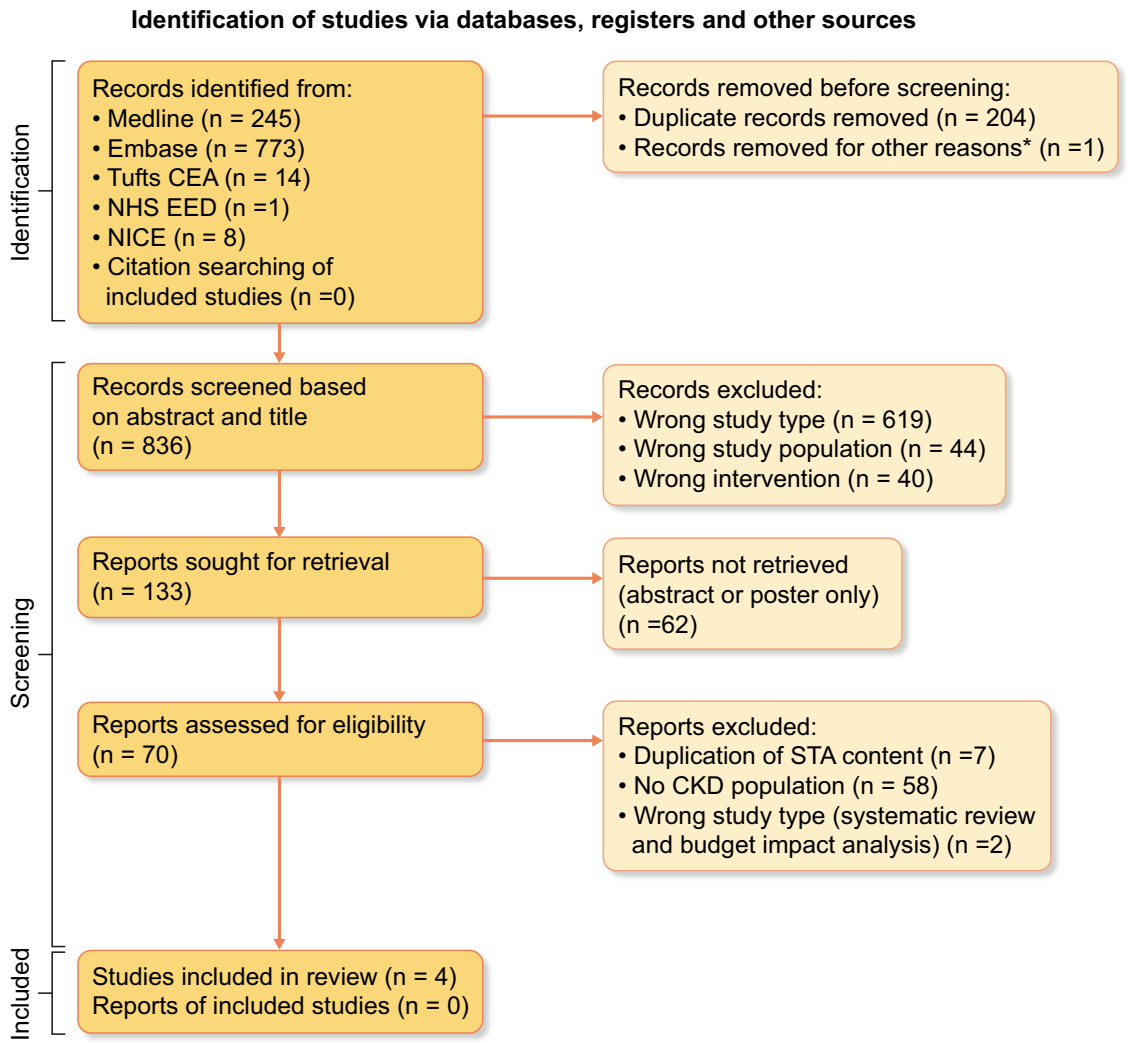

FIGURE 2: PRISMA flow diagram. *NHS EED record not available in the public domain. STA: single technology appraisal; NHS EED: National Health Service Economic Evaluation Database; NICE: National Institute for Health and Care Excellence.

CKD, although none of the studies were focused solely on a CKD population. All studies simulated the effects of PCSK9is for secondary prevention in stable ASCVD populations from Germany [17, 18], The Netherlands [19] and the USA [20]. Two studies modelled the benefits of both commercially available PCSK9is, alirocumab and evolocumab [18, 19], and the other two modelled the cost–benefits of evolocumab alone [17, 20]. All four articles used prospective observational studies for their source cohorts.

Study descriptions

Berkelmans *et al.* [19] generated a microsimulation of 10000 patients from repeated sampling of the Second Manifestation of ARTerial disease (SMART) cohort. SMART consisted of Dutch nationals with established diagnoses of ASCVD. The authors applied the SMART-Reduction of Atherothrombosis for Continued Health (REACH) model to estimate life expectancy free from recurrent cardiovascular events over a lifetime and 10-year time horizon [19]. They estimated the treatment effect of alirocumab (the cheaper of the two PCSK9is available in the Netherlands) based on pooled relative risk reduction models and estimated LDL cholesterol reductions of 50% (extrapolated from clinical trial data for this agent) [21]. Healthcare costs (including hospitalizations, medical visits, procedural costs, pathology, pharmacy and drug costs) were derived from national observational studies and registry data and reported 2016 costs in euros. Two models of treatment allocation were compared, that based on 10-year risk and a lifetime benefit model.

Blaum *et al.* [17] constructed a Monte Carlo simulation model using German 'INTERCATH' study participants who had angiographically documented coronary artery disease or a history of peripheral artery disease or stroke. They simulated the impacts of different intensities of lipid-lowering medications, including PCSK9is, on a treatment-naïve cohort in order to meet the LDL cholesterol targets of three iterations of the European Society of Cardiology's (ESC) guidelines: 2016, 2017 update and 2019. Applying the 2019 ESC guidelines saw 42% of individuals requiring PCSK9i therapy on top of maximal conventional therapy, as opposed to 31.9% by applying the 2016 guideline and only 5% by the 2017 update. They then estimated the cost per prevented

Table 1. Study characteristics and evidence of CKD

First author, year of publication (country of origin)	Study type	Type of economic evaluation	Population characteristics	Evidence of CKD participants in study cohort	Source of funding (conflicts of interest)
Berkelmans [19] 2020 (Netherlands)	CEA, microsimulation	Cost-utility analysis	Participants with symptomatic ASCVD: 10 000 simulated participants generated from 7519 individuals in SMART cohort	Average creatinine of all simulated patients 89 µmol/L (70–111) and 107 µmol/L (86–129) in those with highest 10-year risk-reduction benefit. Source cohort had 24% prevalence of CKD with KDIGO CKD stages ranging from 1 to 5 (14)	Not-for-profit sponsorship (none declared)
Blaum [17] 2021 (Germany)	CEA, microsimulation	Cost-effectiveness analysis	Participants with ASCVD with a recorded cholesterol level and specified lipid-lowering therapy status: 1 780 000 simulated participants from the INTERCATH cohort	Average serum creatinine 88.42 µmol/L (IQR 74–109). CKD stages not explicitly reported; however, dialysis-dependent CKD participants were excluded. Those with CKD (eGFR <60 mL/min/1.73 m^2) classed as having increased risk severity	Publicly funded (two authors have unrelated industry affiliations)
Dressel [18] 2019 (Germany)	CEA, Markov	Cost-utility analysis	Participants referred for coronary angiography with stable CAD with known causes of death: 1530 participants of LURIC cohort	eGFR <60 mL/min/1.73 m^2 included as additional risk factor for modified TRS2P scoring of increased ASCVD risk. CKD stages not explicitly reported	Not reported
Fonarow [20] 2019 (USA)	CEA, Markov	Cost-utility analysis	Participants with established ASCVD and LDL cholesterol level of at least 70 mg/dL (mean 104 mg/dL) while receiving statin therapy deemed VHR; number of participants not reported	Those with CKD grouped with others with very high cardiovascular risk. CKD stages 1–5 were included in source cohorts [FOURIER, NHANES (23, 27)]. A total of 71% participants in FOURIER had CKD	Industry-sponsored (several authors report industry affiliations and financial interests)

TRS2P: Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention.

cardiovascular event and annual treatment cost (per 1 000 000 ASCVD patients) resulting from the application of different guideline targets to the study population.

Dressel *et al.* [18] adopted a subgroup of the single-centre Ludwigshafen Risk and Cardiovascular Health (LURIC) study selected for having known causes of death rather than relying on simulated outcomes. They then assessed the cost-effectiveness of lifelong PSCK9i by modelling the impact of PCSK9i (in addition to maximal conventional lipid-lowering therapy) on direct healthcare costs. They derived costs for cardiovascular events from analyses of national registry data [18].

Fonarow *et al.* [20, 22] used a specific subset of participants with known ASCVD and an LDL cholesterol level ≥70 mg/dL (1.8 mmol/L) despite statin therapy from the North American National Health and Nutrition Examination Survey (NHANES) study. They modelled five different scenarios of baseline cardiovascular event rates within the 2018 American College of Cardiology/American Heart Association guideline definition of a very high risk (VHR) population: an event rate of 6.4 per 100 patient-years on a statin with or without ezetimibe (Scenario 1), and then the same base rate scenario with ezetimibe (Scenario 3), an event rate of 12.3 events per 100 patient-years on a statin with or without ezetimibe (Scenario 2), and then with ezetimibe (Scenario 4), and a base-case rate of 4.4 cardiovascular events per 100 patient-years (Scenario 5) [20]. Case scenarios in Fonarow *et al.* [22] were derived from US population CV event rates as representative of real-world event rates in high-risk populations, whereas conservative estimates of events were derived from licensing trial participants. These authors derived direct medical costs from US claims data and pharmaceutical market costs and indirect costs were from national registry reports of cardiovascular disease burden [20].

Table 2. Summary of results from included economic evaluations

First author	Intervention; comparator; disease state; outcome	Currency (reference year for costs)	Discount rate (%)	Perspective (time horizon)	Total health benefit	Total cost (per patient)	ICER/ICUR
Berkelmans [19]	PCSK9i; no treatment; symptomatic, stable ASCVD; survival free of recurrent CVD	Euro (2016)	Costs: 4; outcomes: 1.5	Healthcare (lifetime and 10-year risk reduction)	NB: QALYs Lifetime benefit (i) 5% highest estimated benefit: 6.7057 (ii) 10% highest estimated benefit: 6.8014 (iii) 20% highest estimated benefit: 6.9704 10-year risk (i) 5% highest estimated benefit: 6.6755 (ii) 10% highest estimated benefit: 6.7443 (iii) 20% highest estimated benefit: 6.8846 No treatment: (i) 5% highest estimated benefit: 6.5897 (ii) 10% highest estimated benefit: 6.5935 (iii) 20% highest estimated benefit: 6.5893	Lifetime benefit (i) 5% highest estimated benefit: €15 400 (ii) 10% highest estimated benefit: €19 416 (iii) 20% highest estimated benefit: €26 950 10-year risk (i) 5% highest estimated benefit: €15 307 (ii) 10% highest estimated benefit: €19 212 (iii) 20% highest estimated benefit: €26 633 No treatment (i) 5% highest estimated benefit: €11 173 (ii) 10% highest estimated benefit: €11 173 (iii) 20% highest estimated benefit: €11 162	Lifetime benefit (i) 5% highest estimated benefit: €36 440/QALY gained (ii) 10% highest estimated benefit: €39 650/QALY gained (iii) 20% highest estimated benefit: €41 426/QALY gained 10-year risk (i) 5% highest estimated benefit: €48 187/QALY gained (ii) 10% highest estimated benefit: €53 368/QALY gained (iii) 20% highest estimated benefit: €52 390/QALY gained
Blaum [17]	PCSK9i; maximally tolerated statin and ezetimibe; chronic, stable ASCVD; prevented CV events analysed in three scenarios based on revisions of ESC guidelines	Euro (NR)	NR	NR	NB: Incremental benefit Scenario 1 (ESC 2019): @2% CV event rate: 0.001909; @3% CV event rate: 0.002863; @4% CV event rate: 0.003818; @5% CV event rate: 0.004772; @6% CV event rate: 0.005727; @7% CV event rate: 0.006681; @8% CV event rate: 0.007635 Scenario 2 (ESC 2016): @2% CV event rate: 0.001583; @3% CV event rate: 0.002374; @4% CV event rate: 0.003165; @5% CV event rate: 0.003956; @6% CV event rate: 0.004748; @7% CV event rate: 0.005539; @8% CV event rate: 0.00633 Scenario 3 (ESC 2017): @2% CV event rate: 0.000422; @3% CV event rate: 0.000633; @4% CV event rate: 0.000845; @5% CV event rate: 0.001056; @6% CV event rate: 0.001267; @7% CV event rate: 0.001478; @8% CV event rate: 0.001689	Scenario 1 (ESC 2019): €2540.80 Scenario 2 (ESC 2016): €1930.14 Scenario 3 (ESC 2017):€302.263	Scenario 1 (ESC 2019): @2% CV event rate: €1 330 958/prevented CV event @3% CV event rate: €887 305/prevented CV event; @4% CV event rate: €665 479/prevented CV event; @5% CV event rate: €532 383/prevented CV event; @6% CV event rate: €443 653/prevented CV event; @7% CV event rate: €380 274/prevented CV event; @8% CV event rate: €380 274/prevented CV event Scenario 2 (ESC 2016): @2% CV event rate: €1 219 295/prevented CV event; @3% CV event rate: €812 863/prevented CV event; @4% CV event rate: €609 647/prevented CV event; @5% CV event rate: €487 718/prevented CV event; @6% CV event rate: €406 432/prevented CV event; @7% CV event rate: €348 370/prevented CV event; @8% CV event rate: €304 824/prevented CV event Scenario 3 (ESC 2017): @2% CV event rate: €716 263/prevented CV event; @3% CV event rate: €477 509/prevented CV event; @4% CV event rate: €358 131/prevented CV event; @5% CV event rate: €286 505/prevented CV event; @6% CV event rate: €238 754/prevented CV event; @7% CV event rate: €204 627/prevented CV event; @8% CV event rate: €179 066/prevented CV event

Table 2. Continued.

First author	Intervention; comparator; disease state; outcome	Currency (reference year for costs)	Discount rate (%)	Perspective (time horizon)	Total health benefit	Total cost (per patient)	ICER/ICUR
Dressel [18]	PCSK9i; maximal tolerated statin therapy; stable ASCVD; reduction in ASCVD events	Euro (NR)	Costs and benefits: 3	NR (lifetime)	Men: 14.91 QALYs with PCSK9i Men 13.67 QALYs with no treatment Women: 15.50 QALYs with PCSK9i Women: 14.27 QALYs with no treatment	NB: Incremental Cost Men: €135 920 Women: €137 230	Men: €108 660/QALY gained Women: €112 530/QALY gained
Fonarow [20]	PCSK9i; maximally tolerated statin therapy ± ezetimibe; known ASCVD; reduction in ASCVD events analysed in five scenarios of varying risk profiles of baseline event rates	USD (2017)	Costs and benefits: 3	Societal (lifetime)	NB: QALYs Scenarios 1 and 3: 7.23 with standard therapy, 7.62 with PCSK9i Scenarios 2 and 4: 5.48 with standard therapy and 5.93 with PCSK9i Scenario 5: 8.11 with standard therapy and 8.44 with PSCK9i	Scenario 1: €223 299 ($234 877) standard therapy versus €244 431 ($257 105) with PCSK9i Scenario 2: €245 775 ($258 519) standard therapy versus €249 019 ($261 931) with PCSK9i Scenario 3: €249 728 ($262 677) standard therapy versus €271 859 ($285 955) with PCKS9i Scenario 4: €266 406 ($280 221) standard therapy versus €270 885 ($284 931) with PCSK9i Scenario 5: €216 239 ($227 451) standard therapy versus €245 042 ($257 748) with PCSK9i	Scenario 1: €53 862 ($56 655)/QALY gained Scenario 2: €7289 ($7667)/QALY gained Scenario 3: €56 406 ($59 331)/QALY gained Scenario 4: €10 062 ($10 584)/QALY gained Scenario 5: €87 094 ($91 610)/QALY gained

Comparators

All studies examined PCSK9i use in addition to standard care. Standard care comprised statin therapy with or without ezetimibe, which are considered first- and second-line agents in the treatment of hypercholesterolaemia [24, 25]. Treatment effects were modelled using cardiovascular event rates and LDL-lowering effects extrapolated from clinical trials and meta-analyses of PCSK9is and applied to last as long as the time horizons [8, 23].

CKD population

No primary study undertook a differential analysis between participants with and without CKD and consequently a comparison of cost-effectiveness between these groups could not be performed. The two key sources of clinical efficacy data for the included studies were the FOURIER and ODYSSEY trials. FOURIER randomized >27 000 participants with established ASCVD and an LDL cholesterol >1.8 mmol/L despite maximal tolerated statin with or without ezetimibe to evolocumab or placebo for 48 weeks. The evolocumab group had a reduced risk of the primary composite endpoint of cardiovascular morbidity and mortality {hazard ratio [HR] 0.85 [95% confidence interval (CI) 0.79–0.92]} and a 59% reduction in LDL cholesterol compared with placebo [23]. Although participants with an eGFR >20 mL/min/1.73 m^2 were eligible, only 1064 and 208 of a total of 27 564 participants had CKD stages 3b and 4, respectively [23]. Alirocumab achieved similar LDL lowering (55%) and composite cardiovascular endpoint risk reduction [HR 0.85 (95% CI 0.78–0.93)] in the ODYSSEY trials with 18 924 participants of the same ASCVD risk profile followed for 4 years [26]. The ODYSSEY trial's inclusion criteria required an eGFR >45 mL/min/1.73 m^2 and ODYSSEY OUTCOMES required an eGFR >30 mL/min/1.73 m^2; their CKD secondary analyses are yet to be published [9, 26].

Fonarow *et al.* [20] and Dressel *et al.* [18] used a diagnosis of CKD (defined as eGFR <60 mL/min/1.73 m^2) as an additional risk factor to grade individuals as very high cardiovascular risk, in keeping with international guidelines [24, 25]. As Fonarow *et al.* [23, 27] detailed the source cohort for their calculations as an amalgamation of the FOURIER trial and NHANES cohort, it could be determined that 71% of individuals in the FOURIER trial had CKD (54% with stage 2 and 16.1% with ≥stage 3) and 13.5–14.3% of the NHANES cohort had CKD (stages 1–5, with a 6.5–6.6% prevalence of stages 3–5). Similarly, Berkelmans *et al.*'s [28] source cohort had a CKD prevalence of 24% (CKD stages 1–5). This calculation was supported by a median creatinine of their simulated cohort of 89 µmol/L [interquartile range (IQR) 70–111] and thus a projected 25% with probable CKD in view of a serum creatinine >111 µmol/L [19]. Blaum *et al.* [17] reported a median serum creatinine of 88.4 µmol/L (IQR 74–109), similarly suggesting a quarter of participants who were likely to have CKD. Moreover, a diagnosis of CKD (defined as eGFR <60 mL/min/1.73 m^2) was used as an additional risk factor in grading the risk of ASCVD events [17].

QALYs and other benefits of PCSK9is

All studies showed small but positive incremental benefits with the use of PCSK9is. Blaum *et al.* [17] did not report any QALYs but rather cardiovascular events avoided as a measure of incremental benefit of therapy. Dressel *et al.* [18] estimated an incremental 1.23 and 1.23 QALYs gained per person for women and men, respectively, over a lifetime. Berkelmans *et al.* [19] and Fonarow *et al.* [20] had similar observed total QALYs that varied depending on baseline cardiovascular risk, with lower total QALYs for those at higher baseline cardiovascular risk (see Table 2). Incremental QALYs for Fonarow *et al.* [20] ranged from 0.33 to 0.44, from lowest to highest cardiovascular risk at baseline, respectively, on a lifetime horizon. Berkelmans *et al.* [19] found an incremental QALY of 1.16 for a lifetime model of risk versus 0.09 for a 10-year risk assessment model when the top 5% of eligible patients were treated. Incremental QALYs were then 0.2 for lifetime risk versus 0.15 for 10-year risk and 0.38 for lifetime and 0.3 for 10-year risk assessments for treatment of the top 10% and 20% of patients, respectively.

Cost-effectiveness results

A summary of the economic findings of the included studies is presented in Table 2. Figure 3 presents the ICERs for the three included studies that reported this outcome [18–20]. Berkelmans *et al.* [19] observed lower ICERs for PCSK9i use when a lifetime model, as opposed to 10-year risk calculation, was used to allocate treatment. Cost-effectiveness was greater among populations with higher baseline ASCVD risk. Similarly, Blaum *et al.* [17] found greater incremental benefits for participants with higher CVD event rates. Total costs were greatest when the newer guidelines were used to determine PCSK9i prescriptions, in keeping with a higher percentage of participants requiring their use to achieve the guideline LDL cholesterol targets. Dressel *et al.* [18] observed a gender difference in cost-effectiveness of PCSK9i use, with a lower ICER in women than men and overall; these values bordered on equivocal cost-effectiveness. Fonarow *et al.* [20] found that PCSK9i therapy was cost-effective in VHR individuals across a broad range of baseline CV event rates (4.4–12.3 events per 100 patient-years) after the introduction of the reduced cost of PCSK9i therapy. North American ICERs were considerably lower than those seen in the European studies.

Overall, estimates centred on an ICUR of ~€50 000 per QALY gained (although with some estimates as high as €100 000) and with evidence that cost-effectiveness may vary inversely with the cardiovascular risk of the underlying population.

Appraisal of studies

The completeness of reporting of the studies encompassed in this review was assessed using the CHEERS checklist and is presented in Supplementary data, Table S4. In brief, completeness of reporting varied, ranging from 14 of 24 (58%) to 23 of 24 (96%) of the checklist items. Items typically not reported included details on heterogeneity between subgroups, particulars on study parameters such as reference ranges and probability distributions and methods for adjusting estimated unit costs and resource quantities. In line with the CHEERS statement aims, this analysis was performed to help explore the completeness of economic reporting and was not a direct measure of study quality [29].

DISCUSSION

This review of available health economic analyses found PCSK9is were moderately cost-effective using accepted willingness-to-pay thresholds in high-risk populations that included a proportion of individuals with CKD. We were unable to find health economic studies that examined the cost-effectiveness of any novel lipid-lowering therapy in a

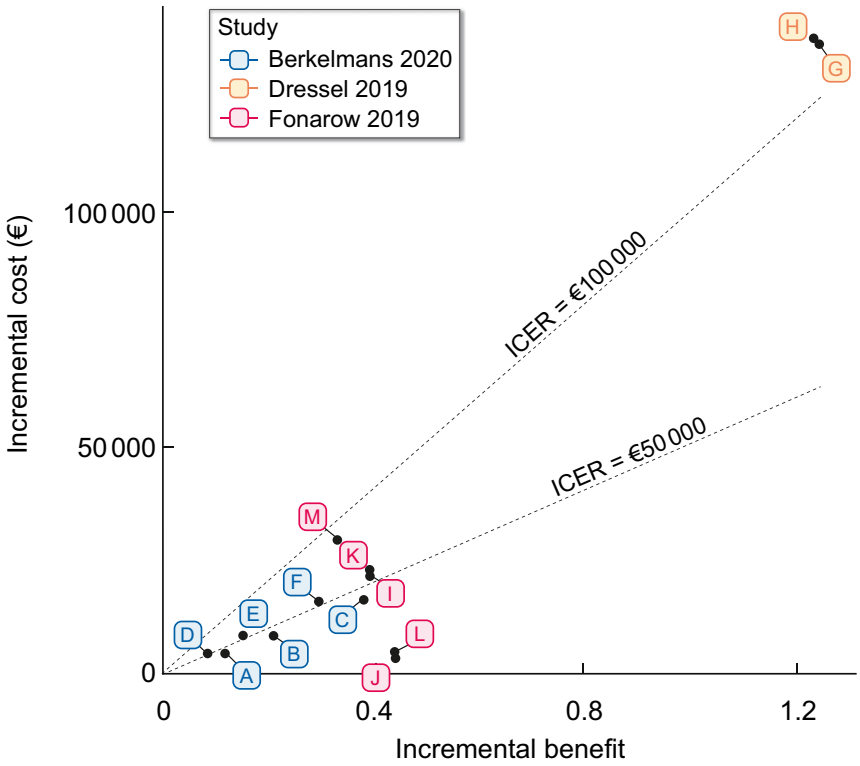

FIGURE 3: Incremental costs versus incremental benefits of included studies. **(A)** 5% estimated benefit, lifetime horizon; **(B)** 10% estimated benefit, lifetime horizon; **(C)** 20% estimated benefit, lifetime horizon; **(D)** 5% estimated benefit, 10-year time horizon; **(E)** 10% estimated benefit, 10-year time horizon; **(F)** 20% estimated benefit, 10-year time horizon; **(G)** men; **(H)** women; **(I)** patients at VHR in US clinical practice, event rate of 6.4 events per 100 patient-years; **(J)** patients at VHR in US clinical practice, event rate of 12.3 events per 100 patient-years; **(K)** patients at VHR in US clinical practice, event rate of 6.4 events per 100 patient-years; **(L)** patients at VHR in US clinical practice, event rate of 12.3 events per 100 patient-years; **(M)** patients at VHR in the FOURIER trial, event rate of 4.4 events per 100 patient-years. ICERs of included studies that reported this outcome (three of four included studies). Results have been standardized to one currency (2017 euros). The two bars outline conventionally accepted cost-effectiveness threshold, with ICERs <€50 000/QALY gained being considered cost-effective and those >€100 000 being considered not cost-effective. Two of three included studies (Foranow *et al.* [20] and Berkelmans *et al.* [19]) reported estimates that were around the upper limit of cost-effectiveness (€50 000/QALY gained). Higher baseline cardiovascular risk and lifetime estimates of cardiovascular risk (as opposed to 10-year prediction of risk) resulted in a greater likelihood of cost-effectiveness.

CKD-specific cohort. In the context of the high cardiovascular risk faced by those with CKD, and their more complex ASCVD pathophysiology, our study underlines the need for primary studies of lipid-lowering therapy to specifically focus on this patient population and later inform cost-effectiveness analyses.

Of the studies reporting ICERs (Figure 3), one did not find PCSK9is to be cost-effective, with ICERs exceeding the generic cost-effectiveness threshold of €100 000/QALY gained [18]. The other two were cost-effective, with better value-for-money seen in populations with higher estimated baseline cardiovascular risk [19, 20]. Baseline cardiovascular risk in the latter two studies was determined by using a tiered application of risk scoring based on international treatment guidelines superimposed on 10-year and lifetime risk [19] or escalating base-care cardiovascular event rates [20]. At most, this implies PCSK9is may be cost-effective in a high-risk population such as those with CKD. A high degree of uncertainty surrounds this assessment and these conclusions cannot be assumed to extend to those with ESKD.

The extent to which PCSK9is are already in use in the CKD population is unclear. Their use is tacitly encouraged (in the face of limited evidence for efficacy in a CKD population) by clinical practice guidelines that include PCSK9is in the treatment algorithm for those at high or very high risk of ASCVD and simultaneously recognize CKD as an independent risk factor, placing patients with moderate-to-severe CKD in this category [24, 25, 30]. Current product labelling in the USA and European Union for PCSK9is notes the limited data in CKD populations but does not make a recommendation for or against their use in this group. The KDIGO guidelines for lipid management in CKD predate the availability of PCSK9is and other novel agents and thus provide no guidance for their use [31]. The evidence for these agents is largely derived from the FOURIER and ODYSSEY clinical trials, which provide reasonable strength of evidence for mild CKD but not its advanced subtypes such as renal transplantation or dialysis.

The clinical benefit of PCSK9is in individuals with significant CKD is uncertain, as this population was excluded from the key trials. This necessitates post hoc analyses of the safety and efficacy of these agents in the small numbers of included participants in these trials with mild renal impairment and provides no evidence of efficacy for individuals with advanced CKD, such as dialysis populations, transplant recipients and those with nephrotic range proteinuria, the very subgroups with the greatest cardiovascular risk. Without evidence of clinical efficacy, cost-effectiveness cannot be accurately modelled. Caution is warranted given that prior assumptions of benefit in a kidney disease population based on basic science principles or surrogate population data have resulted in the use of treatments

later proven ineffectual or even deleterious in randomized trials [32, 33].

Our review failed to identify specific cost-effectiveness studies of other novel lipid-lowering therapies in CKD. PCSK9i therapies have biologically plausible benefit in more advanced CKD, with studies showing an augmented PCSK9 level when normalized for LDL cholesterol in states of significant renal impairment (Loutradis *et al.*, unpublished work). On the same biological principal, and with signs of preserved safety and efficacy in eGFRs as low as 15 in phase 1 clinical trials, inclisiran, the first-in-class of short-interfering RNAs for PCSK9, offers the same promise of clinical efficacy in advanced CKD and two phase 3 studies with comparable efficacy to the PCSK9i class [34, 35]. Phase 3 trials for the use of bempedoic acid have shown clinical efficacy in a general ASCVD population, but <16% of participants have an eGFR <60 mL/min/1.73 m^2 across all published trials and none recruited participants with moderate or severe stages of renal impairment, nor are any subgroup analyses published looking at this CKD subset [36]. The evidence for ApoB antisense oligonucleotide and ApoAI mimic peptide drug classes remains mostly restricted to familial forms of hypercholesterolaemia and thus efficacy for a CKD population is not yet established [37].

The strengths of the present study are the inclusive and broad search strategy and the inclusion of four studies all addressing the clinically relevant question of efficacy of PCSK9is for secondary prevention in source populations with very high baseline cardiovascular risk, three of which used CKD as one of their risk enhancers to qualify as high ASCVD risk [17, 18, 20]. The most notable limitation of this study results from the lack of available dedicated subgroup analyses of the cost-effectiveness within the CKD population. A further limitation is the restricted generalizability of the available data, with three of the included studies in a European setting and one in the USA. The applicability of our findings to regions in the southern hemisphere or to low- and middle-income countries with differently arranged healthcare systems may be limited.

A final broad caveat to the present review comes from the use of different thresholds for cost-effectiveness. What constitutes good 'value for money' is dependent on the context and structure of the healthcare service within which a novel therapy is being considered [38]. As a rough guide, some governments use a threshold of ICERs <€50 000/QALY gained whereas those >€100 000/QALY gained are thought not to be a good value for the money [20, 38]. This methodology of measuring value is reflective of demand and society's willingness to pay for an intervention and does not always reflect displacement of services or the true value of the technology in question [39]. Moreover, while cost-effectiveness thresholds may set broad parameters of acceptable cost for health utilities gained, the true willingness to pay by different countries may actually be much lower when determining where to invest limited health finances [39]. Beyond cost-effectiveness, funders may also consider the opportunity costs of their decisions; that is, what alternative treatments and technologies are forgone through the funding of a novel therapy [39]. In the context of CKD, a funder might consider the impact that funding lipid-lowering therapies would have on the ability to provide other therapies, such as sodium–glucose transport protein 2 inhibitors or novel mineralocorticoid receptor antagonists, which will also improve cardiovascular and kidney outcomes in this population [40–42]. Such considerations may not only be challenging, but also underline the need for high-quality information to inform decision-makers.

CONCLUSION

Our study found moderate cost-effectiveness of novel lipid-lowering therapies compared with standard care in a high ASCVD population with a demonstrable CKD subcohort. However, the cost-effectiveness of novel lipid-lowering therapies in a CKD-specific population remains unclear. Dedicated trials exploring the clinical efficacy of these agents in advanced CKD, dialysis and transplantation are needed. As yet, there are no current trials planned according to publicly available registers. Future efficacy trials should include a cost-effectiveness analysis to ensure that the opportunity cost of these novel therapies is quantified for a CKD population with significant risk for atherosclerotic cardiovascular death.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

CONFLICT OF INTEREST STATEMENT

None declared.

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