Rethinking Cardiovascular Prevention: Cost-Effective Cholesterol Lowering for Statin-Intolerant Patients in Australia and the UK

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Abstract

Background: Approximately 1 in 11 people are intolerant to statins. There have been no studies evaluating the cost-effectiveness of early intervention for primary prevention of cardiovascular disease (CVD) with three non-statin drugs (ezetimibe, proprotein convertase subtilisin–kexin type 9 inhibitors (PCSK9i; inclisiran and evolocumab), and bempedoic acid). We aimed to evaluate the cost-effectiveness of these therapies when initiated at age 40 years.

Methods: We used a published microsimulation model populated with 108 statin-intolerant individuals. The model simulated the ageing of individuals from 40 to 85 years. We calculated the incremental cost-effectiveness ratio (ICER) when non-statin lipid lowering strategies were initiated at age 40 years compared to no intervention until a cardiovascular event. ICERs were compared to Australian and UK cost-effectiveness thresholds of 28,000 AUD and 25,000 GBP per QALY gained, respectively. We adopted each countries national healthcare system perspective (2022 AUD/GBP) and discounted health economic results by 5% annually for Australia and 3.5% annually for the UK.

Results: At current prices in Australia, ezetimibe was cost-effective in 34/108 (31.4%) individuals simulated; bempedoic acid in 17/108 (15.7%); bempedoic acid and ezetimibe in combination in 14/108 (13.0%); whilst inclisiran and evolocumab were not cost-effective in any individuals. Corresponding numbers for the UK were 98/108 (90.7%); 5/108 (4.6%); 11/108 (10.2%); 0/108 (0.0%); and 0/108 (0.0%). Cost-effectiveness of bempedoic acid was predominantly among individuals with an LDL-C of at least 4.0 mmol/L and systolic blood pressure of at least 140 mmHg in Australia and 5.0mmol/L and 160 mmHg in the UK, respectively.

Conclusion: Ezetimibe and bempedoic acid, both alone and in combination, are cost-effective for long-term primary prevention of CVD in a range of people with statin-intolerance, depending on their baseline risk of CVD.

Lay Summary

Approximately 1 in 11 people are intolerant to the main drug used to lower cholesterol, statins, but there have not been any studies looking at the cost-effectiveness of the drugs available to treat people who can't take statins. We assessed the cost-effectiveness of five strategies to lower cholesterol in Australia and the UK. We found:

- The lifetime risk of having a heart attack or stroke is much lower when therapy is initiated early in life compared to not at all.
- Lots of people could benefit (in a cost-effective way) from the drugs we tested, including the new drug known as bempedoic acid.

Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide.[1] A key strategy for prevention of CVD is early lowering of low-density lipoprotein-cholesterol (LDL-C): exposure to high levels of LDL-C over time causes cumulative damage to arteries and elevates the risk of CVD.[2, 3] We have recently shown that using statins to lower LDL-cholesterol (LDL-C) early in life is not only a more effective, but also a more cost-effective strategy than lowering LDL-C later in life for primary prevention of CVD.[4]

However, approximately 1 in 11 people are intolerant to statins,[5] meaning other lipid-lowering strategies will be required to lower LDL-C in these people. There are three available non-statin pharmacological lipid lowering strategies that have been shown to reduce CVD risk: ezetimibe,[6] proprotein convertase subtilisin–kexin type 9 inhibitors (PCSK9i),[7] and bempedoic acid.[8] However, to our knowledge, the cost-effectiveness of these therapies for early primary prevention of CVD across a range of people who are intolerant to statins (rather than just high-risk primary prevention groups) has not been studied.

Therefore, in the present study, we used the health economic model for the primary prevention of cardiovascular disease (HEM-PPCVD)[9] to evaluate the cost-effectiveness of five lipid-lowering strategies (ezetimibe, bempedoic acid, bempedoic acid and ezetimibe, inclisiran (PCSK9i), and evolocumab (PCSK9i)) initiated at age 40 years from the Australian public health system and UK National Health Service perspectives.

Methods

All analysis syntax and a more detailed explanations of the methods are available in an online protocol (link TBD). All analyses were conducted in Stata, Version 17.0 (StataCorp, Texas, USA). We have completed this study in accordance with the CHEERS statement.[10]

Model overview

Construction, calibration, and validation of the HEM-PPCVD has been previously described in detail.[9] Briefly, the HEM-PPCVD is a microsimulation model, based on the UK Biobank (n~480,000), that simulates the ageing of individuals in 0.1-year cycles from 40 to 85 years. The model tracks incident and repeat fatal and non-fatal myocardial infarction (MI) and stroke, diabetes, and death. The model has the following health states: No CVD or diabetes; MI, stroke, and diabetes; all combinations thereof; and death. In the model, risk of MI, stroke, diabetes, and death is influenced by LDL-C, systolic blood pressure (SBP), diabetes (yes/no), and smoking. For LDL-C, SBP, and smoking, the model incorporates the cumulative impact of these risk factors, via simulation of lifetime trajectories, on MI, stroke, and certain causes of death.

The association between each risk factor and clinical outcome was derived from Mendelian randomisation studies. Mendelian randomisation quantifies the effect of each risk factor over the lifetime; for LDL-C, we applied these estimates by assuming that age and sex-specific CVD risk was proportional to the weighted mean cumulative LDL-C at a given age, an assumption consistent with the literature.[9] This was done using the formula $R_a = R \times M^{(x-\mu)}$ where R_a is the adjusted age and sex-specific rate of CVD, R the original/unadjusted age- and sex-specific rate of CVD for the whole population, M the measure of association from a Mendelian Randomisation study, x the time-weighted mean cumulative level of the risk factor (or LSI) for the individual in the simulation, and μ the time-weighted mean cumulative level of the risk factor (or LSI) across the population used to derive the unadjusted age- and sex- specific rate for the whole population.

The primary source for the epidemiological data for the model was the UK Biobank study,[11] which contains clinical and demographic data for over 500,000 participants who enrolled between 2006 and 2010 and with follow-up data available up to 2021. Data on the lifetime risk of diabetes were derived from Pal et al.[12] The remaining inputs – the effect of risk factors on CVD outcomes, utilities, costs, and interventions – were all sourced from published studies. We were not aware of any evidence to suggest that people with statin intolerance have different risk factor values, CVD risk (in the absence of statin use), or response to therapy that would warrant specific study of a statin-intolerant population; thus, we have assumed people with statin intolerance (our model population) can be represented by these studies. However, we were unaware of an Australian dataset comparable to the UK Biobank in which we could validate our model in an Australian setting. All model inputs are listed in Table 1 and Supplementary Tables 1-3.

Population, intervention, and control

To determine the cost-effectiveness of non-statin lipid-lowering therapies across a range of individuals, we simulated individuals with all possible combinations of the following risk factors: LDL-C of 3.0, 4.0, and 5.0 mmol/L; SBP of 120, 140, and 160 mmHg; with and without diabetes; and current, previous, and never smoker (54 unique risk factor profiles). We elected to use simulated individuals, and not actual individuals, to present more specific assessments of cost-effectiveness at a given risk factor profile, given that it there were no risk factor thresholds for this study that could be arrived at *a priori*. We present outcomes as specific to each one of these individuals (simulated 10,000 times), stratified by sex. We simulated individuals from age 40 years (30, 50, and 60 were simulated in scenario analyses), as our previous study showed this was the most cost-effective age to intervene in primary prevention.[4]

There were five interventions in this study: 1) ezetimibe 10 mg daily; 2) bempedoic acid 180 mg daily; 3) bempedoic acid 180 mg and ezetimbe 10 mg both daily; 4) inclisran 284 mg twice yearly; and 5) evolocumab 140 mg every 2 weeks; the control scenario in the base case was no lipid-lowering therapy, given that none of the above therapies have previously been shown to be cost-effective for the primary

prevention of CVD with use beginning at younger ages. Nevertheless, because ezetimibe is already widely available in both Australia and the UK, we also compared all other intervention scenarios to ezetimibe in a secondary analysis. Dosing of each intervention was selected as either the only available or most effective form of the intervention. In each intervention, the medication was initiated at screening at age 40 years. The interventions were assumed to mediate their effects on CVD only via their effects on LDL-C. The LDL-C lowering effects of the interventions were as follows. Ezetimibe 10 mg reduced LDL-C 18.6% (17.5, 19.7), which was derived from a systematic review and meta-analysis of placebo-controlled trials.[13] Bempedoic acid reduced LDL-C 24.9% (22.1, 27.7), again derived from a systematic review and meta-analysis of randomised trials.[14] Bempedoic acid and ezetimibe reduced LDL-C 38.0% (29.6, 46.5), an estimate derived from a randomised clinical trial.[15] Inclisiran reduced LDL-C 51.5% (49.0, 53.9), an estimate based on a weighted average of the results of the ORION-10 and ORION-11 trials.[16] Evolocumab reduced LDL-C by 67.6% (63.9, 71.3), which was derived from a pooled analysis of phase II trials.[17] We assumed full compliance with therapies in the base case analysis.

Quality of life

The utilities used in this study were derived from the EuroQol—five dimensions (EQ-5D) questionnaire.[18] For people in Australia without CVD or diabetes, utility values were derived from a cross-sectional study of the Australian general population,[19] and took age and sex-specific values. The utility for people without CVD or diabetes in the UK was derived from a study using the Health Survey for England,[20] and was set using the following equation: $0.9454933 + 0.0256466 \times \text{male} - 0.0002213 \times \text{age} - 0.0000294 \times \text{age}^2$. The chronic utility values for people with diabetes, MI, or stroke were derived from systematic reviews of utility values for people with these diseases,[21-23] and were set at 0.785 (95%CI: 0.681, 0.889), 0.79 (0.73, 0.85), and 0.65 (0.63, 0.67), respectively; these were applied multiplicatively to the age and sex-specific values from each country. Chronic disutility values for people with diabetes and MI and diabetes and stroke were derived from the same systematic review,[21] and set at -0.055 (-0.067, -0.042) for diabetes and

MI and -0.164 (-0.222, -0.105) for diabetes and stroke (and diabetes and MI and stroke); these were applied additively to the diabetes utility and the resulting utility was multiplied by the age and sex specific utility for each country. The systematic review for type 2 diabetes was selected as it had a stringent and hierarchical approach to selection of health state utility values. The systematic reviews for MI and stroke were selected as the most recent available. Reviews were selected over individual studies to give more accurate and precise estimates of quality of life.

We also applied acute disutility values for MI and stroke to reflect the drop in quality of life associated with the events themselves. For MI, this was set at -0.045 (±20%) and applied for 3 months (2.5 cycles); this value was derived from a clinical trial that assessed quality of life 3 months following an MI.[24] For stroke, the acute disutility was derived from a systematic review of utility values in stroke and was set at -0.12 (±20%) and applied for 3 months (2.5 cycles).[23] These were applied additively in addition to the chronic disutility before multiplying by the age and sex specific utility for each country.

Healthcare costs

For the Australian analyses, the Australian public healthcare system perspective was adopted. For the UK analyses, a National Health Service perspective was adopted. We only included direct costs in both analyses. All costs were in 2022 Australian dollars ($ hereafter) or 2022 Great British pounds (£ hereafter), inflated using the Australian Health Price index or NHS cost inflation index, respectively.[25, 26] All cost inputs are shown in Table 1.

For Australian costs, the chronic costs of diabetes, MI, and stroke were derived from cohort studies,[27, 28] which were selected as the most recent costing studies for these conditions in Australia. The acute cost of non-fatal MI and stroke were derived from an Australian linked data study of people with diabetes (but the costs were assumed to be applicable to people with and without diabetes).[29] Annual costs of ezetimibe and evolocumab were derived directly from the Australian Pharmaceutical Benefits Scheme

in June of 2022.[30] Because they are not currently available on the PBS, the annual cost of bempedoic acid was derived from a previous health economic analysis,[31] and the annual cost of inclisiran was assumed to match that for evolocumab.

For UK costs, the chronic costs for all health states were derived from a study by Public Health England (Table 1).[32] The acute costs of MI and stroke were derived from the UK National Health Service Cost Schedule in 2021/22.[33] Fatal MIs and strokes were assumed to result in hospitalisation 23% and 84% of the time (in both Australia and the UK),[9] and acute event costs were adjusted accordingly. The annual costs of ezetimibe, bempedoic acid, bempedoic acid and ezetimibe, and evolocumab were derived from the NHS drug tariff.[34] The annual cost of inclisiran was derived from the NHS dictionary of medicines and devices, actual medicinal product pack.[35]

Outcomes

We tracked incident MI, stroke, and diabetes, repeat MI and stroke, years of life lived and quality adjusted life years (QALYs) in each health state, and acute and chronic healthcare costs. These were used to generate our primary outcome, the incremental cost-effectiveness ratio (ICER), defined as the incremental healthcare costs divided by the incremental QALYs for each individual for the intervention versus control. All health economic outcomes underwent discounting at 5% per year in Australia, per Australian guidelines,[36] and 3.5% in the UK, per UK guidelines.[37]

Total QALYs, healthcare costs, and the ICERs were presented for all individuals. Full results and results of sensitivity analyses were presented for a single, moderate-risk individual (with an LDL-C of 4.0 mmol/L, SBP of 140 mm Hg, no diabetes, and past smoker; individual 26) because there were too many results to present each for every individual. We summarised results by presenting the number of individuals in which each intervention was cost-effective, using a willingness-to-pay threshold of $28,000 per QALY for Australia[38] and £25,000 per QALY (the midpoint of the recommended £20,000 to £30,000 per QALY range in UK guidelines[37]) for the UK.

Sensitivity and scenario analyses

We conducted one-way sensitivity analyses and presented the results in Tornado diagrams. We conducted probabilistic sensitivity analyses using 1,000 Monte Carlo simulations based on the uncertainty in the model parameters as outlined in Table 1 and Supplementary Tables 1-3; this is the source for 95% uncertainty intervals (UIs). We also conducted five scenario analyses. In the first three, we varied the age of intervention to 30, 50, and 60 years, respectively. In the fourth, we assumed adherence to therapy would drop to 50% immediately after initiation of therapy. In the fifth, we reduced the discounting rate to 0%.

Results

Base-case

The lifetime risk (to age 85 years) of individuals in the sample ranged from 5% to 93% without treatment, and treatment lowered risk commensurate with the degree of LDL-C lowering (Table 1 and 2). QALY gain with treatment was proportional to lifetime risk of CVD and degree of LDL-C lowering (Figure 1 and Supplementary Tables 4-13). In Australia, ezetimibe was cost-effective (at the $28,000 per QALY threshold) in 12/54 females and 22/54 males (Table 3 and Supplementary Table 4), each of whom was modelled in 10,000 simulations. Corresponding figures for bempedoic acid, bempedoic acid and ezetimibe, inclisiran, and evolocumab were 5/54 females and 12/54 males, 4/54 females and 10/54 males, 0/54 females and 0/54 males, and 0/54 females and 0/54 males, respectively (Supplementary Tables 5-8). Moreover, ezetimibe, bempedoic acid, and bempedoic acid and ezetimibe were dominant (i.e., led to a gain in QALYs and were cost-saving) in 4/54 females and 10/54 males, 0/54 females and 2/54 males, and 0/54 females and 2/54 males, respectively (Table 3). The risk factor profiles for whom some interventions were cost-effective were predominantly those with an LDL-C of 5.0 mmol/L and SBP of 140 or 160 mmHg in females and those with an LDL-C of 4.0 or 5.0 mmol/L and SBP of 140 mmHg or 160 mmHg in males. When the control group was changed to ezetimibe, bempedoic acid and ezetimibe was cost-effective in 0/54 females and 4/54 males, and no other medications were cost-effective in females or males (Supplementary Figure 1 and Supplementary Table 14).

For the UK setting, ezetimibe, bempedoic acid, bempedoic acid and ezetimibe, inclisiran, and evolocumab were cost-effective (at a £25,000 per QALY threshold) in 46/54 females and 52/54 males, 0/54 females and 5/54 males, 3/54 females and 8/54 males, 0/54 females and 0/54 males, and 0/54 females and 0/54 males, respectively (Table 3 and Supplementary Tables 9-13). Ezetimibe was dominant in 28/54 females and 43/54 males, while no other interventions were dominant in the base-case. While ezetimibe was cost-effective among most risk factor profiles simulated, bempedoic acid was cost-

effective predominantly among individuals with an LDL-C of 5.0 mmol/L and SBP of 160 mmHg. When the control group was changed to ezetimibe, no other medications were cost-effective in females or males (Supplementary Figure 1 and Supplementary Table 14).

Scenario analyses

While more CVD events were prevented with earlier intervention, the number of individuals in which the interventions were cost-effective decreased (relative to the base case of 40 years) when the intervention was implemented at age 30 years, whereas the number of individuals in which the interventions were cost-effective increased with intervention at 50 years for Australia, but was similar in the UK for age 50 years and both Australia and the UK from age 60 years (Supplementary Tables 15-17).

Modifying adherence had little effect on cost-effectiveness (Supplementary Table 18). Conversely, removing discounting increased the number of individuals in whom ezetimibe, bempedoic acid, and bempedoic acid and ezetimibe were cost-effective, while both PCSK9i remained not cost-effective in any individual at current prices (Supplementary Table 19).

Sensitivity analyses

Tornado diagrams from one-way sensitivity analysis are shown in Supplementary Figure 2-11. For Individual 26, the ICER was most sensitive to transition probabilities for MI, the effects of interventions on LDL-C, the effect of LDL-C on MI, and the chronic utility for people with MI. Results from the probabilistic sensitivity analysis are shown in Supplementary Tables 20-24 and Supplementary Figures 12-13. Uncertainty around model outcomes was generally low, with cost-effectiveness overwhelmingly influenced by medication cost.

Discussion

We have shown that ezetimibe is cost-effective for the primary prevention of CVD in moderate and high-risk statin-intolerant individuals in Australia, and nearly all individuals simulated in the UK. Bempedoic acid and bempedoic acid and ezetimibe were also cost-effective in several high-risk individuals in both countries, especially in Australia. Inclisiran and evolocumab were not cost-effective for primary prevention of CVD in any simulated individuals, even those with an untreated lifetime risk of CVD as high as 93%.

Our results build on our prior studies that showed that earlier lowering of LDL-C is cost-effective compared to lowering of LDL-C later in life,[4, 9] results which support a shift from using short-term absolute risk to guide selection of people for primary prevention of CVD to initiating early and sustained lowering of LDL-C in people with a high lifetime risk of CVD. We extend these studies by demonstrating that in addition to statin-based lipid lowering strategies, ezetimibe, bempedoic acid, and bempedoic acid and ezetimibe can also be cost-effective when statins are not tolerated. It is important to note that, when statins are tolerated, they are more efficacious than ezetimibe and bempedoic acid and should remain first line lipid lowering therapy in this setting.[39]

However, for both the PCSK9i we tested, the high current prices meant that they were not cost-effective in any of the individuals tested, including those with an extremely high lifetime risk of CVD. PCSK9i have not been found to be cost-effective in the secondary prevention populations of Australia or the UK either,[40-42] suggesting price reductions will be needed if the benefits of these medications are to be made available to the public (we expect this will likely need to be at least a 70-80% price reduction, to bring prices closer to bempedoic acid and ezetimibe given the comparable efficacy). Nevertheless, PCSK9i are significantly more effective and could lead to much higher long-term adherence than oral therapies to lower LDL-C (although this has never been shown),[43] meaning find cost-effective ways to make these therapies available for the primary and secondary prevention settings is an important priority.

It is also worth noting that discounting rates in both Australia and the UK markedly impacted cost-effectiveness estimates – our scenario analysis without discounting showed a major increase in the number of people for whom bempedoic acid and bempedoic acid and ezetimibe in combination would be cost-effective. Evidently, constant discounting has implications for the choice between acute and preventive interventions. Future studies should consider how current discounting practices influence the cost-effectiveness of preventive interventions. In addition to discounting, the contrast between the results in Australia in the UK demonstrates that the economic impact of medications is highly influenced by drug pricing practices in a country.

The main strength of this study is the use of the HEM-PPCVD, which was based on a very large population, simulates lifetime trajectories of risk factors, and accounts for cumulative changes in risk using causal data from Mendelian randomisation studies. There are, nevertheless, limitations of this study that warrant mention. First, we have assumed that people with statin intolerance do not differ systematically from the general population in terms of risk factor values, CVD risk (in the absence of statin use), or response to therapy. We are aware of no evidence to suggest that they do. Second, Mendelian randomisation is not a substitute for a randomised clinical trial, and while a clinical trial of the length represented by our model will never be conducted, our results should nevertheless be interpreted with this limitation in mind. Third, the epidemiological structure of the HEM-PPCVD was based on a UK population, which may not be representative of the Australian population; there is no study comparable to the UK Biobank in Australia and thus we could not validate the HEM-PPCVD in an Australian context. Indeed, the lifetime risk of type 2 diabetes and MI are both higher in Australia than the UK,[4,44] which could have led to overestimation of cost-effectiveness in the Australian analyses. Conversely, the UK Biobank has a considerable health volunteer bias,[45] which would have led to underestimation of cost-effectiveness in both Australian and the UK. Fourth, this population is also predominantly of European ancestry, which may limit generalisability. Fifth, the HEM-PPCVD only includes MI and stroke as CVDs, but it is likely that other CVDs would be influenced by LDL-C lowering.[9] Sixth, the results apply

only to the individuals we simulated – higher risk populations, such as people with familial hypercholesterolaemia or existing CVD, will require other analyses. Finally, we did not account for intolerance to the non-statin drugs we simulated.

In conclusion, ezetimibe and bempedoic acid, both alone and in combination, are cost-effective for primary prevention of CVD in a range of people with statin-intolerance, depending on their baseline risk factors and lifetime risk of CVD. Conversely, PCSK9i were not cost-effective at current prices. It may be worthwhile reconsidering pricing practices to address the priority of long-term treatment to lower LDL-C in the primary prevention population, thereby maximising the availability of therapies and clinical benefits in this population.

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Duality of Interest

DL declares previous grants, participation in advisory boards and receipt of honoraria from AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Edwards Lifesciences, Novartis, Pfizer, Sanofi, and Shire outside of the submitted work. GFW declares financial support for research, conference travel or advisory boards from Amgen, Arrowhead, Novartis, Pfizer, Sanofi, Esperion, and CRISPR Therapeutics outside of the submitted work. SZ reports payment to Monash University from Eli Lilly Australia Ltd, Boehringer-Ingelheim, MSD Australia, AstraZeneca, Novo Nordisk, Sanofi and Servier outside of the submitted work. SJN has received research support from AstraZeneca, Amgen, Anthera, CSL Behring, Cerenis, Cyclarity, Eli Lilly, Esperion, Resverlogix, New Amsterdam Pharma, Novartis, InfraReDx and Sanofi-Regeneron and is also a consultant for Amgen, Akcea, AstraZeneca, Boehringer

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Author Contributions

JIM contributed to study design, constructed the model, performed the analysis and literature search, contributed to acquisition and interpretation of data, wrote the protocol, and wrote and revised the manuscript. JIM is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ZA is senior author and obtained funding, contributed to study design, design of the model, acquisition and interpretation of data, revision of the manuscript, and supervision. All other authors contributed to study design, interpretation of data, and revision of the manuscript. All authors read and approved the final manuscript and made the decision to submit for publication.

Data availability

Data from the UK Biobank study was used for this study. The dataset is accessible to researchers via https://www.ukbiobank.ac.uk/register-apply/

Patient and Public Involvement

Patients and the public were not involved in the design or conduct of this study.

References

1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021.
2. Ference BA, Bhatt DL, Catapano AL, et al. Association of Genetic Variants Related to Combined Exposure to Lower Low-Density Lipoproteins and Lower Systolic Blood Pressure With Lifetime Risk of Cardiovascular Disease. JAMA. 2019;322(14):1381-91.
3. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459-72.
4. Morton JI, Marquina C, Lloyd M, et al. Lipid-Lowering Strategies for Primary Prevention of Coronary Heart Disease in the UK: A Cost-Effectiveness Analysis. PharmacoEconomics. 2023.
5. Bytyçi I, Penson PE, Mikhailidis DP, et al. Prevalence of statin intolerance: a meta-analysis. Eur Heart J. 2022;43(34):3213-23.
6. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. New England Journal of Medicine. 2015;372(25):2387-97.
7. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. New England Journal of Medicine. 2017;376(18):1713-22.
8. Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. New England Journal of Medicine. 2023.
9. Morton JI, Liew D, Ademi Z. A causal model for primary prevention of cardiovascular disease: the health economic model for the primary prevention of cardiovascular disease (HEM-PPCVD). Value in Health.
10. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. BMJ. 2022;376:e067975.
11. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
12. Pal K, Horsfall L, Sharma M, Nazareth I, Petersen I. Time trends in the incidence of clinically diagnosed type 2 diabetes and pre-diabetes in the UK 2009-2018: a retrospective cohort study. BMJ Open Diabetes Res Care. 2021;9(1).
13. Pandor A, Ara RM, Tumur I, et al. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. J Intern Med. 2009;265(5):568-80.
14. Dai L, Zuo Y, You Q, Zeng H, Cao S. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: A systematic review and meta-analysis of randomized controlled trials. Eur J Prev Cardiol. 2021;28(8):825-33.
15. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. Eur J Prev Cardiol. 2020;27(6):593-603.
16. Ray KK, Wright RS, Kallend D, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. New England Journal of Medicine. 2020;382(16):1507-19.
17. Schludi B, Giugliano RP, Sabatine MS, et al. Time-averaged low-density lipoprotein cholesterol lowering with evolocumab: Pooled analysis of phase 2 trials. J Clin Lipidol. 2022;16(4):538-43.
18. Rabin R, Oemar M, Oppe M, Janssen B, Herdman M. EQ-5D-5L user guide. Basic information on how to use the EQ-5D-5L instrument Rotterdam: EuroQol Group. 2011;22.
19. McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. Health Qual Life Outcomes. 2016;14(1):133.

20. Ara R, Brazier JE. Populating an Economic Model with Health State Utility Values: Moving toward Better Practice. Value in Health. 2010;13(5):509-18.
21. Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. Value Health. 2014;17(4):462-70.
22. Betts MB, Rane P, Bergrath E, et al. Utility value estimates in cardiovascular disease and the effect of changing elicitation methods: a systematic literature review. Health Qual Life Outcomes. 2020;18(1):251.
23. Joundi RA, Adekanye J, Leung AA, et al. Health State Utility Values in People With Stroke: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2022;11(13):e024296.
24. Lacey EA, Musgrave RJ, Freeman JV, Tod AM, Scott P. Psychological morbidity after myocardial infarction in an area of deprivation in the UK: evaluation of a self-help package. Eur J Cardiovasc Nurs. 2004;3(3):219-24.
25. The Australian Institute of Health and Welfare (2023) Health Expenditure Australia 2021-22. Available from https://www.aihw.gov.au/reports/health-welfare-expenditure/health-expenditure-australia-2021-22/data Accessed 5 Jan 2024.
26. Personal social services research unit. Unit costs of health and social care 2022. 12 Sources of information. 12.1 Inflation indices. 12.1.1 The NHS cost inflation index (NHSCII). Available at: https://kar.kent.ac.uk/100519/ [Accessed 12 January 2024].
27. Cobiac LJ, Magnus A, Barendregt JJ, Carter R, Vos T. Improving the cost-effectiveness of cardiovascular disease prevention in Australia: a modelling study. BMC Public Health. 2012;12:398.
28. Lee CM, Colagiuri R, Magliano DJ, et al. The cost of diabetes in adults in Australia. Diabetes Res Clin Pract. 2013;99(3):385-90.
29. Morton JI, Marquina C, Shaw JE, et al. Projecting the incidence and costs of major cardiovascular and kidney complications of type 2 diabetes with widespread SGLT2i and GLP-1 RA use: a cost-effectiveness analysis. Diabetologia. 2023;66(4):642-56.
30. The Pharmaceutical Benefits Scheme. PBS and RPBS section 85 date of supply data. 2023. available at: https://www.pbs.gov.au/info/statistics/dos-and-dop/dos-and-dop [accessed: 5 January 2024].
31. Perera K, Kam N, Ademi Z, Liew D, Zomer E. Bempedoic acid for high-risk patients with CVD as adjunct lipid-lowering therapy: A cost-effectiveness analysis. J Clin Lipidol. 2020;14(6):772-83.
32. Public health england. The health and social care costs of a selection of health conditions and multi-morbidities. July 2020. Available at: https://www.gov.uk/government/publications/health-and-social-care-costs-of-a-selection-of-health-conditions [Accessed: 12 January 2024].
33. National health service. 2021/22 national cost collection for the NHS. Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ [Accessed: 12 January 2024].
34. National health service. Prescription services. NHS electronic drug tariff june 2022. Available at: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff/back-copies-drug-tariff [Accessed: 10 January 2024].
35. National health service dictionary of medicines and devices. Actual medicinal product pack (ampp). Leqvio 284mg/1.5ml solution for injection pre-filled syringes (Novartis Pharmaceuticals UK LTD) 1 pre-filled disposable injection. Available at: https://dmd-browser.nhsbsa.nhs.uk/amp/view/160939 [Accessed: 10 January 2024].

36. Department of Health. The Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines. Available at: https://pbac.pbs.gov.au [Accessed: 28 September 2021].
37. Guide to the methods of technology appraisal. National Institute for Health and Clinical Excellence (NICE) London, UK, 2013.
38. Edney LC, Haji Ali Afzali H, Cheng TC, Karnon J. Estimating the Reference Incremental Cost-Effectiveness Ratio for the Australian Health System. Pharmacoeconomics. 2018;36(2):239-52.
39. Adams SP, Tsang M, Wright JM. Lipid-lowering efficacy of atorvastatin. Cochrane Database Syst Rev. 2015;2015(3):Cd008226.
40. Michaeli DT, Michaeli JC, Boch T, Michaeli T. Cost-Effectiveness of Icosapent Ethyl, Evolocumab, Alirocumab, Ezetimibe, or Fenofibrate in Combination with Statins Compared to Statin Monotherapy. Clin Drug Investig. 2022;42(8):643-56.
41. Kumar R, Tonkin A, Liew D, Zomer E. The cost-effectiveness of PCSK9 inhibitors - The Australian healthcare perspective. International Journal of Cardiology. 2018;267:183-7.
42. Kam N, Perera K, Zomer E, Liew D, Ademi Z. Inclisiran as Adjunct Lipid-Lowering Therapy for Patients with Cardiovascular Disease: A Cost-Effectiveness Analysis. Pharmacoeconomics. 2020;38(9):1007-20.
43. Gencer B, Mach F. Inclisiran in primary prevention: reality or fiction? Eur Heart J. 2022 Dec 21;43(48):5058-5060.
44. Tomic D, Morton JI, Chen L, et al. Lifetime risk, life expectancy, and years of life lost to type 2 diabetes in 23 high-income jurisdictions: a multinational, population-based study. Lancet Diabetes Endocrinol. 2022 Nov;10(11):795-803.
45. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol. 2017 Nov 1;186(9):1026-1034.