# Economic evaluation of lipid lowering with PCSK9 inhibitors in patients with familial hypercholesterolemia –methodological aspects

Torbjørn Wisløff1,2

Liv J Mundal3,4

Kjetil Retterstøl3,4

Jannicke Igland5

Ivar Sønbø Kristiansen1

1 Department of Health Management and Health Economics, University of Oslo, Oslo, Norway

2 Department of Infectious Disease Epidemiology and Modelling, Norwegian Institute of Public Health, Oslo, Norway

3 The Lipid Clinic, Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway

4 Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

5 Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

Short running title: Economic evaluation of PCSK9 inhibitors for FH

Corresponding author:

Torbjørn Wisløff

Address: Norwegian Institute of Public Health, Postboks 222 Skøyen, 0213 Oslo, Norway

Email: torbjorn.wisloff@medisin.uio.no

Word count: 3514 (excluding Title Page, Abstract, References, Tables and Figures Legends)

## ABSTRACT

### Background and aims

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have proved to reduce low density lipoprotein cholesterol levels in numerous clinical trials. In two large clinical trials PCSK9 inhibitor treatment reduced the risk of cardiovascular disease. Our aim was to explore the impact of varying assumptions about clinical effectiveness on health and economic outcomes for patients with familial hypercholesterolemia.

### Methods

We used a previously published and validated Norwegian model for cardiovascular disease. The model was updated with recent data from the world’s second largest registry of patients with genetically confirmed familial hypercholesterolemia. We performed analyses for 24 different subgroups of patients based on age, gender, statin tolerance and previous history of cardiovascular disease.

### Results

In 1 out of 24 subgroups, PCSK9 inhibitors were cost-effective when effectiveness was modelled using direct relative efficacy as reported in the FOURIER trial. When using assumptions as suggested in a recent consensus statement from the European Atherosclerosis Society, 14 subgroups were cost-effective.

### Conclusion

Cost-effectiveness of PCSK9 inhibitors depends highly on assumptions regarding effectiveness. Basing assumptions only on randomised controlled trials and not taking into account varying effect based on baseline cholesterol level results in much fewer groups being cost-effective.

## Introduction

Familial hypercholesterolemia (FH) is characterized by increased plasma low density lipoprotein (LDL) cholesterol concentrations and severely increased risk of premature cardiovascular disease (CVD) (1). FH is usually caused by mutations in genes encoding key proteins that clear serum of LDL cholesterol (LDL-C). Heterozygous FH is more common than previously believed, with a prevalence of approximately 1:250 (2). This would mean that globally approximately 30 million people suffer from FH, among whom more than 20,000 individuals live in Norway (The United States Census Bureau. Worldometers Current world population. http://www.worldometers.info/world-population (accessed 01 February 2018)). Since the cause of the clinical manifestations lies in elevated LDL-C levels, reducing LDL-C is crucial for preventing CVD events (3).

Using register data we have previously showed that FH patients younger than 40 years old have a tenfold increased risk of CVD events (4). We have also showed that cardiovascular mortality in this age group is four times higher compared to the Norwegian population (5). In young patients with CVD, one study recently reported that 71% of those hospitalized for myocardial infarction (MI) before age 35 years had definite or possible FH (6). Another study reported that, depending on country, 5-10% of those hospitalized for MI before 50 years of age had FH (7). The risk of coronary artery disease in FH was recently reported to be 22-fold increased in patients with an FH-mutation in combination with an LDL-C level ≥ 4.9 mmol/L compared with a reference group with LDL-C < 4.2 mmol/L and no mutation (8).

In 2015, two monoclonal antibodies, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, alirucomab and evolucomab, were approved by both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for use to lower LDL-C (9). These medications are given as subcutaneous injection every 2 or 4 weeks and lowers LDL-C by 50-60%, also when added to statin treatment (10). Both types were recently shown to reduce cardiovascular events (11, 12).

Statins in combination with ezetimibe represent the basis of current FH treatment. This treatment is inexpensive and effective, but even with maximal dose it is often insufficient to achieve the treatment target in patients with FH due to their particularly high LDL-C levels. Thus, PCSK9 inhibitors represent a new tool in those who do not reach treatment targets. The high price of PCSK9 inhibitors, however, raise questions about their cost-effectiveness. Using unique register data on CVD events among patients with FH and a previously published economic model, the aim of this study was to explore how choice of input variables influence the estimated cost-effectiveness of PCSK-9 inhibitors. We placed particular focus on the difference between modelling based directly on the recently published FOURIER trial (11) and three alternative approaches.

## Methods

### Efficacy

The efficacy of PCSK9-inhibitors has been a much-discussed topic in the research literature, not least after the results from the FOURIER-trial were published. FOURIER is the first large randomised controlled trial (RCT) with “hard”, clinically relevant outcomes (11).

Essentially, there are two different ways of incorporating effectiveness of PCSK9 inhibitors in health economic models; either (1) by assuming that relative hazards observed in RCT(s) apply to all populations, regardless of LDL-C level and other risk factors, or (2) by assuming that patients with higher LDL-C levels have a larger relative effect of cholesterol reduction as shown in meta-analyses of randomised controlled trials (13). The first is standard assumption in evidence-based medicine and most economic evaluations, the latter is based on results from several meta-analyses, first of statin trials (13), later also confirmed for other interventions such as ezetimibe and PCSK9-inhibitors (14). Given the convincing evidence of increasing relative effectiveness of LDL-C reduction with higher baseline LDL-C (14), we aimed to explore both approaches in modelling the cost-effectiveness of PCSK9 inhibitors. We therefore incorporated into our model both the hazard ratios observed in the first large-scale RCT currently available for any PCSK9-inhibitor (11) and varying relative effectiveness depending on baseline LDL-C level. We will in the following refer to the “standard” evidence based medicine approach as “FOURIER direct”, as this method uses the hazard ratios from the FOURIER trial directly (Table 1).

With respect to the second approach, a well-recognized way of estimating the effectiveness of LDL-C reduction is published in a consensus statement by the European Atherosclerosis Society (EAS). It concludes that a “22% reduction in risk per millimole per litre (mmol/l) reduction in LDL-C” summarizes current evidence of “the proportional reduction in short-term risk” (14). EAS proposes the following formula to calculate the relative risk reduction of atherosclerotic CVD events for patients at different levels of baseline LDL-C (14): 1- RRFLDL\*(RRm), where RRF is the relative reduction in CVD risk per mmol/l reduction in LDL-C, LDL is the baseline LDL-C level and RRm is the treatment effectiveness measured as percentage reduction in mmol/l. The EAS statement concluded that a Cholesterol Treatment Trialists’ Collaboration (CTTC) meta-analysis from 2010 (13) represents best current evidence on the relationship between LDL-C reduction and CVD outcomes, resulting in the number 22% (or RRF = 0.78). The recent FOURIER trial described by Sabatine and colleagues (11) estimated an RRm of 59%, hence the formula used is 1-0.78LDL\*0.59, where LDL in our model can be varied to analyse different patient groups with different baseline LDL-C. This second approach is in the following referred to as “EAS consensus”.

As both approaches are plausible in their own merit, one solution may be to incorporate a midpoint between the two approaches. The hazard ratio reported by Sabatine and colleagues in the FOURIER trial is the best available evidence, but the baseline LDL-C in that trial (2.4 mmol/l) is far lower than in most FH populations, even when FH is treated with potent statins plus ezetimibe (15). With a fixed treatment effectiveness in terms of percentage LDL-C reduction, the absolute change in mmol/L increase proportionally with increasing baseline LDL-C levels (13, 14). Thus, given a fixed dose of a lipid lowering medication, the higher baseline LDL-C and the more LDL will be cleared from the circulation. To incorporate an alternative that both uses the FOURIER trail and also incorporates information about LDL-C level in the population, we would have to adjust the observed hazard ratio (HR) of cardiovascular events based on the assumed baseline LDL-C level in different populations. This can be done by transforming the observed HR from FOURIER into a natural logarithmic scale, do calculations on that scale and exponentiate to get back to HR scale: HRadj = EXP(LN(HRs)-(LDL-LDLs)\*RRm\*(1-RRF)), where HRS = 0.73, as reported by Sabatine et al, LDLs = baseline LDL-C observed in Sabatine et al (2.4 mmol/l), and LDL, RRF and RRm is as defined above. This scenario with an adjustment of the original FOURIER results according to baseline LDL-C, is in the following called “FOURIER adjusted”.

Although the EAS statement refers to a 22% reduction as the main effect of LDL-C on CVD (14), there has been suggestions to divide CVD into it’s most common components AMI and stroke (16). The mentioned CTTC analyses reports a 29% and 31% reduction of AMI and stroke respectively. We incorporated this alternative as a fourth modelling option, using the name “CTTC subgroups”.

In addition to the mentioned four modelling options, there are numerous different ways of calculating effect of treatment and the number is increasing with increasing publications on this topic. In Table 1, we have listed 3 further potential analyses that could have been performed, but were not included in the present model.

We analysed our model for two different levels of LDL-C, representing FH patients who were statin tolerant and intolerant. For statin tolerant patients, we assumed an average LDL-C of 3.5 mmol/l on current treatment, approximately as reported in the Norwegian FH registry (17), while for the statin intolerant, we assumed an LDL-C level of 6.0 mmol/l (18). In addition, we also analysed men and women who had previously experienced a cardiovascular event, *i.e.* secondary prevention. For this latter group, we assumed LDL-C level of 3.5 on average (17) and otherwise similar assumptions as for other patients with previous CVD event. The assumptions about LDL-C and resulting assumed hazard ratios for the four different calculation methods are summarized in Table 1.

### Other modelling assumptions

Lifetime costs and QALYs were estimated based on the Norwegian Cardiovascular Disease model (NorCaD)(19), which has been used in several publications previously (20-22). Briefly, the model is a health state transition model (Markov model) with 4 primary CVD events and 11 health states (Figure 1). Health outcomes are measured until all are dead or 100 years old and expressed in terms of quality adjusted life years (QALYs). Unit costs are based on market prices, the Norwegian DRG system and various fee schedules as appropriate (19).

We used incidence data recently derived from a Norwegian FH registry (4). Unit costs in the model were updated to 2017 costs based on current prices of pharmaceuticals (as of May 2017) and fees and averages as reported in official documents (23, 24). All costs were measured in Norwegian kroner, but reported in European Euros (€) to ease comparison (1 € = 9.5 NOK). Future health and costs were discounted at 4% per year and analysed using a health care sector perspective, as described in Norwegian guidelines (25).

Guidelines developed by the Norwegian Directorate of Health in 2005 (25) state that interventions are cost-effective for incremental cost-effectiveness ratios (ICERs) below €62,443 per Quality Adjusted Life Year (QALY). We adjusted this value for inflation and adopted a threshold of €70,000 per QALY. Although empirical evidence has confirmed this as an approximate willingness to pay for health gains (26), for comparison, we also evaluated cost-effectiveness with a threshold of €40,000 per QALY), based on estimation of opportunity cost of health care resources in the UK (27, 28).

### Sensitivity and analyses

Lately, it has been suggested not to discount future health outcomes in Norway (29). Although this suggestion is not based on all the latest research on this issue (30-32), we performed scenario analyses without discounting future health to test how this suggestion may affect conclusions.

The official price of one year’s use of the least expensive PCSK9 inhibitors is listed at NOK 48,104 (€5064) in the Norwegian Medicines Agency database (Legemiddelverket.no). As PCSK9 manufacturers offer confidential discounts for the Norwegian health care system, we performed one-way sensitivity analyses on price. Scenario analyses with up to 50% lower price are presented for statin intolerant women for four different age groups.

All uncertain parameters in the NorCaD model, including those added to the model for this specific analysis, are incorporated as probability distributions. When running simulations of the model, each uncertain parameter is represented by 1000 realizations from the specified probability distribution. Probabilistic results are shown only as cost-effectiveness acceptability curves (CEACs) for 40-year-old statin intolerant women with FH. In the CEAC, the proportion of simulations in which a PCSK9 inhibitor is cost-effective is shown for all possible cost-effectiveness thresholds between 0 and 120 000 €/QALY.

## Results

When we used the EAS consensus approach or the FOURIER adjusted approach for baseline LDL-C, PCSK9 inhibitors were cost-effective in 15, respectively 13 out of 24 subgroups of FH patients (Table 2, further details in Appendix table 1). Direct use of the FOURIER HRs yielded less optimistic results with only one cost-effective subgroup (statin intolerant men aged 60). With the CTTC subgroup approach PCSK9 treatment was cost-effective in 21 groups.

When setting the discount rate for outcomes at zero, treatment in all subgroups was cost-effective except when modelling FOURIER results directly (Appendix table 2). With the latter approach, treatment of 16 of 24 groups was cost-effective, compared with 1 of 24 when discounting health outcomes at 4%.

Probabilistic sensitivity analysis of 40-year-old statin intolerant women using FOURIER HRs directly indicate a zero probability that PCSK9 inhibitors are cost-effective at a cost-effectiveness threshold of €70,000 per QALY, increasing to 80% with FOURIER adjusted for LDL-C, 95% with the EAS consensus, and 96% with CTTC subgroups (Figure 2).

One-way sensitivity analysis indicates that price reductions have considerable impact on the cost-effectiveness of PCSK9 inhibitors. For statin intolerant women, a 50% reduction in the price would make PCSK9 inhibitors cost-effective for all ages and ways of modelling effectiveness (at a threshold of €70,000 per QALY), except 30-year-old women modelled through direct use of FOURIER HRs (Figure 3). Similar analyses are also presented for men (Appendix Figure 1).

## Discussion

We have shown that cost-effectiveness of PCSK9 inhibitors depends heavily on the way the effectiveness is modelled. Assuming PCSK9 inhibitors reduces risk of AMI and stroke as reported in the FOURIER trial (11) (27% and 21% risk reduction, respectively) results in PCSK9 inhibitors being cost-effective in only one of 24 analysed risk groups at current prices. Allowing for reduction of other CVD outcomes or modelling effectiveness as proposed by EAS (14) may lead to all groups being cost-effective.

Advances in treatment and prevention of CVD have contributed to considerably decreased CVD mortality rates during the past four decades. One of the most pronounced consequence is that CVD to a lesser extent is a middle-age disease today, compared to only a few decades ago. For patients with FH, however, CVD is still a great threat even in younger age groups (5), and it is therefore important to start treatment early (33). An example from our own analyses that illustrates this (Appendix table 1) shows that if treatment for 30-year-olds is withheld until age 40, up to 0.69 QALYs may be lost on average per person. These QALYs are lost because the patient develops CVD or dies before becoming 40 years old, corresponding to for instance 2% dying and loosing 34.5 remaining QALYs.

Our results are presented from a Norwegian setting based on Norwegian data. Generally, the transferability of health economic evaluations is limited. However, a recent review of economic evaluations of PCSK9 inhibitors found that differences between countries were much smaller than other differences between studies, such as those explored in the present analysis (34). That review found incremental health effects among FH patients of more than 2 QALYs in two studies and less than 1 QALY in three studies. The two studies with the high QALY gains concluded that PCSK9 inhibitors are cost-effective, while the other three concluded PCSK9 inhibitors were not. Similarly, we found that all 32 analyses with a gain of more than 1 QALY were cost-effective, while most of our analyses with a QALY gain below 1 were not cost-effective (52 out of 64). Based on recent price reductions in some countries, PCSK9 inhibitors may be more cost-effective in the countries where large rebates have been given. Official prices (maximum approved price) as reported by the Norwegian Medicines Agency has, however, not been reduced in the past few years ([www.legemiddelverket.no](http://www.legemiddelverket.no), accessed 11th January 2019).

### Strength and Limitations

In Norway, all individuals with genetically verified FH diagnosis are registered in a patient registry. As of October 2018, 8220 patients are registered with a pathogenic FH mutation in Norway, making this registry the second largest in the world of its kind. In the present paper we used data on hospitalizations and death in a complete cohort of all Norwegian patients with known FH mutation to estimate the cost-effectiveness of PCSK9 treatment in FH by applying the previously described health economic model (NORCAD) (19).

The NorCaD model used in the present work is comprehensive and models specifically some aspects of cardiovascular disease that are not included in all other cardiovascular models, such as nursing home care. We have previous shown with the NorCaD model that off-patent antihypertensive drugs are cost-saving largely due to the reduction in future hospitalization and nursing home admittance (20). In contrast to other CVD models, NorCaD may capture reductions in the risk of angina and heart failure. Even though such reductions have yet not been shown for PCSK9 inhibitors, they are plausible from the LDL level reductions and make treatment cost-effective in wider groups. These model differences should be noticed when comparing our results to those published by others (34).

A high number of genotyped FH patients and the complete follow-up in Norwegian registries provide a sound basis for the estimates of the present study. All AMI and CHD hospitalizations all FH patients genotyped in Norway are therefore included in the calculated incidence.

Still, the study has several limitations. Information on AMI subtypes (ST-elevation versus non-ST-elevation) is not available. Further, factors that could influence AMI morbidity and hospitalization frequencies, e.g. smoking habits, LDL-C values and statin treatment, were not accounted for. Further, even though in Norway physicians can request genetic FH-test free of charge for physicians and patients, the FH register may contain a selected group of patients. In the present study, we based the assumption of baseline LDL-C level for statin tolerant on the Norwegian registry that includes all diagnosed with FH in Norway, but we do not know what proportion of patients who are statin intolerant. This may impact our assumption about LDL levels among statin tolerant and intolerant patients. The impact of this limitation, however, is likely minimal because only a small proportion of the FH patients are statin intolerant.

Atherosclerosis is a slow process with lipids accumulating in the arterial wall. LDL-cholesterol is a major driver of the process and reduction of LDL may slow down and even reverse the atherosclerosis. Cholesterol years is a concept to calculate the result of the accumulated cholesterol load on intima, similar to the concept pack-years regarding cigarette smoking. It was first used to evaluate risk in homozygous patients with FH and total cholesterol values of 20-30 mmol / l (35). In this conceptual understanding, inhibiting the atherosclerosis process during a study period will provide sustained effects even after the end of the study. The slowing of the atherosclerosis process will likely generate health benefits later in life. The long term follow-up up of statin trials like the WOSCOPS trial provide support for this view (36) with no significant effect on total mortality the first 6 years, but highly reduced total mortality 20 years after end of study. The early results of the FOURIER study (11) may therefore prove

different from the long term results. In several statins trials, like in the 4S study (37), the survival curves for placebo and statin, did not diverge until about 1.5 years follow-up. In the FOURIER study the median duration of follow-up was 2.2 years, which is a short period when studying the slow process of atherosclerosis.

Two large RCT’s of PCSK9 inhibitors available (11, 12). Our analyses are based on the trial that was published first. In large, the two trials did not differ much in results, for instance both reported a hazard ratio (HR) of 0.85 on their primary outcome. When split into the detailed outcomes directly used in modelling, the differences are somewhat larger, HRAMI: 0.73 vs 0.86 and HRStroke: 0.79 vs 0.73. Hence, we would have found somewhat different results if analyses were performed based on ODYSSEY instead of FOURIER.

As can be seen from the previous paragraph, the primary endpoint in the FOURIER and ODYSSEY trials indicate a lower effect than the estimates on what we regarded as the most relevant outcomes in our model; AMI and stroke. If we had used the estimates of effect on this composite endpoint instead of the endpoints for separate outcomes, we would have observed a smaller effect, and therefore that PCSK9 inhibitors were not cost-effective in any subgroups.

A recent analysis similar to the CTTC meta-analysis found effects to be somewhat smaller, with approximately RR of 0.86 instead of 0.78 per mmol/l. as can be seen from our Table 1, these effect estimates are between the FOURIER direct and FOURIER adjusted, hence we would likely get somewhere between 1 and 10 risk groups to be cost-effective if this analysis had been done.

## Conclusions

Our model predictions suggests that PCSK9 inhibitors with the maximum approved price in Norway are cost-effective for some groups of FH patients, particularly when CVD risk reduction from LDL level reductions is based on the CTTC meta-analyses as suggested by EAS. When using clinical relevant endpoints from the FOURIER trial, the proportion of FH patient groups that is cost-effective to treat with PCSK9 inhibitors is lower. Price discounts may make it cost-effective in all patient groups.

### Acknowledgements

None

### Sources of funding

This work was not receive any external funding. The research was done as part of regular work assignments.

### Disclosures

Dr. Retterstøl reports personal fees from Oslo Economics, Amgen, Mills DA, Norwegian Medical Association, and Chiesi. Dr. Kristiansen reports funding from Amgen through Oslo Economics. Dr. Wisløff reports personal fees from Amgen through Oslo Economics. Dr. Igland and Dr. Mundal reports no potential conflicts of interest.

### Contributions

All authors contributed to the planning of the paper and contributed to analyses and discussions. All authors have contributed to the writing of the manuscript and has approved the final version. TW conducted all analyses based on a model that was in previous projects, see references (19) and (20).

## References

1. Brown MS, Goldstein JL. Familial hypercholesterolemia: A genetic defect in the low-density lipoprotein receptor. N Engl J Med. 1976;294(25):1386-90.

2. Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open. 2017;7(9):e016461.

3. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. European heart journal. 2013;34(45):3478-90a.

4. Mundal LJ, Igland J, Veierod MB, Holven KB, Ose L, Selmer RM, et al. Impact of age on excess risk of coronary heart disease in patients with familial hypercholesterolaemia. Heart. 2018;104(19):1600-7.

5. Mundal L, Igland J, Ose L, Holven KB, Veierod MB, Leren TP, et al. Cardiovascular disease mortality in patients with genetically verified familial hypercholesterolemia in Norway during 1992-2013. European journal of preventive cardiology. 2017;24(2):137-44.

6. Rallidis LS, Triantafyllis AS, Tsirebolos G, Katsaras D, Rallidi M, Moutsatsou P, et al. Prevalence of heterozygous familial hypercholesterolaemia and its impact on long-term prognosis in patients with very early ST-segment elevation myocardial infarction in the era of statins. Atherosclerosis. 2016;249:17-21.

7. De Backer G, Besseling J, Chapman J, Hovingh GK, Kastelein JJ, Kotseva K, et al. Prevalence and management of familial hypercholesterolaemia in coronary patients: An analysis of EUROASPIRE IV, a study of the European Society of Cardiology. Atherosclerosis. 2015;241(1):169-75.

8. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. J Am Coll Cardiol. 2016;67(22):2578-89.

9. CardioPulse Articles. Eur Heart J. 2016;37(17):1341-52.

10. Lipinski MJ, Benedetto U, Escarcega RO, Biondi-Zoccai G, Lhermusier T, Baker NC, et al. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. Eur Heart J. 2016;37(6):536-45.

11. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-22.

12. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018.

13. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81.

14. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, 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.

15. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478-90a.

16. Villa G, Lothgren M, Kutikova L, Lindgren P, Gandra SR, Fonarow GC, et al. Cost-effectiveness of Evolocumab in Patients With High Cardiovascular Risk in Spain. Clin Ther. 2017;39(4):771-86 e3.

17. Leren TP, Berge KE. Subjects with molecularly defined familial hypercholesterolemia or familial defective apoB-100 are not being adequately treated. PLoS One. 2011;6(2):e16721.

18. Stein EA, Ose L, Retterstol K, Tonstad S, Schleman M, Harris S, et al. Further reduction of low-density lipoprotein cholesterol and C-reactive protein with the addition of ezetimibe to maximum-dose rosuvastatin in patients with severe hypercholesterolemia. J Clin Lipidol. 2007;1(4):280-6.

19. Wisløff T, Selmer R, Halvorsen S, Kristiansen IS. Norwegian Cardiovascular Disease Model (NorCaD) – a simulation model for estimating health benefits and cost consequences of cardiovascular interventions. 2008 2008. Report No.: 23.

20. Wisloff T, Selmer RM, Halvorsen S, Fretheim A, Norheim OF, Kristiansen IS. Choice of generic antihypertensive drugs for the primary prevention of cardiovascular disease--a cost-effectiveness analysis. BMC Cardiovasc Disord. 2012;12:26.

21. Hamidi V, Wisløff T, Ringerike T, Linnestad KK, Harboe I, Klemp M. Behandling av pasienter med akutt hjerneslag i slagenheter (med og uten tidlig støttet utskriving). 2010 2010. Report No.: 18.

22. Wisløff T, Hamidi V, Ringerike T, Harboe I, Klemp M. Intravenøs trombolytisk behandling av hjerneinfarkt i akuttfasen og sekundær blodproppforebyggende behandling (platehemmende behandling og antikoagulasjonsbehandling) etter hjerneslag. 2010 2010. Report No.: 22.

23. [Performance-based financing 2016] In Norwegian. ISBN: 978-82-8081-417-3: Norwegian Directorate of Health, 2015.

24. Normal tariff for contract specialists 2015-2016. The Norwegian Medical Association.

25. [Socioeconomic analyses in the health care sector - a guideline] In Norwegian. Norwegian Directorate of Health, 2011.

26. Foss P. [The pharmaceutical insdustry view on health economics] In Norwegian. 2016.

27. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. Value Health. 2016;19(8):929-35.

28. Wisloff T. [New Norwegian threshold value for a good life year?] In Norwegian. Tidsskr Nor Laegeforen. 2017;137(7):518.

29. Helsedepartementet. Åpent og rettferdig - prioriteringer i helsetjenesten. 2014. p. 1-220.

30. Paulden M, O'Mahony JF, McCabe C. Discounting the Recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine. Pharmacoeconomics. 2017;35(1):5-13.

31. O'Mahony JF, Paulden M. NICE's selective application of differential discounting: ambiguous, inconsistent, and unjustified. Value Health. 2014;17(5):493-6.

32. Claxton K, Paulden M, Gravelle H, Brouwer W, Culyer AJ. Discounting and decision making in the economic evaluation of health-care technologies. Health Econ. 2011;20(1):2-15.

33. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015;36(36):2425-37.

34. Korman MJ, Retterstol K, Kristiansen IS, Wisloff T. Are PCSK9 Inhibitors Cost Effective? Pharmacoeconomics. 2018.

35. Hoeg JM, Feuerstein IM, Tucker EE. Detection and quantitation of calcific atherosclerosis by ultrafast computed tomography in children and young adults with homozygous familial hypercholesterolemia. Arterioscler Thromb. 1994;14(7):1066-74.

36. Vallejo-Vaz AJ, Robertson M, Catapano AL, Watts GF, Kastelein JJ, Packard CJ, et al. Low-Density Lipoprotein Cholesterol Lowering for the Primary Prevention of Cardiovascular Disease Among Men With Primary Elevations of Low-Density Lipoprotein Cholesterol Levels of 190 mg/dL or Above: Analyses From the WOSCOPS (West of Scotland Coronary Prevention Study) 5-Year Randomized Trial and 20-Year Observational Follow-Up. Circulation. 2017;136(20):1878-91.

37. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383-9.

## Figure legends

Figure 1 Simplified model structure

Figure 2 Cost-effectiveness acceptability curve for 40-year-old statin intolerant women with FH

Figure 3 One-way sensitivity analysis on price reduction of PCSK9 inhibitor for statin intolerant women in four age groups (upper left: 30 yrs, upper right: 40 yrs, lower left: 50 yrs, lower right: 60 yrs)

## Tables

Table 1 Seven different approaches for calculating effectiveness of PCSK9 inhibitors (approaches with \* not analyzed)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Statin tolerant |  |  |  |  |  |
| **Evidence of efficacy directly based on**  | **LDL level without PCSK9 inhibitor (mmol/l)** | **LDL-C reduction (mmol/l)** | **LDL-C with PCSK9 inhibitor (mmol/l)** | **Hazard ratio for AMI** | **Hazard ratio for stroke** |
| FOURIER directa | 3,5 | 2,1 | 1,4 | 0,73 | 0,79 |
| FOURIER adjustedb | 3,5 | 2,1 | 1,4 | 0,64 | 0,69 |
| EAS consensusb,c | 3,5 | 2,1 | 1,4 | 0,60 | 0,60 |
| CTTC subgroupsb | 3,5 | 2,1 | 1,4 | 0,48 | 0,45 |
| \*Navarese et al 2018d | 3,5 | 2,1 | 1,4 | 0,72 | 0,72 |
| \*FOURIER MACEe | 3,5 | 2,1 | 1,4 | 0,86 | 0,86 |
| \*ODYSSEY OUTCOMESf | 3,5 | 1,9 | 1,6 | 0,86 | 0,73 |
|  |
| Statin intolerant |  |  |  |  |  |
| **Evidence of efficacy directly based on**  | **LDL level without PCSK9 inhibitor (mmol/l)** | **LDL reduction (mmol/l)** | **LDL with PCSK9 inhibitor (mmol/l)** | **Hazard ratio for AMI** | **Hazard ratio for stroke** |
| FOURIER directa | 6,0 | 3,5 | 2,5 | 0,73 | 0,79 |
| FOURIER adjustedb | 6,0 | 3,5 | 2,5 | 0,46 | 0,50 |
| EAS consensusb,c | 6,0 | 3,5 | 2,5 | 0,41 | 0,41 |
| CTTC subgroupsb | 6,0 | 3,7 | 2,3 | 0,28 | 0,26 |
| \*Navarese et al 2018d | 6,0 | 3,7 | 2,3 | 0,58 | 0,58 |
| \*FOURIER MACEe | 6,0 | 3,5 | 2,5 | 0,86 | 0,86 |
| \*ODYSSEY OUTCOMESf | 6,0 | 3,3 | 2,7 | 0,86 | 0,73 |
| a: Same hazard ratio for all levels of baseline LDL-C b: Higher hazard ratio with higher baseline LDL-C c: Same hazard ratio for AMI and stroked: Results from meta-regression by Navarese et al 2018e: results on major acute coronary event (MACE) as reported by Sabatine et al 2017 (FOURIER)f: Results from Schwartz et al 2018 (ODYSSEY OUTCOMES) |

Table 2 Incremental cost-effectiveness ratios (ICER) for 24 different subgroups and 4 different ways of modelling effectiveness (€/QALY)

|  |
| --- |
| ICERs for FH patients, evidence of efficacy directly based on FOURIER hazard ratios |
| Age | Women primary prevention | Women secondary prevention | Men primary prevention | Men secondary prevention | Women statin intolerant | Men statin intolerant |
| 60 | 108 680 | 110 144 | 86 567 | 143 101 | 82 648 | 69 735 |
| 50 | 142 460 | 141 823 | 101 978 | 99 297 | 96 322 | 80 056 |
| 40 | 219 258 | 230 669 | 148 678 | 140 749 | 137 530 | 103 172 |
| 30 | 346 790 | 349 803 | 232 801 | 221 002 | 208 313 | 146 734 |
|  |  |  |  |  |  |  |
| ICERs for FH patients, evidence of efficacy based on FOURIER HRs adjusted for LDL |
| Age | Women primary prevention | Women secondary prevention | Men primary prevention | Men secondary prevention | Women statin intolerant | Men statin intolerant |
| 60 | 75 661 | 71 350 | 59 627 | 67 386 | 34 728 | 27 238 |
| 50 | 100 092 | 90 023 | 70 613 | 63 104 | 41 790 | 31 466 |
| 40 | 155 477 | 145 181 | 103 837 | 86 174 | 61 203 | 41 831 |
| 30 | 247 478 | 218 744 | 163 599 | 133 310 | 94 486 | 61 497 |
|  |  |  |  |  |  |  |
| ICERs for FH patients, evidence of efficacy based on EAS consensus & FOURIER LDL levels |
| Age | Women primary prevention | Women secondary prevention | Men primary prevention | Men secondary prevention | Women statin intolerant | Men statin intolerant |
| 60 | 66 672 | 57 436 | 51 990 | 49 281 | 31 003 | 23 954 |
| 50 | 88 696 | 71 541 | 61 901 | 49 586 | 37 590 | 27 705 |
| 40 | 138 516 | 114 990 | 91 486 | 65 223 | 55 413 | 37 163 |
| 30 | 221 279 | 172 159 | 144 666 | 99 824 | 85 939 | 55 021 |
|  |  |  |  |  |  |  |
| ICERs for FH patients, evidence of efficacy based on CTTC subgroups & FOURIER hazard ratios |
| Age | Women primary prevention | Women secondary prevention | Men primary prevention | Men secondary prevention | Women statin intolerant | Men statin intolerant |
| 60 | 40 570 | 28 359 | 31 129 | 21 734 | 20 175 | 14 864 |
| 50 | 55 109 | 34 165 | 37 655 | 24 133 | 25 145 | 17 228 |
| 40 | 87 908 | 55 130 | 56 715 | 28 256 | 38 060 | 23 942 |
| 30 | 142 410 | 82 098 | 90 992 | 42 618 | 60 133 | 36 449 |

FOURIER = The FOURIER trial (11)

CTTC = Cholesterol treatment trialists collaboration

Green boxes = incremental cost-effectiveness ratios (ICERs) below €70,000 per QALY

Red boxes = ICERs above €70,000 per QALY

## Figures

Figure 1 Simplified model structure



Footnotes to Figure 1:

* Established CVD is three different health states based on whether the CVD event was angina, AMI or stroke.
* Stroke Sequelae is two different health states; moderate and severe sequelae
* Heart failure is divided into three health states based on time since heart failure was established
* Dead is two different health states based on whether death was a result of CVD or not.

Figure 2 Cost-effectiveness acceptability curve for 40-year-old statin intolerant women with FH

The estimated threshold for cost-effectiveness is about €40,000 per QALY, while the empirical threshold is about €70,000 per QALY.

Figure 3 One-way sensitivity analysis on price reduction of PCSK9 inhibitor for statin intolerant women in four age groups (upper left: 30 yrs, upper right: 40 yrs, lower left: 50 yrs, lower right: 60 yrs)

