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

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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

88   cost-effectiveness. Using unique register data on CVD events among patients with FH and a

89   previously published economic model, the aim of this study was to explore how choice of

90   input variables influence the estimated cost-effectiveness of PCSK-9 inhibitors. We placed

91   particular focus on the difference between modelling based directly on the recently

92   published FOURIER trial (11) and three alternative approaches.

93

94   ## Methods

95

96   ### Efficacy

97   The efficacy of PCSK9-inhibitors has been a much-discussed topic in the research literature,

98   not least after the results from the FOURIER-trial were published. FOURIER is the first large

99   randomised controlled trial (RCT) with "hard", clinically relevant outcomes (11).

100   Essentially, there are two different ways of incorporating effectiveness of PCSK9 inhibitors in

101   health economic models; either (1) by assuming that relative hazards observed in RCT(s)

102   apply to all populations, regardless of LDL-C level and other risk factors, or (2) by assuming

103   that patients with higher LDL-C levels have a larger relative effect of cholesterol reduction as

104   shown in meta-analyses of randomised controlled trials (13). The first is standard

105   assumption in evidence-based medicine and most economic evaluations, the latter is based

106   on results from several meta-analyses, first of statin trials (13), later also confirmed for other

107   interventions such as ezetimibe and PCSK9-inhibitors (14). Given the convincing evidence of

108   increasing relative effectiveness of LDL-C reduction with higher baseline LDL-C (14), we

109   aimed to explore both approaches in modelling the cost-effectiveness of PCSK9 inhibitors.

110   We therefore incorporated into our model both the hazard ratios observed in the first large-

111   scale RCT currently available for any PCSK9-inhibitor (11) and varying relative effectiveness

112   depending on baseline LDL-C level. We will in the following refer to the "standard" evidence

113   based medicine approach as "FOURIER direct", as this method uses the hazard ratios from

114   the FOURIER trial directly (Table 1).

115   With respect to the second approach, a well-recognized way of estimating the effectiveness

116   of LDL-C reduction is published in a consensus statement by the European Atherosclerosis

117   Society (EAS). It concludes that a "22% reduction in risk per millimole per litre (mmol/l)

118 reduction in LDL-C" summarizes current evidence of "the proportional reduction in short-

119 term risk" (14). EAS proposes the following formula to calculate the relative risk reduction of

120 atherosclerotic CVD events for patients at different levels of baseline LDL-C (14):

121 $1 - RR_F^{LDL*(RRm)}$, where RR_F is the relative reduction in CVD risk per mmol/l reduction in LDL-C,

122 LDL is the baseline LDL-C level and RRm is the treatment effectiveness measured as

123 percentage reduction in mmol/l. The EAS statement concluded that a Cholesterol Treatment

124 Trialists' Collaboration (CTTC) meta-analysis from 2010 (13) represents best current evidence

125 on the relationship between LDL-C reduction and CVD outcomes, resulting in the number

126 22% (or $RR_F = 0.78$). The recent FOURIER trial described by Sabatine and colleagues (11)

127 estimated an RRm of 59%, hence the formula used is $1-0.78^{LDL*0.59}$, where LDL in our model

128 can be varied to analyse different patient groups with different baseline LDL-C. This second

129 approach is in the following referred to as "EAS consensus".

130 As both approaches are plausible in their own merit, one solution may be to incorporate a

131 midpoint between the two approaches. The hazard ratio reported by Sabatine and

132 colleagues in the FOURIER trial is the best available evidence, but the baseline LDL-C in that

133 trial (2.4 mmol/l) is far lower than in most FH populations, even when FH is treated with

134 potent statins plus ezetimibe (15). With a fixed treatment effectiveness in terms of

135 percentage LDL-C reduction, the absolute change in mmol/L increase proportionally with

136 increasing baseline LDL-C levels (13, 14). Thus, given a fixed dose of a lipid lowering

137 medication, the higher baseline LDL-C and the more LDL will be cleared from the circulation.

138 To incorporate an alternative that both uses the FOURIER trail and also incorporates

139 information about LDL-C level in the population, we would have to adjust the observed

140 hazard ratio (HR) of cardiovascular events based on the assumed baseline LDL-C level in

141 different populations. This can be done by transforming the observed HR from FOURIER into

142 a natural logarithmic scale, do calculations on that scale and exponentiate to get back to HR

143 scale: $HR_{adj} = EXP(LN(HR_s)-(LDL-LDL_s)*RRm*(1-RR_F))$, where $HR_s = 0.73$, as reported by

144 Sabatine et al, LDL_s = baseline LDL-C observed in Sabatine et al (2.4 mmol/l), and LDL, RR_F

145 and RRm is as defined above. This scenario with an adjustment of the original FOURIER

146 results according to baseline LDL-C, is in the following called "FOURIER adjusted".

147 Although the EAS statement refers to a 22% reduction as the main effect of LDL-C on CVD

148 (14), there has been suggestions to divide CVD into it's most common components AMI and

149 stroke (16). The mentioned CTTC analyses reports a 29% and 31% reduction of AMI and

150 stroke respectively. We incorporated this alternative as a fourth modelling option, using the

151 name "CTTC subgroups".

152 In addition to the mentioned four modelling options, there are numerous different ways of

153 calculating effect of treatment and the number is increasing with increasing publications on

154 this topic. In Table 1, we have listed 3 further potential analyses that could have been

155 performed, but were not included in the present model.

156 We analysed our model for two different levels of LDL-C, representing FH patients who were

157 statin tolerant and intolerant. For statin tolerant patients, we assumed an average LDL-C of

158 3.5 mmol/l on current treatment, approximately as reported in the Norwegian FH registry

159 (17), while for the statin intolerant, we assumed an LDL-C level of 6.0 mmol/l (18). In

160 addition, we also analysed men and women who had previously experienced a

161 cardiovascular event, *i.e.* secondary prevention. For this latter group, we assumed LDL-C

162 level of 3.5 on average (17) and otherwise similar assumptions as for other patients with

163 previous CVD event. The assumptions about LDL-C and resulting assumed hazard ratios for

164 the four different calculation methods are summarized in Table 1.

165

166

167 Other modelling assumptions

168

169 Lifetime costs and QALYs were estimated based on the Norwegian Cardiovascular Disease

170 model (NorCaD)(19), which has been used in several publications previously (20-22). Briefly,

171 the model is a health state transition model (Markov model) with 4 primary CVD events and

172 11 health states (Figure 1). Health outcomes are measured until all are dead or 100 years old

173 and expressed in terms of quality adjusted life years (QALYs). Unit costs are based on market

174 prices, the Norwegian DRG system and various fee schedules as appropriate (19).

175

176 We used incidence data recently derived from a Norwegian FH registry (4). Unit costs in the

177 model were updated to 2017 costs based on current prices of pharmaceuticals (as of May

178 2017) and fees and averages as reported in official documents (23, 24). All costs were

179   measured in Norwegian kroner, but reported in European Euros (€) to ease comparison (1 €

180   = 9.5 NOK). Future health and costs were discounted at 4% per year and analysed using a

181   health care sector perspective, as described in Norwegian guidelines (25).

182

183   Guidelines developed by the Norwegian Directorate of Health in 2005 (25) state that

184   interventions are cost-effective for incremental cost-effectiveness ratios (ICERs) below

185   €62,443 per Quality Adjusted Life Year (QALY). We adjusted this value for inflation and

186   adopted a threshold of €70,000 per QALY. Although empirical evidence has confirmed this as

187   an approximate willingness to pay for health gains (26), for comparison, we also evaluated

188   cost-effectiveness with a threshold of €40,000 per QALY), based on estimation of

189   opportunity cost of health care resources in the UK (27, 28).

190

191   Sensitivity and analyses

192

193   Lately, it has been suggested not to discount future health outcomes in Norway (29).

194   Although this suggestion is not based on all the latest research on this issue (30-32), we

195   performed scenario analyses without discounting future health to test how this suggestion

196   may affect conclusions.

197

198   The official price of one year's use of the least expensive PCSK9 inhibitors is listed at NOK

199   48,104 (€5064) in the Norwegian Medicines Agency database (Legemiddelverket.no). As

200   PCSK9 manufacturers offer confidential discounts for the Norwegian health care system, we

201   performed one-way sensitivity analyses on price. Scenario analyses with up to 50% lower

202   price are presented for statin intolerant women for four different age groups.

203

204   All uncertain parameters in the NorCaD model, including those added to the model for this

205   specific analysis, are incorporated as probability distributions. When running simulations of

206   the model, each uncertain parameter is represented by 1000 realizations from the specified

207   probability distribution. Probabilistic results are shown only as cost-effectiveness

208   acceptability curves (CEACs) for 40-year-old statin intolerant women with FH. In the CEAC,

209   the proportion of simulations in which a PCSK9 inhibitor is cost-effective is shown for all

210   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

242   reported in the FOURIER trial (11) (27% and 21% risk reduction, respectively) results in

243   PCSK9 inhibitors being cost-effective in only one of 24 analysed risk groups at current prices.

244   Allowing for reduction of other CVD outcomes or modelling effectiveness as proposed by

245   EAS (14) may lead to all groups being cost-effective.

246

247   Advances in treatment and prevention of CVD have contributed to considerably decreased

248   CVD mortality rates during the past four decades. One of the most pronounced consequence

249   is that CVD to a lesser extent is a middle-age disease today, compared to only a few decades

250   ago. For patients with FH, however, CVD is still a great threat even in younger age groups (5),

251   and it is therefore important to start treatment early (33). An example from our own

252   analyses that illustrates this (Appendix table 1) shows that if treatment for 30-year-olds is

253   withheld until age 40, up to 0.69 QALYs may be lost on average per person. These QALYs are

254   lost because the patient develops CVD or dies before becoming 40 years old, corresponding

255   to for instance 2% dying and loosing 34.5 remaining QALYs.

256

257   Our results are presented from a Norwegian setting based on Norwegian data. Generally,

258   the transferability of health economic evaluations is limited. However, a recent review of

259   economic evaluations of PCSK9 inhibitors found that differences between countries were

260   much smaller than other differences between studies, such as those explored in the present

261   analysis (34). That review found incremental health effects among FH patients of more than

262   2 QALYs in two studies and less than 1 QALY in three studies. The two studies with the high

263   QALY gains concluded that PCSK9 inhibitors are cost-effective, while the other three

264   concluded PCSK9 inhibitors were not. Similarly, we found that all 32 analyses with a gain of

265   more than 1 QALY were cost-effective, while most of our analyses with a QALY gain below 1

266   were not cost-effective (52 out of 64). Based on recent price reductions in some countries,

267   PCSK9 inhibitors may be more cost-effective in the countries where large rebates have been

268   given. Official prices (maximum approved price) as reported by the Norwegian Medicines

269   Agency has, however, not been reduced in the past few years (www.legemiddelverket.no,

270   accessed 11th January 2019).

271

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

304 this limitation, however, is likely minimal because only a small proportion of the FH patients

305 are statin intolerant.

306

307 Atherosclerosis is a slow process with lipids accumulating in the arterial wall. LDL-cholesterol

308 is a major driver of the process and reduction of LDL may slow down and even reverse the

309 atherosclerosis. Cholesterol years is a concept to calculate the result of the accumulated

310 cholesterol load on intima, similar to the concept pack-years regarding cigarette smoking. It

311 was first used to evaluate risk in homozygous patients with FH and total cholesterol values of

312 20-30 mmol / l (35). In this conceptual understanding, inhibiting the atherosclerosis process

313 during a study period will provide sustained effects even after the end of the study. The

314 slowing of the atherosclerosis process will likely generate health benefits later in life. The

315 long term follow-up up of statin trials like the WOSCOPS trial provide support for this view

316 (36) with no significant effect on total mortality the first 6 years, but highly reduced total

317 mortality 20 years after end of study. The early results of the FOURIER study (11) may

318 therefore prove

319 different from the long term results. In several statins trials, like in the 4S study (37), the

320 survival curves for placebo and statin, did not diverge until about 1.5 years follow-up. In the

321 FOURIER study the median duration of follow-up was 2.2 years, which is a short period when

322 studying the slow process of atherosclerosis.

323

324 Two large RCT's of PCSK9 inhibitors available (11, 12). Our analyses are based on the trial

325 that was published first. In large, the two trials did not differ much in results, for instance

326 both reported a hazard ratio (HR) of 0.85 on their primary outcome. When split into the

327 detailed outcomes directly used in modelling, the differences are somewhat larger, HR_{AMI}:

328 0.73 vs 0.86 and HR_{Stroke}: 0.79 vs 0.73. Hence, we would have found somewhat different

329 results if analyses were performed based on ODYSSEY instead of FOURIER.

330

331 As can be seen from the previous paragraph, the primary endpoint in the FOURIER and

332 ODYSSEY trials indicate a lower effect than the estimates on what we regarded as the most

333 relevant outcomes in our model; AMI and stroke. If we had used the estimates of effect on

334 this composite endpoint instead of the endpoints for separate outcomes, we would have

335 observed a smaller effect, and therefore that PCSK9 inhibitors were not cost-effective in any

336 subgroups.

337

338 A recent analysis similar to the CTTC meta-analysis found effects to be somewhat smaller,

339 with approximately RR of 0.86 instead of 0.78 per mmol/l. as can be seen from our Table 1,

340 these effect estimates are between the FOURIER direct and FOURIER adjusted, hence we

341 would likely get somewhere between 1 and 10 risk groups to be cost-effective if this analysis

342 had been done.

343

344 ## Conclusions

345 Our model predictions suggests that PCSK9 inhibitors with the maximum approved price in

346 Norway are cost-effective for some groups of FH patients, particularly when CVD risk

347 reduction from LDL level reductions is based on the CTTC meta-analyses as suggested by

348 EAS. When using clinical relevant endpoints from the FOURIER trial, the proportion of FH

349 patient groups that is cost-effective to treat with PCSK9 inhibitors is lower. Price discounts

350 may make it cost-effective in all patient groups.

351

Contributions

366 All authors contributed to the planning of the paper and contributed to analyses and

367 discussions. All authors have contributed to the writing of the manuscript and has approved

368 the final version. TW conducted all analyses based on a model that was in previous projects,

369 see references (19) and (20).

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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)

485 *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 direct[a]	3,5	2,1	1,4	0,73	0,79
FOURIER adjusted[b]	3,5	2,1	1,4	0,64	0,69
EAS consensus[b,c]	3,5	2,1	1,4	0,60	0,60
CTTC subgroups[b]	3,5	2,1	1,4	0,48	0,45
*Navarese et al 2018[d]	3,5	2,1	1,4	0,72	0,72
*FOURIER MACE[e]	3,5	2,1	1,4	0,86	0,86
*ODYSSEY OUTCOMES[f]	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 direct[a]	6,0	3,5	2,5	0,73	0,79
FOURIER adjusted[b]	6,0	3,5	2,5	0,46	0,50
EAS consensus[b,c]	6,0	3,5	2,5	0,41	0,41
CTTC subgroups[b]	6,0	3,7	2,3	0,28	0,26
*Navarese et al 2018[d]	6,0	3,7	2,3	0,58	0,58
*FOURIER MACE[e]	6,0	3,5	2,5	0,86	0,86
*ODYSSEY OUTCOMES[f]	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 stroke

d: Results from meta-regression by Navarese et al 2018

e: results on major acute coronary event (MACE) as reported by Sabatine et al 2017 (FOURIER)

f: Results from Schwartz et al 2018 (ODYSSEY OUTCOMES)

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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

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Figures

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498 *Figure 1 Simplified model structure*
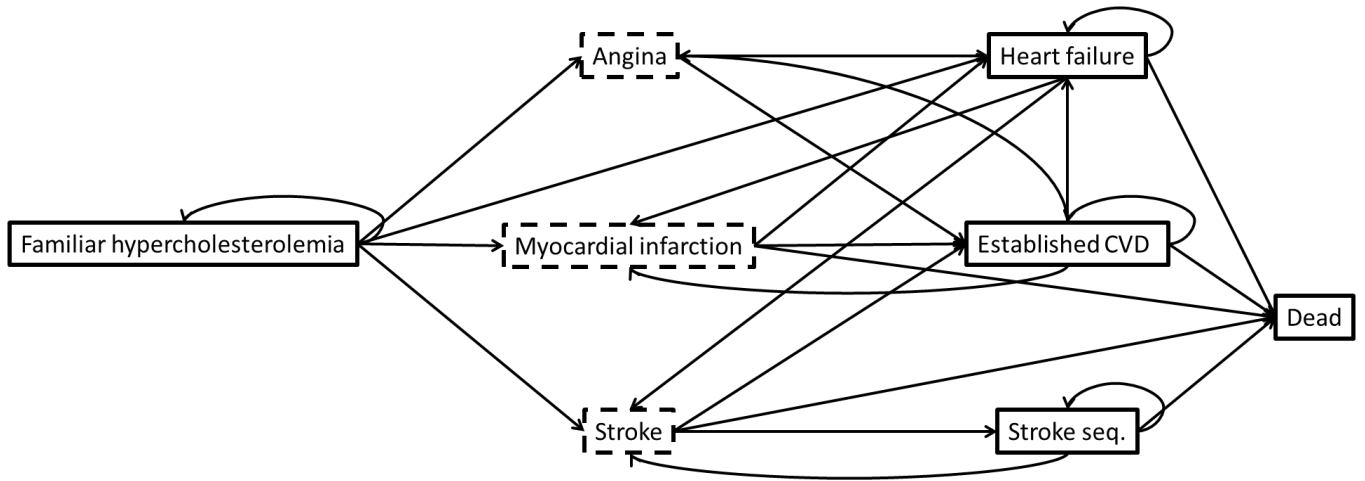
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500 Footnotes to Figure 1:

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

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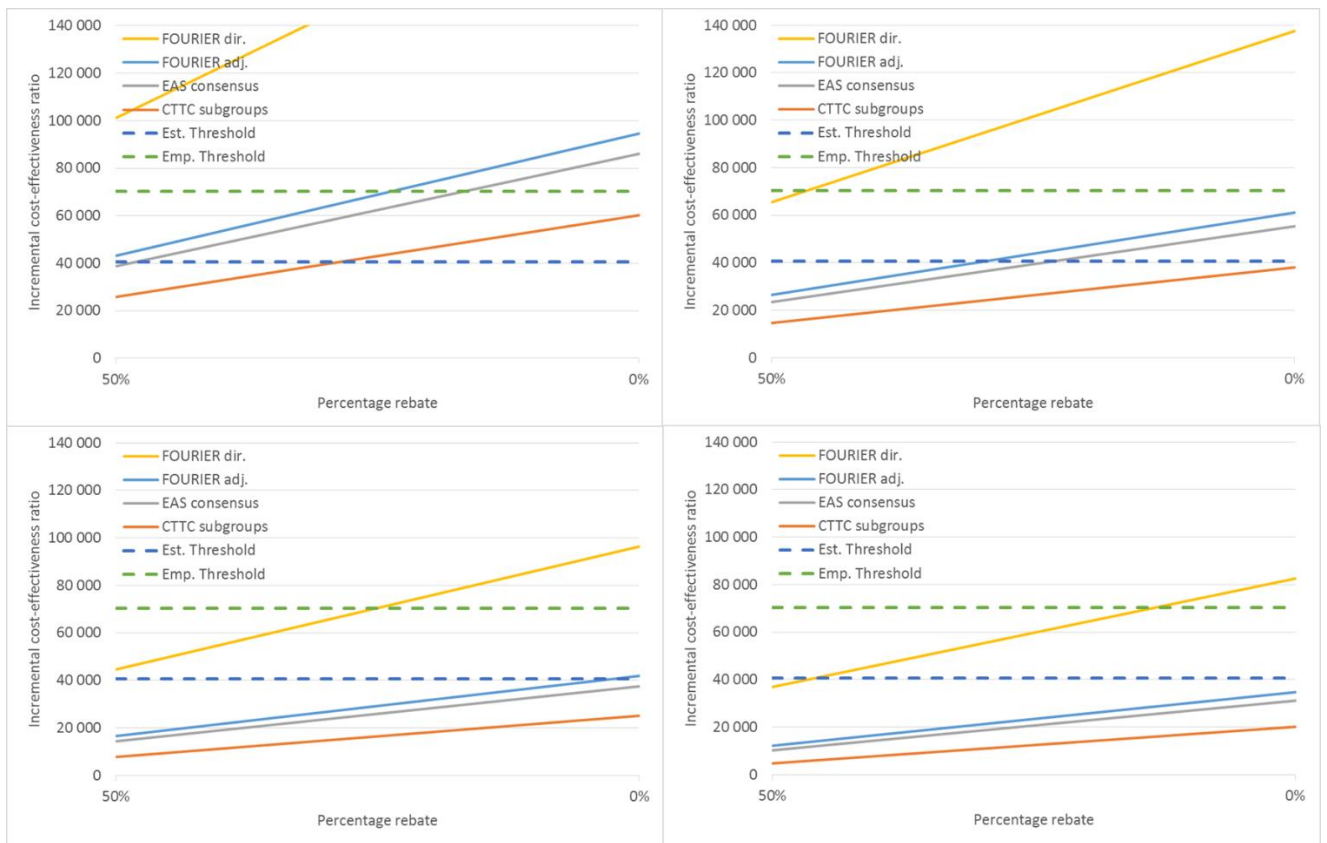507 *Figure 2 Cost-effectiveness acceptability curve for 40-year-old statin intolerant women with FH*
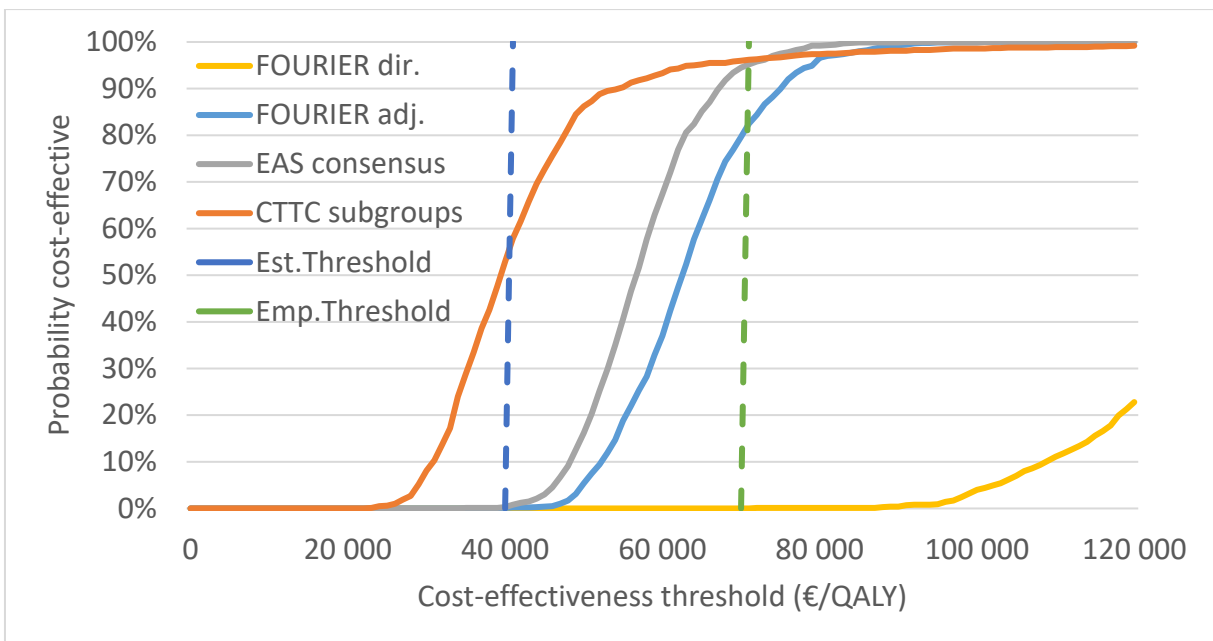
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509 The estimated threshold for cost-effectiveness is about €40,000 per QALY, while the empirical

510 threshold is about €70,000 per QALY.

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512   *Figure 3 One-way sensitivity analysis on price reduction of PCSK9 inhibitor for statin intolerant women in four age groups*

513   *(upper left: 30 yrs, upper right: 40 yrs, lower left: 50 yrs, lower right: 60 yrs)*

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