Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: A Single Technology Appraisal

Erratum

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(i) Estimation of transition probabilities for people prior to receiving evolocumab and/or ezetimibe.

(ii) Estimation of the relative reduction in CVD events associated with the use of evolocumab and/or ezetimibe based on reductions in LDL-C observed in RCTs.[23,24]

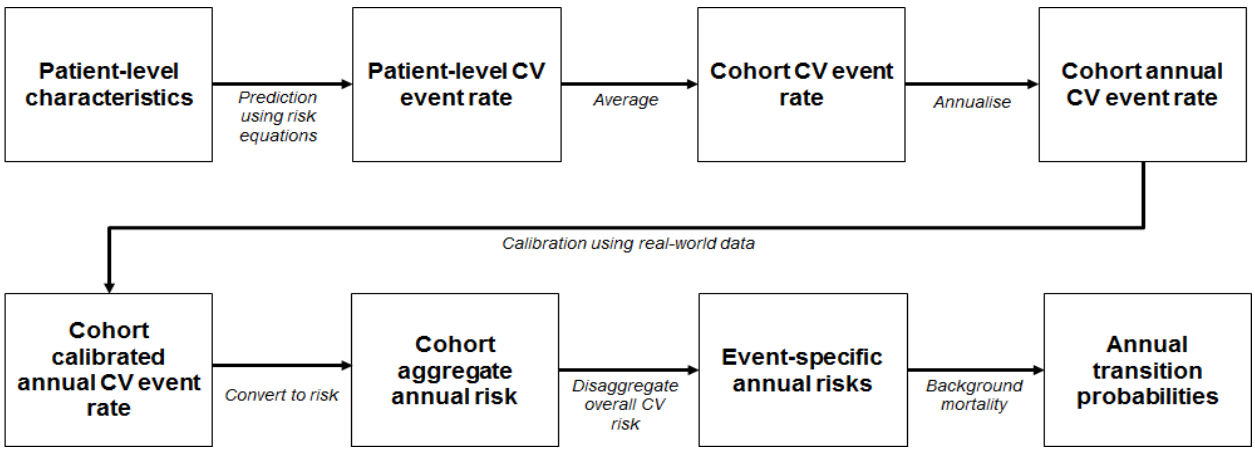
(iii) Estimation of transition probabilities in patients receiving evolocumab, ezetimibe or evolocumab plus ezetimibe.

(iv) Estimation of QALYs, costs and cost-effectiveness.

(i) Estimation of transition probabilities for people prior to receiving evolocumab and/or ezetimibe

The steps used by the company to estimate transition probabilities in the absence of evolocumab and/or ezetimibe (referred to as "population CV event rates" in the CS) are described in Figure 5.

Figure 5: Step-wise sequence of estimating event-specific transition probabilities from patient-level characteristics (reproduced from CS,[13] Figure 5-4 page 182)



CV - cardiovascular

Published risk equations[53,54] are applied to individual patient data (IPD) from the subgroup of patients enrolled in the LAPLACE-2 trial[23] who had a baseline LDL-C>2.5mmol/L and from the modified ITT population of the RUTHERFORD-2 trial[21] to estimate the average aggregate risk of the next CVD event for males and females separately. The Framingham equations for males and females[53] are used to estimate the risk of a first CVD event in people who do not have a history of CVD. The REduction of Atherothrombosis for Continued Health (REACH) Registry equations[54] are used to predict the risk of experiencing a fatal or any CVD event (assumed incorrectly to be non-fatal by the company) in people who have a history of CVD. The company assumes (incorrectly) that the risk predicted for "cardiovascular death" and "next cardiovascular event" from the REACH equations are independent of each other and can be added (effectively producing a total CVD risk~~). It should also be noted that the predicted risks from both the Framingham and REACH equations are actually probabilities which are bounded between 0 to 1, but are not treated as such within the company's model; these are instead~~

~~assumed to be "event rates" (see Figure 5, box 2 "patient level CV event rate"). This error in logic is discussed in more detail in Section 5.3.~~

The calculated average aggregate risks of CVD events (10-year risk from Framingham[53] and 20-month risk from REACH[54]) are then transformed into annualised rates; these are calculated separately for males and females (using a sex-specific equation from Framingham and a covariate for sex within the REACH equation). Limited details are provided within the CS[13] regarding this step in the process. From the company's model, the age coefficients (for males and females separately) from the risk equations are used to obtain annual age- and sex-specific rates under the assumption that the event rate follows an exponential distribution such that the sum of the CVD event risks is equal to the average aggregate 10-year risk of CVD using the following formula:

$$risk(t)=\partial \times exp(\varphi)^{ln(\frac{age(t)}{\rho}} \quad [i]$$

Where:

risk(t)=annual risk at a given age

∂=risk prediction by risk equation

φ=age coefficient in the risk equation

age(t)=current age

ρ=mean age

The annual age-specific risks obtained for males and females are then averaged to obtain an average annual age-specific risk; these are capped at a maximum age of 86 years (i.e. the risk is assumed to remain constant after age 85 years) and are subsequently multiplied by either: (a) state-specific calibration factors to reflect the performance of the risk equations in the UK for the non-familial primary hypercholesterolaemia populations (based on the LAPLACE-2 trial[23]), or (b) an overall calibration factor to reflect the differences in the risk of CVD events between HeFH and non-HeFH patients (HeFH analyses only). Following this process, the company transform the resulting risks onto the probability scale using the following formula:

$$probability = 1-exp(-rate) \quad [ii]$$

The average aggregate annual age-specific probabilities of CVD events are then apportioned according to specific CVD events based on multinomial logistic regression models (see Section 5.2.2). The average aggregate risks for first CVD events derived from the Framingham equations[53] after calibration are apportioned into ECVD, ACS, IS, HF, CHD death and stroke death events. The risks for subsequent CVD events derived from the REACH Registry equations[54] after calibration are

Section 5.2.2). The ERG notes that based on information provided within the CS[13] and during the clarification process,[35] the baseline risk of experiencing CV events could have been estimated directly from the company's CPRD and HES analysis, and that the use of the Framingham and REACH equations is not necessary as it does not appear to provide additional information compared with using the CPRD and HES data. In effect, the company's approach involves estimating CV risk using equations then adjusting these to reflect real-world CPRD/HES data rather than using the CPRD/HES data directly. The ERG sought clarification from the company regarding this matter (see clarification response,[35] question B33). The company's response stated that:

"…*the economic model could indeed have directly used the CPRD study event rates to model an overall high-risk population as per the study cohort definitions. However, this approach would not have permitted us to assess specific high-risk populations such as those with existing CVD with 1 or 2 additional risk factors who remain at the highest residual risk*."

The ERG considers the company's response to be unsatisfactory because: (a) the analyses in individuals with additional risk factors (AF and 2/3 vascular beds) are presented only within the company's subgroup analyses and do not reflect the main population specified in the NICE scope,[4] and; (b) the company's analysis in patients with existing CVD with one or two additional risk factors employs arbitrary manipulations of the IPD which will ultimately produce biased risk estimates. The ERG considers that it would have been more appropriate to estimate baseline CVD risk from the CPRD/HES data and to subsequently adjust these using relative risks from the published literature to reflect these additional risk factors. It is also noteworthy that the company's process for estimating CVD risk in all populations requires several other assumptions (e.g. removing the effect of age and sex), the validity of which are unclear.

(d) Model implementation and misspecification of evidence inputs

Upon scrutinising the company's model, the ERG identified a number of inconsistencies and errors in the model's implementation and logic, which appear to be due to a misinterpretation or misuse of evidence. These are described in below.

~~Firstly, the company's model treats the predictions from the Framingham[53] and REACH Registry[54] risk equations as event rates (see CS,[13] Figure 5-4, page 182). However, in response to a request for clarification from the ERG, the company recognised that the risk predicted by these equations are actually probabilities which are bounded between 0 to 1 (see clarification response,[35] question B17).~~

~~In addition,~~ The company's model misinterprets what the REACH Registry risk equations[54] are predicting. As detailed in Section 5.2, the REACH Registry risk equations predict: (i) the risk of any