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Editorial

When economy meets physiopathology: A novel cost-effectiveness model finally considers the cumulative effect of LDL cholesterol burden

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Familial hypercholesterolemia (FH) is a prevalent hereditary autosomal dominant lipoprotein metabolic disorder marked by increased levels of LDL-cholesterol (LDL-C) and a higher risk of developing early cardiovascular disease [1]. Heterozygotic FH affects 1 in 250–300 individuals worldwide, and less than 1% of those subjects have been diagnosed to date [2,3].

Early screening helps prevent or delay coronary artery disease (CAD) by guiding proper treatment to lower the high cholesterol burden associated with lifelong cardiovascular risk. According to the most recent recommendations, LDL-C should be reduced in adults with FH to 50% of baseline values, or to achieve 2.5 mmol/l (100 mg/dL) [4,5]. However, in clinical practice, adherence to these recommendations is low for several reasons, including the effectiveness of lipid-lowering therapies (LLTs), genetic background, medical education, as well as the costs of screening and therapies.

FH phenotype is highly heterogeneous even among heterozygotes. Among them, high-dose statins and ezetimibe will reduce LDL-C levels by 25–65% [6]. Genetic variations affect the therapeutic efficacy of lipid-lowering drugs, with SORT1/CELSR2/PSRC1 and PCSK9 mutations being related with improved responses and mutations in the *ApoE*, *LPA,* and *SLCO1B1* genes being associated with decreased responses [6–8].

In fact, less than 12% of individuals with FH actually reach optimal LDL-C levels. Of those not reaching LDL-C goals, 70% are on high-intensity statin plus ezetimibe, and in 30%, the main reason for goal achievement failure was the acceptance of a higher target level of LDL-C by the treating physician [9]. Although several novel LLTs such as bempedoic acid and PCSK9 inhibitors are available, the access to these therapies is not always trivial and medical education can also be an issue. In the real world, the availability of such treatments does not necessarily convert into prescriptions and goal accomplishment [9].

To justify an effort, it is innate to think that the benefit must outweigh the cost. However, (i) when the benefit is not immediately clear or (ii) when marginal gains decrease by adding new therapies or (iii) when the cost scales in a non-linear fashion (i.e. the cost to reduce 1 mmol/L of LDL-C is much lower in statin-naïve individuals than in those taking high-dose statins plus ezetimibe [10]), it is difficult to make clinicians conscious of the benefit of achieving LDL-C goals. To improve the quality of care for people with FH, the concept of cost-benefit or cost-effectiveness must be stressed and must be consistent with disease mechanistic framework.

The average lifetime levels of LDL-C multiplied by the number of years lived define the atherosclerotic burden of any individual. The cumulative LDL-C over years is highly associated with CAD when above 160mmol (Fig. 1). This is not a new concept [11,12], however, it is not well defined the optimal screening and treatment window to avoid crossing the threshold of cumulative LDL-C associated with higher risk of CAD. Available cost-effectiveness studies did not consider the impact of cholesterol burden, ignoring such physiopathological component.

In this issue of *Atherosclerosis*, Faria et al. [13] evaluated the impact of the cholesterol burden in the incremental cost-effectiveness for screening and treating individuals with FH at different ages and baseline cardiovascular risk. The authors found that when LDL-C burden is considered, in all individuals with pre-treatment LDL-C $\geq$ 4 mmol/L, and in those with pre-treatment LDL-C $\geq$ 2 mmol/L aged $\geq$50 years or who have CVD history had positive net health gains from diagnosis and treatment at the cost-effective threshold of £15,000/QALY.

If cholesterol burden is not considered, diagnosis and treatment resulted in lower net health gain, but still positive in children aged 10 years with pre-treatment LDL-C $\geq$ 6 mmol/L and adults aged 30 years with pre-treatment LDL-C $\geq$ 4 mmol/L. Higher LDL-C levels and longer age at diagnosis result in greater net health improvements, which raises the risk of CAD in those individuals.

The cumulative lifetime burden of LDL-C highlights the importance

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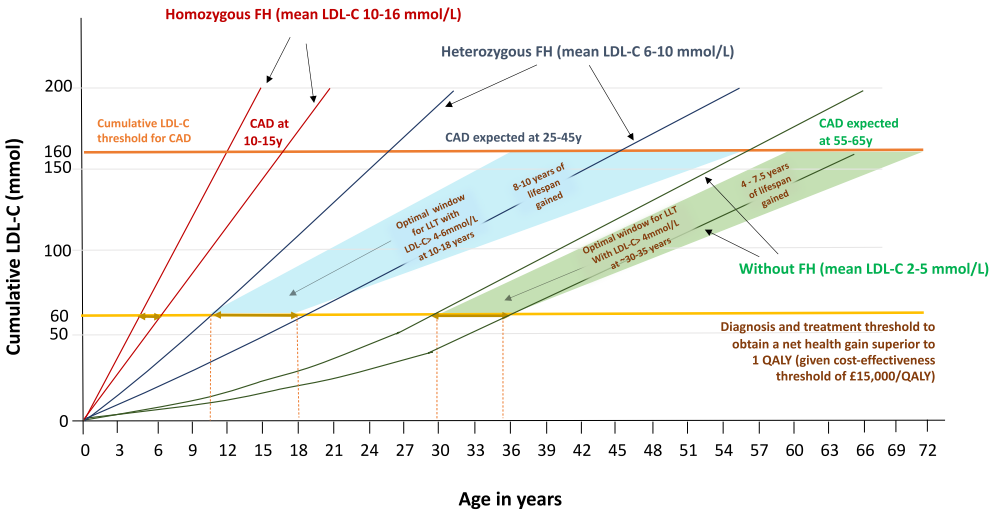

Fig. 1. LDL-C load and optimal windows for initiating therapy throughout life in relation to net health gain in homozygous, heterozygous, and non-FH individuals.
The cumulative LDL cholesterol burden of individuals with CAD is typically 160 mmol (data derived from Refs. [10,11]). Optimal treatment windows for heterozygous FH consider the threshold to obtain a net health gain superior to 1 QALY (given cost-effectiveness threshold of £15, 000/QALY) as reported by Faria et al. [13]. In non-FH individuals, we also consider the LDL-C levels necessary to accumulate 100mmol over 25 years (from 30 to 55 years) and the exposure to normal levels of LDL-C during childhood and adolescence (~1.8–2.2 mmol/L from 2 to 19 years) according to LDL-C nomograms in several populations [15–19]. CAD: coronary artery disease, FH: familial hypercholesterolemia, LDL-C: low-density lipoprotein; LLT: lipid-lowering therapies, QALY: quality-adjusted life years.

of early intervention. The new economic models by Faria et al. [13] and net health gains with early diagnosis and treatment are highly consistent with existing physiopathological models. With the new data, it is possible to ascertain an optimal treatment window for heterozygous FH at 10–18 years with LDL-C $\geq$ 6 mmol/L, considering the threshold to obtain a net health gain superior to 1 QALY (given cost-effectiveness threshold of £15,000/QALY) (Fig. 1). If left untreated, a heterozygous FH individual reaches a risky LDL-C burden at 25-45 years-old [14]. If diagnosed and treated appropriately with LLT in the optimal time window, life expectancy will increase by 8–10 years [13].

Although the model was based in a cohort of individuals with FH, there is a considerable proportion of individuals with pre-treatment LDL-C levels between 2 and 4 mmol/L, what may indicate non-FH were also included in CPRD-FH cohort. This information stands as a limitation to whole model as an FH-specific model, but also permit a reasonable extrapolation to non-FH individuals. With the data by Faria et al. it is also possible to consider an optimal treatment window for the general population at 30–35 years with LDL-C $\geq$ 4 mmol/L. Three key reasons justify this window: (i) it provides a net health gain superior to 1 QALY (given cost-effectiveness threshold of £15,000/QALY); (ii) most non-FH individuals will reach a LDL-C burden of 60–70 mmol at their 30–35 years [15–19]; (iii) if a 30-year old individual carries a LDL-C level of 4mmol/L for 25 years, there is a high propensity of reaching the risky 160 mmol threshold at 55 years. With this window for diagnosis and treatment, life expectancy is projected to be increased by 4–7.5 years [13].

These findings can guide the development of diagnostic guidelines that focus on people with various features (e.g., cascade screening versus universal screening with LDL-C in childhood). The cost-effectiveness model can also be easily modified to assess new treatments and medications that may result in greater LDL-C reductions but higher costs, as well as to use inputs from other countries to provide country-specific results.

Limitations are well acknowledged by the study authors, but it is noteworthy that these findings might not apply to those who have homozygous FH. In addition, CPRD-FH cohort data had follow-up data limited to 10 years, leading to extrapolation of long-term cardiovascular risk with limited validity. Given the variation in management approaches across the country and over time, as well as individual LDL-C responses, another area of ambiguity is to the impact of diagnosis and therapy on LDL-C and post-diagnostic monitoring expenses.

In conclusion, the novel economic models developed by Faria et al. are highly consistent with the physiopathological background of FH and atherosclerotic artery disease. More specifically, the study helps to define the ideal windows for screening and treatment to maximize lifespan at the lowest cost to society. Of course, the model is designed to the UK healthcare system. As so, due to the substantial variation in the organization of healthcare systems between countries, optimal cholesterol thresholds for screening and treatment might be country-specific and may be defined with appropriate local economic data.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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