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Original Article

Achieved LDL cholesterol levels in patients with heterozygous familial hypercholesterolemia: A model that explores the efficacy of conventional and novel lipid-lowering therapy

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BACKGROUND: A large proportion of patients with heterozygous familial hypercholesterolemia (heFH) do not reach low-density lipoprotein cholesterol (LDL-c) levels advocated by international guidelines (<70 mg/dL or <100 mg/dL).

OBJECTIVE: We set out to model which proportion of patients reach targets using conventional and novel therapies.

METHODS: We performed a cross-sectional analysis in a large cohort of genetically identified heFH patients and calculated the proportion reaching treatment targets in four scenarios: (1) after 50% LDL-c reduction (representing maximal dose statin); (2) after 70% LDL-c reduction (maximal dose statin + ezetimibe); (3) additional 40% LDL-c reduction representing cholesteryl ester transfer protein inhibitor (CETPi); and (4) 60% LDL-c reduction (proprotein convertase subtilisin/kexin type 9 inhibitors [PCSK9i]), on top of scenario 2. We applied 100% adherence rates and literature-based adherence rates from 62% to 80%.

RESULTS: We included 1059 heFH patients with and 9420 heFH patients without coronary heart disease (CHD). With maximal dose statin, 8.3% and 48.1% of patients with and without CHD would

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reach their recommended LDL-c targets, respectively. This increases to 54.3% and 93.2% when ezetimibe is added. Addition of CETPi increases these numbers to 95.7% and 99.7%, whereas adding PCSK9i would result in 99.8% and 100% goal attainment. Using literature-based adherence rates, these numbers decrease to 3.8% and 27.3% for maximal dose statin, 5.8% and 38.9% combined with ezetimibe, 31.4% and 81.2% when adding CETPi, and 40.3% and 87.1% for addition of PCSK9i.

CONCLUSIONS: Less than 10% with and 50% of heFH patients without CHD would reach treatment targets with maximal dose statin, but this substantially increases on addition of ezetimibe, CETPi, or PCSK9i. However, considering recently published adherence data, this might be lower in real life, especially in heFH patients with CHD.

Introduction

Heterozygous familial hypercholesterolemia (heFH) is a common autosomal dominant genetic disorder affecting approximately 1 in 200–250 persons and is caused by mutations in the low-density lipoprotein receptor, apolipoprotein B (*APOB*), or proprotein convertase subtilisin/kexin 9 (*PCSK9*) genes.[1,2] Patients with heFH are characterized by high plasma low-density lipoprotein cholesterol (LDL-c) levels and increased risk for premature coronary heart disease (CHD). The hazard ratio or odds ratio for CHD is 3.6 to 22.3 times higher in heFH patients compared with that of non-heFH controls.[3–5] Current clinical guidelines recommend striving for LDL-c levels below 70 mg/dL (1.8 mmol/L) or below 100 mg/dL (2.6 mmol/L) in these patients with and without a history of CHD, respectively.[6]

Several observational studies have shown that these levels are not reached in a large proportion of patients, despite the use of lipid-lowering therapy (LLT) (ie, statin with or without ezetimibe).[7,8] In recent years, additional LDL-c–lowering agents were developed to address this unmet clinical need. Inhibitors of cholesteryl ester transfer protein inhibitor (CETPi) and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) have been extensively studied in heFH patients. Anacetrapib, an oral CETPi, was shown to result in an additional 40% LDL-c reduction compared to placebo in heFH patients who were using maximally tolerated LLT in the REALIZE trial,[9] and recently it was stated in a press release that in the REVEAL trial, anacetrapib significantly decreases major coronary events.[10] In a similar trial design in the RUTHERFORD studies and ODYSSEY familial hypercholesterolemia (FH) studies, subcutaneous injections of alirocumab or evolocumab, both monoclonal antibodies directed against PCSK9, resulted in an approximately 60% additional LDL-c decrease.[11–13] However, patients enrolled in these clinical trials do not necessarily represent "the general heFH patient" because the in- and exclusion criteria of such studies usually result in selection of patients whose LDL-c levels are higher compared to heFH patients not participating in a clinical trial.[14] In addition, the enrolled populations are heterogeneous, as both genetically and clinically defined heFH patients could participate in these trials. Moreover, adherence to medication in real life has shown to be substantially lower compared to the adherence in clinical trials.[15–18] Therefore, we set out to calculate which fraction of heFH patients identified by cascade screening, would reach the recommended LDL-c levels with maximally conventional LLT (maximal dose statin combined with ezetimibe) and additional CETPi or PCSK9i at different adherence rates.

Methods

Data collection and study cohort

The data used in present study were collected during the FH cascade screening program in the Netherlands, which ran from 1994 to 2014. Details have been described previously.[19,20] In short, a cascade started with the identification of a carrier of an FH causing mutation. Subsequently, molecular analysis took place in first degree relatives. Blood was drawn in fasting state, and demographic and clinical data of participants were collected by a certified genetic field worker. Lipids and lipoproteins were measured by default in all participants since 2004. In the present study, we included heFH patients with a pathogenic mutation 3 aged 18 years or above and of whom a lipid profile and information about the use of LLT was available. Homozygous and compound heterozygous FH patients were excluded. All patients provided written informed consent. This study was approved by the Medical Ethical Committee of the Academic Medical Centre, University of Amsterdam, the Netherlands and the scientific board of the Landelijk Expertisecentrum Familiaire Hypercholesterolemie, the nonprofit organization in charge of the data collection.

Measurement of lipid levels

The lipid profile was measured with the LDX-analyzer (Cholestech Corporation, Hayward, CA, USA).[21] Levels of LDL-c were subsequently calculated with the Friedewald formula, unless triglycerides were above 400 mg/dL (4.5 mmol/L).[22] Off-treatment LDL-c levels in patients using LLT at the time of screening were calculated based on type and dose of medication, according to the adjustment coefficients as previously described.[17,23]