Archives of Cardiovascular Disease (2019) 112, 75—78

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Elsevier Masson France EM|consulte www.em-consulte.com/en

SCIENTIFIC EDITORIAL

Hypercholesterolaemia and coronary artery disease: A silent killer with several faces

Hypercholestérolémie et maladie coronaire : un tueur silencieux à plusieurs visages

Jean Ferrières

Department of Cardiology and Department of Epidemiology, Health Economics and Public Health, UMR Inserm 1027, Toulouse-Rangueil University Hospital, Toulouse University School of Medicine, 31059 Toulouse, France

Received 5 November 2018; accepted 8 November 2018
Available online 31 December 2018

KEYWORDS
Familial hypercholesterolaemia;
Coronary artery disease;
Ezetimibe;
Statins;
PCSK9 monoclonal antibodies

MOTS CLÉS
Hypercholestérolémie familiale ;
Maladie coronaire ;
Ezétimibe ;
Statines ;
Anticorps monoclonaux anti-PCSK9

From the works of Anitschkow in 1908 [1] to the success of monoclonal antibodies in 2017 [2], cholesterol has come out of the shadows and into the light. Experimental models have made it possible to put forward hypotheses, and cohort studies have promoted cholesterol to the rank of a major risk factor. However, unlike tobacco and arterial hypertension, cholesterol testing belongs to the field of laboratory medicine. The perception that doctors and their patients have of cholesterol-related risk is therefore difficult to assess.

The consequences of exposure to cholesterol can be measured at the population level and at the individual level. In a recently published study [3], we analysed the predictive value of cardiovascular risk factors in the general population. Our sample consisted of 3208 French subjects, representative of the general population, who were followed for 10 years. In an analysis that was adjusted for all risk factors for cardiovascular disease, a low-density lipoprotein cholesterol (LDL-C) concentration $\geq$ 5.2 mmol/L was associated with a significant relative risk of 1.62 for total mortality (compared with individuals whose LDL-C concentration was < 5.2 mmol/L). This means that cumulative exposure to high LDL-C concentrations shortens the life expectancy of ordinary French subjects in the general population.

In another recent study [4], in which we followed 4930 subjects for 8.6 years, we sought to determine whether the risk could be stratified according to LDL-C concentration. To

Abbreviations: LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

E-mail address: jean.ferrieres@univ-tlse3.fr

https://doi.org/10.1016/j.acvd.2018.11.007

better illustrate the relationship between LDL-C and risk, we chose the LDL-C concentrations used by the Dutch Lipid Clinic Network and recommended by the European Society of Cardiology [5] to identify familial hypercholesterolaemia. There were four LDL-C concentration thresholds: 4 mmol/L, 5 mmol/L, 6.5 mmol/L and 8.5 mmol/L. We carried out several multivariable analyses before and after the exclusion of patients who were treated with statins. Whatever the multivariable model, a dose-effect relationship was observed between LDL-C concentration and total mortality risk. The risk of death increased significantly when the LDL-C concentration rose above 4 mmol/L. The relative risk was 8.17 when the LDL-C concentration was > 8.5 mmol/L (compared with individuals whose LDL-C concentration was < 4 mmol/L). In other words, LDL-C concentration recorded at a given time had a cumulative effect on long-term risk that was far from negligible. In a work that reached similar conclusions [6], American colleagues from the Cooper Center studied 36 375 participants with no history of cardiovascular disease or diabetes, who were followed for 26.8 years. As in our own work, a significant relationship was found between LDL-C concentration and cardiovascular risk. In addition, a dose-effect relationship was observed between LDL-C and cardiovascular mortality.

At an individual level, hypercholesterolaemia consists of two different nosological entities. On the one hand, polygenic hypercholesterolaemia corresponds to complex interactions between nutrition and certain genetic polymorphisms that promote the development of hypercholesterolaemia. On the other hand, heterozygous familial hypercholesterolaemia is a monogenic disorder, where exposure to LDL-C intervenes from birth. This monogenic disorder is caused by low-density lipoprotein (LDL) receptor dysfunction, and its causes and treatment have been studied intensively.

Most studies show that only 10% of patients who are carriers of familial hypercholesterolaemia are diagnosed [7]; this is because it is a disease that progresses slowly from birth, and cholesterol deposits build up insidiously in the arteries. As a result, the first diagnosis is generally acute coronary syndrome or effort angina. If the cardiologist does not pay particular attention to the family history, genetic hypercholesterolaemia blends in with all the cases of pure and mixed hypercholesterolaemia that are met with every day in cardiology.

The LDL receptor gene, perfectly well identified, is sited on chromosome 19; it contains 18 exons that correspond to the different parts of the LDL receptor, including the transmembrane section that captures LDL lipoproteins. The prevalence of heterozygous familial hypercholesterolaemia is 1 in 200 or 1 in 250 subjects [5]; it is by far the most common genetic abnormality in medicine, well ahead of cystic fibrosis, the prevalence of which is 10 times lower in the general population. At the present time, more than 1700 mutations have been identified in the gene coding for the LDL receptor, as well as a small number of mutations in the gene that codes for apolipoprotein B and several dozens of mutations in the gene that codes for proprotein convertase subtilisin/kexin type 9 (PCSK9).

Clinical diagnosis of heterozygous familial hypercholesterolaemia is easy when extravascular cholesterol deposits are present; these are tendon xanthomas, xanthelasmas and premature corneal arcus in subjects aged < 45 years. At the present time, such extravascular deposits are less frequent, as subjects with high cholesterol concentrations are treated earlier than in the past. For this reason, clinical scores have been developed to facilitate screening for this genetic disorder. The most popular of these diagnostic scores is the Dutch Lipid Clinic Network score (Dutch score) [5], which combines a family history of cholesterol and premature cardiovascular disease with a personal clinical history of extravascular deposits and premature cardiovascular disease as well as LDL-C concentrations before initiation of pharmacological treatment. Obviously, if a mutation is present, this confirms the diagnosis of heterozygous familial hypercholesterolaemia.

The most severe clinical form of familial hypercholesterolaemia is homozygous hypercholesterolaemia. Here, the receptors may still be partly functional or may be totally non-functional; it is in the clinical form where the LDL receptors are totally non-functional that LDL-C concentration is highest and cardiovascular risk is greatest. In heterozygous familial hypercholesterolaemia, which is the most common, we find a very severe form (with an inactive LDL receptor) and a serious form (with a partially inactive LDL receptor). The role of the geneticist is to translate the genetic information about the modification of DNA nucleotides into clinical information about the functional capacity of the LDL receptor in a given patient. It is on this residual functional capacity of the LDL receptor that the patient's coronary risk depends.

In a series of 632 patients examined in our cardiology department [8], we identified 344 patients who potentially presented with familial hypercholesterolaemia (i.e. with an LDL-C concentration > 4.9 mmol/L). Among these 344 patients, we found 197 mutations, or 57% of patients with a definite genetic diagnosis. Among these 197 patients, one patient had homozygous familial hypercholesterolaemia, while in 17 cases the geneticist was unable to reach a conclusion about the pathogenic nature of the mutation identified. Thus, only 179 of 326 patients, or 55%, carried a pathogenic mutation of the LDL receptor or apolipoprotein B receptor. In the whole patient population, 13% had already presented with premature coronary disease (i.e. before the age of 55 years in men and 60 years in women). Premature coronary disease developed at the age of 48 years in patients who were carriers of a positive mutation. These patients with a pathogenic mutation had an LDL-C concentration of 7.6 mmol/L, compared with 6.9 mmol/L in patients with no identified mutation. In the multivariable analysis, the presence of premature coronary artery disease and an LDL-C concentration > 8.5 mmol/L were associated with a greater probability of bearing a positive mutation, whereas high concentrations of high-density lipoprotein cholesterol and triglycerides were associated with a lower probability of having a positive mutation. When we analyse the factors that are associated with the presence of premature coronary artery disease, findings novel to the medical literature are revealed. An LDL-C concentration > 8.5 mmol/L and the presence of a mutation are, in fact, both independently associated with premature coronary disease. In other words, LDL-C concentration is not in itself enough to predict the

presence of premature coronary disease. This justifies the search for a mutation in routine practice to better target the risk of accelerated atherosclerosis.

The first stage in the treatment of hypercholesterolaemia will always remain the introduction of lifestyle and nutritional measures and the promotion of endurance physical exercises. Nevertheless, in familial hypercholesterolaemia, the impact of dietary measures does not exceed a 10% decrease in LDL-C concentration. In another respect, at the other extreme of therapeutic measures is LDL apheresis. This is a remarkable treatment that stabilizes coronary atherosclerotic plaques and improves vital prognosis in the most severely affected patients [9]. For cardiology centres that are equipped with LDL apheresis facilities, this last-resort treatment can save a large number of patients, and maintain them in a condition compatible with a normal life. There are, nevertheless, social and professional constraints, as two half-days per month must be devoted to the apheresis sessions.

In general, familial hypercholesterolaemia is treated with medication. There are two modalities for lowering LDL-C. On the one hand, medications can be prescribed to decrease very-low-density lipoprotein (VLDL) production, such as statins, mipomersen and lomitapide. On the other hand, medications can be prescribed to promote expression of the LDL receptor, such as statins, ezetimibe and PCSK9 monoclonal antibodies. All of these treatments are complementary, and must be used sequentially, starting with statins and then ezetimibe. Only in the event of resistance to these basic treatments do we consider prescribing PCSK9 monoclonal antibodies or LDL apheresis.

The European Society of Cardiology has expressed its opinion on the prescription of PCSK9 monoclonal antibodies in cardiology [10]. The first situation concerns patients who have a cardiovascular disorder and whose LDL-C concentration is higher than that recommended. If the patient is an ''ordinary'' patient with coronary artery disease, an LDL-C concentration of 3.6 mmol/L has been proposed as a threshold for initiating PCSK9 monoclonal antibodies. For subjects who have a cardiovascular condition and whose atherosclerosis is progressing in an alarming manner, or who combine the cardiovascular condition with familial hypercholesterolaemia or diabetes, an LDL-C threshold of 2.6 mmol/L has been selected.

For patients who are carriers of heterozygous familial hypercholesterolaemia, but have no cardiovascular involvement, other thresholds have been proposed. If the patient has true familial hypercholesterolaemia that is not controlled by conventional treatments, an LDL-C threshold of 4.5 mmol/L has been chosen for prescription of PCSK9 monoclonal antibodies. On the other hand, if patients who are carriers of heterozygous familial hypercholesterolaemia combine high LDL-C with high lipoprotein(a), diabetes, other risk factors or a family history of premature cardiovascular disease, an LDL-C threshold of 3.6 mmol/L has been selected for prescription of PCSK9 monoclonal antibodies.

Cumulative exposure to high LDL-C concentrations calls for early detection and treatment of LDL abnormalities. This refers back to the notion of ''cholesterol legacy'' that was demonstrated in the WOSCOPS study [11] and the ASCOT study [12], where treatment with statins over a relatively short period led to a very marked improvement in very long-term prognosis. To reduce the atheroma burden, the level of elevation of LDL-C must be taken into consideration, together with the duration of exposure. Reducing the LDL-C concentration is in line with the history of clinical trials; the LDL-C concentrations obtained were 1.6 mmol/L in the PROVE-IT study [13], 1.4 mmol/L in the IMPROVE-IT study [14] and 0.78 mmol/L in the FOURIER study [2]. In summary, the lower the LDL-C concentration, the better the prognosis [15]. Cumulative exposure of the coronary arteries to LDL-C is not a new idea; it is a highly realistic concept leading on from the pathophysiology of atherosclerosis, where the level and severity of a risk factor always influence cardiovascular prognosis. This notion has a double clinical impact: on the one hand, screening for high LDL-C must be done from childhood; and on the other, the cardiologist must search obsessively for infraclinical vascular lesions.

To conclude, heterozygous familial hypercholesterolaemia is the most common genetic disease in medicine. In the spectrum of gravity of hypercholesterolaemia, familial hypercholesterolaemia is the most demonstrative example of accelerated coronary atherosclerosis. Familial hypercholesterolaemia does not raise any problem in terms of clinical diagnosis. Nevertheless, it is diagnosed late when cardiovascular complications occur, such as an acute coronary syndrome. Precise genetic diagnosis is available for all patients, and is very effective for optimal evaluation of coronary risk. The cardiologist's mission is to identify, among the constant flow of patients, those whose LDL-C concentration is highest, and who warrant particular attention with regard to diagnosis, prognosis and treatment.

Disclosure of interest

J. F. has received lecture fees from the companies Amgen, AstraZeneca, MSD, Sanofi and Servier.

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