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Scientific editorial

Aortic valve stenosis in familial hypercholesterolaemic: Should we systematically screen?

Juliette Lutun[a], Ariel Cohen[a,b], Hélene Eltchaninoff[c], Franck Boccara[a,d,*]

[a] Department of Cardiology, Saint-Antoine and Tenon Hospital, AP–HP, 75012 Paris, France
[b] INSERM UMRS-ICAN 1166 and Sorbonne université, 75013 Paris, France
[c] Department of cardiology, Rouen University Hospital, CHU-hôpitaux de Rouen, 1, rue de Germont, 76031 Rouen, France
[d] Sorbonne université, GRC n°22 (C2MV-Complications Cardiovasculaires et Métaboliques chez les patients vivant avec le Virus de l'immunodéficience humaine), Inserm UMR_S 938, centre de recherche Saint-Antoine, institut Hospitalo-Universitaire de cardio-métabolisme et nutrition (ICAN), 75571 Paris, France

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1. Abbreviations

AoVC	Aortic valve calcification
AVS	Aortic valve stenosis
CAC	Coronary artery calcification
CT	Computed tomography
CYS	Cholesterol year score
HeFH	Heterozygous familial hypercholesterolaemia
HoFH	Homozygous familial hypercholesterolaemia
LDL-C	Low-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin/kexin type 9
TTE	Transthoracic echocardiography

* Corresponding author. Cardiology Department, Assistance Publique-Hôpitaux de Paris, Sorbonne University, 184, rue du faubourg St-Antoine, 75571 Paris Cedex 12, France.
E-mail address: franck.boccara@aphp.fr (F. Boccara).

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2. What is familial hypercholesterolemia and how should we deal with it?

Familial hypercholesterolaemia is an autosomal-dominant disorder characterized by abnormally high low-density lipoprotein concentrations since intra-utero life. It is caused by a mutation in the low-density lipoprotein receptor (in 80% of cases), apolipoprotein B and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes. Familial hypercholesterolaemia affects about 30 million subjects worldwide [1]. Two forms exist: the homozygous form (HoFH) is characterized by having two mutated alleles and the heterozygous form (HeFH) by having one mutated allele. HoFH has a prevalence of approximately 1 in a million, and carries a much worse prognosis than HeFH, which has a prevalence of 1 in 300 [2].

Detecting and treating familial hypercholesterolaemia as early as possible is essential to prevent the development of cardiovascular atherosclerotic disease, especially coronary artery disease. Therapy includes dietary modification, medication (statins, ezetimibe, PCSK9 inhibitors) and lipid apheresis. Besides coronary artery disease, aortic valve stenosis is also more prevalent among people with versus those without familial hypercholesterolaemia.

3. Aortic valve calcifications and valvulopathy in familial hypercholesterolaemia

Aortic valve calcifications (AoVC) are present in more of half of individuals aged 75 years. The development of calcifications is associated with male sex, smoking, hypertension, diabetes, obesity and hypercholesterolaemia [3,4]. The extent of calcification correlates with the severity of the stenosis and the development of coronary

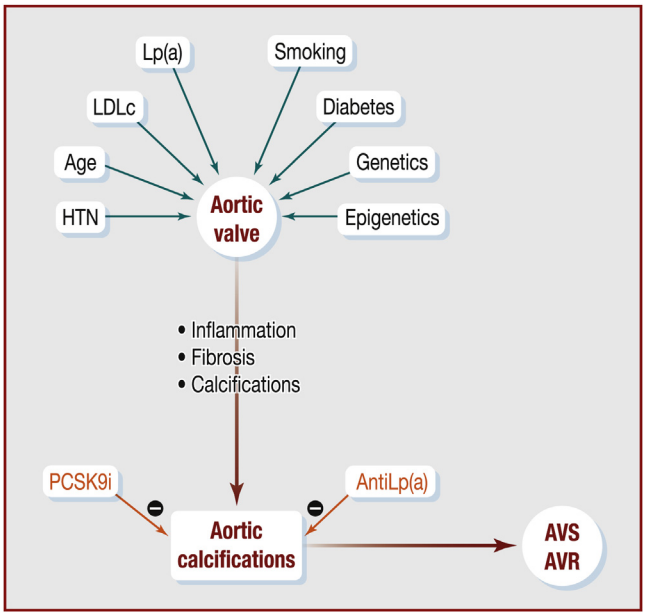

Fig. 1. Factors associated with aortic valve stenosis in familial hypercholesterolaemia. AntiLp(a): anti-lipoprotein(a); AVS: aortic valve stenosis; AVR: aortic valve regurgitation; HTN: hypertension; Lp(a): lipoprotein(a); LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9.

events [5]. AoVC share the same pathophysiology and vascular risk factors as coronary artery disease. Briefly, endothelial damage of the valve, lipid infiltration, inflammation, fibrosis, myofibroblast apoptosis and calcifications are involved in the development of AoVC [6].

Aortic root impairment, including aortic valve stenosis, in familial hypercholesterolaemia was first identified in the 1970s; it concerns both HoFH and HeFH forms [7] and can be fatal [8]. The type of aortic damage has evolved from supra-valvular aortic stenosis before statins were introduced, to valvular aortic stenosis following the widespread use of statins [9].

Valvulopathy associated with hypercholesterolaemia occurs mainly in the left-sided valves, especially the aortic valve, and one of the early signs is aortic regurgitation. The prevalence of AoVC in HeFH ranges from 33–41% [4,5,10] and aortic valve stenosis (AVS) from 31–39% [11,12]. The damage caused by elevated cholesterol in familial hypercholesterolaemia is similar to age-related "degenerative" calcific aortic stenosis observed in individuals without familial hypercholesterolaemia [6]. In a study by Fahed et al. [12], AVS was found to exist without necessarily AoVC, but this study was based on echocardiograms, which are less sensitive than cardiac computed tomography (CT) scanning in detecting AoVC. It seems that in HoFH, the aortic valve is injured by the extremely high concentrations of cholesterol over a relatively short period, whereas in HeFH additional risk factors are required to develop a valvulopathy, leading to a later expression [6]. This leads to the question of how hypercholesterolaemia and AoVC interact and which factors are involved (Fig. 1).

In a study involving 192 individuals (mean age 68 years) Messika-Zeitoun et al. [3] observed that low-density lipoprotein cholesterol (LDL-C) concentration was higher in individuals who developed AoVC de novo versus those who remained free of AoVC, and that faster progression of pre-existing AoVC was linked to higher baseline AoVC score. Gert-Jane et al. [5] showed that in individuals with HeFH, AoVC extent evaluated by the Agatston score using cardiac CT was associated with age, untreated maximum LDL-C, low-density lipoprotein receptor-negative mutational HeFH and diastolic blood pressure, whereas sex, smoking, hypertension, diabetes and obesity were not associated with AoVC burden. The authors also reported that < 4% of individuals without coronary artery calcifications (CAC) had AoVC, but > 39% of those without AoVC had CAC [5]. Rallidis et al. [13] found that age, elevated total cholesterol and elevated LDL-C at diagnosis were associated with aortic valve thickening. In another study involving 112 individuals, aortic peak velocity (V_{max}) and AoVC correlated with untreated LDL-C concentration [14]. Moreover, many studies found that cholesterol year score (CYS) was a significant independent predictor for the development of AVS and AoVC [4,11,13]. Finally, duration of statin use and treated LDL-C concentrations were inversely associated with extent of AoVC[4–6]. Mean aortic valve gradient deteriorated with age and at a faster rate in HeFH individuals than in controls [14].

Vongpromek et al. [4] showed that lipoprotein(a) concentration was positively correlated with the presence and severity of AoVC. In fact, lipoprotein(a) is a major carrier of oxidized phospholipids. Oxidized phospholipids have been established as a causal risk factor for AVS in several genetic and population studies [15]. Moreover, lipoprotein(a) is associated with AVS and AoVC progression, along with oxidized phospholipid–apolipoprotein B [16,17]. Together, these studies highlight that lipoprotein(a) and its cargo, oxidized phospholipids, are involved in the development of AVS and AoVC. Moreover, in the FOURIER trial, lipoprotein(a) was independently associated with aortic stenosis whereas LDL-C corrected for lipoprotein(a) concentration was not [18]. Altogether, the role of lipoprotein(a) in the progression of AVS and AoVc and its association with aortic stenosis events may be a key target for the prevention of AVS and aortic valve regurgitation.

4. When and how to screen for AVS in familial hypercholesterolaemia?

The need for early screening is undeniable to prevent AVS complications. Meanwhile, stabilizing or slowing progression of AoVC or AVS remains a medical challenge. Early control of LDL-C and other vascular risk factors associated with the development of AVS may be beneficial.

Clinical examination must be the first step during each consultation when searching for aortic murmur. However, transthoracic echocardiography (TTE) should be systematically performed–it is widely available, cost-effective and does not require X-rays. TTE should be performed in children with HoFH as they are at higher risk of AoVC and AVS earlier than children with HeFH due to the very high concentrations of LDL-C. As suggested by Fahed et al. [12], annual TTE follow-up in the presence of AoVC or AVS and every 2 years in the absence of AoVC or AVS should be recommended in adults with familial hypercholesterolaemia (Fig. 2). Furthermore, AoVC could be used as a marker of subclinical coronary artery disease, leading to more intense risk factor management.

5. Role of aortic CT scans

Aortic CT scans are efficient in detecting AoVC [18] but expose the patient to irradiation, limiting their use, particularly in the young population. However, the development of new CT scans associated with the measurement of CAC score and coronary CT angiogram exploring coronary artery disease with lower levels of irradiation may change the usual follow-up with TTE in the near future.

We suggest evaluation by CT scan and TTE initially in very high-risk adults with familial hypercholesterolaemia to detect AoVS (including patients with HoFH, with multiple vascular risk factors, high CYS, elevated lipoprotein(a) concentration and low duration of

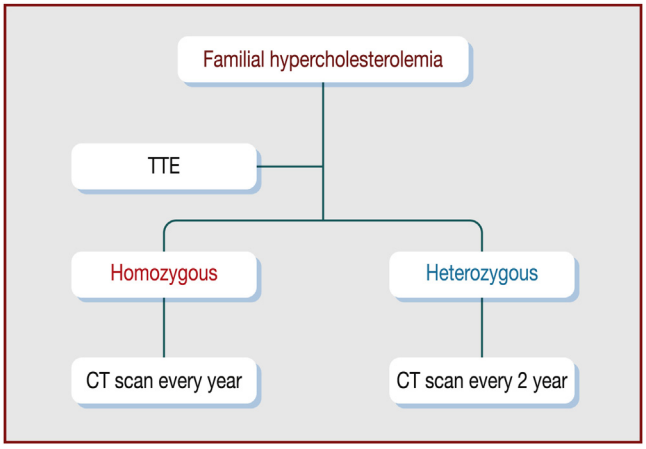

Fig. 2. Proposal of transthoracic echocardiography and CT scan follow up for familial hypercholesterolemia subjects. CT: computed tomography; TTE: transthoracic echocardiography.

exposure to statins). Both examinations appear necessary to detect aortic stenosis without calcifications [12].

6. How to prevent aortic valve stenosis in familial hypercholesterolaemia?

Statin therapy has failed to prevent the evolution of AoVC to aortic stenosis [18].

In a post-hoc analysis of the FOURIER trial [19], aortic stenosis events (defined as site-reported adverse events of new or worsening AVS or aortic valve replacement) occurred in 63 patients over a median follow-up of 2.2 years. The authors found that the overall hazard ratio (HR) for AVS events with evolocumab was 0.66 [95% confidence interval (CI), 0.40–1.09], with no apparent association in the first year (HR, 1.09, 95% CI, 0.48–2.47) but with an HR of 0.48 (95% CI, 0.25–0.93) after the first year of treatment.

In a recent meta-analysis [20], AVS was less prevalent in carriers of the *PCSK9 R46L* variant. PCSK9 is produced and secreted by aortic valves. In vitro, PCSK9 inhibition may lower calcification in aortic valves cells. Therefore, PCSK9 inhibition could present a potent therapeutic strategy for preventing or stabilizing AVS.

New anti-lipoprotein(a) therapy using siRNA or oligonucleotide antisense may be a promising treatment for this challenge. The Lp(a)FRONTIERS CAVS study (NCT0564638) will enrol 500 subjects with mild aortic valve stenosis into a randomized, double-blind, placebo-controlled, multicentre trial assessing the effect of lipoprotein(a) lowering with pelacarsen (TQJ230) on the progression of calcific AVS.

7. Conclusions

AVS prevention remains an important unmet medical need. Individuals with familial hypercholesterolaemia are at higher risk of AVS and aortic valve replacement, which is associated with longer and higher exposure to raised concentrations of LDL-C but also to higher concentrations of lipoprotein(a). There is an urgent need for aortic valve stratification in familial hypercholesterolaemia using regular TTE. Recommendations on the role of aortic CT scanning must be defined. No pharmacological therapies can slow or revert AVS. New treatments using PCSK9 or lipoprotein(a) inhibitors may be promising options for slowing the progression of AVS, with important question on when to start these therapies in the life course of individuals with familial hypercholesterolaemia to better prevent AVS.

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Disclosure of interest

The authors declare that they have no competing interest.

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