JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 24, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.09.087

ORIGINAL INVESTIGATIONS

Increased Aortic Valve Calcification in Familial Hypercholesterolemia

Prevalence, Extent, and Associated Risk Factors

Gert-Jan R. ten Kate, MD,*†‡ Sven Bos, MD,§ Admir Dedic, MD,*†‡ Lisan A. Neefjes, MD, PhD,*†‡ Akira Kurata, MD, PhD,* Janneke G. Langendonk, MD, PhD,§ Anho Liem, MD, PhD,¶ Adriaan Moelker, MD, PhD,* Gabriel P. Krestin, MD, PhD,* Pim J. de Feyter, MD, PhD,*‡ Jeanine E. Roeters van Lennep, MD, PhD,§ Koen Nieman, MD, PhD,*‡ Eric J. Sijbrands, MD, PhD§

ABSTRACT

BACKGROUND Familial hypercholesterolemia is typically caused by LDL receptor (LDLR) mutations that result in elevated levels of LDL cholesterol (LDL-C). In homozygous FH, the prevalence of aortic valve calcification (AoVC) reaches 100% and is often symptomatic.

OBJECTIVES The objective of this study was to investigate the prevalence, extent, and risk-modifiers of AoVC in heterozygous FH (he-FH) that are presently unknown.

METHODS Asymptomatic patients with he-FH and 131 non-familial hypercholesterolemia controls underwent CT computed tomography calcium scoring. AoVC was defined as the presence of calcium at the aortic valve leaflets. The extent of AoVC was expressed in Agatston units, as the AoVC-score. We compared the prevalence and extent of AoVC between cases and controls. In addition, we investigated risk modifiers of AoVC, including the presence of LDLR mutations without residual function (LDLR-negative mutations), maximum untreated LDL-cholesterol (maxLDL), LDL-C, blood pressure, and coronary artery calcification (CAC).

RESULTS We included 145 asymptomatic patients with he-FH (93 men; mean age 52 ± 8 years) and 131 non-familial hypercholesterolemia controls. The prevalence (%) and AoVC-score (median, IQR) were higher in he-FH patients than in controls: 41%, 51 (9–117); and 21%, 21 (3–49) ($p < 0.001$ and $p = 0.007$). Age, untreated maxLDL, CAC, and diastolic blood pressure were independently associated with AoVC. LDLR-negative mutational he-FH was the strongest predictor of the AoVC-score (OR: 4.81; 95% CI: 2.22 to 10.40; $p = <0.001$).

CONCLUSIONS Compared to controls, he-FH is associated with a high prevalence and a large extent of subclinical AoVC, especially in patients with LDLR-negative mutations, highlighting the critical role of LDL-C metabolism in AoVC etiology. (J Am Coll Cardiol 2015;66:2687–95) © 2015 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the *Department of Radiology, Erasmus Medical Centre, Rotterdam, the Netherlands; †Interuniversitair Cardiologisch Instituut Nederland, Utrecht, the Netherlands; ‡Department of Cardiology, Thorax Centre Rotterdam, Rotterdam, the Netherlands; §Department of Internal Medicine, Erasmus Medical Centre Rotterdam, Rotterdam, the Netherlands; and the ¶Department of Cardiology, Sint Franciscus Gasthuis, Rotterdam, the Netherlands. This work was supported by grant 2006T102 from the Dutch Heart Foundation and the Interuniversitair Cardiologisch Instituut Nederland. Dr. Krestin has served as a consultant for Bracco Diagnostics. Dr. Nieman has received institutional research support from Siemens Medical Solutions, GE Healthcare, and Bayer Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. ten Kate and Bos contributed equally to this work.

Manuscript received September 4, 2015; revised manuscript received September 24, 2015, accepted September 28, 2015.

ABBREVIATIONS AND ACRONYMS

AoVC = aortic valve calcification

CAC = coronary artery calcification

CAD = coronary artery disease

CT = computed tomography

FH = familial hypercholesterolemia

he-FH = heterozygous familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

LDLR = low-density lipoprotein receptor

maxLDL = maximum low-density lipoprotein cholesterol

NACP = nonanginal chest pain

Aortic valve calcification (AoVC) has an estimated prevalence of >50% in the elderly (i.e., those aged >75 years) and is associated with an elevated risk of coronary (72%) and cardiovascular (50%) events (1,2). In addition, the degree of AoVC correlates with severity of stenosis, disease progression, and the development of coronary and cardiovascular events (3–5).

In the general population, AoVC is associated with age, male sex, smoking, hypertension, diabetes, obesity, and hypercholesterolemia (6,7). Patients with familial hypercholesterolemia (FH) have extremely high levels of low-density lipoprotein cholesterol (LDL-C) and may be at high risk for developing AoVC. FH is an autosomal inherited disorder caused by mutations in the LDL receptor (*LDLR*) gene, the apolipoprotein B (*APOB*) gene, or the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene (8). LDLR mutations can be classified as mutations with residual LDLR function (LDLR-defective mutations) or without LDLR function (LDLR-negative mutations) (9).

SEE PAGE 2696

In patients who are homozygous for FH, the prevalence of AoVC reaches 100%, and surgical intervention of functional valvular disease is often needed (10,11). Compared with homozygous FH, heterozygous familial hypercholesterolemia (he-FH) is associated with less aortic valve dysfunction on echocardiography (12–15). However, the prevalence of AoVC in he-FH is unknown.

The purpose of the present single-center study was to determine the prevalence and extent of AoVC in asymptomatic statin-treated patients, heterozygous for FH. In addition, we evaluated which variables were associated with the presence and extent of AoVC. In the molecular context of the patients, AoVC was compared between he-FH patients with and without LDLR-negative mutations.

METHODS

STUDY POPULATION. Between February 2008 and June 2011, a total of 145 consecutive patients with he-FH were included in the study. Between November 2006 and January 2011, we also included 131 consecutive patients with nonanginal chest pain (NACP) as a control group. Patients with NACP were used as a substitute for asymptomatic patients without he-FH because the radiation exposure limits the choice of control subjects to patients with an indication for cardiac computed tomography (CT) scanning.

Patients with NACP were referred by their general practitioner for the evaluation of chest pain and underwent stress testing and cardiac CT scanning. They had no history of coronary artery disease (CAD). NACP was defined as chest pain or discomfort that was not provoked by exertion or emotional stress or relieved by rest or nitroglycerin (16).

Patients with he-FH were recruited from our tertiary outpatient lipid clinic. he-FH was determined either by the presence of a confirmed *LDLR* or *APOB* gene mutation (the patients did not have *PCSK9* mutations) or clinically as having untreated LDL-C levels above the 95th percentile for sex and age in combination with at least 1 of the following: the presence of typical tendon xanthomas in the patient or a first-degree relative; an LDL-C level above the 95th percentile for sex and age in a first-degree relative; or proven CAD in a first-degree relative aged <60 years (17).

DNA samples were taken of all patients with a clinical suspicion of he-FH and were sent to a central laboratory for mutational screening (18). A complete overview of the mutations found and clinical characteristics of both LDLR-negative and LDLR-defective he-FH has been published previously (19). Plasma lipid levels were measured by using the fasting blood samples at the time of inclusion. Cholesterol levels before statin treatment were obtained from patient medical records, and they were used as the variable untreated maximum total cholesterol and untreated maximum low-density lipoprotein cholesterol (maxLDL).

Exclusion criteria were: symptoms of CAD, history of CAD, rheumatic fever, or known aortic valve pathology (although cardiac ultrasounds were not routinely performed before study inclusion). Patients with a secondary cause of hypercholesterolemia (e.g., renal, liver, or thyroid disease) were also excluded from the study. Further exclusion criteria were renal insufficiency (serum creatinine >120 μmol/l), known contrast allergy, and irregular heart rhythm (atrial fibrillation). In patients with asymptomatic he-FH, the inclusion age was 40 to 70 years for men; women were included if they were older than childbearing age because of potential radiation-induced harm to the fetus or ovaries. Women's inclusion age was thus 45 to 70 years.

This study complied with the Declaration of Helsinki, and the institution's human research committee approved the study protocol. All patients provided written informed consent.

CT CALCIUM SCORE. To quantify the AoVC, as well as the coronary calcium score, a cardiac CT scan without contrast medium was performed, which enabled