The role of LDL cholesterol on excess risk of aortic valve stenosis: a prospective registry study in familial hypercholesterolemia

Liv J. Mundal MD, PhD[1], Anders Hovland MD, PhD[2,3] , Morten Vetrhus, MD, PhD Jannicke Igland PhD[4,5], Marit B. Veierød PhD[7], Kirsten B. Holven PhD[6,8], Martin Prøven Bogsrud MD, PhD[8,9], Grethe S. Tell MPH, PhD[5,10], Trond P. Leren MD, PhD[9], Kjetil Retterstøl MD, PhD[1,6]

[1]The Lipid Clinic, Oslo University Hospital, Oslo, Norway,[2]Division of Internal Medicine, Nordland Hospital, Bodø, Norway, [3]Department of Clinical Medicine, University of Tromsø, Tromsø, Norway, [4]Department of Health and Social Science, Centre for Evidence-Based Practice, Western Norway University of Applied Science, Bergen, Norway, [5]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway, [6]Department of Nutrition, University of Oslo, Oslo, Norway, [7]Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, University of Oslo, Oslo, Norway, [8]National Advisory Unit on Familial Hypercholesterolemia, Oslo University Hospital, Oslo, Norway, [9]Unit for Cardiac and Cardiovascular Genetics, Oslo University Hospital, Oslo, Norway, [10]Division of Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway.

Corresponding author:

Anders Hovland

Division of Internal Medicine

Nordland Hospital

N-8092 Bodø

Telephone: +4775534000

E-mail : anders.w.hovland@gmail.com

Keywords: Familial hypercholesterolemia; LDL-cholesterol; aortic valve stenosis.

Manuscript word count (excluding cover page, references, acknowledgements, table): 1453.

Revision date : 8 August 2019.

Key points

Question: Is patients with genetically proven familial hypercholesterolemia at excess risk of aortic valve stenosis compared to the general population?

Findings: In this registry-based, prospective cohort study of all Norwegian genotyped patients with familial hypercholesteremia, during 18300 person years follow-up, we demonstrate an increased incidence of aortic valve stenosis compared to the total Norwegian population stratified by sex and age. The standardized incidence ratio (95% CI) for patients with familial hypercholesterolemia was 7.9 (6.1-10.4).

Meaning: In this prospective cohort study we demonstrated a significant higher incidence of aortic valve stenosis in patients with familial hypercholesterolemia compared to the total Norwegian population.

Tweet: Persons with familial hypercholesterolemia have increased risk of aortic valve stenosis.

Twitter handle: @AWHovland

IMPORTANCE

Aortic valve stenosis (AS) is the most common valve disease. Elevated levels of low-density lipoprotein (LDL)-cholesterol is a risk factor, however, lipid-lowering treatment seems not to prevent progression of AS. The importance of LDL-cholesterol in the development of AS thus remain unclear. People with familial hypercholesterolemia (FH) have elevated LDL-cholesterol levels from birth and until lipid lowering treatment starts. Thus, FH may serve as a "model disease" to study the importance of LDL-cholesterol for the development of AS.

OBJECTIVE

To relate the incidence of AS per year in all genetically proven FH patients in Norway to the incidence of these diseases in the total Norwegian population of about 5 million people.

DESIGN

This is a registry-based prospective cohort study.

SETTING

Study of all Norwegian FH patients with regard of first time AS during 2001-2009.

PARTICIPANTS

All genotyped patients with FH in Norway were compared to the total Norwegian populations through linkage with the Cardiovascular Disease in Norway project and the Norwegian Cause of Death Registry regarding occurrence of first-time AS.

MAIN OUTCOMES AND MEASURES

Standardized incidence ratios (SIRs).

RESULTS

In total, 53 cases of AS occurred among 3161 persons (46.6% men) with FH during 18300 person years of follow-up. Mean (range) age at inclusion and at time of AS were 39.9 (8-91) and 65 (44-88) years, respectively. Total SIR (95% CI) for women and men combined was 7.9 (6.1-10.4), 8.5 (5.8-12.4) in women and 7.4 (5.0-10.9) in men respectively, indicating marked increased risk of AS compared to the general Norwegian population.

CONCLUSIONS AND RELEVANCE

In this prospective registry study we demonstrate a marked increase in risk of AS in persons with FH.

Aortic valve stenosis (AS) is the most common valvular disease in the western world. The underlying pathophysiology of AS is divided into an *initiation* phase resembling atherosclerosis including lipid infiltration, oxidation and inflammation and a *propagation* phase characterized by fibrosis and calcification.[1] Even if low-density lipoprotein (LDL)-cholesterol may be important in the initiation phase, lipid lowering therapy with statins and ezetimibe has been unsuccessful in halting the disease.[2]

Familial hypercholesterolemia (FH) is a disorder with increased levels of LDL-cholesterol and increasing the risk of atherosclerotic diseases, in particular coronary heart disease.[3] In the severe homozygous form of FH, AS is seen frequent and more often in null mutations with even higher LDL-cholesterol than in defective mutations.[4] The risk of AS in heterozygous FH mutation carriers is not known. The current study was designed as a prospective registry study to assess the risk of AS in a large cohort of genetically verified heterozygous FH patients compared with the total Norwegian population.

Methods

The study was approved by the Regional Committee for Medical and Health Research Ethics, and the cohort, study design and methods have been described previously.[3]

In brief, this is a registry-based prospective cohort study of all genotyped patients with FH in Norway. Characteristics of 714 out of the 3161 patients in the FH cohort have been reported previously in a retrospective study on collection of data from medical charts.[5] These subjects had been followed at a lipid clinic for 11.1 (7.9) years and 89 % subjects were treated with statin and 58% received ezetimibe with an achieved LDL-cholesterol of mean (SD) 3.4 (1.3) mmol/L (131 (50) mg/dL.

All patients with genetically diagnosed FH in Norway are included in the National UCCG Registry after written informed consent. This registry was coupled with all hospitalizations in Norway during 1994–2009 for AS from the Cardiovascular Disease in Norway project (CVDNOR, http:// www.cvdnor.no), a collaborative project between the University of Bergen and the Norwegian Knowledge Centre for the Health Services. We obtained data regarding death from the Norwegian Cause of Death Registry (NCoDR) containing information on date and cause of death (underlying, contributing and immediate causes) for all deaths among Norwegian residents.

We followed patients for endpoints through linkage with the NCoDR and CVDNOR by using the unique personal identification number for each Norwegian resident. Data were given according to the International Classification of Diseases, version 9 (ICD9) or version 10 (ICD10), (AS: ICD9: 424.1, ICD10: I35.0, I35.2). Aortic valve replacements were coded according to Nordic Medico-Statistical Committee (NOMESCO) classification for medical procedures (NCMP): FMD00, FMD10, FMD12, FMD13, FMD20, FMD96).

Persons were followed from time of FH diagnosis until the first occurrence of AS, death from other causes or December 31th 2009, whichever occurred first. Similarly, we also calculated time to the first occurrence of valve replacement. To analyze the first time events only, we required 7 years of observation free of events prior to the start of follow-up. Incidence rates were thus calculated for the period 2001-2009 among persons with FH aged 25 and above. We calculated unadjusted incidence rates for each endpoint (AS diagnosis and valve replacement) in 2001-2009 stratified by sex and age. For each age stratum, the incidence rates were calculated as the number of events per 1000 person-years of follow-up for FH patients and the entire Norwegian population. We calculated standardized incidence ratios (SIR)s for each endpoint using indirect standardization with incidence rates for the total Norwegian

population as reference rates.[6] Expected number of incident events was calculated for each combination of 1-year age group and calendar year in the UCCG Registry as time spent in the cohort multiplied by the incidence rate for the same combination of birth year and calendar year in the total Norwegian population. Calculations were performed for men and women separately and in combination. Total expected number of incident events were obtained by summing expected number of events over 1-year age groups and calendar years. SIR was calculated as the observed number of events divided by the expected number of events. Confidence limits were obtained using the normal approximation to the Poisson distribution.

Results

In total, 53 cases of AS occurred among 3161 persons (46.6% men) with FH during 18300 person years of follow-up. Mean (range) age at inclusion (date of genetic FH diagnosis) and AS (date of first AS diagnosis) were 39.9 (8-91) and 65.0 (44-88) years, respectively. Total SIR (95% CI) for women and men combined was 7.9 (6.1-10.4), 8.5 (5.8-12.4) in women and 7.4 (5.0-10.9) in men respectively, indicating marked increased risk of AS compared to the general Norwegian population (Table 1). In the FH group the total SIR (95% CI) for aortic valve replacements was 7.7 (5.2-11.5), and SIR was significant for both women and men (Table 2).

Discussion

As far as we know, this is the largest, prospective registry study to date demonstrating increased risk of AS in persons with FH compared to the general population. The estimated SIR of 7.9, is higher than we previously have demonstrated for coronary artery disease, heart failure, atrial fibrillation and cerebrovascular disease.[3,7,8] Furthermore, the significant increased risk of aortic

valve replacements in the FH group, indicates that the AS are severe, and in need of surgical treatment.

Acknowledging the contribution of age to the risk of AS, mean age at hospitalization for AS was 65 years in our cohort of FH mutation carriers. In an epidemiological study from Norway the prevalence of AS was 0.2% in the 50-59 years cohort, 1.3% in the 60-69 years cohort and 3.9% in the 70-79 years cohort.[9] Previously, Ten Kate et al have demonstrated increased aortic valve calcification assessed by cardiac computed tomography in asymptomatic, heterozygous FH patients (mean age 52 years) when compared to controls.[10] A large mendelian randomization study found that genetic predisposition of high LDL-cholesterol increased the risk of aortic valve calcification and AS.[11] Our data support that increased LDL-cholesterol due to FH may indeed increase the risk of AS. Although LDL-cholesterol lowering therapy have failed to reduce the risk in established AS, the importance of LDL-cholesterol in AS development suggests that early initiation of LDL-cholesterol lowering therapy could prevent development of AS. Persons with FH with increased incidence of AS could be an ideal group to test this hypothesis in prospective studies. Whether other patient groups with increased risk of AS including those with bicuspid aortic valves, would benefit from lipid lowering therapy remains unknown. An European consensus on FH states that one could screen for asymptomatic coronary artery disease, AS, however is not mentioned.[12] Our finding of increased risk of AS in heterozygous FH might indicate a need for some form of echocardiographic evaluation in this large patient group.

Strengths and limitations

All AS hospitalizations and the corresponding reported AS related deaths from the NCoDR for the entire Norwegian population during 2001-2009 were included. Data on all registered

AS hospitalizations in Norway were included in the analyses, but there is always a risk of misclassification due to errors in diagnostic coding at the hospitals. We do not know about any validation studies on the accuracy of the AS diagnosis in Norwegian hospital data. We do however not expect the rate of misclassification to differ between persons with and without FH. Important risk factors for AS were not accounted for, that is, smoking habits, body mass index, LDL-cholesterol values, lipoprotein(a) values, statin treatment, other lipid lowering treatment, dietary habits. There might be a detection bias as FH patients may have closer monitoring possible leading to detection of murmurs and hence echocardiography, leading to detection of AS. Patients with homozygous FH are well known for having an increased risk of AS. Three of the 3161 patients in our total FH population were homozygous. We were not able to exclude them from the analyses because they were not flagged in the anonymized data file. In a sensitivity analysis were we excluded the three AS-cases with shortest time from baseline to AS-diagnosis (as a worst-case scenario) the total SIR was reduced from 7.9 to 7.5. Since all the three homozygous probably do not have AS the true bias caused by inclusion of the three homozygous FH patients is even smaller.

Selection bias is important in register studies. Participants in the present study account for almost one-third of the total number of patients diagnosed with a pathogenic FH mutation in Norway, given a prevalence of 1:300. This large proportion of the total number reduce the possibility of any major selection bias. Testing is free of charge for physicians and patients in Norway, probably reducing the risk of bias due to economic reasons.

Conclusions

In this prospective registry study, spanning more than 18000 person years, we demonstrate a marked increase in risk of AS in persons with FH.

Acknowledgements

We thank the patients for allowing us to study the data presented here, and in particular Margaretha Hamrin for the important contribution in leading the patient organization FH Norway (FH-Norge) and for being editor of the bi-annual FH-magazine (http://www.f-h.no/). We thank referring physicians for many years of shipping samples for testing and the staff at the UCCG and at the Lipid Clinic in Oslo. We thank Tomislav Dimoski at the Norwegian Institute of Public Health, Oslo, Norway for developing the software necessary for obtaining data from Norwegian hospitals, conducting the data collection and quality assurance of data in this project. We thank Dr. Leiv Ose who established the Lipid Clinic in Oslo and headed the clinic for more than 30 years. Without his great efforts in the field of FH, this article would not have been possible. We have obtained written permission to include these names.
This work was funded by the South-Eastern Norway Regional Health Authority, Oslo, Norway, Throne Holst Foundation for Nutrition Research, Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo. The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Jannicke Igland had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

References

1. Peeters FECM, Meex SJR, Dweck MR et al. Calcific aortic valve stenosis: hard disease in the heart: A biomolecular approach towards diagnosis and treatment. *Eur Heart J*. 2018;39(28):2618-2624.

2. Zhao Y, Nicoll R, He YH, Henein MY. The effect of statins on valve function and calcification in aortic stenosis: A meta-analysis. *Atherosclerosis*. 2016;246:318-324.

3. Mundal LJ, Igland J, Veierød MB et al. Impact of age on excess risk of coronary heart disease in patients with familial hypercholesterolaemia. *Heart*. 2018;104(19):1600-1607.

4. Alonso R, Díaz-Díaz JL, Arrieta F et al. Clinical and molecular characteristics of homozygous familial hypercholesterolemia patients: Insights from SAFEHEART registry. *J Clin Lipidol*. 2016;10(4):953-961.

5. Bogsrud MP, Græsdal A, Johansen D et al. LDL-cholesterol goal achievement, cardiovascular disease, and attributed risk of Lp(a) in a large cohort of predominantly genetically verified familial hypercholesterolemia. *Journal of Clinical Lipidology*. 2019;13(2)279-286.

6. Kirkwood BR, Sterne JAC. Essential medical statistics. 2 Rev Ed: Wiley-Blackwell 2003:268-270)

7. Hovland A, Mundal LJ, Igland J et al. Increased risk of heart failure and atrial fibrillation in heterozygous familial hypercholesterolemia. *Atherosclerosis*. 2017;266:69-73.

8. Hovland A, Mundal LJ, Igland J et al. Risk of Ischemic Stroke and Total Cerebrovascular Disease in Familial Hypercholesterolemia. *Stroke*. 2019;50(1):172-174.

9. Eveborn GW, Schirmer H, Heggelund G et al. The evolving epidemiology of valvular aortic stenosis. The Tromsø Study. *Heart*. 2013;99(6):396-400.

10. Ten Kate GR, Bos S, Dedic A et al. Increased Aortic Valve Calcification in Familial Hypercholesterolemia: Prevalence, Extent, and Associated Risk Factors. *J Am Coll Cardiol*. 2015;66(24):2687-2695.

11. Smith JG, Luk K, Schulz CA et al. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. *JAMA*. 2014;312(17):1764-1771.

12. Nordestgaard BG, Chapman MJ, Humphries SE et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. *Eur heart J* .2013;34(45):3478-3490a.

Table 1. Incidence rate and standardized incidence ratios (SIR) for aortic valve stenosis among 3161 persons with genetically verified familial hypercholesterolemia during 2001-2009.

Sex and age	Incident cases	Person years in 1000	Crude incidence rate per 1000 person years (95% CI)	Expected number of cases	SIR (95% CI)*
Total 25-49	3	11.5	0.3 (0.08-0.8)	0.5	**6.3 (2.0-19.4)**
Total 50-69	28	5.9	4.8 (3.3-6.9)	2.8	**9.9 (6.8-14.3)**
Total 70+	22	0.9	25.1 (16.5-38.0)	3.4	**6.5 (4.3-9.9)**
Total 25+	53	18.3	2.9 (2.2-3.8)	6.7	**7.9 (6.1-10.4)**
Women 25-49	2	6.0	0.3 (0.1-1.3)	0.1	**13.8 (3.4-55.1)**
Women 50-69	8	3.2	2.5 (1.3-5.0)	1.0	**7.7 (3.9-15.5)**
Women 70+	17	0.5	31.5 (19.6-50.7)	2.0	**8.5 (5.3-13.7)**
Women 25+	27	9.7	2.8 (1.9-4.1)	3.2	**8.5 (5.8-12.4)**
Men 25-49	1	5.5	0.2 (0.0-1.3)	0.3	3.0 (0.4-21.2)
Men 50-69	20	2.7	7.5 (4.8-11.6)	1.8	**11.1 (7.1-17.2)**
Men 70+	5	0.3	14.8 (6.1-11.6)	1.4	**3.6 (1.5-8.8)**
Men 25+	26	8.6	3.0 (2.1-4.5)	3.5	**7.4 (5.0-10.9)**

*Age- and sex-standardized using incidence rates for the total Norwegian population during 2001-2009 in 1-year age groups as reference rates
SIR: standardized incidence ratio. Bold text denotes statistical significance.

Table 2.. Incidence rate and standardized incidence ratios (SIR) for aortic valve replacements among 3161 persons with genetically verified familial hypercholesterolemia during 2001-2009.

	Incident cases	Person years in 1000	Crude incidence rate per 1000 person years (95% CI)	Expected number of cases	SIR (95%CI)*
Total 25+	24	18.4	1.3 (0.9-1.9)	3.1	**7.7 (5.2-11.5)**
Women 25+	14	9.8	1.4 (0.8-2.4)	1.2	**11.4 (6.8-19.3)**
Men 25+	10	8.6	1.2 (0.6-2.1)	1.9	**5.3 (2.9-9.9)**

*Age- and sex-standardized using incidence rates for the total Norwegian population during 2001-2009 in 1-year age groups as reference rates
SIR: standardized incidence ratio. Bold text denotes statistical significance.