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RESEARCH LETTER
Peripheral Arterial Disease

Increased risk of peripheral artery disease in persons with familial hypercholesterolaemia: a prospective registry study

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Peripheral artery disease (PAD) is associated with a cluster of traditional risk factors for atherosclerosis such as smoking, diabetes, and elevated cholesterol.[1,2] The isolated role of low-density lipoprotein (LDL) cholesterol in the development of PAD is less clear. However, the recent 2019 European Guidelines for the Management of Dyslipidemias state that patients with PAD are considered high risk of new cardiovascular events and LDL cholesterol should be lowered to below 55 mg/dL (1.4 mmol/L).[3]

In this study, we aimed to study the isolated role of LDL cholesterol in the development of PAD. Familial hypercholesterolaemia (FH) could be considered as a 'model disease' for studying the effect of LDL cholesterol on atherosclerosis, and thus the development of PAD. This is particularly important as persons with FH have elevated LDL cholesterol due to mutation rather than lifestyle. The primary aim of this prospective cohort study was to compare the incidence of hospitalization for PAD in persons with a proven FH mutation to the incidence in the total Norwegian population of ~5 million people, adjusted for age, sex, and calendar years.

The Regional Committee for Medical and Health Research Ethics approved the study, and the study design and methods have been described previously.[4] Briefly, this is a registry-based prospective cohort study including 4489 persons ≥25 years with a genetically verified FH during 1992–2009.

Peripheral artery disease was defined according to the International Classification of Diseases, version 9 (ICD9: 440 and 443) or version 10 (ICD10: 170 and 173). Information on hospitalizations due to PAD was obtained from the Cardiovascular Disease in Norway Project (www.cvdnor) and death (date and cause) was obtained from the Cause of Death Registry.[5] Data on hospitalizations were obtained for the period 1994–2009, but to make sure that the study population was free of PAD at start of follow-up, we used 1994–2000 as a washout period to search for previous events and estimated incidence rates and SIR for the period 2001–2009. Persons with PAD or death before 2001 were excluded. After exclusion, the cohort contained 3162 persons. Persons were followed from 1 January 2001 or the time of FH diagnosis (if FH diagnosis after 1 January 2001) until the first hospitalization with PAD as primary or secondary diagnosis, death from other causes or 31 December 2009, whichever occurred first. We calculated standardized incidence ratios (SIRs) for PAD as the ratio of observed to expected number of cases using indirect standardization with incidence rates for the total Norwegian population in 1-year age groups (obtained from the Cardiovascular Disease in Norway project) as reference rates.[6]

A total of 40 patients were hospitalized due to PAD in the FH cohort (*Table 1*). Risk of PAD was nearly tripled in the FH cohort compared to the total Norwegian population, and increased risks were found both in women [SIR = 3.2, 95% confidence interval (CI) (2.0–5.0)] and men [SIR = 2.7, 95% CI (1.8–4.1)].

As far as we know, this is the largest prospective registry of persons with genetically confirmed FH and thus with high levels of LDL cholesterol from birth. Pereira *et al.*[7] studied 202 persons with genetically confirmed heterozygous FH (mean age 51 years) and 524 controls from the 'Heart of Brazil Project' (mean age 43 years) and found PAD

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Table 1 Incidence rates and standardized incidence ratios for peripheral artery disease during 2001–2009 among 3162 persons with familial hypercholesterolaemia in Norway

Sex and age group	Incident cases	Person-years in 1000	Crude incidence rate per 1000 person-years (95% CI)	Expected number of cases	SIR (95% CI)
Women					
25–49	3	6.0	0.5 (0.2–1.6)	0.6	4.9 (1.6–15.1)
50–69	11	3.2	3.4 (1.9–6.2)	3.0	3.6 (2.0–6.6)
70+	5	0.6	8.2 (3.4–19.6)	2.3	2.2 (0.9–5.2)
Total	19	9.8	1.9 (1.2–3.0)	6.0	3.2 (2.0–5.0)
Men					
25–49	6	5.5	1.1 (0.5–2.4)	0.7	8.7 (3.9–19.3)
50–69	12	2.7	4.5 (2.5–7.9)	4.9	2.5 (1.4–4.3)
70+	3	0.4	8.4 (2.7–26.0)	2.2	1.4 (0.4–4.2)
Total	21	8.6	2.4 (1.6–3.8)	7.8	2.7 (1.8–4.1)
Men and women combined					
25–49	9	11.5	0.8 (0.4–1.5)	1.3	6.9 (3.6–13.2)
50–69	23	5.9	3.9 (2.6–5.9)	7.9	2.9 (1.9–4.4)
70+	8	1.0	8.3 (4.1–15.5)	4.5	1.8 (0.9–3.5)
Total	40	18.3	2.2 (1.6–3.0)	13.7	2.9 (2.1–4.0)

CI, confidence interval; SIR, standardized incidence rate.

(diagnosed by ankle-brachial index) in 17.3% of the FH patients compared to 2.3% in the controls. Perez de Isla *et al.*[8] studied 2752 genetically confirmed FH persons (mean age 44 years) with 993 unaffected relatives (mean age 40 years) and observed PAD (symptoms and signs of PAD or revascularization for PAD) in 39 (1.2%) of the FH persons compared to 2 (0.2%) in the control group. Using clinical criteria for FH, Emanuelsson *et al.*[9] found increased odds of PAD (ICD diagnose and/or PAD symptoms and/or ankle-brachial index) in persons with probable or definitive FH (mean age 59 years) compared to unlikely FH (mean age 54 years) in the Copenhagen General Population Study [Odds Ratio (OR) = 1.36, 95% CI (1.00–1.84)]. These earlier studies indicate an increased risk of PAD in persons with FH. The present prospective registry study adds further information indicating increased risk of PAD in all age groups and both sexes, but especially in persons younger than 50 years.

Data on all PAD hospitalizations in Norway were included in the analyses, but some misclassification may have occurred due to errors in diagnostic coding at the hospitals. We do not know of validation studies on the accuracy of the PAD diagnosis in Norwegian hospital data. However, we do not expect misclassification to differ between persons with and without FH. The estimated prevalence of FH is 1 in 250 persons in Norway; participants in the present cohort therefore account for almost one-third of the total number of FH in Norway. The risk of selection bias is reduced as such a large proportion of all FH cases are included in the study. The fact that secondary diagnoses of PAD are also included could also be a bias, as patients with FH may be more prone to be evaluated for PAD. Other risk factors including smoking status, diabetes, and hypertension are not available for this cohort, but our group has previously demonstrated that Norwegian FH patients have lower levels of smoking-associated cancer, possibly indicating a healthier lifestyle.[10] Lipid-lowering therapy and LDL cholesterol levels are not available in this cohort, but we have previously shown that, in Norwegian normal-risk FH patients, 86% take a statin, and the average LDL cholesterol is 3.5 mmol/L.[11]

In conclusion, we found a three-fold increased risk of hospitalization for PAD in persons with an FH mutation, with no difference between sexes. The excess risk of hospitalization for PAD seemed to be particularly high in FH persons younger than 50 years. These results indicate that a high LDL cholesterol level is important in the development of PAD.

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