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# Accelerated subclinical coronary atherosclerosis in patients with familial hypercholesterolemia

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ABSTRACT

*Objectives:* We determined the extent, severity, distribution and type of coronary plaques in cardiac asymptomatic patients with familial hypercholesterolemia (FH) using computed tomography (CT).
*Background:* FH patients have accelerated progression of coronary artery disease (CAD) with earlier major adverse cardiac events. Non-invasive CT coronary angiography (CTCA) allows assessing the coronary plaque burden in asymptomatic patients with FH.
*Materials and methods:* A total of 140 asymptomatic statin treated FH patients (90 men; mean age 52 ± 8 years) underwent CT calcium scoring (Agatston) and CTCA using a Dual Source CT scanner with a clinical follow-up of 29 ± 8 months. The extent, severity (obstructive or non-obstructive plaque based on >50% or <50% lumen diameter reduction), distribution and type (calcified, non-calcified, or mixed) of coronary plaque were evaluated.
*Results:* The calcium score was 0 in 28 (21%) of the patients. In 16% of the patients there was no CT-evidence of any CAD while 24% had obstructive disease. In total 775 plaques were detected with CT coronary angiography, of which 11% were obstructive. Fifty four percent of all plaques were calcified, 25% non-calcified and 21% mixed. The CAD extent was related to gender, treated HDL-cholesterol and treated LDL-cholesterol levels. There was a low incidence of cardiac events and no cardiac death occurred during follow-up.
*Conclusion:* Development of CAD is accelerated in intensively treated male and female FH patients. The extent of CAD is related to gender and cholesterol levels and ranges from absence of plaque in one out of 6 patients to extensive CAD with plaque causing >50% lumen obstruction in almost a quarter of patients with FH.



## 1. Introduction

Familial hypercholesterolemia (FH) is an inherited autosomal dominant disorder of the lipoprotein metabolism with a prevalence of about 1 in 500 people. FH causes highly elevated serum levels of LDL cholesterol which might accumulate in large and medium sized arteries inducing development of early coronary atherosclerosis [1].

Cardiac CT has evolved as a safe, non-invasive imaging modality to assess coronary atherosclerosis in symptomatic [2,3] and in asymptomatic high-risk patients [4–7]. Detection of subclinical coronary atherosclerosis in patients with FH may provide insights into the accelerated development of coronary artery disease (CAD) in these asymptomatic subjects. Only few studies are available that report about the calcium score or coronary plaque burden in patients with FH [8–10]. Recently we reported the first results of CT coronary angiography (CTCA) in 101 asymptomatic patients with FH, describing the accelerated atherosclerosis in these patients compared to patients with non anginal chest pain [11]. In this present prospective cohort study of an extended patient population of 140 asymptomatic men and women with FH, who have been treated with high dosages of statins, we sought to evaluate in depth not only the CAD severity but also the extent,

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anatomical distribution and plaque composition of subclinical coronary atherosclerosis, using CT-coronary imaging. Additionally we assessed the relation of occult CAD with patient related variables and the occurrence of adverse cardiac events and all cause death during the follow-up period.

## 2. Methods and materials

### 2.1. Study population

Between February 2008 and July 2010 we prospectively invited 214 eligible cardiac asymptomatic statin treated patients with familial hypercholesterolemia to participate in this study as part of continuing recruitment of asymptomatic patients with FH. These patients visit the outpatient preventive clinic of the internal medicine department in our hospital at least once a year for optimization of the medical therapy and early detection of complications. All patients met the criteria for FH according to van Aalst-Cohen et al. [12], which can be summarized as either (1) the presence of a documented LDL-receptor mutation, or (2) an LDL-cholesterol level above the 95th percentile for gender and age in combination with the presence of typical tendon xanthomas in the patient or in a first degree relative, or (3) an LDL-cholesterol level above the 95th percentile for gender and age in a first degree relative or proven CAD in the patient or in a first degree relative under the age of 60. Patients with secondary causes of hypercholesterolemia such as renal, liver, or thyroid disease were excluded. In addition, all participants were asymptomatic for CAD, i.e. absence of symptoms suggestive of ischemic heart disease or history of CAD. Inclusion age for women was between 45 and 70 years, for men between 40 and 70 years. Exclusion criteria for CTCA were renal insufficiency (serum creatinine >120 μmol/l) ($n=4$), known contrast allergy ($n=3$) and irregular heart rhythm (atrial fibrillation) ($n=11$).

Finally 140 patients with FH could be included after written informed consent, 90 men and 50 women, with a mean age $52 \pm 8$ years (range 40–68 years).

The institutional Ethical Review Board approved the study protocol.

During their clinical work-up all patients were genetically screened for a LDL-receptor mutation. Lipid levels were obtained by standard methods in patients that were fasting for at least 12 h. The total cholesterol-years score (mg-y/dl) was calculated as follows: (total cholesterol level at time of FH diagnosis × age at time of diagnosis) + (total cholesterol level after start statin treatment × years of statin treatment) [13]. Presence of tendon xanthomas was clinically evaluated by palpation by experienced clinicians during yearly clinical visits to our hospital.

### 2.2. Computed tomography coronary angiography

#### 2.2.1. Patient preparation

Patients with a heart rate above 65 beats/min received an oral dose of beta-blockers (100 mg metoprolol) 1 h before the scan, in the absence of contraindications. Just prior to the scan all patients received nitroglycerin (0.4 mg/dose) sublingually.

#### 2.2.2. Scan protocol

All scans were performed on a Dual Source CT scanner (First 101 scans: Somatom Definition, last 39 scans: Somatom Definition FLASH, Siemens Medical Solutions, Forchheim, Germany). For the non-enhanced scan we used a prospective ECG-triggered scan protocol with a tube current of 76 mAs at 70% of the RR-interval. Images were reconstructed with a slice thickness of 3 mm and an increment of 1.5 mm using a medium convolution kernel (B35f). The contrast enhanced CTCA was obtained using a retrospective ECG-gated scan protocol in the first 101 patients and a prospective ECG-triggered protocol in the last 39 patients. The maximum tube current was 380 mAs. We applied an optimized heart rate-dependent ECG-pulsing (retrospective) or ECG-padding (prospective) protocol with full dose during 62–75% of the RR-interval for heart rates <65 beats/min and 31–75% for heart rates >65 beats/min [14]. In addition, automated tube-current modulation was applied. Tube voltage was 120 kV. Pitch (mean 0.25, range 0.2–0.34) and scan time (mean 10.0 s, range 6.9–14.3 s) of the retrospective ECG-gated scans varied with the heart rate. Data of the prospective triggered scans were acquired during 3 or 4 heart beats dependent of the required scan length. Iodinated contrast agent (Ultravist 370 mgI/ml, Bayer Schering Pharma, Berlin, Germany), with a scan time dependent volume (94 ml (80–100 ml)), was administered at a flow rate of 5.5 ml/s through an antecubital vein, followed by a saline chaser of 40 ml at 5.5 ml/s. CTCA datasets were reconstructed at a slice thickness of 0.75 mm, an increment of 0.4 mm, a medium-soft convolution kernel (B26) or a sharp convolution kernel (B46) when calcium was present. All datasets were sent to a dedicated workstation (MMWP, Siemens Medical Solutions, Forchheim, Germany).

The mean estimated radiation dose per CTCA, calculated by multiplying the dose length product (DLP) by the conversion coefficient of $0.014\,\mathrm{mSv\,mGy^{-1}\,cm^{-1}}$ for the chest, was $7.9\,\mathrm{mSv} \pm 2.4\,\mathrm{mSv}$ (range 3.9–16.4 mSv) [15].

#### 2.2.3. CT analysis

No complications occurred during or after scanning and all scans were included in the analysis. Using the non-enhanced CT scan the calcium score was calculated semi-automatically. The coronary calcium score is expressed as the Agatston score per patient.

Two experienced readers analyzed all CTCA scans separately and discrepancies in their evaluations were resolved by consensus. Per segment, using the modified AHA 17-segment model, the absence or presence of a coronary plaque was determined, as was the severity of the lumen narrowing (0, >0–20%, >20–50%, >50–70% and >70% diameter reduction). Obstructive CAD was defined as plaque causing >50% lumen diameter reduction.

We assessed a clinical CAD extent score per patient based on the severity of plaque per coronary segment. The score is the sum of the luminal stenosis of each individual segment ($0 = 0\%$, $1 \geq 0$–$20\%$, $2 \geq 20$–$50\%$, $3 \geq 50$–$70\%$ or $4 \geq 70\%$ lumen diameter reduction). This results in a CAD extent score ranging from 0 to a theoretical maximum of 68.

Additionally the plaque composition was classified as (1) calcified: highly attenuating tissue for >70% of the plaque volume which could be clearly separated from the contrast enhanced coronary lumen, (2) non-calcified: low attenuating lesions that could be clearly separated from the coronary lumen and the surrounding epicardial fat or myocardium and (3) mixed: containing both calcified and non-calcified tissue. The presence of positive remodeling (diameter at the lesion site at least 10% larger than at the reference site) was assessed in all non-calcified lesions. Vessel segments <1.5 mm in diameter were excluded from analysis.

CTCA results were blinded for treating physicians and patients which precludes treatment decisions made based on these results.

### 2.3. Risk scores

The Framingham risk score (according to the NECP/ATPIII report 2002 [16]) was calculated in all FH patients. In this NECP/ATPIII report diabetes mellitus is considered an equivalent of coronary heart disease and for this study patients with diabetes mellitus were considered to have a 10-years risk of 20%.

### 2.4. Follow-up

Patient files were examined for follow-up data and patients were approached by telephone when recent information was lacking in the files. Cardiac events (myocardial infarction, acute coronary syndrome (ACS), stable or unstable angina pectoris (AP), percutaneous coronary intervention and coronary artery bypass graft (CABG)) and (all cause) death were inventoried.

### 2.5. Statistical analysis

Continuous variables are shown as mean [±SD] or median [IQR]. Categorical variables are expressed as number [frequency]. We used the Mann–Whitney test to compare the CAD extent between male and female patients, between patients without and with diabetes mellitus type 2 and between patients without and with a cardiac event during follow-up time and to compare the Framingham risk score between patients without and with obstructive CAD.

The relationship between the calculated CAD extent and patient characteristics, cardiovascular risk factors and lipid levels was assessed using linear regression analysis. Variables with a univariate relationship ($p < 0.2$) with the presence of obstructive coronary CAD were entered in the multivariate regression model using backward elimination ($p < 0.1$). A $p$-value of <0.05 was considered statistically significant.

Inter-observer and intra-observer agreement is described with the κ statistics. All analyses were performed using SPSS for windows (version 15.0, SPSS, Chicago, USA).

## 3. Results

### 3.1. Baseline

The patient characteristics are shown in Table 1. A positive family history for cardiovascular disease was reported in 71% (99/140) of the patients, hypertension in 26% (37/140), diabetes mellitus in 6% (9/140) and smoking in 29% (40/140). In 66% (93/140) of the patients a mutation in the LDL-receptor mutation has been identified. The 34% other patients were diagnosed with FH on clinical grounds.

### 3.2. CT analysis

#### 3.2.1. Coronary artery disease per patient

A negative calcium score was present in 20% (28/140) of our patients. The median coronary calcium score was 51 (IQR 2–350) (Table 1). The total calcium score significantly increased with higher age (3 age categories, 40–49, 50–59, and 60–69 years) in both men (15.4 (0–287), 194 (38–488), and 521 (135–1001), respectively, $p < 0.001$) and women (0 (0–4), 32 (8–136), and 96 (51–662), respectively, $p < 0.001$).

CTCA showed no plaques in 16% (23/140) of the patients. In 60% (84/140) of the patients only lesions causing <50% lumen obstruction were present and in 24% (33/140) one or more lesions of >50% lumen diameter stenosis were detected. Four patients had obstructive lesions in all three coronaries (3-vessel disease), 9 in 2 vessels and 20 in 1 vessel. Presence and severity of CAD per patient (no CAD, non-obstructive CAD and obstructive CAD) was significantly higher in patients at higher age in men ($p = 0.03$) and in women ($p = 0.01$).

A calcium score of zero excluded obstructive CAD in this cohort of patients with FH. Patients with a calcium score of >400 exhibited obstructive CAD in 69% (22/32).

**Table 1**
Patients characteristics.

| Variable | $n = 140$ |
|---|---|
| Gender (male) | 90 (64%) |
| Age (years) | 52 (8) |
| **Riskfactors** | |
| Smoker[b] | 40 (29%) |
| Hypertension[c] | 37 (26%) |
| Diabetes[d] | 9 (6%) |
| CAD positive in family history[e] | 99 (71%) |
| Body mass index (kg/m$^2$) | 26.6 (3.7) |
| **Lipids (treated)** | |
| Total cholesterol (mmol/l) | 5.5 (1.4) |
| LDL-cholesterol (mmol/l) | 3.5 (1.3) |
| HDL-cholesterol (mmol/l) | 1.4 (0.4) |
| Triglycerides (mmol/l) | 1.5 (1.5) |
| Total cholesterol-years score[f] (mg-years/dl) | 18321 (5112) |
| **FH related characteristics** | |
| Known genetic disorder | 93 (66%) |
| Age at start statin use (years) | 43 (10) |
| Duration of statin use (years) | 9 (7) |
| Maximum untreated total cholesterol (mmol/l) | 9.7 (2.4) |
| Tendon xanthomas | 33 (24%) |
| Arcus cornealis | 31 (22%) |
| **Calcium Score** | |
| Total calcium score[a] (Agatston) | 51 (2–350) |
| 0 | 28 (20%) |
| 0–100 | 51 (36%) |
| 101–400 | 29 (21%) |
| >400 | 32 (23%) |
| **CT cornary angiography** | |
| Presence of cornary plaque | 23 (16%) |
| CAD extent[g] | 7 (3-16) |

Continuous data is expressed as mean (SD) and dichotomous data as $n$ (%).

[a] The calcium score and the CAD extent are expressed as median (Inter Quartile Range). CAD, Coronary Artery Disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[b] Currently and/or in the past.

[c] Blood pressure >140/90 mmHg or treatment for hypertension.

[d] Treatment with oral anti-diabetic medicine or insulin.

[e] Premature CAD in 1st degree relative.

[f] Score according to Hoeg et al. [13] (pre treatment cholesterol × age at start treatment + post treatment cholesterol × years of treatment).

[g] Score based on the sum of the severity of plaque per segment (0% lumen diameter stenosis = 0; >0–20% = 1; >20–50% = 2; >50–70% = 3; >70% = 4).

#### 3.2.2. Coronary plaque analysis

After exclusion of 16 segments because of non-diagnostic image quality 1918 segments were available for analysis. Sixty percent (1144/1918) of the segments showed no signs of coronary artery disease. In 4% (70/1918) of the segments a lesion of more than 50% lumen diameter stenosis was detected. The CAD extent score increased at increasing age. In men the median CAD extent score (10 [4–17]) was significantly higher than in women (5 [2–11]; $p = 0.004$)

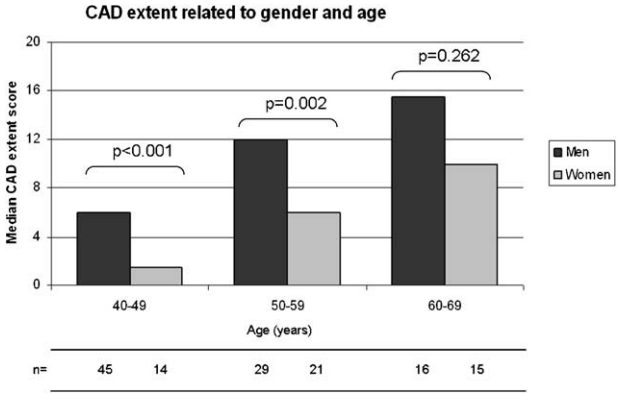


**Fig. 1.** Extent of coronary artery disease in relation to gender at different ages. CAD, coronary artery disease.

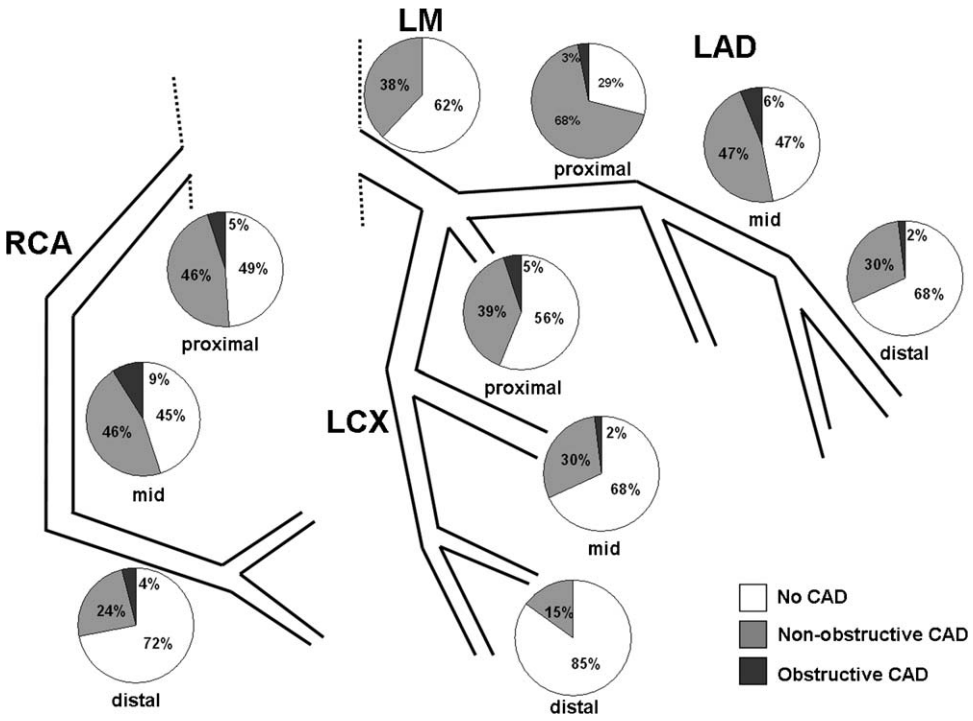


**Fig. 2.** Distribution of presence and severity of coronary plaque in the proximal, mid and distal segments of the coronary tree. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main; RCA, right coronary artery. The distal RCA comprises segment 3, the posterior descending artery and the postero-lateral artery. The mid LAD includes segment 7 and the first diagonal, the distal LAD includes segment 8 and the second diagonal. The proximal LCX comprises segment 11 and the intermediate branch; the mid LCX segment 13 and the first marginal obtuse branch; the distal LCX includes segment 15 and the second obtuse marginal branch.

(Fig. 1). The CAD extent score was slightly higher in patients with a known LDL-mutation (10 (IQR 3–17) compared to patients without such mutation (6 (IQR 2–13)) although not significantly ($p = 0.06$). A sub analysis in patients without ($n = 131$) and with ($n = 9$) diabetes mellitus type II showed no significant difference in calcium score (51 (2–346) vs. 89 (5–1580), respectively, $p = 0.57$) and CAD extent (8 (3–16) vs. 5 (2–21), respectively, $p = 0.86$).

#### 3.2.3. Plaque composition

Overall 54% (419/775) of the plaques were calcified, 25% (192/775) were non-calcified and 21% (163/775) were mixed. The percentage of calcified plaques increased with increasing age in both men and women. Most non-calcified plaques (146/192 (76%)) caused <20% lumen obstruction while the more severe plaques (>50% lumen diameter stenosis) were mainly caused by lesions containing calcium (calcified and mixed plaques) (60/70 (86%)). Of all non-calcified plaques 9 showed positive remodeling (9/192 (5%)).

#### 3.2.4. Distribution and localization of coronary plaque

The majority of the plaques were located in the proximal and mid-parts of the coronary arteries of which the proximal (99/140 (71%)) part of the LAD showed plaque most frequently, while the mid-segment of the RCA showed the highest number of obstructive lesions (12/132 (9%)). The distal LCX showed the least atherosclerotic disease. The presence and the severity of CAD per coronary segment are shown in Fig. 2.

### 3.3. Risk scores

The median adjusted Framingham risk score in patients without obstructive CAD (4 (1–10)) is significantly lower than in patients with obstructive CAD (8 (5–12), $p < 0.001$).

### 3.4. Follow up

Mean follow-up time was $29 \pm 8$ months (range 9–43 months). None of the patients died during the follow-up period, 2 patients experienced stable AP, 1 patient suffered an ACS and one patient had a positive exercise test without symptoms. All these 4 patients underwent CABG. The 4 patients requiring CABG had a significant higher CAD extent (median 24 (IQR 22–31)) than patients without a cardiac event (median CAD extent 7 (IQR 3–15), $p < 0.01$) and they all 4 exhibited obstructive CAD.

### 3.5. Relationship between patients characteristics and the CAD extent

The results of the linear regression analysis are presented in Table 2. The independent variables were gender ($B$ −6.15, 95% CI −9.35 to −2.89, $p < 0.01$), treated HDL-values ($B$ −4.77, 95% CI −8.97 to −0.56, $p = 0.03$), and treated LDL-values ($B$ 1.48, 95% CI 0.25–2.61, $p = 0.02$).

The κ statistics of the inter-observer agreement for the evaluation of the stenosis severity per plaque and the plaque composition were 0.78 and 0.83, respectively and of the intra-observer agreement 0.81 and 0.84, respectively.

## 4. Discussion

FH is associated with an increased risk of adverse coronary artery disease although some FH patients with this condition reach a high age without significant complications. Non-invasive CT coronary plaque imaging is able to identify absence, presence and extent of CAD and could be used as a tool to differentiate asymptomatic patients with advanced CAD from those who are relatively unaffected, and thereby guide preventive or therapeutic measures. In our cross-sectional study of 140 asymptomatic statin treated patients with FH we found that 84% had detectable coronary plaque,

**Table 2**
Predictive value of traditional risk factors for the CAD extent score per patient.[a]

| $n = 140$ | Univariate linear regression | | | | Multivariate linear regression | | | |
|---|---|---|---|---|---|---|---|---|
| | *B* | SE of *B* | 95% CI | *p*-Value | *B* | SE of *B* | 95% CI | *p*-Value |
| **Age (years)** | **0.32** | **0.09** | **0.15–0.50** | **0.000** | 0.24 | 0.13 | −0.17–0.498 | 0.068 |
| **Gender (female)** | **−4.30** | **1.44** | **−7.14 to −1.45** | **0.003** | **−6.15** | **1.63** | **−9.35 to −2.89** | **0.000** |
| Smoker[b] | 0.99 | 1.57 | −2.13–4.10 | 0.532 | | | | |
| Diabetes[b] | 0.65 | 2.90 | −5.08–6.39 | 0.822 | | | | |
| **Hypertension[b]** | **2.47** | **1.60** | **−0.69–5.64** | **0.125** | – | – | – | – |
| Positive family history[b] | −1.53 | 1.56 | −4.61–1.55 | 0.327 | | | | |
| **Body mass index (kg/m²)** | **0.40** | **0.19** | **0.02–0.78** | **0.038** | – | – | – | – |
| **Known genetic disorder** | **−2.48** | **1.51** | **−5.47–0.51** | **0.103** | – | – | – | – |
| **Total cholesterol-years score** | **0.02** | **0.01** | **0.01–0.03** | **0.001** | 0.02 | 0.01 | −0.00–0.03 | 0.064 |
| **LDL-cholesterol (mmol/l)** | **1.23** | **0.56** | **0.13–2.32** | **0.029** | **1.48** | **0.56** | **0.25–2.61** | **0.018** |
| **HDL-cholesterol (mmol/l)** | **−5.47** | **1.85** | **−9.12 to −1.82** | **0.004** | **−4.77** | **2.12** | **−8.97 to −0.56** | **0.027** |
| Triglycerides (mmol/l) | 0.35 | 0.48 | −0.60–1.29 | 0.467 | | | | |
| **Tendon xanthomas** | **3.02** | **1.70** | **−0.34–6.38** | **0.077** | – | – | – | – |

Variables in bold ($p < 0.2$) were entered in the multivariate regression model. Backward elimination was used in the multivariate model ($p < 0.10$). B, regression coefficient; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error.

[a] Score based on the sum of the severity of plaque per segment (0% lumen diameter stenosis = 0; >0–20% = 1; >20–50% = 2; >50–70% = 3; >70% = 4).

[b] Definition as in Table 1.

and 24% had obstructive CAD (>50% diameter stenosis). Men exhibited more advanced coronary disease at a younger age than women.

Only 20% of this FH cohort had a zero calcium score, which is much lower than the 44–51% shown in 3 large scale population studies, i.e. MESA [17], HNR [18] and Budoff et al. [2] or the 35–80% of normal calcium scans in other asymptomatic populations [4,19]. Notably a zero calcium score did not completely rule out presence of CAD, because non-calcified plaque was present in 4% of these calcium free patients. However, none of these plaques caused >50% luminal obstruction.

CTCA enables assessment of the total extent of coronary plaque per patient, which provides a more comprehensive evaluation of the coronary atherosclerosis than the assessment of the presence of obstructive lesions alone. In addition it has been reported that sudden adverse coronary outcomes are usually caused by vulnerable plaques and that the severity of stenosis is of less importance than the composition and the size of these plaques [20]. Min et al. showed that CTCA examination of the extent of CAD in symptomatic patients, including a stenosis severity score which is largely comparable to our CAD extent score, is of incremental value to assess all cause death [21].

CTCA did not reveal any CAD in 16% of this cohort of patients with FH, which is within the range of the absence of CAD in 7–36% asymptomatic diabetic patients [6,7], but much lower than the 32–79% of other high risk asymptomatic patients [4,5]. In addition we found obstructive CAD in 24% of our FH patients, although all were asymptomatic for CAD. In asymptomatic diabetic patients a comparable prevalence has been described [6,7], but in other high risk asymptomatic populations the prevalence of obstructive CAD of approximately 5–16% was much lower [4,5].

A previous study by Miname et al. [9] showed a lower prevalence of plaque (48%) in asymptomatic patients with FH than we found in our current study (84%). Calcium score (0 (IQR 0–748)) and prevalence of obstructive CAD (19%) were only slightly lower. However, the patient population of Miname et al. was younger ($45 \pm 13$ years) than ours ($52 \pm 8$ years) and comprised 64% women compared to 36% women in our population. Additionally none of the patients were on statin treatment during the study, whereas only 66% had been treated with statins previously.

The majority of coronary plaques were localized in the proximal and mid parts of the coronary arteries which is largely similar to the anatomical features of CAD in symptomatic patients. The proximal LAD exhibited plaque in 80% of the patients which might be of concern because lesions in the proximal LAD were associated with worse prognostic outcome [22].

With increasing age in men and in women the percentage of calcified plaque increased and consequently the percentage of non-calcified plaques decreased. This is in line with other CTCA studies in asymptomatic patients [4] and in symptomatic patients [23] and it corresponds with the suggestion that the advanced stages of coronary atherosclerosis are reflected by more intense calcifications [24]. There is still debate whether coronary plaque calcification is associated with stability or instability of a coronary plaque leading to coronary thrombosis. It has been shown that plaques that have a low CT density (non-calcified lipid plaques) and evidence of positive remodeling were associated with a higher likelihood of adverse coronary events [23,25]. In our study we found positive remodeling in a small number of non-calcified plaques, but due to cross-talk of lumen attenuation and absolute plaque density [26], we could not accurately distinguish between fibrous and lipid tissue in those mainly small plaques.

We demonstrated that gender, treated HDL-cholesterol and treated LDL-cholesterol were significantly associated with the extent of CAD. Previously Junyent et al. also have shown the strong independent predictive value of HDL-cholesterol levels (negatively) for preclinical carotid atherosclerosis in patients with FH. Our results therefore confirm their suggested important role for HDL-raising therapies in future treatment strategies in patients with FH [27].

It has been shown that traditional risk factors do play an important role in patients with FH but the predictive value might be different than in the general population [28]. However, we could not confirm a significant relation between the traditional risk factors age, smoking, hypertension, diabetes or the specific FH related presence of tendon xanthomas or presence of a LDL-receptor mutation and the extent of CAD. This was probably the result of the limited number of patients with FH that were studied causing insufficient statistical power.

Nine patients with diabetes mellitus type 2 were included in our study and these patients may have a more extensive expression of CAD. However, a separate analysis of the patients with diabetes mellitus type 2 compared to patients without diabetes did not reveal a difference in extent of CAD.

Using an adjusted Framingham Risk Score we could demonstrate that there was a direct relation between the Framingham Risk Score and the presence of obstructive CAD. The FRS has been based on a general population and patients with FH were not enough represented in that study. Nevertheless, although the FRS in our population might underestimate the total 10-year CHD risk,

it shows the positive relation between the risk factors and the CAD extent.

As has been recently reported by Hadamitzky et al. cardiac CT has incremental prognostic value in asymptomatic individuals [19]. In our study though, there was a low incidence of cardiac events during 29 months follow-up. We found a higher extent of CAD in the patients that developed stable angina or acute coronary syndrome followed by CABG during FU than in patients without development of clinical symptoms of CAD. Additional studies are warranted to establish whether it is reasonable to intensify medical preventive treatment in patients with evident CAD on CT to prevent progression of disease and development of adverse events and to continue or even lower current medical treatment in patients without subclinical coronary atherosclerosis on CT. Cardiac CT might lead to a more cost-effective allocation of preventive efforts.

Radiation exposure of CT coronary angiography remains a matter of concern. By using a dual source scanner with optimized scan protocols the mean estimated effective dose of a CTCA in our study was 7.9 mSv. To minimize the lifetime attributable risk of cancer and in women the risk of birth abnormalities in their offspring we included only women of at least 45 years and men of at least 40 years of age. However, due to recent technical improvements the effective radiation dose of a CTCA currently can be <3.0 mSv [29]. Decreasing the radiation dose is of positive influence on the harm–benefit ratio of CTCA, which might even induce extended use of CTCA for screening purposes or repetitive scanning for CAD progression follow up when CT-scanning below 1 mSv is definitively available.

### 4.1. Limitations

CTCA may not be able to detect very early coronary atherosclerosis which is beyond the spatial resolution of current CT-technology. CTCA tends to overestimate or underestimate the severity of obstructive CAD and in particular calcified plaques hinder precise severity assessment, due to blooming effects. In patients with a calcium score >10 (Agatston) and more explicit >400, the diagnostic accuracy of CTCA to exclude or detect obstructive CAD is hampered compared to patients with less calcium [30]. Our patients with FH were treated with intense lipid lowering drugs which will have modified the natural history of plaque progression. We included only patients aged 40–70 years old that may have affected the prevalence of CAD considering the strong relation of age and CAD in the elderly. However we sought to include patients in whom additional long lasting measures to prevent progression of CAD could be beneficial.

## 5. Conclusion

CT coronary imaging uniquely allows for non-invasive assessment of the extent, severity, anatomic distribution and plaque composition of coronary artery disease in asymptomatic patients with FH. The extent of CAD in this high risk population is related to lipid blood values and ranges from absence of detectable CAD in less than one out of six patients to obstructive CAD in nearly a quarter of patients despite the absence of symptoms. The anatomical distribution and composition of coronary plaques is similar to that of patients without FH.

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## Conflict of interests

None.

## References

[1] Austin MA, Hutter CM, Zimmern RL, Humphries SE. Familial hypercholesterolemia and coronary heart disease: a HuGE association review. Am J Epidemiol 2004;160:421–9.
[2] Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007;49:1860–70.
[3] Meijboom WB, van Mieghem CA, Mollet NR, et al. 64-Slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. J Am Coll Cardiol 2007;50:1469–75.
[4] Choi EK, Choi SI, Rivera JJ, et al. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. J Am Coll Cardiol 2008;52:357–65.
[5] Iwasaki K, Matsumoto T, Aono H, Furukawa H, Samukawa M. Prevalence of subclinical atherosclerosis in asymptomatic diabetic patients by 64-slice computed tomography. Coron Artery Dis 2008;19:195–201.
[6] Rivera JJ, Nasir K, Choi EK, et al. Detection of occult coronary artery disease in asymptomatic individuals with diabetes mellitus using non-invasive cardiac angiography. Atherosclerosis 2009;203:442–8.
[7] Zeina AR, Odeh M, Rosenschein U, Zaid G, Barmeir E. Coronary artery disease among asymptomatic diabetic and nondiabetic patients undergoing coronary computed tomography angiography. Coron Artery Dis 2008;19:37–41.
[8] Gidding SS, Bookstein LC, Chomka EV. Usefulness of electron beam tomography in adolescents and young adults with heterozygous familial hypercholesterolemia. Circulation 1998;98:2580–3.
[9] Miname MH, Ribeiro 2nd MS, Parga Filho J, et al. Evaluation of subclinical atherosclerosis by computed tomography coronary angiography and its association with risk factors in familial hypercholesterolemia. Atherosclerosis 2010;213:486–91.
[10] Santos RD, Meneghelo RS, Chacra AP, Martinez TL, Ramires JA, Carvalho JA. Detection of subclinical atherosclerosis by electron beam tomography in females with heterozygous familial hypercholesterolaemia. Heart 2004;90:92–4.
[11] Neefjes LA, Ten Kate GJ, Rossi A, et al. CT coronary plaque burden in asymptomatic patients with familial hypercholesterolaemia. Heart 2011;97:1151–7.
[12] van Aalst-Cohen ES, Jansen AC, Tanck MW, et al. Diagnosing familial hypercholesterolaemia: the relevance of genetic testing. Eur Heart J 2006;27:2240–6.
[13] Hoeg JM, Feuerstein IM, Tucker EE. Detection and quantitation of calcific atherosclerosis by ultrafast computed tomography in children and young adults with homozygous familial hypercholesterolemia. Arterioscler Thromb 1994;14:1066–74.
[14] Weustink AC, Mollet NR, Pugliese F, et al. Optimal electrocardiographic pulsing windows and heart rate: effect on image quality and radiation exposure at dual-source coronary CT angiography. Radiology 2008;248:792–8.
[15] Shrimpton P. Assessment of patient dose in CT: appendix C—European guidelines for multislice computed tomography. European Commission project MSCT: CT safety & efficacy—a broad perspective, http://www.msct.eu/PDF_FILES/Appendix%20paediatric%20CT%20Dosimetry.pdf; 2004 [accessed 20.11.08].
[16] National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
[17] McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2006;113:30–7.
[18] Schmermund A, Mohlenkamp S, Berenbein S, et al. Population-based assessment of subclinical coronary atherosclerosis using electron-beam computed tomography. Atherosclerosis 2006;185:177–82.
[19] Hadamitzky M, Meyer T, Hein F, et al. Prognostic value of coronary computed tomographic angiography in asymptomatic patients. Am J Cardiol 2010;105:1746–51.
[20] Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657–71.
[21] Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol 2007;50:1161–70.
[22] Mark DB, Nelson CL, Califf RM, et al. Continuing evolution of therapy for coronary artery disease. Initial results from the era of coronary angioplasty. Circulation 1994;89:2015–25.
[23] Bamberg F, Dannemann N, Shapiro MD, et al. Association between cardiovascular risk profiles and the presence and extent of different types of coronary atherosclerotic plaque as detected by multidetector computed tomography. Arterioscler Thromb Vasc Biol 2008;28:568–74.
[24] Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on

Arteriosclerosis, American Heart Association. Arterioscler Thromb Vasc Biol 1995;15:1512–31.
[25] Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009;54:49–57.
[26] Cademartiri F, Runza G, Palumbo A, et al. Lumen enhancement influences absolute noncalcific plaque density on multislice computed tomography coronary angiography: ex vivo validation and in vivo demonstration. J Cardiovasc Med (Hagerstown) 2010;11:337–44.
[27] Junyent M, Cofan M, Nunez I, Gilabert R, Zambon D, Ros E. Influence of HDL cholesterol on preclinical carotid atherosclerosis in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2006;26:1107–13.
[28] Civeira F. International Panel on Management of Familial H. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis 2004;173:55–68.
[29] von Ballmoos MW, Haring B, Juillerat P, Alkadhi H. Meta-analysis: diagnostic performance of low-radiation-dose coronary computed tomography angiography. Ann Intern Med 2011;154:413–20.
[30] Meijs MF, Meijboom WB, Prokop M, et al. Is there a role for CT coronary angiography in patients with symptomatic angina? Effect of coronary calcium score on identification of stenosis. Int J Cardiovasc Imaging 2009;25:847–54.