Impact of Family History of Coronary Artery Disease in Young Individuals (from the CONFIRM Registry)

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Although family history (FH) of coronary artery disease (CAD) is considered a risk factor for future cardiovascular events, the prevalence, extent, severity, and prognosis of young patients with FH of CAD have been inadequately studied. From 27,125 consecutive patients who underwent coronary computed tomographic angiography, 6,308 young patients (men aged <55 years and women aged <65 years) without known CAD were identified. Obstructive CAD was defined as >50% stenosis in a coronary artery >2 mm diameter. Risk-adjusted logistic regression, Kaplan-Meier, and Cox proportional-hazards models were used to compare patients with and without FH of CAD. Compared with subjects without FH of CAD, those with FH of CAD (FH+) had higher prevalences of any CAD (40% vs 30%, p <0.001) and obstructive CAD (11% vs 7%, p <0.001), with multivariate odds of FH+ increasing the likelihood of obstructive CAD by 71% (p <0.001). After a mean follow-up period of 2 ± 1 years (42 myocardial infarctions and 39 all-cause deaths), FH+ patients experienced higher annual rates of myocardial infarction (0.5% vs 0.2%, log-rank p = 0.001), with a positive FH the strongest predictor of myocardial infarction (hazard ratio 2.6, 95% confidence interval 1.4 to 4.8, p = 0.002). In conclusion, young FH+ patients have higher presence, extent, and severity of CAD, which are associated with increased risk for myocardial infarction. Compared with other clinical CAD risk factors, positive FH in young patients is the strongest clinical predictor of future unheralded myocardial infarction. **(Am J Cardiol 2013;111:1081−1086)**

From numerous population-based studies, family history (FH) of coronary artery disease (CAD) has been established as an independent risk factor for CAD[1−4] and myocardial infarction (MI).[5−7] Importantly, an inverse relation between risk and age exists for subjects with FH of CAD (FH+), wherein the strength of risk is higher with younger age of onset.[2,5] However, these studies have been constrained to patients who have already experienced clinical CAD events, and the prospective relation of positive FH to CAD presence, extent, severity, and prognosis remains inadequately examined. In a study of patients who underwent coronary computed tomographic angiography (CCTA), we evaluated the impact of positive FH on the presence, extent, and severity of CAD, as well as the association with MI for patients with and without FH.

Methods

Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (CONFIRM) is an international, multicenter, observational registry of 27,125

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See page 1085 for disclosure information.

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0002-9149/13/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2012.12.042

consecutive patients who underwent ≥64−detector row CCTA for suspected CAD at 12 centers from 2003 to 2009. The study design has been previously described.[8] Each center obtained approval from an ethics or institutional review board. Of 27,125 adult patients, we excluded 2,350 with known CAD (previous MI and/or coronary revascularization) and 7,453 patients for whom FH information was lacking. Among the remaining 17,322 patients, 6,308 young patients (men aged <55 years and women aged <65 years) met the inclusion criteria for the study, with cut points for young patients chosen on the basis of age strata from the National Cholesterol Education Program Adult Treatment Panel[9] and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[10] A "very young" group of 2,934 patients (men aged <45 years and women aged <55 years) was examined in secondary analyses.

Before CCTA, we prospectively collected information on the presence of CAD risk factors. Hypertension was defined as a history of high blood pressure or treatment with antihypertensive medications. Diabetes mellitus was defined by previously made diagnosis and/or the use of insulin or hypoglycemic agents. Dyslipidemia was defined as known but untreated dyslipidemia or current treatment with lipid-lowering medications. Smoking history was defined as current smoking or cessation <3 months before testing. Positive FH was defined as MI, cardiac death, or need for coronary revascularization in a first-degree relative with early onset. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Angina typicality was diagnosed by the interviewing physician at the time of CCTA.

CCTA was performed using a single-source 64-slice scanner or a dual-source scanner. Timing bolus or automated bolus tracking at the proximal ascending aorta was used to determine the time from contrast injection to optimal coronary artery enhancement. Contrast (80 to 140 ml, depending on site) was injected at 5 to 6 ml/s, and whole-volume image acquisition was completed in a single breath-hold. In selected patients, noncontrast computed tomography was also performed to quantify coronary calcium score, according to the method of Agatston et al.[11] Acquired image data were initially reconstructed in mid-diastole (always) and end-systole (when available). Reconstructed data were evaluated by ≥1 highly experienced reader (level III equivalent and/or board certified in CCTA) using all necessary postprocessing techniques to determine the presence of CAD in any visible segment ≥2 mm in diameter.

Coronary computed tomographic angiographic interpretation was performed in an intent-to-diagnose fashion, with any uninterpretable segment scored as having the same stenosis severity as the most adjacent proximal evaluable segment, in accordance with previous multicenter studies.[12,13] A 16-segment American Heart Association coronary artery tree model was used.[14] Coronary lesions were quantified for luminal diameter stenosis by visual estimation and graded as none (0% luminal stenosis), mild (1% to 49%), moderate (50% to 69%), or severe (≥70%). Plaque composition in each coronary segment was classified as calcified, noncalcified, or partially calcified,[15] as we have previously described. Plaque severity was scored at per patient, per vessel, and per segment levels. Any CAD was defined as any plaque, irrespective of grade of stenosis. On a per patient basis, obstructive CAD was defined at the ≥50% stenosis threshold, with nonobstructive CAD defined as by a 0% to 49% maximal stenosis. Per vessel CAD was defined by ≥50% stenosis in 0, 1, 2, or 3 coronary artery vessels. Per segment analysis was graded for individual coronary artery segments.[16] The numbers of segments with calcified, noncalcified, and partially calcified plaque were calculated. The ratios of the number of segments with plaque were calculated as the number of segments with a specific plaque type divided by 16 and multiplied by 100. A segment involvement score (SIS) was calculated as the total number of segments with plaque, irrespective of the grade of luminal stenosis within each segment (minimum 0, maximum 16). A segment stenosis score (SSS), measuring overall plaque extent, was graded as follows: each individual segment was graded as having no to severe plaque (i.e., scores from 0 to 3). Then, the extent scores of all 16 segments were summed to yield a total score ranging from 0 to 48.[15] The primary clinical end points were time to nonfatal MI and all-cause death. MI was adjudicated at each site and was defined in accordance with the World Health Organization's universal definition of myocardial infarction.[17] Death status for centers outside the United States was collected by clinical visits, telephone contacts, and questionnaires sent by mail, with verification of all reported events by hospital records or direct contact with a patient's attending physician. Death status for United States centers was ascertained either by query of the Social Security Death Index or by interview by physician and/or nurse study investigators.

All statistical calculations were performed using Stata version 11 (StataCorp LP, College Station, Texas) and SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) for Windows. Categorical variables are presented as frequencies and continuous variables as mean ± SD. Variables were compared using chi-square statistics for categorical variables and Student's unpaired t tests for continuous variables. Comparisons of body mass index, coronary calcium score, SIS, SSS, and the number and ratio of segments with plaque were performed using Kruskal-Wallis nonparametric tests. Coronary calcium score in the overall population was compared after logarithmic transformation to adjust for its non-normal distribution. Stepwise multivariate logistic regression analysis including age, gender, and coronary risk factors was performed to determine the association between these variables and the presence of obstructive CAD; these relations were expressed as odds ratios and 95% confidence intervals. A p value <0.05 was considered significant. Times to MI and death were calculated using Cox proportional-hazards models. In each case, the proportional-hazards assumption was met. Adjusted models were also devised including multivariate stepwise models adjusting for baseline demographics and cardiac risk factors. A hazard ratio and 95% confidence interval were calculated from the Cox models. A 2-tailed p value <0.05 was considered statistically significant.

Results

Among 6,308 patients, 42 MIs and 39 all-cause deaths over a mean follow-up period of 2 ± 1 years occurred. In 2,934 very young subjects, 13 MIs and 11 all-cause

Table 1
Baseline patient characteristics

Variable	All Patients (n = 6,308)	FH+ (n = 1,981)	FH− (n = 4,327)	p Value
Age (yrs)	49 ± 9	49 ± 8	50 ± 9	0.23
Men	45%	45%	45%	0.35
Body mass index (kg/m^2)*	26 (24−30)	27 (24−31)	26 (23−29)	<0.0001
Diabetes mellitus	11%	11%	11%	0.94
Dyslipidemia	52%	55%	51%	0.007
Hypertension	43%	45%	43%	0.13
Current smoking	17%	22%	15%	<0.001
Typical angina pectoris	11%	13%	10%	<0.001
Diamond-Forrester probability	27 ± 26	27 ± 26	27 ± 25	0.86

Data are expressed as mean ± SD, as percentages, or as median (interquartile range).

* Analysis of body mass index was performed in 6,143 patients (97%) (1,948 patients with FH and 4,195 patients without FH).

Table 2
Coronary calcium score, stenosis severity, and plaque composition for patients with and without family history of coronary artery disease

Variable	FH+ (n = 1,981)	FH− (n = 4,327)	p Value
Log coronary calcium score, median (interquartile range)	0 (0−3)	0 (0−2)	<0.0001
Per-patient analysis*			
Presence of CAD			
Normal	60%	70%	<0.001
Nonobstructive CAD	28%	23%	<0.001
Obstructive CAD	11%	7%	<0.001
Any CAD	40%	30%	<0.001
Presence of plaque			
Calcified	14%	14%	0.84
Noncalcified	16%	10%	<0.001
Partially calcified	16%	10%	<0.001
Anomalous coronary arteries†	1%	2%	0.034
Number of obstructive vessels*			
1	7%	5%	<0.001
2	3%	1%	<0.001
3	1%	0%	0.040

* Per patient and per vessel analyses were performed in 6,303 patients (99.9%) (1,979 patients with FH and 4,324 patients without FH).

† Anomalous coronary artery analysis was performed in 5,270 patients (83.5%) (1,521 patients with FH and 3,749 without FH).

Table 3
Extent of coronary plaque and number of segments with plaque for patients with any plaque

Variable	FH+ (n = 783)	FH− (n = 1,305)	p Value
Coronary calcium score	30 (1−138)	20 (0−106)	0.0025
Per segment analysis			
SIS	2 (1−4)	2 (1−3)	<0.0001
SSS	3 (1−5)	2 (1−4)	<0.0001
Number of segments with plaque			
Calcified	0 (0−1)	0 (0−1)	0.0016
Noncalcified	0 (0−1)	0 (0−1)	0.0039
Partially calcified	0 (0−1)	0 (0−1)	0.0006
Ratio of segments with plaque (%)			
Calcified	0 (0−6)	0 (0−6)	0.0016
Noncalcified	0 (0−6)	0 (0−6)	0.0039
Partially calcified	0 (0−6)	0 (0−6)	0.0006

Data are expressed as median (interquartile range).

Table 4
Multivariate predictors of obstructive coronary artery disease on coronary computed tomographic angiography in young patients (n = 6,308)

Variable	Odds Ratio	95% Confidence Interval	p Value
Age	1.07	1.05−1.08	<0.001
Male gender	2.56	2.03−3.21	<0.001
Hypertension	1.51	1.24−1.82	<0.001
Diabetes	1.74	1.36−2.22	<0.001
Dyslipidemia	1.61	1.31−1.96	<0.001
Current smoking	1.71	1.37−2.13	<0.001
FH of CAD	1.71	1.42−2.07	<0.001

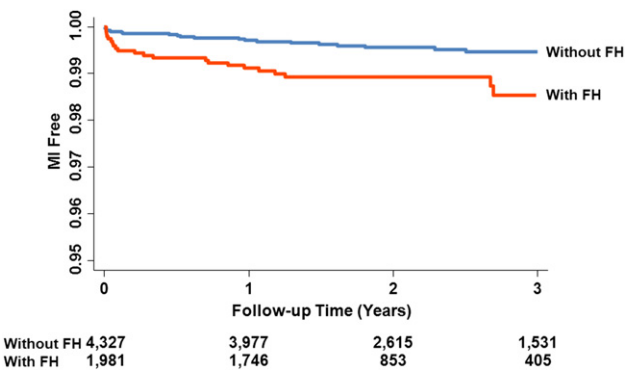

Figure 1. Unadjusted 3-year Kaplan-Meier analysis estimates for MI. Log-rank p = 0.0012.

deaths occurred. Of 6,308 total patients, there were 1,981 FH+ patients (31%) and 4,327 patients without FH of CAD (FH−) (69%) (Table 1). Compared with FH− patients, those with positive FH had higher body mass indexes and greater prevalences of dyslipidemia, current smoking, and typical angina. There was no significant difference in Diamond-Forrester pretest likelihood of obstructive CAD between FH+ and FH− patients. FH+ and FH− patients possessed generally low log coronary calcium scores, with high prevalences of normal coronary arteries and nonobstructive CAD (Table 2). Compared with FH− patients, FH+ patients exhibited higher frequencies of any and obstructive CAD. Noncalcified plaque was observed more often in FH+ patients than in FH− patients, with no significant difference in the frequency of calcified plaques. Anomalous coronary arteries were observed more often in FH− patients than FH+ patients (Table 2). Among patients with CAD (n = 2,088), FH+ patients had higher coronary calcium scores, SIS, and SSS than FH− patients (Table 3).

In multivariate logistic regression analyses considering age and CAD risk factors, FH+ state remained an independent predictor of obstructive CAD (Table 4). FH+ patients experienced higher annual rates of MI compared

Table 5
Multivariate predictors of myocardial infarction or all-cause death on coronary computed tomographic angiography in young patients (n = 6,308)

Variable	MI			All-Cause Death		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.03	0.99−1.08	0.14	0.97	0.93−1.01	0.15
Male gender	1.08	0.53−2.22	0.83	1.05	0.48−2.32	0.90
Hypertension	1.26	0.67−2.35	0.48	2.33	0.86−6.31	0.10
Diabetes	1.46	0.63−3.37	0.38	0.47	0.20−1.09	0.08
Dyslipidemia	0.86	0.46−1.60	0.63	0.68	0.32−1.42	0.30
Current smoking	1.68	0.84−3.38	0.14	1.32	0.53−3.31	0.55
FH of CAD	2.60	1.41−4.79	0.002	1.73	0.68−4.41	0.25

CI = confidence interval; HR = hazard ratio.

Table 6
Multivariate predictors of obstructive coronary artery disease on coronary computed tomographic angiography in very young patients (n = 2,934)

Variables	Odds Ratio	95% Confidence Interval	p Value
Age	1.05	1.01−1.08	0.009
Male gender	1.47	0.91−2.38	0.12
Hypertension	1.63	1.14−2.33	0.008
Diabetes	2.56	1.62−4.07	<0.001
Dyslipidemia	1.56	1.09−2.24	0.016
Current smoking	1.78	1.21−2.62	0.003
FH of CAD	1.59	1.12−2.26	0.009

Table 7
Multivariate predictors of myocardial infarction or all-cause death on coronary computed tomographic angiography in very young patients (n = 2,934)

Variable	MI			All-Cause Death		
	HR	95% CI	p Value	HR	95% CI	p Value
Dyslipidemia	1.03	0.34−3.07	0.96	0.16	0.02−1.38	0.10
Current smoking	0.73	0.16−3.31	0.68	1.07	0.03−44.1	0.97
FH of CAD	1.98	0.66−5.94	0.22	2.96	0.26−33.4	0.38

Abbreviations as in Table 5.

with FH− patients (Figure 1). In multivariate Cox proportional-hazards analysis, risk for MI associated with FH+ state was higher than age, gender, or any other traditional CAD risk factor (Table 5). In contrast, risk for death was not associated with any CAD risk factor (Table 5). Importantly, positive FH remained a predictor of MI even after adjustment for age, gender, CAD risk factors, and SSS or SIS. In contrast, for very young patients, considering age and CAD risk factors, positive FH was a predictor of the presence of obstructive CAD (Table 6) but not MI or all-cause death (Table 7).

Discussion

In this study, we identified higher prevalence, extent, and severity of CAD by CCTA in young patients with reported FH of CAD. This significantly increased overall coronary plaque burden for FH+ subjects was associated with coronary calcium scores, which although significantly higher than in FH− subjects were still within ranges generally considered low. Furthermore, the increased CAD extent and severity identified in FH+ patients was directly associated with an increased risk for MI over age, gender, or any other traditional CAD risk factor.

Previous studies have investigated the association between positive FH and CCTA. Bamberg et al[18] evaluated 195 patients (mean age 55 ± 12 years), of whom 44 reported FH of CAD. In their study, positive FH was associated with noncalcified plaque. These data generally agree with those of Sunman et al,[19] who examined 349 patients (mean age 58 ± 11 years), of whom 168 reported FH of CAD, and reported higher prevalences of CAD and noncalcified plaque in FH+ than FH− patients. In contrast, Rivera et al[20] reported in 1,015 asymptomatic patients (mean age 53 ± 10 years) FH+ state in 131 and observed no significant association with the presence of any CAD in FH+ subjects.

Given these discordant results, our study findings directly extend previous studies by prospectively examining a larger population that was strictly restricted to a younger cohort that may be considered most likely to be influenced by having a positive FH. Importantly, we noted the presence of noncalcified plaque to be higher in young patients with FH than in those without FH. Furthermore, we observed that positive FH was associated with the presence of obstructive CAD and future MI. Previous studies have reported higher frequencies of FH in young patients with previous MIs than in older patients with previous MIs.[21,22] Further data have corroborated these findings, demonstrating that FH of CAD increases with younger age of onset. In the Framingham study, positive FH was associated with higher offspring event rates, with a threefold increase for offspring aged 30 to 59 years and a twofold difference for older offspring.[2] Similarly, in the present study, we noted positive FH to be predictive of obstructive CAD in very young patients (men aged <45 years and women aged <55 years). However, positive FH in very young patients did not risk for future MI, as it did in the entire cohort of young patients. Myriad potential explanations may account for these findings; 1 example may be that positive FH enables premature development of CAD but that the risk for future events is temporally related to the duration of obstructive CAD presence.

One notable finding in our present study is that positive FH was also associated with the presence of noncalcified plaque. Combined with our study findings of the generally low coronary calcium scores in these young subjects with FH of CAD, it is conceivable that coronary calcium scoring may not be uniformly effective in identifying young subjects with FH of CAD, who have no or low detectable levels of coronary calcium and nevertheless may be at heightened risk for unheralded MI. Some early adopters of CCTA have advocated for its use for asymptomatic subjects for risk stratification, although current appropriate use criteria indicate its use as “inappropriate” in this population. Whether young patients with FH of CAD may represent a small minority of patients who may benefit from CCTA in lieu of calcium scoring remains to be determined.

This study was not without limitations. First, positive FH was gleaned from direct patient history or query. However, our study findings indicate a strong relation of CAD presence and prognosis by self-report in a manner that would be expected to be done clinically in daily practice. Second, our study findings were derived from a cohort of subjects who were referred for clinically indicated CCTA by their physicians, and thus extrapolation of our study findings to population-based cohorts should be done with caution. Finally, although we noted a strong relation between the presence, extent, severity, and risk for CAD in FH+ subjects compared with FH− subjects, the mechanism of these findings remains unknown. Although limited studies suggest an association between reduced arterial elasticity[23] and impaired endothelial function in FH+ subjects,[24−26] the mechanism of subclinical atherosclerosis in patients with FH of CAD has not been definitively determined. For this, future prospective longitudinal studies are likely necessary.

Disclosures

Dr. Achenbach received grant support from Siemens Healthcare, Erlangen, Germany, and Bayer Schering Pharma AG, Berlin, Germany, and has served as a consultant for Servier, Neuilly-sur-Seine, France. Dr. Al-Mallah received support from the American Heart Association, Dallas, Texas; the Blue Cross Blue Shield of Michigan Foundation, Detroit, Michigan; and Astellas Pharma Inc., Tokyo, Japan. Dr. Cademartiri received grant support from GE Healthcare and has served on the speakers' bureau of Bracco, Milan, Italy, and as a consultant for Servier. Dr. Chinnaiyan received grant support from Bayer Schering Pharma AG and Blue Cross Blue Shield Blue Care Michigan, Detroit, Michigan. Dr. Chow received research and fellowship support from GE Healthcare; research support from Pfizer, Inc., New York, New York, and AstraZeneca, Wilmington, Delaware; and educational support from TeraRecon, Foster City, California. Dr. Hausleiter received a research grant from Siemens Medical Systems, Forchheim, Germany. Dr. Maffei received grant support from GE Healthcare. Dr. Kaufmann received institutional research support from GE Healthcare and grant support from the Swiss National Science Foundation, Bern, Switzerland. Dr. Raff received grant support from Siemens Healthcare, Blue Cross Blue Shield Blue Care Michigan, and Bayer Schering Pharma AG. Dr. Min received modest speakers' bureau and medical advisory board compensation and significant research support from GE Healthcare, Milwaukee, Wisconsin.

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