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VIEWPOINT

Cardiac CT findings in patients with family history of premature CAD: an observational study

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ABSTRACT

Introduction: A family history of premature CAD may promote enhanced development of coronary atherosclerosis in a sibling population. Baseline CV algorithms may underestimate the risk of coronary incidents in individuals at familial risk. Cardiac CT provides high diagnostic performance for the detection of coronary plaques. There is little data on the use of this technology in the initial diagnostic approach of these patients. The prognostic value of early detection of coronary plaques by cardiac CT remains unknown in this population.

Objectives: The study aimed to estimate the global CV risk and the pre-test probability of CAD in patients with a family history of premature CAD. We investigated the potential role of cardiac CT imaging in the assessment of coronary risk in patients from high-risk families. We sought to remind the 2019 ESC guidelines for screening for CAD in asymptomatic subjects.

Methods: Fifty siblings of patients with premature CAD were investigated. The pre-test probability of CAD was determined with the Clinical Model of the CAD consortium. The risk of CV disease was calculated and compared with three different risk algorithms (SCORE, FRS, PROCAM). All patients underwent cardiac CT with both non-contrast and contrast imaging. Coronary artery calcium (CAC) scoring was calculated and CT angiograms were analyzed. Patients with suspected CT obstructive CAD underwent coronary angiography. Clinical outcomes in terms of treatment were analyzed.

Results: The pre-test probability of CAD was low: CAD consortium <10% in 60%, SCORE <5% in 100%, FRS <10% in 88%, CAC scoring <100% in 68%. However, PROCAM was <10% in 16 cases (32%). Only 12 patients (24%) presented normal CCTA findings. In patients with abnormal CCTA findings ($n = 38$), PROCAM was higher than FRS in 20 patients (53%). Coronary angiography was performed in 31 cases (62%) for suspected CT obstructive CAD. Most patients presented no significant lesions (55%). Revascularization was performed in 8 patients (16%), 6 of them (75%) presented CAC scoring <100, 4 of them (50%) presented CAC scoring <400. After investigation, lipid-lowering therapy was enhanced by 66%.

Conclusion: Coronary atherosclerotic-phenotyping using cardiac CT may provide discriminatory information allowing earlier identification of patients at familial risk of premature CAD. This diagnostic workup strategy may help to guide and improve the management of these patients. However, there is a paucity of data concerning the prognostic significance of this technology in relatives at familial risk of premature CAD. Therefore, further randomized controlled trials are needed to assess the incremental risk-predictive value of this approach in this population.

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Coronary atherosclerosis; cardiac computed tomography; coronary artery calcium scoring; cardiovascular risk assessment

Introduction

Parental premature history of cardiovascular (CV) disease represents a risk factor for coronary artery disease (CAD). Family history of premature CAD is absent from traditional CV risk algorithms. Therefore, baseline predictive models may underestimate the risk of coronary incidents [1–3]. Cardiac computed tomography (CT) provides high diagnostic performance for the detection of coronary plaques [4]. However, scientific data on the use of this non-invasive imaging modality in the initial diagnostic approach of asymptomatic subjects at familial risk are limited. Thereby, the prognostic value of early detection of coronary plaques by cardiac CT remains uncertain in these patients.

Objectives

The study aimed to estimate the global CV risk and the pre-test probability of CAD in patients with a family history of premature CAD. We investigated the potential role of cardiac CT imaging in the assessment

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of coronary risk in patients from high-risk families. We sought to remind the 2019 ESC guidelines for screening for CAD in asymptomatic subjects.

Methods

In this observational study, we analysed coronary artery calcium (CAC) scoring and coronary computed tomographic angiography (CCTA) findings in patients without known coronary artery disease (CAD). Fifty siblings of patients with premature coronary events were investigated. All subjects were aged <55 years and presented a family history of premature CAD in a first-degree relative (men <55 years, women <60 years). Family history included strong coronary incidents including sudden cardiac death, acute coronary syndrome, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass grafting (CABG). We used the Clinical Model of CAD consortium to determine the pre-test probability of CAD. Based on more than 5500 patients from 18 hospitals across the United States and Europe, the Clinical Model estimates the presence of CAD based on age, sex, symptoms, and cardiovascular risk factors including diabetes, hypertension, dyslipidemia, smoking history, and coronary calcium score [5]. Three cardiovascular risk algorithms were calculated and compared: Systematic Coronary Risk Estimation (SCORE), Framingham Risk Score (FRS), and Prospective Cardiovascular Münster (PROCAM) Score. The SCORE cardiovascular risk chart estimates the 10-year risk of fatal CV disease based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol [6]. The FRS provides an estimate of the 10-year risk of CV disease based on age, sex, smoking status, total cholesterol, HDL-cholesterol, systolic blood pressure, and diabetes [7]. The PROCAM Score is used to predict 10-year risk of acute coronary event based on the following parameters: age, diabetes, smoking, family history of myocardial infarction <60 years in a first-degree relative, LDL-cholesterol, HDL-cholesterol, triglycerides, and systolic blood pressure [8].

Finally, all patients underwent cardiac CT with CAC scoring and multi-slice CT angiography. CAC scores were obtained with non-contrast-enhanced cardiac CT and expressed as Agatston scores. CCTA examinations were performed on a 128×0.625 mm detector row/256 slices per rotation multidetector CT (Brilliance iCT; Philips, Cleveland, OH). Significant CAD was defined as ≥50% reduction in coronary luminal diameter. Patients with a suspected CT obstructive CAD underwent cardiac catheterisation for diagnostic coronary angiography.

Results

In this analysis, we explored CV risk profile and the presence of coronary atherosclerosis in middle-aged adults with a reported sibling history of premature CAD. The results of our investigations are summarised in Table 1.

Table 1. Participant CV risk assessment, pre-test probability of CAD, CAC scoring, CCTA findings, coronary angiography, and treatment.

CV risk assessment	Pre-test probability of CAD	CAC scoring
10-year risk of fatal CV disease:	<5%: 15 (30%)	0: 22 (44%)
SCORE <5%: 50 (100%)	5-10%: 15 (30%)	<100: 12 (24%)
10-year risk of CV disease:	10-15%: 11 (22%)	100-400: 12 (24%)
FRS <5%: 25 (50%)	15-20%: 6 (12%)	>400: 4 (8%)
FRS 5-10%: 19 (38%)	>20%: 3 (6%)	
FRS >10%: 6 (12%)		
10-year risk of acute coronary event:		
PROCAM <5%: 16 (32%)		
PROCAM 5-10%: 18 (36%)		
PROCAM >10%: 16 (32%)		

CCTA findings	Coronary angiography	Treatment
Normal: 12 (24%)	Normal: 2 (6%)	New statin therapy: 26 (52%)
Single-vessel CAD: 12 (24%)	Non-obstructive single-vessel CAD: 8 (26%)	Higher statin dose: 7 (14%)
Two-vessel CAD: 17 (34%)	Non-obstructive two-vessel CAD: 6 (19%)	PTCA: 6 (12%)
Three-vessel CAD: 9 (18%)	Non-obstructive three-vessel CAD: 3 (10%)	*CAC scoring <100: 2*
	Obstructive single-vessel CAD: 8 (26%)	*CAC scoring 100-400: 2*
	Obstructive two-vessel CAD: 3 (10%)	*CAC scoring >400: 2*
	Obstructive three-vessel CAD: 1 (3%)	CABG: 2 (4%)
		CAC scoring >400: 2

Abbreviations: CV: cardiovascular; SCORE: Systematic Coronary Risk Estimation; FRS: Framingham Risk Score; PROCAM: Prospective Cardiovascular Münster; CAD: coronary artery disease; CAC: coronary artery calcium; CCTA: coronary computer tomography angiography; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting.

Overall, the pre-test probability of CAD was low (<10% in 60%). Remarkably, the SCORE was <5% in all patients and the FRS was <10% in 88 percent of cases. By contrast, The PROCAM score which introduces a family history of myocardial infarction at precocious age was >10% in 32 percent of cases. Regarding cardiac CT findings, the prevalence of subclinical CAD defined by abnormal CCTA findings was not negligible (76%). While CAC scoring was low in most patients (<100% in 68%), only 12 patients (24%) presented normal CT angiograms. Interestingly, in patients with abnormal CCTA findings ($n = 38$), the PROCAM score was higher than the FRS in 20 patients (53%). After coronary angiography, most patients presented no significant lesions (55%). Only eight patients (16%) underwent myocardial revascularization. Strikingly, six of them (75%) presented CAC scoring >100 and four of them (50%) presented CAC scoring >400. Importantly, our investigations helped improve preventive therapy with lipid-lowering medications in a significant proportion of the population (66%).

Illustrations

Some examples of our CT imaging findings are illustrated in Figures 1–3.

Discussion

The global CV risk estimation requires flexibility. Indeed, there is significant variability between individuals in the development and progression of coronary atherosclerosis. Several modifiable and non-modifiable risk factors interfere. In particular, age, ethnic background and family history of coronary heart disease represent non-modifiable parameters that influence the global CV risk. However, the prediction of incident premature CAD using baseline algorithms may be underestimated in the siblings of patients with coronary events at precocious age [9–11].

In our situation, we pointed out the underestimation of the atherosclerotic burden by the classical risk

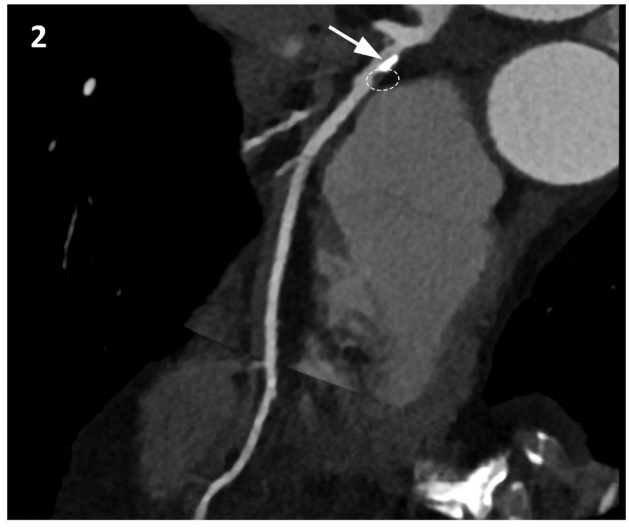

Figure 2. Computed tomography coronary angiography images with curved multiplanar reconstruction and segmental vessel analysis of the left anterior descending artery. Visualisation of a mixed coronary atherosclerotic lesion with an extensive calcification (arrow) and a soft plaque (circle).

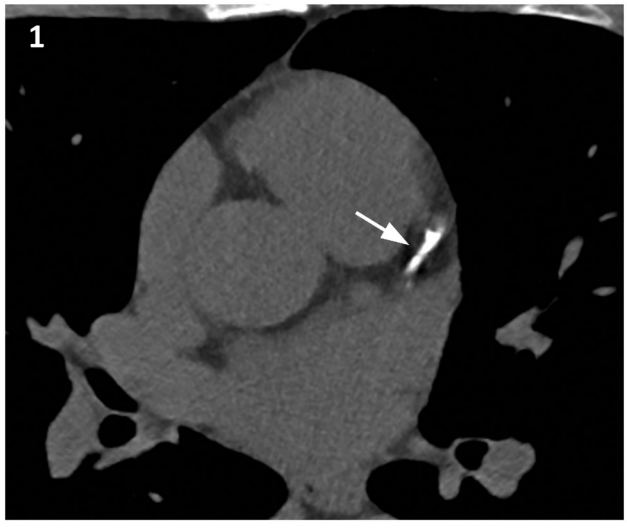

Figure 1. Non-contrast-enhanced cardiac computed tomography with axial oblique maximum intensity projection images showing single-vessel calcified coronary artery disease. Coronary artery calcium predominates at the level of the mid-segment of the left anterior descending artery (arrow).

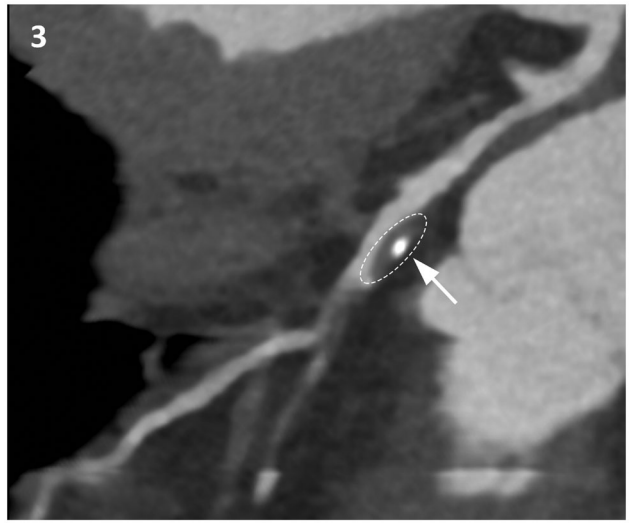

Figure 3. Computed tomography coronary angiography images with curved multiplanar reconstruction and segmental vessel analysis of the right coronary artery. Visualisation of a bulky atheroma (circle) with a focal calcification (arrow) at the level of the second segment of the right coronary artery.

scores as compared to when CT findings are considered. Approximately 75% of participants presented abnormal CCTA findings. As a result, the standard risk stratification may deprive middle-aged at-risk patients of an appropriate prevention strategy for CV disease. Remarkably, the SCORE was <5% in all patients. This could partly be explained by the effect of age. Also, we used the standard SCORE risk chart without including recalibration related to the family-specific frailty. Concerning the FRS, Vaidya et al. underlined in a prospective cohort that the baseline FRS failed to predict the 10-year CAD events in siblings [12]. Besides, we limited our data to the conventional FRS while several distinct Framingham risk models have been developed (e.g. 'FRS for hard coronary heart disease'). The PROCAM score tends to reclassify susceptible individuals by including a family history of myocardial infarction at precocious age in addition to traditional risk markers. Accordingly, this scoring system may help to indicate an increased risk of coronary events in patients at inherited risk. Thereby, almost a third of our study population presented a PROCAM score above 10%.

With regard to the European guidelines on CV disease prevention in clinical practice, it is recommended to use the SCORE risk model to predict the 10-year risk of fatal CV disease. Because the family history of CV disease has been recognised as a non-modifiable risk factor for CAD, the Task Force for the management of dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society has proposed to increase the SCORE risk by 1.7-fold in women and by 2.0-fold in men [13]. In 2019, the Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology detailed recommendations concerning the screening for CAD in asymptomatic subjects. Accordingly, assessment of the family history of premature CAD is recommended as part of CV risk estimation. The use of a validated risk algorithm is recommended to assess the CV risk of patients aged <50 years with a family history of premature CAD in a first-degree relative. CAC scoring may be considered as a risk modifier, as well as atherosclerotic plaque detection by carotid artery ultrasound and ankle-brachial index. To a lesser degree, CCTA may be considered for CV risk assessment in high-risk asymptomatic individuals [14]. For our part, we decided to use this approach in our analysis because of the strong family history of CAD.

The clinical effectiveness of cardiac CT in the investigation of suspected CAD has been validated. Non-contrast-enhanced CT imaging enables coronary calcium detection and quantification using the Agatston score. The correlation between the burden of coronary calcium and the increased risk of CV disease has widely been demonstrated in prospective studies. In fact, CAC screening provides incremental prognostic value for the prediction of coronary outcomes and all-cause mortality in asymptomatic patients [15–17]. The ability of CCTA for the detection of coronary plaques and the evaluation of luminal narrowing has been validated in the literature. The high diagnostic performance of CCTA to detect CAD provides to physicians the opportunity to reliably exclude significant stenosis of coronary arteries [18]. In addition, CT characterisation of coronary plaques in terms of composition and geometry provides reliable information on plaque stability and risk of rupture [19,20].

In conclusion, this observational study emphasises the importance of CV risk reclassification in middle-aged adults from families with early-onset CAD. Our data and clinical pictures suggest that predicting the risk of CAD with traditional risk models may underestimate the global CV risk profile in the siblings of patients with premature myocardial infarction. In this regard, we are convinced that family history questioning and reclassification of CV risk profile represent fundamental issues for preventive cardiology and medical research. Therefore, we think that developing additional markers for CV risk prediction beyond baseline algorithms is key for CV risk assessment in the sibling population. Particularly, the use of calibrated CV risk equations should be commonly applied in first-degree relatives from high-risk families. Likewise, quantification of CAC and detection of coronary atherosclerotic plaques using cardiac CT may help to promote appropriate preventive therapies at an earlier stage in individuals at inherited risk. Moving forwards, further studies are necessary to determine whether this approach may help to improve CV risk prediction and protection in this targeted population. Similarly, the development of larger studies on non-invasive cardiac imaging for the detection of coronary atherosclerosis in patients at familial risk becomes fundamental.

Study limitations

This study was a single-centre, prospective, observational analysis of a small cohort of middle-aged patients addressed for CV risk assessment and cardiac CT imaging. Actually, we only discussed 50 patients in the study sample, which is a low number, considering

that the classical risk scores are based on large samples, and hardly account for individual variabilities.

Despite very low pre-test probabilities, cardiac CT explorations were only performed for compelling reasons (e.g. acute coronary syndrome and sudden cardiac death in first-degree relatives at precocious age). Accordingly, we did not create a control group for the comparison of CT imaging findings. Although recent advances in CT technology have reduced exposure to radiation, we found it not acceptable to perform scanning procedures in a control group without a strong family history of CAD.

The interpretation of excess clustering of CAD as an additional risk factor for CV events is questionable in this sample. This hypothesis is intuitive because there was no control group, and not yet proven by evidence on large scale. Previous studies have investigated the association between family history and cardiac CT findings. For example, Sunman et al. reported that the prevalence of CAD and soft plaques were higher in patients with family history [21]. Parikh et al. demonstrated the relationship between parental premature CV disease and CAC. However, sibling history of premature CV disease was not investigated [22].

Lastly, the clinical impact of our cardiac CT findings must be interpreted with caution. To date, there remains a paucity of data regarding the prevalence of subclinical CAD in the siblings of patients with premature CAD. Also, the management of asymptomatic individuals with a positive screening test for CAD remains unclear. As described in the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes, the routine use of non-invasive imaging tests for screening for CAD in asymptomatic subjects is not recommended. Indeed, scientific data demonstrating the incremental prognostic benefit for the routine use of scanning procedures in this population are still lacking.

Conclusion

Prediction of the coronary incident in apparently healthy people with a family history of premature CAD remains challenging. Development and validation of improved algorithms for the stratification of CV risk in this population are advised. Coronary atherosclerotic-phenotyping using cardiac CT may also provide discriminatory information allowing earlier identification of susceptible individuals. This diagnostic workup strategy may help to guide and improve the management of these patients. However, there is a paucity of data concerning the prognostic significance of this technology in relatives at risk. Further randomised controlled trials are needed to assess the incremental risk-predictive value of this approach in patients at familial risk of premature CAD.

Disclosure Statement

This manuscript has been approved by all authors and has not been previously published. To our best knowledge, no conflict of interest, financial or other, exists.

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