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The Added Value of Cardiac Computed Tomography in Early Detection of Coronary Artery Disease: A single-centre Retrospective Analysis of Asymptomatic Individuals with low-to-medium pre-test probability

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ABSTRACT

Purpose: To evaluate the contribution of Cardiac Computed Tomography (CCT) in the early detection of coronary atheromatosis in asymptomatic individuals with or without risk factors for Coronary Artery Disease (CAD).

Materials and Methods: This is a retrospective, single centre study of 373 asymptomatic individuals with low-to-medium pre-test probability for CAD who performed CCT to exclude CAD, between September 2020 and November 2021. All individuals had a Coronary Artery Calcium (CAC) test, followed by a Coronary Computed Tomography Angiography (CCTA), unless CAC scoring (CACS) was above 1000 with the Agatston scoring system. CAC was estimated with the Agatston scoring system and the CAD-RADs system was used to assess the presence and extent of CAD.

Results: 58.4% of the participants were detected with coronary atheromatosis (CACS>0) when the CAC test was considered, with 16% of those having CAC>400 with a high likelihood of at least one coronary stenosis. When assessed with CCTA, 68% of the participants were detected with coronary atheromatosis and any degree of CAD, 11.6% with significant stenosis and 7.8% with severe stenosis. Nine (9)

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participants without risk factors were detected with minimal atheromatosis and one with moderate atheromatosis. Fifteen participants were under 40y with three (3) of them detected with minimal and two (2) with mild atheromatosis.
Conclusions: CCTA has the potential of becoming the established method for the early diagnosis of coronary atheromatosis and CAD. CCTA is superior to CAC for the early diagnosis of coronary atheromatosis and CAD. Individuals who may benefit from CCTA are diabetics, young males with multiple risk factors for CAD and middle-aged males with no risk factors for CAD.

KEY WORDS
Asymptomatic Patient, Coronary Artery Disease, Cardiac Computed Tomography, Coronary Computed Tomography Angiography, Coronary Artery Calcium

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally. In 2019, 17.9 million deaths (32% of all deaths worldwide) were due to CVDs with 85% of them occurring from heart attack and stroke (WHO 2021). Ischaemic heart disease (IHD), also referred as coronary artery disease (CAD), affects 1.7% of the world population resulting approximately in 9 million deaths annually [1]. Prevention and early detection of the underlying pathology of atheromatosis is considered as the key point for the elimination of the disease.

Prevention is succeeded through control of the behavioural risk factors such as unhealthy diet, physical inactivity, tobacco use etc which may show up as increased arterial pressure, dyslipidaemia, diabetes mellitus and increased BMI.

For the early detection of atheromatosis, various tests have been used during the past decades [2].

Nowadays, computed tomography offers two tests with the capability of detection and imaging of the atheromatous plaque in the coronaries:

Coronary Artery Calcium (CAC): Calcium as a component of the atheromatous plaque can be detected at the coronaries and their segments and, also, its burden can be calculated. [3]

Coronary Computed Tomography Angiography (CCTA): The atheromatous plaque and its components apart from calcium can be imaged and the degree of stenosis caused can be calculated [4].

CAC, being the first to be introduced in the 90's with the Electronic Beam Computed Tomography (EBCT), identifies calcified coronary plaques and, at its time, improved the prediction of cardiac events beyond traditional risk scores [3,5]. However, its inability to detect non-calcified plaques and calculate the degree of stenosis is a major disadvantage when compared to CCTA. On the other hand, several big-scale studies have suggested that in symptomatic patients, CCTA data when combined to CAC data, may be of added value for prediction of future coronary events [6,7]. Eventually, in 2016 the National Institute for Health and Care Excellence [8,9] in UK, recommended cardiac CT as the first-line test for the evaluation of stable coronary artery disease in chest pain pathways.

At the same time, the value of CCTA in the detection of subclinical CAD in asymptomatic population was under investigation. Smaller studies, in targeted groups of asymptomatic individuals have been very promising [10, 11, 12] giving evidence that CCTA may detect occult atheromatosis and CAD and, also add prognostic value beyond cardiac risk factors and/or CAC for the prediction of MACE (Major Adverse Cardiovascular Events) in asymptomatic population. More importantly, in the most recently published large-scale study of the Swedish population, Bergstrom [13] showed that silent coronary atherosclerosis is not uncommon in general population with one or more risk factors for CAD and can be detected with CCTA in contrast with CAC, where CAC 0 does not exclude atherosclerosis.

The goal of this study was to contribute at the evaluation of CCTA in the early detection of coronary atheromatosis in asymptomatic individuals with or without risk factors for CAD and its possible advantages when compared to CAC.

Materials and Methods

Study Design

This is a retrospective, single-centre study of individu-

Table 1. Population demographics and risk factors for developing coronary artery disease

	N	SMOKER	FAMILY HISTORY	BMI>26	AH	DL	DM	MULTI RISK FACTORS
TOTAL	373	39.1%	43.2%	37.5%	46.9%	63.5%	17.4%	95.4%
MALE	276 (74%)	40.2%	43.5%	38%	46%	65.6%	17%	96.4%
FEMALE	97 (26%)	36.1%	42.3%	36.1%	49.5%	57.7%	18.6%	92.8%
30 - 40	15 (4%)	26.7%	53.3%	33.3%	13.3%	53.3%	0	93.3%
41 - 50	67 (18%)	44.8%	49.3%	34.3%	16.4%	55.2%	13.4%	94%
51 - 60	146 (39.1%)	47.9%	47.3%	38.4%	40.4%	61%	13.7%	95.9%
61 - 70	111 (29.8%)	31.5%	37.8%	41.4%	65.8%	70.3%	21.6%	94.6%
71+	34 (9.1%)	20.6%	26.5%	29.4%	88.2%	79.4%	35.3%	100%

BMI: Body Mass Index, AH: Arterial Hypertension, DL: dyslipidaemia, DM: Diabetes Mellitus

als referred for a CCTA in a non-urgent basis, between September 2020 and November 2021, at a primary care diagnostic centre, specially dedicated in the detection of cardiovascular disease.

The inclusion criterion was absence of either typical or non-typical thoracic pain.

Known CAD (previous MI, percutaneous coronary intervention with or without stenting and coronary bypass grafting) was the only exclusion criterion. Patient's medical history was obtained with a personal interview by one of the authors (P.K.) and was confirmed by their hospital records.

Study Population

During the above-mentioned period, 1,456 individuals were referred for a CCTA in a non-urgent basis for various reasons. Of those, 373 met the study's inclusion criterion.

All included individuals were assessed for pre-test probability of CAD depending on the presence or absence of one of the following entities: arterial hypertension (AH), dyslipidaemia (DL), family history (FH), increased body weight, smoking and diabetes mellitus (DM). (**Table 1.**)

Definitions were according to the latest ESC guidelines (14,15): arterial hypertension (systolic blood pressure (SBP) >140 bpm or diastolic BP >90 bpm), dyslipidaemia (total cholesterol >200 mg/dL or high-density lipoprotein <40 mg/dL), family history (MI or sudden cardiac death in an immediate male relative <55 years or female<65 years), increased body weight (Body Mass Index BMI >25 kg/m^2), smoker (current smoker or those who quit in the past 6 months) and diabetes mellitus. Most of the individuals were under treatment for their underlying pathology (arterial hypertension, dyslipidaemia or diabetes mellitus). In case an ECG-treadmill test had been performed previously, the individuals were included only if the test was inconclusive due to physical incompetence or co-morbidity, non-specific pathological or borderline for myocardial ischaemia [16]. All data for the inclusion criteria were collected from the medical records of the patients.

Image Acquisiton and Analysis

CCTA was performed by using a 128-slice system (Go. Top – SIEMENS HEALTHNEERS) and a dedicated cardiac software was used for the assessment of the calcium burden and the atheromatosis of coronary arteries.

Initially, a non-contrast scan was obtained (detector collimation 64×0.6 mm, 120 kV, ECG-gating, slice thickness 3mm), images were reconstructed (36f HeartView medium CaScore), CAC was identified and scored with the syngo.via calcium scoring software and CAC score

Table 2. Coronary atheromatosis was detected both with measurement of CAC (Coronary Artery Calcium), using the Agatston Scoring System and with detection of plaques and estimation of stenosis with the CAD-RADs system [18].

ASSESSEMENT OF ATHEROMATOSIS										
	N	CAC_0	CAC_1	CAC_2	CAC_3	CR_0	CR_1	CR_2	CR_3+	CRN
TOTAL	373 (100%)	155 (41.6%)	99 (27%)	58 (15.5%)	61 (16%)	120 (32%)	157 (42.1%)	53 (14.2%)	20 (5.4%)	23 (6.2%)
MALE	276 (74%)	35.5%	28.6%	17.4%	18.5%	25.7%	43.8%	15.9%	3.6%	8%
FEMALE	97 (26%)	58.8%	20.6%	10.3%	10.3%	50.5%	35.1%	9.1%	3.1%	1%
30 - 40	15 (4%)	66.7%	26.7%	6.7%	0	66.7%	13.3%	20%	0	0
41 - 50	67 (18%)	64.2%	23.9%	7.5%	6%	44.8%	43.3%	7.5%	4.5%	0
51 - 60	146 (39.1%)	43.2%	28.1%	15.8%	12.3%	36.3%	42.5%	11%	4.1%	4.8%
61 - 70	111 (29.8%)	29.7%	27.9%	17.1%	25.2%	21.6%	40.5%	21.6%	2.7%	10.8%
71+	34 (9.1%)	17.6%	20.6%	29.4%	32.4%	8.8%	55.9%	14.7%	2.9%	11.8%

in Agatston Units was calculated. Then, the participants were categorized into 4 groups: Group 0 (CAC = 0), Group 1 (1-100), Group 2 (101- 400), Group 3 (above 400).

In case that Agatston score was below 1000, a CCTA was performed. In Agatston scores >1000, the patient was dismissed, as the accuracy of CCTA decreases dramatically above this point [17]. However, these patients were included in the overall statistical analysis as CAD-RADs_N and considered as severe CAD with non-diagnostic stenosis.

Based on the patient's heart rate (HR) and body mass index (BMI) two different scan protocols were used: patients with BMI> 24kg/m^2 and HR either above 65 bpm or irregular HR were scanned with retrospective ECG-gating, whereas in patients with regular HR<65bpm and BMI<24 kg/m^2, prospective ECG-gating was used. In order to obtain HR around 65bpm and dilated coronary arteries, a β-blocker and a sublingual glyceryl nitrate were administered, when not contraindicated.

Tube voltage was 100 kV in patients with BMI <26 kg/m^2 and 120 kV in patients with BMI >26 kg/m^2.

An iodine contrast agent with 350mg/ml iodine concentration was used for intravenous bolus injection during the arterial phase, followed by 40cc of saline. The bolus tracking technique was applied using 100 Hounsfield Units (HU) as a threshold and the injection rate was 4-6 ml/sec. The total volume of CA injected depended on patient's BMI and scan time and ranged between 90 and 120cc.

Reconstruction of axial images followed with slice width 0.75mm, using a medium-smooth kernel (B36f). The coronary arteries were evaluated with multiplanar reformation by two cardiac radiologists, one with more than 15 years practice in the field and the other more than three years. For the assessment of total atherosclerosis and grading stenoses the CAD-RADs system was used **(Table 2.)** [18] as this system involves at the same time information about the presence or not of atheromatosis independent of stenosis, plaque characteristics and degree of stenosis. Patients were then categorized into 6 groups:

- Group 0: CR_0 (no atheromatosis detected)
- Group 1: CR_1 (CAD-RAD=1: minimal stenosis [1%-24%] or plaque without stenosis),
- Group 2: CR_2 (CAD-RAD=2: mild stenosis [25%-49%] – mild non-obstructive CAD),
- Group 3: CR_3 (CAD_RAD=3 moderate stenosis [50%-69%]),

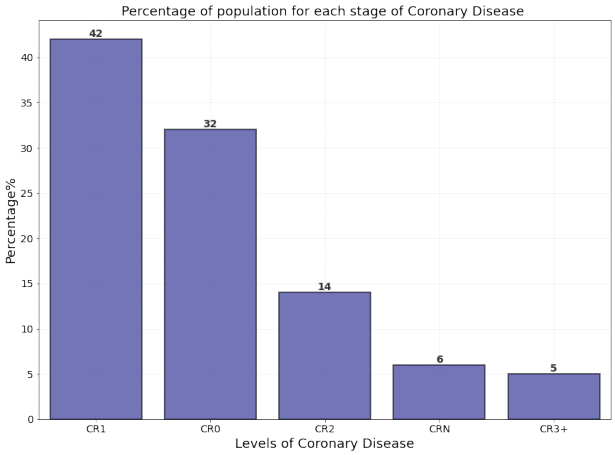

Fig 1. No atheromatosis was detected with CCTA in 32% of our asymptomatic population, mild atheromatosis in 42 % and more severe atheromatosis in 25%.

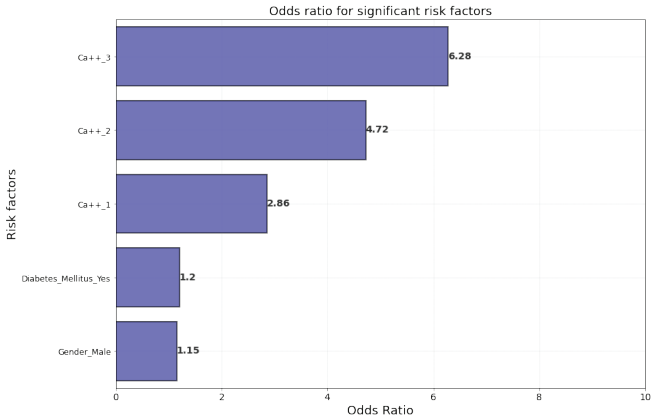

***Fig.2.** Risk factors with a significant impact in CAD are diabetes mellitus and gender male. Presence of Ca++ is a hallmark of CAD: the higher the Ca++, the more significant the impact.*

- Group 4: CR_4 (CAD-RAD=4A [70%-99% stenosis] or 4B [left main>50% or 3-vessel obstructive>70% disease]),
- Group 5: CR_5 (CAD-RAD=5 total occlusion),
- Group N: CR_N= non-diagnostic study (obstructive CAD cannot be excluded)

Participants in categories 4A and 4B formed one group (Group 4) as distinction between two subgroups may be useful in diagnosis and treatment but it was irrelevant for the purposes of the current study.

Data analysis

The first section of our study was about investigating how many asymptomatic patients have coronary disease (CR_1,2,3+, N) or not (CR_0), detected with CCTA. The second part is about investigating if and how much specific risk and demographic factors such as (age, gender, Ca++, BMI>26, Smoking, Family history, Diabetes Mellitus, Arterial Hypertension and Dyslipidaemia) impact the stage of coronary disease. The coronary disease feature is our dependent variable, and its values describe the different levels of stenosis (0-5, N), with 0 indicating no coronary disease present and N describing an overly high stenosis. Therefore, an ordinal logistic regression model was selected for our analyses, as we can measure the level of significance and the impact of the factors mentioned.

Results

Of the 373 individuals included in the study, 276 (73.9%) were male with an age range from 26-85yo (mean=56.29yo) and 97 (26.1%) were female with an age range 35-85yo (mean=62.13). The participants were categorized into 5 age-groups, one age group per decade from 30yo to above 70yo (**Table 1.)**

Depending on the presence of risk factors, participants were categorized into low risk (0, 1, 2 risk factors) and high risk (3 and more risk factors). Only 17 of the participants (4.55% of the total population) were free of risk factors: 10 males (3.62% of all males) and 7 females (7.21% of all females).

Among the 373 participants, any CCTA-detected atherosclerosis (CAD-RADs_1,2,3,4,5, N) was found in 68%, any significant stenosis >50% (CAD-RADs 3,4,5, N) in 11.6% and severe stenosis >70% (CAD-RADs 4,5, N) in 7.8% **(Fig.1).** When atherosclerosis was assessed solely with CAC scoring, the prevalence was lower (58,4% of the 373 had Ca++>0).

When assessed with CCTA, 71.3% of all males were detected with any kind of atheromatosis, with moderate to severe stenoses counting to 11,6%. **(Table 2.)** In females, any kind of atheromatosis was detected in 49.5%, with moderate to severe stenoses counting to 4,1%. As demonstrated with the regression analysis model, males are 1.155 times (or 15%) more likely of be-

Table 3. Analytical display of the participants below 40y of age

ASSESSEMENT OF ATHEROMATOSIS									
GENDER	AH	DL	DM	BMI>26	FAMILY HISTORY	SMOKING	MULTI RISK FACTORS	Ca++>0	CR
M	N	Y	N	Y	N	N	2.0	0.0	CR0
F	N	N	N	Y	N	N	1.0	0.0	CR0
M	Y	Y	N	N	Y	N	3.0	0.0	CR0
F	N	N	N	N	Y	N	1.0	0.0	CR0
M	N	Y	N	N	Y	Y	3.0	0.0	CR0
F	N	N	N	Y	Y	N	2.0	0.0	CR0
M	N	N	N	N	Y	N	1.0	0.0	CR0
M	N	Y	N	N	Y	N	2.0	0.0	CR0
M	N	N	N	N	N	N	0.0	0.0	CR0
M	N	Y	N	Y	N	N	2.0	0.0	CR0
M	N	Y	N	N	N	N	2.0	1.0	CR1
M	Y	Y	N	Y	Y	Y	6.0	1.0	CR1
M	N	N	N	N	N	Y	2.0	1.0	CR2
M	N	N	N	N	N	Y	3.0	2.0	CR2
M	N	Y	N	N	Y	N	3.0	1.0	CR2

ing asymptomatic with a higher-level coronary disease than females. Also, there was a sharp increase with age: any kind of atheromatosis was detected in 22% of participants at the age group 30-50yo and in 68.9% at the age groups 51 – 70 yo.

Furthermore, after running the regression model, we exponentiated the coefficients because the Ordinal Logistic Regression returns the coefficients in a log form and the odds ratio is calculated only for the values that were significant (P<0.05). We can see that age, positive family history, arterial hypertension, dyslipidaemia, being overweight and being a smoker did not have a significant impact on our dependent variable (P>0.05). The two risk factors that have a significant impact (p<0.05) are **(Fig. 2)**:

- diabetes mellitus as it is 20% more likely of being asymptomatic with a higher-level coronary disease than a patient without and
- male gender.

Finally, two subgroups were of special interest:

- **Subgroup I:** Young participants, under 40y of age. **(Table 3.)**
- **Subgroup II**: Participants with detected atheromatosis (CR>0) without any risk factor.

Subgroup I: Fifteen (15) participants were under 40y, 12 males and 3 females. Fourteen (14) of those had one or more risk factors. They were all males and minimal atheromatosis (CR_1) was detected in 2 (13.3%) whereas mild atheromatosis was detected in 3 (20%). There was no correlation between the number of risk factors and the level of atheromatosis.

Subgroup II: Nine (9) out of 373 participants (2.41%,) without any risk factor, were detected with atheromatosis: n=8 with minimal atheromatosis (CR_1) and n=1

with moderate atheromatosis (CR_3+). Of those 8 were males above 50y.

Discussion

Coronary artery disease, a significant cause of death worldwide, may develop silently and lead to fatal events - CAD accounts for the 25% of the 17 million sudden deaths annually [19]. Identification of individuals at risk for a coronary event is a major challenge of the medical community. Several factors are associated with increased risk for an adverse cardiac event; however, when comes to assess the individual risk, their hazard rate is too small. Even when these factors are combined at various risk scoring systems, such as the Framingham score, the accuracy of the estimation of the individual risk is still low [20]. So, for the early diagnosis of CAD at the level of individuals, a screening tool is needed. The gold standard method for the diagnosis of CAD is the invasive coronary angiography but, due to its invasive nature, it cannot be used as a screening tool.

The simplest and most common test is the ECG exercise test with a high specificity of 89% for prediction of CAD death but countered by a low sensitivity of 61% [21]. Another test widely used as a screening tool for low-to-medium probability patients during the past thirty years is radionuclide myocardial perfusion scintigraphy. However, with its low specificity of 64% [22], it may lead to further unnecessary investigations. Further on, exercise test echocardiography indicates a positive predictive value of 89% [23] in a meta-analysis not concentrating on asymptomatic patients. This is countered by a negative predictive value of 61% and a major drawback of the method: the intolerance of many patients to dobutamine.

During the past two decades, cardiac computed tomography has been increasingly considered as the method that can detect atheromatosis on coronary arteries on an individual basis and thus, estimate the atheromatic burden and guide for treatment options [24]. It is the only examination for the exclusion of CAD, with a negative predictive value of above 98% since its early days [25, 26]. Currently, it has been established as the first line examination to evaluate stable CAD in chest pain pathways. Still, its role as a screening tool for symptomless population, whether at risk for developing CAD or not, has not been established yet. The reason for this is twofold: the method involves radiation exposure and data from large-scale studies on asymptomatic population are still missing. However, nowadays with the evolution of both the multidetector scanners to systems of 128 slices and above and the various kinds of dedicated radiation protection software, the exposure doses are adequately addressed [27]. At the same time, data from both small and large scale studies are accumulating.

Our retrospective study was based on these grounds. For once, the increasing number of asymptomatic individuals referred for a CAC plus CCTA examination for exclusion for CAD, mainly because of increased risk factors and/or equivocal results of other non-invasive tests, made us question our role as radiologists responsible for the radiation protection of the population: should we accept all these referrals or should we put a cut-off point? On the other hand, our referring physicians, mainly cardiologists, were at a dead end: low-to-medium probability patients, asymptomatic, with equivocal results from other tests of non-direct detection of atheromatosis and not established guidelines to use cardiac CT. Should they use cardiac computed tomography and, if so, should they refer for CAC only or for both CAC+CCTA.

Our results justified the use of cardiac CT to exclude CAD in asymptomatic population:

- When using the Ca++ scoring test, 58.4% of the participants had CAC>0, that means established atheromatosis [28]. Of those, 16% had CAC>400 with a high likelihood of at least one coronary artery stenosis and 6.2% had CAC>1,000.
- With a CCTA, 68% of the participants were detected with any level of atheromatosis. Of those, 42,1% had a mild type with no stenoses (CAD-RADs_1) and 14,2% with minimal stenoses (CAD-RADs_2). These are the patients that will benefit from preventive factor modification: apart from improving their lifestyle, medication has to be considered (if not already given) or doses have to be increased (if already given). The rest are the patients with silent CAD, the ones at a very high risk for a sudden acute event and must be treated accordingly.

So, both examinations are clinically useful as they add important information. However, CCTA not only detects a higher percentage of individuals with ather-

omatosis than CAC but, also, stratifies more distinctly these patients as for the treatment they need.

Another question to be answered is whether any particular groups of the population get the most benefit from a CCTA examination. Diabetics are definitely such a group as our regression analysis demonstrated. Also, young patients with at least one risk factor may have an early diagnosis and right timing for the start of their treatment. Finally, in men above 50y even without risk factors, CCTA may detect mild to moderate atheromatosis.

The main limitation of this retrospective study is the small number of patients. As, however, the results are in accordance with larger scale studies, we can draw some conclusions so as to consult confidently our referring clinicians in their decision making of their asymptomatic patients. Furthermore, based on this study we may design and conduct another larger scale prospective study to address several questions that kept rising as we were working on our data. **R**

Conclusions

- CCTA has the potential of becoming the established method for the early diagnosis of coronary atheromatosis and CAD.
- CCTA is superior to CAC for the early diagnosis of coronary atheromatosis and CAD.
- Individuals who may benefit from CCTA are diabetics, young males with multiple risk factors for CAD and middle-aged males with no risk factors for CAD. **R**

Conflicts of interest

The authors declared no conflicts of interest.

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