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Coronary calcifications as assessed on routine non-gated chest CT; a gatekeeper to tailor downstream additional imaging in patients with stable chest pain

Roos A. Groen [a,1], Paul R.M. van Dijkman [a,1], J. Wouter Jukema [a,c,1,*], Jeroen J. Bax [a,1], Hildo. J. Lamb [b,1], Michiel A. de Graaf [a,1]

[a] Leiden University Medical Center, Department of Cardiology, The Netherlands
[b] Leiden University Medical Center, Department of Radiology, The Netherlands
[c] Netherlands Heart Institute, Utrecht, Leiden, The Netherlands

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ABSTRACT

Background and aims: Currently applied methods for risk-assessment in coronary artery disease (CAD) often overestimate patients' risk for obstructive CAD. To enhance risk estimation, assessment of coronary artery calcium (CAC) can be applied. In 10 % of patients presenting with stable chest pain a previous non-gated computed tomography (CT) has been performed, suitable for CAC-assessment. This study is the first to investigate the clinical utility of CAC-assessment on non-gated CT for risk-assessment of obstructive CAD in symptomatic patients.

Methods: For this analysis, all patients referred for coronary computed tomography angiography (CCTA), in whom a previous non-gated chest CT was performed were included. The extent of CAC was assessed on chest CT and ordinally scored. CAD was assessed on CCTA and obstructive CAD defined as stenosis of ≥70 %. Patients were stratified according to CAC-severity and percentages of patients with obstructive CAD were compared between the CAC groups.

Results: In total, 170 patients of 32–88 years were included and 35 % were male. The percentage of obstructive CAD between the CAC groups differed significantly ($p < 0.01$). A calcium score of 0 ruled out obstructive CAD irrespective of sex, pre-test probability, type of complaints and number of risk factors with a 100 % certainty. Furthermore, a mild CAC score ruled out obstructive CAD in patients with low – intermediate PTP or non-anginal complaints with 100 % certainty.

Conclusion: When available, CAC on non-gated chest CT can accurately rule out obstructive CAD and can therefore function as a radiation-free and cost-free gatekeeper for additional imaging in patients presenting with stable chest pain.

1. Introduction

The accurate evaluation of chest pain for diagnosis of coronary artery disease (CAD) is a key feature of out-patient care in cardiology. Daily, cardiologists and general practitioners are tasked to accurately rule-out obstructive CAD in patients presenting with stable chest pain. Simultaneously, they are expected to limit unnecessary diagnostic testing for ultimate cost-effective patient care and to decrease test and cost burden.

Unfortunately, the tools that can be applied in CAD assessment are limitedly effective. Qualitive risk scores have shown to be limited in their ability to predict coronary events or rule out CAD [1]. Therefore, additional imaging is required based on patients' pre-test probability (PTP). Unfortunately, currently applied methods generally result in an overestimation of patients' PTP for obstructive CAD. Subsequently, additional imaging is often performed. This combination of initial risk-overestimation and often performed additional imaging leads to a low diagnostic yield for obstructive CAD [2].

To enhance patient-tailored risk estimation, guidelines (i.e. ESC and

* Corresponding author at: Leiden University Medical Center, Department of Cardiology, Albinusdreef 2, 2333ZA Leiden, The Netherlands.
E-mail address: j.w.jukema@lumc.nl (J.W. Jukema).
[1] Leiden University Medical Center, Albinusdreef 2, 2333ZA Leiden. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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ACC/AHA) advise additional risk modification based on coronary artery calcium (CAC) as assessed by the Agatston score on a dedicated cardiac computed tomography (CT) scan [3,4]. Studies have shown that CAC severity is equally well determined on routine non-gated chest CT [5–8]. According to recent literature, in 10 % of all patients suspected of CAD [9] a prior non-gated chest CT has been performed for a non-cardiac indication. This scan is suitable for assessment of CAC and thus forms a resource to enhance patient-specific risk assessment for CAD. These data are available at the first consultation at the cardiologists, with no extra costs or radiation exposure. Unfortunately, this source of information on patients' risk for obstructive CAD often remains unexploited. Potentially, this readily accessible method could specify patients' risk and tailor downstream testing with coronary CT angiography (CCTA). Therefore, this study aims to investigate the clinical utility of assessment of CAC on non-gated chest CT for risk stratification of patient with chest pain.

2. Methods

2.1. Patients

The patient population consists of patients referred for a CCTA after presenting with stable chest pain at the outpatient cardiology clinic of the Leiden University Medical Center (LUMC).

For this retrospective analysis, we selected all patients in whom a CCTA was performed between 2010–2021, either for presentation of chest pain or because of increased risk for CAD due to their cardiovascular risk profile. A total of 2159 patients were selected. Subsequently, all patients with known CAD, percutaneous coronary intervention, and coronary artery bypass graft, were excluded. The remainder of patients ($n = 2100$) was screened for previously performed chest CT. Only patients ≥ 30 years old and with a CT performed in ≤ 7 years before the first presentation at the out-patient clinic were included for this study. Ultimately, 170 (8 % of 2100) patients of 32–88 years were included. The selection of patients is depicted in **Supplementary file (Fig. 1)**.

Furthermore, we determined each patient's pre-test probability (PTP) following the ESC guidelines of 2019 [3]. Patients' type of complains were obtained from medical records on their first presentation with stable chest pain complaints at the outpatient cardiology clinic. Complaints were classified according to the traditional classification of suspected anginal symptoms from the current ESC guidelines [3]. Based on type of complaints, triggering factors and response to rest of nitroglycerin. Subsequently, patients were stratified according to PTP-categories, defined as "low" (PTP of ≤ 5 %), "intermediate" (PTP of 6–15 %), or "high" (PTP of > 15 %), and analyzed accordingly. In addition, patients' medical records were screened for presence of cardiovascular risk factors e.g. diabetes mellitus, hypertension, and smoking. These were measured at first presentation at the outpatient cardiology clinic. To analyze generalizability we screened patients without a non-gated CT for the prevalence of comorbidities as well. The hospital's ethical review board waived the need for informed consent.

2.2. Image acquisition and evaluation

Non-gated chest CT has been performed as part of routine non-cardiac care or as a follow-up of other diseases (e.g. lung nodules), prior to patients' referral for CCTA. The specific scan protocol was different per indication (Canon Medical Systems, The Netherlands). CAC was assessed on scans with a slice thickness of 1 mm. Two readers with experience in assessment of CCTA and CAC performed CAC-assessment, without knowledge of patients CCTA and ICA results i.e. CAD burden. They were therefore blinded for CCTA and ICA results.

There are several methods for assessing CAC on non-gated chest CT. According to recent literature, simple visual assessment of CAC with severity quantified on an ordinal scale can accurately predict patients CAD burden, equally well as the Agatston score (AS) [10,11]. For the present study this previously described visual ordinal score was used [12]. This method is most easily applied and time-efficient, with a mean evaluation time under one minute [13]. The assessment of CAC on these non-gated scans in not hampered by differences in axial slice-thickness [5,14], radiation dose [15,16] or contrast enhancement [17]. Furthermore, this method correlates excellently with the AS on cardiac CT ($R = 0.81–0.84$) and with the prognosis of patients [5,7,12]. Calcification was defined as pixels with the same visual brightness as bone (e.g. from the sternum). The extent of calcification in the right coronary artery, the left main, the left anterior descending, and the ramus circumflex including secondary branches (e.g. diagonal, marginal, posterolateral) was graded with a score ranging from 0 to 3. Score 0 indicated no calcification, whereas 1 indicated that less than a third of the overall length (based on simple visual assessment) of coronary artery was calcified, a score of 2 indicated that less than two third of the coronary artery calcified, and 3 more than two third of the coronary artery calcified. The summed score ranged from 0 to 12. For our analysis patients were stratified into 3 categories, defined as no (0), mild [1–3], and severe [4–12] CAC [11,16]. These categories roughly correspond with the Agatston CAC categories 0, 1–100, >100 [7].

CCTA was performed using 320-slice scanners and analyzed according to current guidelines from the Society of Cardiovascular Computed Tomography (Canon Medical Systems, The Netherlands) [18]. Patients were scanned according to a previously described protocol [19]. Patients were screened for atherosclerosis, with plaque categorized as calcified and non-calcified. Obstructive CAD was defined as stenosis for which invasive coronary angiography (ICA) is recommended according to the CAD-RADS [20]. Therefore, obstructive CAD was defined as stenosis of ≥ 70 % and non-obstructive CAD as stenosis of < 70 %. Extensive calcifications herein form a challenge as they increase the risk of overestimation of CAD lesions and false positives [21]. If the blooming artefacts complicated determining the stenosis grade and obstructive CAD could not be ruled out, the patient was categorized as having obstructive CAD.

Ultimately, as the proximal location of CAC in the left main is associated with increased patients' risk [22], we analyzed whether patients showed extensive calcifications in the left main when no CAC was observed in the other arteries.

2.3. Statistical analysis

Statistical analyses were performed using IBM SPSS version 25.0. Dichotomous variables were described as numbers (%) and continuous variables were reported as mean ± standard deviation or median (IQR). CAC severity groups were compared using a One-way ANOVA or a Kruskal Wallis test for numerical outcomes and a Chi-square test for dichotomous outcomes.

Stratified analyses were made for gender, pre-test probability, number of risk factors and type of complaints, to investigate the influence of these factors on the negative predictive value of CAC.

To validate the accuracy and reliability of CAC-assessment performed during this study, the interrater reliability analysis and inter-observer agreement were analyzed with intra class correlation (ICC) and kappa-statistics.

3. Results

Patient characteristics are described in Table 1 and 2. The mean age was 59 ± 10 and was significantly different between the CAC severity groups ($p < 0.01$). The mean BMI was 27 ± 5 kg/m^2 and 35 % were male. A total of 42 % of patients presented with hypertension, 11 % with diabetes, 25 % with hypercholesteremia, and 39 % had a positive family history for CAD. The prevalence of smoking was 39 % and was significantly different among the CAC severity groups ($p < 0.01$). In terms of complaints, the majority of patients presented with non-anginal or atypical complaints (35 % and 30 % respectively). Only 7 % presented

Table 1
Baseline characteristics of the study population*, n = 170.

	All	*No CAC (n = 96)*	*Mild CAC (n = 56)*	*Severe CAC (n = 18)*	P-value
Age, years	58.7 ± 10.3	54.9 ± 9.5	62.3 ± 9.0	67.9 ± 8.4	**<0.01**
Sex, men, %	59 (34.7)	29 (30.2)	23 (41.1)	7 (38.9)	0.37
BMI, kg/m^2	27.2 ± 5.0	27.6 ± 5.3	26.7 ± 4.3	27.0 ± 5.8	0.57
Total Cholesterol, mmol/L	5.5 ± 1.3	5.5 ± 1.2	5.5 ± 1.2	5.6 ± 2.1	0.94
Comorbidities					
Hypertension**, %	72 (42.4)	39 (40.6)	23 (41.1)	10 (55.6)	0.49
Diabetes, %	18 (10.6)	8 (8.3)	5 (8.9)	5 (27.8)	**0.04**
Hypercholesterolemia**, %	42 (24.7)	19 (19.8)	17 (30.4)	6 (33.3)	0.23
ESRD/CKD, %	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
PE, %	6 (3.5)	2 (2.1)	4 (7.1)	0 (0.0)	0.18
Family history					
CAD/MI +	67 (39.4)	39 (40.6)	18 (32.1)	10 (55.6)	0.20
History of					
Cardiovascular disease, %					
AF/AFI	11 (6.5)	5 (5.2)	6 (10.7)	0 (0.0)	0.59
Valvular abn	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
CVA/TIA	6 (3.5)	3 (3.1)	2 (3.6)	1 (5.6)	0.38
PVD	5 (2.9)	2 (2.1)	3 (5.3)	0 (0.0)	0.75
HFrEF	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
HFmEF	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
HFpEF	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Smoking, %					**<0.01**
Yes	66 (38.8)	26 (27.1)	29 (51.8)	11 (61.1)	
Current	18 (10.6)	14 (14.6)	2 (3.6)	2 (11.1)	
Former	48 (28.2)	12 (12.5)	27 (48.2)	9 (50.0)	
Alcohol %					0.24
Yes (≥1/week)	57 (68.7)	35 (72.9)	18 (69.2)	4 (44.4)	
Complaints					
Non-anginal, %	59 (34.7)	38 (39.6)	15 (26.8)	6 (33.3)	0.28
Atypical, %	51 (30)	30 (31.3)	15 (26.8)	6 (33.3)	0.80
Typical, %	12 (7.1)	6 (6.3)	6 (10.7)	0 (0.0)	0.27
Dyspnea d'effort, %	48 (28.2)	22 (22.9)	20 (35.7)	6 (33.3)	0.21

*All data are presented as mean ± SD or as number (%).
AF = Atrial fibrillation, AFI = Atrial flutter, Abn = Abnormalities, BMI = Body mass index, CAD = Coronary artery disease, CKD = Chronic kidney disease, CRP = C-reactive protein, CVA/TIA = Cerebrovascular accident/Transient ischemic attack, DVT = Deep venous thrombosis, ESRD = End-stage renal disease, HFpEF, HFmEF, HFrEF = Heart failure with preserved, mid-range, reduced ejection fraction, PE = Pulmonary embolism, PVD = Peripheral vascular disease.
**Hypertension: a systolic blood pressure > 130 mmHg or a diastolic blood pressure > 80 mmHg or taking medication for hypertension, Hypercholesterolemia: total cholesterol > 200 mg/dL or ratio greater than 5–1.

with typical complaints, and 28 % with dyspnea d'effort. According to PTP, 17 % of patients were categorized as low risk, 48 % categorized as intermediate, and 35 % as high risk.

The comparison of baseline characteristics between patients with and without a non-gated CT to analyze generalizability, is described in **Supplementary file Table 1**. The prevalence of comorbidities between the patient groups was mostly similar, with the exception of age, smoking and family history. Patients with a non-gated CT were older and had a higher prevalence of smoking. Therefore, this study

Table 2
Distribution of risk factors, PTP and CCTA results for CAC categories*, n = 170.

	All	*No CAC (n = 96)*	*CAC mild (n = 56)*	*Severe CAC (n = 18)*	P-value
CCTA					
Obstructive CAD, %	13 (7.6)	0 (0.0)	6 (10.7)	7 (38.9)	**<0.01**
No obstructive CAD, %	157 (92.4)	96 (100.0)	50 (89.3)	11 (61.1)	
Time between chest CT and CCTA, months	8.5 (1–30)	7.5 (1–34)	12 (1–32)	2 (0–23)	0.56
<1 month	34 (20.0)	17 (17.7)	11 (19.6)	6 (33.3)	0.66
≤5 years	124 (72.9)	72 (75.0)	42 (75.0)	10 (55.6)	
>5 years	12 (7.1)	7 (7.3)	3 (5.4)	2 (11.1)	
PTP categories					**<0.01**
PTP low (%)	29 (17.1)	25 (26.0)	4 (7.1)	0 (0.0)	
PTP intermediate (%)	82 (48.2)	49 (51.0)	24 (42.9)	9 (50.0)	
PTP high (%)	59 (34.7)	22 (22.9)	28 (50.0)	9 (50.0)	
N of risk factors					**0.03**
No risk factors, %	32 (18.8)	21 (21.9)	9 (16.1)	2 (11.1)	
One risk factor, %	52 (30.6)	35 (36.5)	16 (28.6)	1 (5.6)	
≥2 Risk factors, %	86 (50.6)	40 (41.7)	31 (55.4)	15 (83.3)	

*All data are presented as median (IQR) or as number (%).
CAC = coronary artery calcium, CAD = coronary artery disease, CT = computed tomography, CCTA = coronary computed tomography angiography, PTP = pre-test probability, PTP low ≤ 5 %, PTP intermediate 6–15 %, PTP high > 15 %.

population was more prone to CAD. The number of risk factors was equally distributed among patients with and without a non-gated CT.

3.1. Chest CT and CCTA results

The interrater reliability between the two observers was excellent, ranging from 0.93 to 0.98 ($p < 0.01$). The overall agreement was excellent as well, with a kappa of 0.96. The ICC and agreement are described in **Supplementary file (Table 2, Fig. 2, Table 3, Figure 3)**.

The CCTA results are described in Table 2 and depicted in Fig. 1. The median time between prior chest CT and the first presentation of patients at the outpatient clinic was 9 (IQR 1–30) months. The majority (93 %) of patients had a prior chest CT within 5 years before the first consult.

After categorization based on CAC severity, in 96 (56 %) patients no CAC was observed, 56 (33 %) patients showed only mild CAC (i.e., a CAC score of 1–3) and 18 (11 %) patients showed severe CAC (i.e. a CAC score of ≥ 4). Of particular interest, the percentage of patients without obstructive CAD on CCTA was significantly different between the CAC severity groups ($p < 0.01$). None of the patients with a CAC score of zero showed obstructive CAD, yielding a negative predictive value (NPV) of 100 %. The time-interval between chest CT and presentation was similar among the CAC severity groups. Only 12 patients had a chest CT performed in > 5 years before the first consult. In these patients a CAC score of 0 yielded a NPV of 100 %. Therefore, no difference in negative predictive power was observed between patients with short (i.e. ≤ 5 years) and long (i.e. > 5 years) time-interval.

In the mild CAC group only a few patients (n = 6) had obstructive CAD, still yielding a NPV of 89 %. When female and male patients were compared, similar trends were observed. In both sexes no patients with a CAC score of zero showed obstructive CAD on CCTA. Furtherly, per increase in severity-category the percentage of patients without

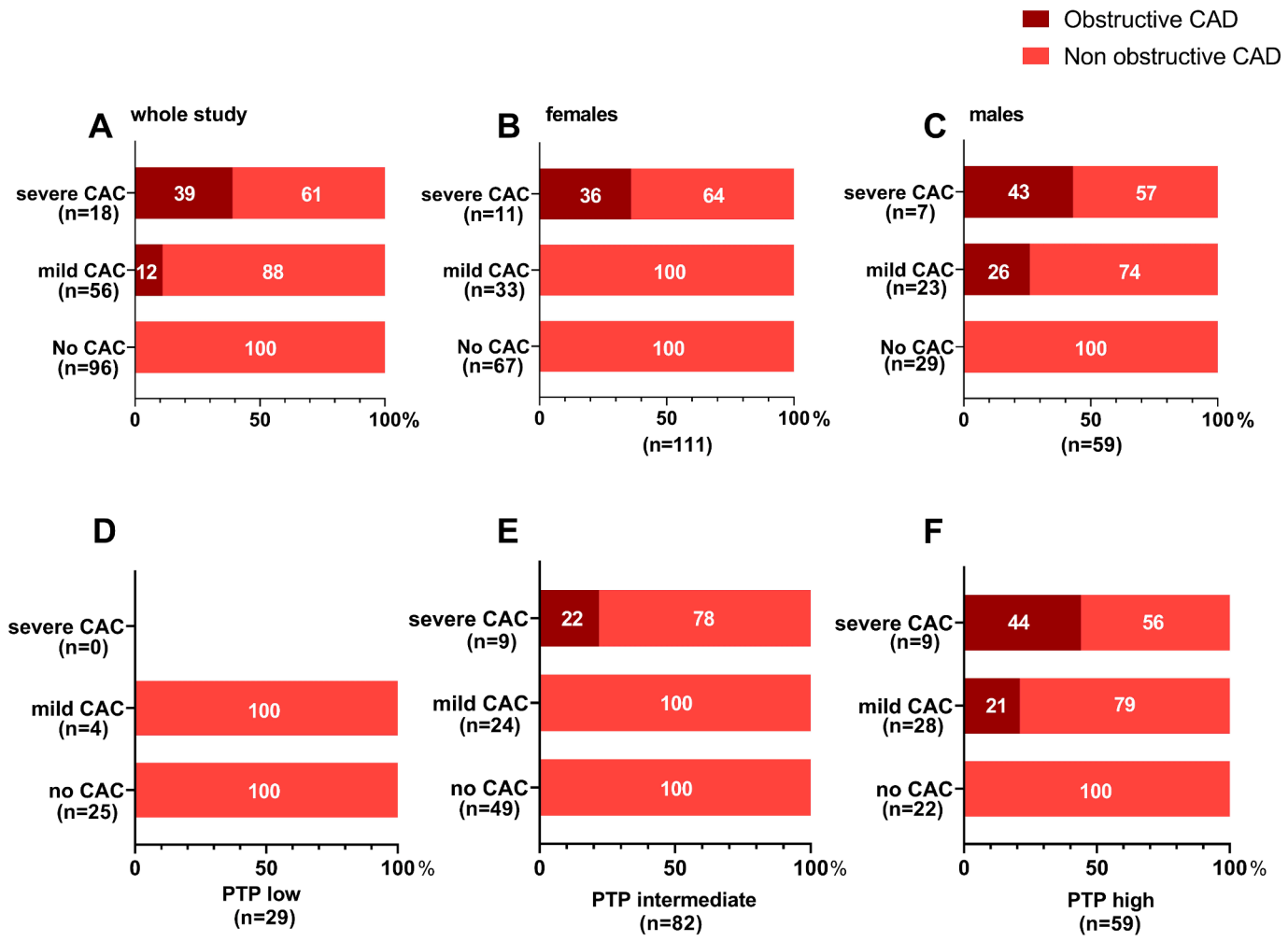

Fig. 1. CCTA results A: Distribution of obstructive vs non-obstructive CAD in all patients B: Distribution of obstructive vs non-obstructive CAD in female patients C: Distribution of obstructive vs non-obstructive CAD in male patients D: Distribution of obstructive vs non-obstructive CAD in patients with a PTP of ≤ 5 % E: Distribution of obstructive vs non-obstructive CAD in patients with a PTP of 6–15 % F: Distribution of obstructive vs non-obstructive CAD in patients with a PTP of > 15 %.

obstructive CAD decreased. In females this was resp. 100 %, 100 % and 55 % ($p < 0.01$) and in males this was resp. 100 %, 75 %, 38 % ($p < 0.01$), following the trend of the entire study cohort.

Of interest, 7 % of patients had a CCTA where stenosis grade was difficult to assess due to the blooming artefacts of extensive calcifications. Furthermore, only 4 patients showed a single calcified spot in the left main when no further calcifications were observed in the other coronary arteries. On CCTA these lesions were defined as wall

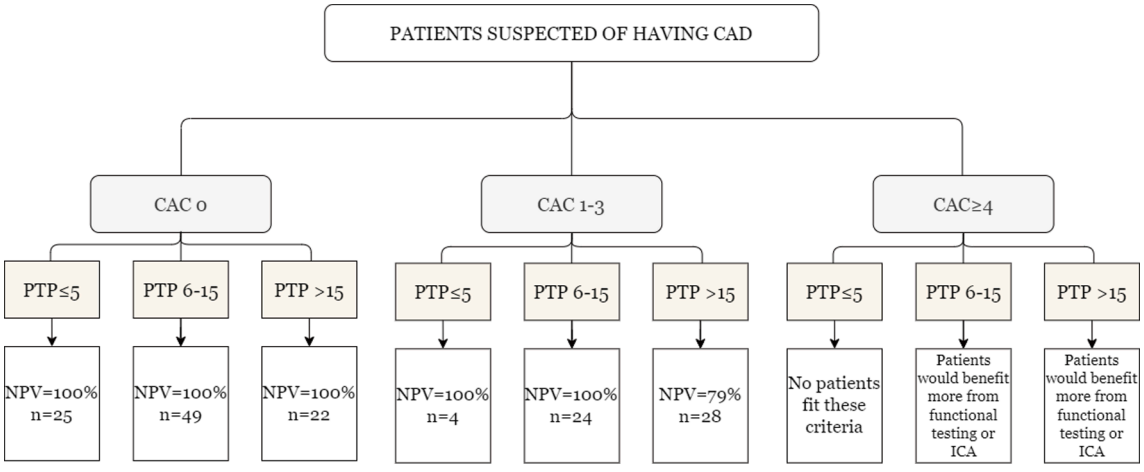

Fig. 2. Decision tree in patients with stable chest pain based on CAC and PTP *CAC = coronary artery calcium, NPV = negative predictive value for obstructive CAD, PTP = pre-test probability.

abnormalities.

3.2. CCTA and PTP categories

Further analyses stratified according to PTP are depicted in Figs. 1 and 2 and described in Table 2. The percentage of patients with obstructive CAD on CCTA was significantly different between the CAC severity groups ($p < 0.01$) in each PTP category. Overall, absence of CAC on non-gated CT ruled out obstructive CAD on CCTA irrespective of PTP. None of the patients with a low PTP (i.e. PTP $\leq$ 5 %, n = 29) showed obstructive CAD, no – mild CAC (i.e. 0, 1–3) yielded a NPV of 100 % for obstructive CAD in this category. More pertinently, even in patients with an intermediate PTP (i.e. PTP 6–15 %, n = 82), a no – mild CAC score ruled out obstructive CAD with a 100 % certainty. In patients with an intermediate PTP and severe CAC, 78 % showed no obstructive CAD. Mentionable, in patients with a high PTP (i.e. PTP > 15 %, n = 59), the prevalence of obstructive CAD was low (22 %). Even in these high-risk patients, the negative predictive value of no – mild CAC was adequate (88 %).

3.3. CCTA and type of complaints

Results of analysis stratified to type of complaints patients presented with are depicted in **Supplementary file (Figure 4 and 5)**. The percentage of obstructive CAD was significantly different between the CAC severity groups ($p < 0.01$) in each stratum. In patients with non-anginal complaints (n = 59) the majority (97 %) had a CCTA without obstructive CAD. The NPV of no – mild CAC for absence of obstructive CAD in this group was 100 %. Similarly, less than 10 % of patients with atypical complaints (n = 51) showed obstructive CAD. No – mild CAC yielded a NPV of 93 %. Unexpectedly, in patients presenting with typical complaints (n = 12) no severe CAC was found. Even in this group the NPV of no – mild CAC was 100 %. Lastly, in patients with complaints of dyspnea d' effort (n = 48) the NPV of no – mild CAC was 93 %.

3.4. CCTA and number of risk-factors

In **Supplementary file (Figure 6 and 7)** the analysis of patients according to number of risk-factors is shown (i.e. no risk factors, one risk factor or $\geq$ 2 risk factors). For this analyses we incorporated the following cardiovascular risk factors: hypertension, diabetes mellitus, hypercholesterolemia, end-stage renal failure or chronic kidney disease, family history of CAD and smoking. A significant difference in percentage of patients without obstructive CAD was observed between the CAC severity groups ($p < 0.01$) in each stratum. The absence of CAC ruled out obstructive CAD, irrespective of the number of risk-factors. Furthermore, none of the patients without risk-factors and mild CAC showed obstructive CAD on CCTA. In patients with one risk-factor, the negative predictive value of no – mild CAC for obstructive CAD was 92 %. When patients had more than one risk-factor, the negative predictive value of no – mild CAC for obstructive CAD decreased slightly to 97 %.

In **Supplementary file (Figure 8)** a case-example is provided from one of the patients in this study population.

4. Discussion

This study is the first to assess the clinical value of CAC on non-gated CT to tailor downstream testing with CCTA in patients with stable chest pain. In 10 % of patients presenting with stable chest pain, a previous CT has been performed on which coronary calcium can be visually assessed. Assessment of CAC has excellent ability to rule out obstructive CAD, thus avoiding unnecessary testing. The absence of CAC on non-gated CT could rule out obstructive coronary artery disease with 100 % certainty, irrespective of gender, pre-test probability, type of complaints and number of risk factors. In patients with a low – intermediate PTP ($\leq$15 %), patients presenting with non-anginal complaints or patients presenting with no risk-factors, even a mild calcium score was found to rule out obstructive CAD wit 100 % accuracy. Performing additional CCTA in these patients could have been waived based on their CAC on freely available CT scans. According to the analysis for generalizability, the patients in this study would be more prone to CAD. However, even in this relatively higher risk population, the majority had CAC 0 and the negative predictive value of no – mild CAC (i.e. 0, 1–3) for obstructive CAD was high.

When analyzing CAC, each vessel was scored based on their individual length, however not based on their proximity to the aorta. Arguably, stenosis in the left main and proximal LAD are of more significance than stenosis in more distal locations. Williams et al.(22) investigated the additive value of commenting on the location of calcifications. They reported that commenting on location was only of value when extensive calcifications were seen in the left main and proximal LAD. However, all of these patients had an increased risk based on their high total Agatston score alone. None of the patients in our study showed extensive calcification in the left main with otherwise normal coronary arteries.

The presentation of chest pain is fairly common, affecting 20 % to 40 % of the general population during a lifetime. In primary care the presentation of stable chest pain takes up 1 % of all consultations per year in the UK [23] and even up to 3 % in the Netherlands and Belgium [24]. Furthermore, CAD is associated with enormous healthcare expenditures [25]. For these reasons, a cost-effective, yet safe diagnostic work-up in patients suspected of CAD is paramount. Non-invasive imaging is performed based on patients' pre-test probability of obstructive CAD. Most guidelines recommend basing patients' PTP on typicality of anginal complaints [3,4,26]. However, studies have shown that physicians often overestimate the typicality of anginal complaints or fear to miss a life-threatening disease [27,28]. According to Vester et al. 82 % of patients referred for additional non-invasive imaging based on their chest pain presentation, does not have CAD[2]. This leaves the diagnostic yield of additional imaging still relatively low, and the need for a stronger gatekeeper high.

Zhou et al compared currently applied strategies for risk assessment (i.e., 2016 NICE, 2019 ESC guidelines and PROMISE-risk tool) with CAC assessment [29] on cardiac CT to accurately rule out CAD. CAC superseded in effectively deferring additional cardiac testing (NPV of 92–94 %). These results coincide with a study by Rijlaarsdam et al. who reported that CAC assessment improved the ability of risk models to safely rule-out obstructive CAD [30]. On top of the ability to improve risk estimation and patient-tailor downstream testing, CAC-assessment appears to reduce health care expenditures as well. Gomes et al. [31] showed that costs per correctly diagnosed patient with CCTA reduced with 40 % when CAC-assessment on cardiac CT was firstly implemented. Our study is the first in exploring this possibility with CAC on non-cardiac CT. The NPV in this study was similar to that of Zhou et al. (100 % for CAC 0 and 89 % for CAC 1–3).

A factor believed to influence the otherwise evident discriminative power of CAC. The association between the extent of CAC and age is strong and previous studies have found a relatively low prevalence (<16 %) of CAC in younger individuals i.e. < 45 years [32]. This raises the question whether performance in patients under the age of 45 years is clinically relevant. Conversely, the presence of CAC in the younger population can early identify high-risk individuals and enables early implementation of preventive therapy. For the present manuscript we have selected patients $\geq$ 30 years old, as pre-test probability estimations include patients $\geq$ 30 years old. Recent studies of The Coronary Artery Calcium Consortium [33,34] show a non-negligible prevalence of CAC among very high-risk young individuals and the strongest association with cardiac death in comparison to older subgroups. When CAC is observed on previously performed scans in a young patients, this could early identify this patient as a high risk individual.

Another theoretical argument against performing CAC assessment as a risk classifier is an inability to identify "non-calcified plaque" or "low-

attenuation plaque". Recent studies have identified this feature of patients' plaque as a high-risk feature for myocardial infarction and reported a prevalence ranging from 6 % to 44 % among patients with a CAC score of 0 [35]. Possibly, in patients with a high suspicion of obstructive CAD a critical non-calcified plaque could be present. Still, for risk stratification of the vast majority of low-risk patients with stable chest pain a rough and robust estimate of disease burden is well above the mark. Lastly, Senoner et al. 2 reported that 26 % of patients with a calcium score of 0 showed CAD on CCTA. Subsequently, only a few patients (0.5 %) experienced MACE.

Several studies have compared the estimation of CAC on ECG-gated cardiac CT versus on non-gated chest CT. Generally, CAC on non-gated CT is reported as a strong predictor of cardiovascular events and mortality. Blair et al. even reported it as equally good as the Agatston score on gated CT [5]. Furthermore, a great to excellent correlation was found between the Agatstson score and ordinally scored calcium ranging from R = 0.81–0.86 [7,9,12].

In terms of clinical utility, the benefit of CAC on non-gated chest CT is the easy applicability and early-on availability (i.e. first consultation). Studies have shown that general practitioners might benefit from safe prediction rules and/or fast accessible tests to enhance efficiency of patients' referral [28]. Additionally, besides ruling out obstructive disease, the assessment of CAC on non-gated chest CT could help in selection of appropriate additional imaging tests; when patients coronary arteries are extensively calcified, the diagnostic yield of anatomical tests like CCTA decreases and deployment of functional tests for ischemia becomes more efficient [21,36]. Despite these benefits, this abundant resource on patient-specific risk information remains untapped and its penetration into clinical practice ultimately minimal. Our recommendation, based on our results, would be to check whether a previously performed non-gated CT is available in patients who present with stable chest pain. When available, the extent of CAC can be used to accurately tailor downstream imaging for CAD.

4.1. Limitations

Due to strict exclusion criteria (**Supplementary file Figure 1**) this study cohort is relatively small. Furthermore, our results have shown that no patients with typical chest pain show severe calcification on their CCTA. Possibly, these results are biased because most patients with typical chest pain are directly referred for invasive testing without a prior CCTA and would therefore not be included in this study. Coincidentally, only 7 % of this study population is formed by patients with typical angina. Another limitation is the use of CCTA as golden standard, as comparison between CCTA and invasive coronary angiogram suggest severity overestimation of stenosis by CCTA [37]. This may be caused by blooming artifacts due to heavily calcified lesions, motion artifacts, or the usage of different reference points for evaluation of luminal size in plaques.

An important factor for the predictability of CAC on non-gated chest CT is the length of the time-interval between the prior chest CT and first presentation of chest pain. The warranty period of CAC on gated CT is described as 3–7 years [38], with the notion that conversion from CAC = 0 to a CAC score of > 10 would take an average 5–8 years depending on ASCVD risk category and age. Furthermore, patients did not convert to severe CAC (CAC > 100) until 9 years and even after 10 years the conversion to severe CAC was rare. These higher CAC scores may be more clinically actionable than low CAC burdens. For the most robust analysis, we have applied a maximal interval of 7 years between the non-gated CT and first consultation at the out-patient clinic. Only 12 patients had a time-interval of > 5 years. In these patients CAC 0 still ruled out obstructive CAD on CCTA. Possibly this patient group is relatively small to extrapolate these results to larger patient cohorts. This study solely focusses on stable patient with suspected chronic coronary syndrome. It would be of interest to explore the applicability in patients with unstable complaints. However, it should be noted that in these patients a plaque rupture can occur also in non-obstructive or non-calcified atherosclerotic lesions.

Although it is beyond the scope of this manuscript, focusing on stable chest pain assessment of CAC on non-gated CT could have clinical value in several other patient populations. In asymptomatic patients CAC assessment can be applied as a tool for cardiovascular risk assessment. Furthermore, in cancer patients, who are more and more prone to CAD due to improved survival and long-term side effects of cancer medication, evaluation of CAC can be used as a tool of cardiac surveillance. Especially, since these patients often undergo routine non-gated CT for follow up on their disease.

4.2. Conclusion

This study is the first to assess the value of CAC on non-gated CT to tailor downstream testing with CCTA. We observed that in patients with stable chest pain an ordinal calcium score of 0 on non-gated chest CT can accurately rule out obstructive CAD. Furtherly, the presence of mild coronary calcifications can accurately rule out obstructive CAD in patients with intermediate PTP, low risk profile or non-anginal symptoms. When available, this radiation-free and cost-free available source of information on patient-specific risk-assessment should be integrated to tailor downstream additional testing in the daily practice of cardiology.

CRediT authorship contribution statement

Roos A. Groen: Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Paul R.M. van Dijkman:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **J. Wouter Jukema:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Jeroen J. Bax:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Hildo. J. Lamb:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Michiel A. de Graaf:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent

The hospital's ethical review board waived the need for informed consent.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101418.

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