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The prognostic value of automated coronary calcium derived by a deep learning approach on non-ECG gated CT images from ^{82}Rb-PET/CT myocardial perfusion imaging

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ABSTRACT

Background: Assessment of both coronary artery calcium(CAC) scores and myocardial perfusion imaging(MPI) in patients suspected of coronary artery disease(CAD) provides incremental prognostic information. We used an automated method to determine CAC scores on low-dose attenuation correction CT(LDACT) images gathered during MPI in one single assessment. The prognostic value of this automated CAC score is unknown, we therefore investigated the association of this automated CAC scores and major adverse cardiovascular events(MACE) in a large chest-pain cohort.

Method: We analyzed 747 symptomatic patients referred for ^{82}RubidiumPET/CT, without a history of coronary revascularization. Ischemia was defined as a summed difference score≥2. We used a validated deep learning (DL) method to determine CAC scores. For survival analysis CAC scores were dichotomized as low(<400) and high(≥400). MACE was defined as all cause death, late revascularization (>90 days after scanning) or nonfatal myocardial infarction. Cox proportional hazard analysis were performed to identify predictors of MACE.

Results: During 4 years follow-up, 115 MACEs were observed. High CAC scores showed higher cumulative event rates, irrespective of ischemia (nonischemic: 25.8% vs 11.9% and ischemic: 57.6% vs 23.4%, *P*-values <0.001). Multivariable cox regression revealed both high CAC scores (HR 2.19 95%CI 1.43–3.35) and ischemia (HR 2.56 95%CI 1.71–3.35) as independent predictors of MACE. Addition of automated CAC scores showed a net reclassification improvement of 0.13(0.022–0.245).

Conclusion: Automatically derived CAC scores determined during a single imaging session are independently associated with MACE. This validated DL method could improve risk stratification and subsequently lead to more personalized treatment in patients suspected of CAD.

1. Introduction

The prognostic and diagnostic role of myocardial perfusion imaging (MPI) in patients suspected of coronary artery disease (CAD) has been very well established during the past decades [1]. However, this functional test modality is not able to detect subclinical atherosclerosis, or nonflow-limiting coronary stenosis. Additional to this, one of the most thoroughly studied test modalities in the establishment of coronary artery disease (CAD) is the coronary artery calcium (CAC) score [2–5]. CAC is seen as a highly specific manifestation of atherosclerosis and therefore considered to be an excellent anatomic measure of plaque burden [5–7]. There is a growing body of evidence showing that quantitative

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assessment of CAC scores improves the prognostic ability of MPI in the detection of major adverse cardiovascular events (MACE) [8–10].

Considering this clear complementary value of using both MPI and CAC scores, it would be ideal to combine both in preferably one imaging session. Most existing studies performed an additional scan to obtain CAC scores. This leads to a higher effective radiation dose for the patient and often requires manual assessment by a trained physician, which is unfavorable in an era of growing interest for algorithms based on machine learning leading to improved accuracy [11].

We used a previously validated deep learning (DL) method to automatically determine CAC scores on non-ECG-gated low-dose attenuation correction CT (LDACT) images during one single imaging session, without additional scanning [12]. A previously performed study investigated the diagnostic role of this DL method in symptomatic patients undergoing Rubidium-82 (^{82}Rb) PET/CT scanning [13]. The AUC to detect obstructive CAD with MPI improved from 0.87 to 0.91 after the addition of the automated CAC score. Whether this automated CAC score is also associated with MACE is unknown. The aim of this study was therefore to determine the association of automated CAC scores (derived during MPI in one single imaging session) with MACE.

2. Method

The MYOMARKER (MYOcardial ischemia detection by circulating bioMARKERs) study is a prospective single-center observational cohort study of consecutively enrolled outpatient clinic patients aged>18 years with suspected CAD. Patients were included between August 2014 and September 2016 at the Meander Medical Center (Amersfoort, the Netherlands). All patients underwent ^{82}Rubidium PET/CT as part of their diagnostic work up. For the purpose of this study only patients without a history of coronary revascularization were included. The study (NL5078) was approved by the regional Medical Ethics Committee and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. Patients were not involved in the design or recruitment of the study.

A detailed description of the MPI protocol has been published previously [13]. In short, patients were asked to discontinue caffeine- or methylaxanthine-containing food/drinks and theophylline and dypiridamol 48 h prior to the PET/CT scan. Scans were acquired using a hybrid scanner (Biograph CT Flow 64-slice scanner, Siemens Healthcare, Knoxville, Tennessee). Standard acquisition parameters were used e.g. 120kVp and 35 mA. Both rest and stress images were acquired in the same session, regadenoson was administered intravenously as pharmacological stress. The estimated effective radiation dose for the patients was 3.7 mSv. Rate-pressure product was calculated for manual correction of rest flow values.

^{82}Rb-PET/CT MPI results were assessed according to the 17-segment model of the American Heart Association [14]. Semi-quantitative analysis was performed using the summed difference score (SDS) for each patient. Patients were assigned to either positive or negative for ischemia on ^{82}Rb-PET/CT, using SDS≥2 as a threshold for ischemia [15].

CAC scores were determined from the LDACT scan, a standard part of MPI for attenuation correction, using a previously developed algorithm [16,17]. No additional ECG-gated CT images were obtained, nor was the MPI protocol adapted to enable the measurement of CAC scores. Briefly, the lungs are excluded first by the software to identify a region of interest. The software then automatically detects voxels above the standard threshold of 130 Hounsfield Units as CAC using a deep learning approach. No adaptation for the threshold of CAC scores was needed since a protocol with 120kVp, typically used for CAC scoring was used [18]. Calcifications were first labelled according to the presumed affected coronary vessel (left anterior descending including left main coronary artery, left circumflex artery and right coronary artery and then the CAC scores were calculated [19]. Since this method is not (yet) able to distinguish previously placed coronary stents from coronary calcium, patients with prior coronary revascularization were excluded from the analysis.

Patients received a questionnaire to inquire information about cardiac events or other medical procedures after 30 days, 1 year and 3 years. Collection of follow-up was performed per batch of approximately 300 patients and started if the last patients reached the 3 year timepoint. As result slight differences in follow up-time occurred. If patients did not respond to the questionnaire they received a reminder by mail, in case of no response their general practitioner was contacted, or their hospital records were used. This thorough attempt to collect as much follow-up details as possible resulted in follow-up details that were received up to 1 year after the initial invitation to deliver the required questionnaire.

The primary outcome, MACE included all cause death, myocardial infarction and coronary revascularization (percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG)) [20]. Early revascularization within 90 days after MPI was considered to be triggered by the MPI result and therefore excluded [21]. In patients with multiple events, only the first event was considered for survival analysis. All endpoints were adjudicated by two members of the research team, in case of disagreement or uncertainty a third member was involved.

Continuous data are presented as mean ± standard deviation, discrete data as frequencies and percentages. To compare the prevalence of abnormal ^{82}Rb-PET/CT by CAC category, Cochrane's Armitage test for trend was performed. To facilitate comparison with prior studies, a binary cut point of the CAC score (≥400) was used for survival analysis [22]. Patients were divided in four groups: considering both the presence or absence of ischemia and high (≥400)/low CAC score (<400). Cumulative event rates were computed for each category with the Kaplan-Meier method. Survival between groups was compared performing the Log-Rank test. To account for multiple testing post-hoc analysis with the Bonferroni correction was performed. An additional subanalysis without revascularization was performed. Cox-proportional hazard regression analysis was used to identify predictors for MACE. To appropriately account for heterogeneity among the study population, the analysis was adjusted for prespecified covariates, encompassing: age, sex, history of CAD and cardiovascular risk factors [23]. For all regression analyses, the proportional hazard assumption was tested with both a formal test and the Schoenfeld residual plots. No violation of the proportional hazard assumption was found.

To assess the potential clinical impact of the use of the use of this automated CAC score the net reclassification improvement (NRI) was calculated [24,25]. First internal validation was performed with bootstrapping to control for optimism and overfitting, additionally the NRI was calculated. For the computation of the NRI we censored follow up times at 4 years. Risk categories were defined as <5%; 5–7.5%; 7.5–20% and >20% as proposed by Greenland et al. [5]. All hypotheses tests were two-sided with a critical significance level of <0.05. Statistical analysis was performed with R software (R software, version 3.5.1).

3. Results

The complete study population of the MYOMARKER cohort consisted of 1265 patients. MPI was not performed in four patients (0.3%), no informed consent was obtained from 13 patients and 1 patient was lost to follow up. Another 500 patients were excluded because of a history of PCI/CABG. The remaining 747 patients are the subject of this report (Fig. 1). Among them a total of 195 (26.1%) showed an ischemic perfusion defect with SDS ≥2 on ^{82}Rb-PET/CT. The baseline characteristics for the complete cohort and stratified by MPI result are summarized in Table 1. Mean age was 67 (±10) and 50.5% were male. Most common risk factors were hypertension (62.1%) and hypercholesterolemia (50.9%). Patients with a ^{82}Rb-PET/CT positive for ischemia were more often male (45.7% vs. 64.1%, *P* value <0.001). No significant differences between both groups were seen regarding the known cardiovascular risk factors. Patients with ischemia more often had a history

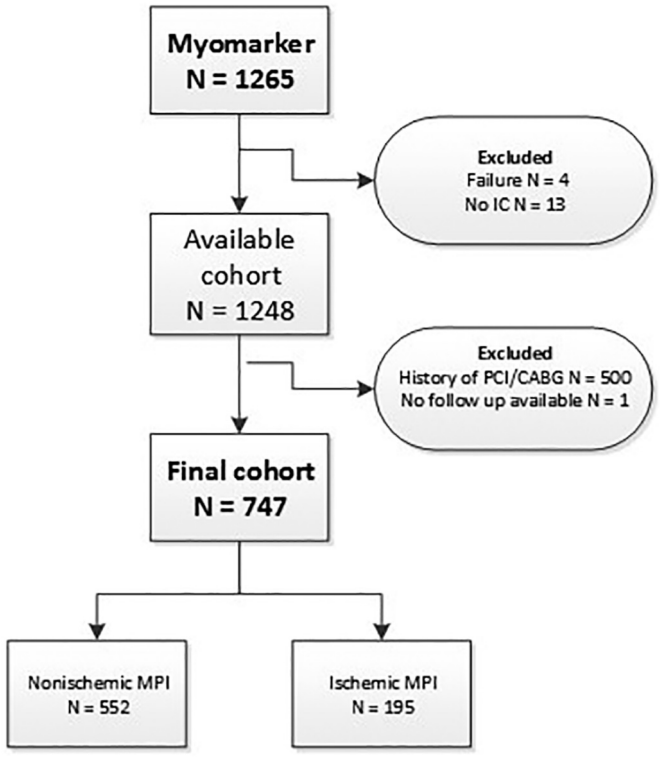

Fig. 1. Flowdiagram for the Myomark study. IC = informed consent, MPI = myocardial perfusion imaging

Table 1
Baseline characteristics.

	Overall	Nonischemic	Ischemic	*P* value[1]
n	747	552	195	
Demographics				
Age, years	67±10	67±10	68±10	0.125
Male sex (%)	377 (50.5)	252 (45.7)	125 (64.1)	<0.001
BMI	27.6±5.2	27.3±5.0	28.3±5.8	0.020
Risk factors				
Current smoking	143 (19.1)	97 (17.8)	44 (22.7)	0.171
Diabetes Mellitus	140 (19.1)	97 (17.8)	42 (21.6)	0.289
Hypertension	464 (62.1)	340 (62.5)	121 (62.4)	1.000
Hypercholesterolemia	380 (50.9)	276 (50.7)	98 (50.5)	1.000
Family history CAD	180 (24.1)	129 (23.7)	49 (25.3)	0.738
Medical history				
Cardiovascular disease	567 (76.0)	413 (75.9)	148 (76.3)	0.996
Coronary artery disease	53 (7.1)	22 (4.0)	31 (16.0)	<0.001
Heart failure	37 (5.0)	24 (4.4)	13 (6.7)	0.288
Atrial fibrillation	119 (15.9)	84 (15.4)	34 (17.5)	0.571
Ischemic CVA	31 (4.1)	20 (3.7)	10 (5.2)	0.494
Drug therapy				
Aspirin	303 (40.6)	211 (38.8)	89 (45.9)	0.101
P2Y12-inhibitors	53 (7.1)	31 (5.7)	21 (10.8)	0.026
Anti-coagulants	140 (18.7)	97 (17.8)	42 (21.6)	0.289
Statin	350 (46.9)	253 (46.5)	92 (47.4)	0.892
ACE/AT-inhibitor	329 (44.0)	229 (42.1)	97 (50.0)	0.069
B-blocker	337 (45.1)	231 (42.5)	105 (54.1)	0.007

Values are shown as mean±SD or frequency with corresponding percentages. CAD = coronary artery disease, CVA = Cerebrovascular accident, AT = Angiontensine II, B-blocker = betablockade.
[1] *P* values for comparison between nonischemic and ischemic ^{82}Rb PET/CT. Ischemia was defined as summed difference score ≥2.

of coronary artery disease (16% vs 4%, *P* value 0.001) and more often used P2Y12 inhibitors (10.8% vs. 5.7%, *P* value 0.026) and beta blockade (54.1% vs. 42.5%, *P* value 0.007).

CAC scores were successfully derived in 726 of the 747 patients. In 21 patients no valid scores could be obtained due to insufficient image quality. In total 126 patients had a CAC score of zero, and a ^{82}Rb-PET/CT positive for ischemia was found in 12% of these patients. The frequency of ^{82}Rb-PET/CT results positive for ischemia increased gradually with an increased CAC score (*P* value for trend <0.001, Fig. 2). An abnormal ^{82}Rb-PET/CT was seen in 38% of patients with a high CAC score (≥400).

Table 2 shows the results of the automatically derived CAC scores stratified by MACE separately for patients with and without ischemia, determined on their ^{82}Rb-PET/CT. The occurrence of MACE was higher in patients with an ischemic ^{82}Rb-PET/CT (31%) result compared to patients without (10%). For both patients with and without ischemia, mean Agatston score was significantly higher in patients with a MACE (400±725 vs. 998±1110, *P* value <0.001 and 593±916 vs. 1443±1427, *P* value <0.001).

Median follow-up time was 3.62 (±0.82) years during which 115 patients reached the outcome MACE. Table 3 shows the occurrence of MACE and its components stratified by MPI result and CAC score. MACE consisted of 24 myocardial infarctions, 48 revascularizations and 43 all cause deaths.

Patients were divided in four groups according to their MPI result and CAC score for the survival analysis. Cumulative event rates differed significantly between the groups (*P* value Log-Rank test <0.001) (Fig. 3). Post-hoc analysis showed, irrespective of the presence of ischemia, a significantly higher MACE rate in patients with high CAC scores compared to patients with low CAC scores (*P* value for both comparisons <0.001). Cumulative event rates in patients without ischemia were 11.9% in patients with low CAC scores and 25.8% in patients with high CAC scores. The difference in cumulative event rates was even more pronounced in patients with ischemia: 23.4% in those with low CAC scores and 57.6% in patients with high CAC scores. Supplemental Fig. 1 shows the same survival analysis but only for the composite endpoint combining all cause death and myocardial infarction. It can be appreciated that the MACE rate was, irrespective of ischemia, significantly higher in patients with high CAC scores (*P* value patients without ischemia <0.001, *P* value patients with ischemia <0.01). These results are consistent with the findings in Fig. 3.

To determine the association of the automated CAC score with MACE, univariable and multivariable cox regression analysis were performed with all preselected covariates (Table 4). Age (HR 1.03 95%CI 1.01–1.05), male sex (HR 2.34 95%CI 1.57–3.48) and a history of CAD (HR 2.77 95%CI 1.69–4.53) were significant clinical predictors of MACE in the univariable analysis. Both established ischemia on ^{82}Rb-PET/CT (HR 3.19 95%CI 2.41–4.60) as well as high automated CAC scores (HR 3.49 95%CI 2.39–5.10) were significant univariable imaging predictors of MACE. After adjustment for all prespecified covariates both ischemia (HR 2.14 95%CI 1.45–3.17) and high automated CAC (HR 2.26 95%CI 1.48–3.46) remained independently associated with MACE.

Addition of the automated CAC scores to a model with all predefined clinical predictors and ischemia yielded a total NRI of 0.13 (95% CI 0.022–0.245) which was significant. The NRI for patients with MACE was not significant 0.070 (95% CI -0.032-0.171) with a correctly reclassification of 19.1% compared to incorrect reclassification of 12.2%. For patients without MACE the NRI was 0.064 (0.018–0.109) In total 19.8% of patients were correctly reclassified compared to incorrect reclassification of 13.4%. Reclassification tables can be found in the supplemental results.

4. Discussion

In this study we showed that automated CAC scores are associated with MACE, irrespective of the MPI results and other prespecified confounders. Our results extend the existing knowledge regarding the combined use of CAC scoring and MPI by the use of an automated DL method that determines CAC from non-ECG-triggered CT images in one single

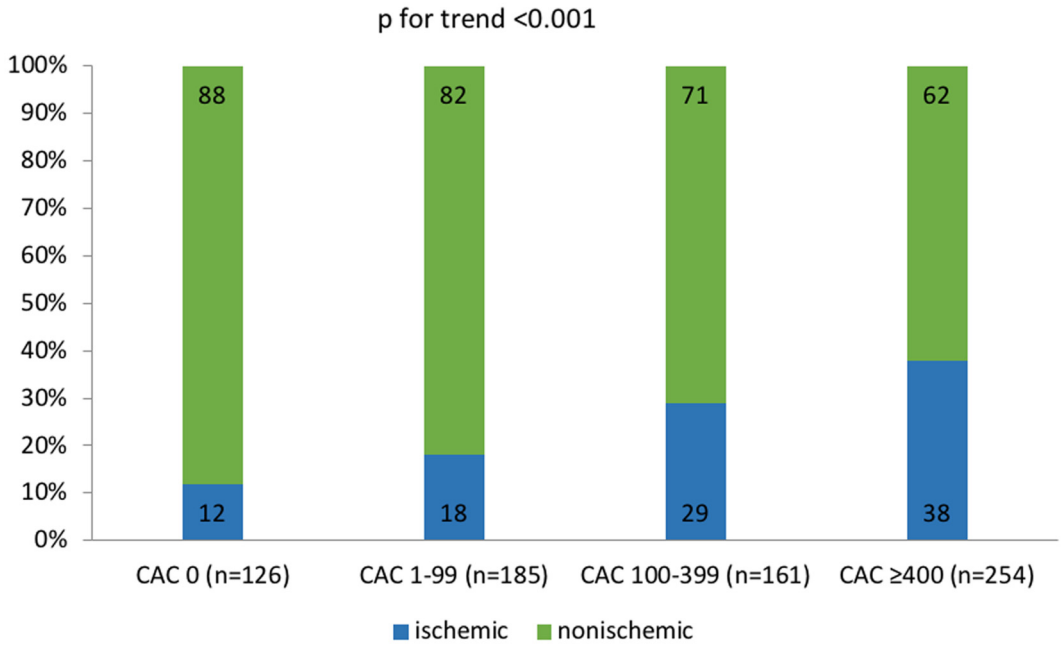

Fig. 2. Prevalence of abnormal MPI results by CAC score. CAC = coronary artery calcium. MPI = myocardial perfusion imaging.

Table 2
CAC results according to MACE stratified by MPI result.

	No MACE	MACE	*P* value
Total	632	115	
Nonischemic	**497**	**55**	
Agatston score	400±725	998±1110	<0.001
Categorical calciumscore			<0.001
0	108 (22.5)	3 (5.5)	
1–99	141 (29.3)	10 (18.2)	
100–399	103 (21.4)	12 (21.8)	
>400	129 (26.8)	30 (54.5)	
Ischemic	**135**	**60**	
Agatston score	593±916	1443±1427	<0.001
Categorical calciumscore			0.001
0	14 (10.8)	1 (1.7)	
1–99	28 (21.5)	6 (10.0)	
100–399	36 (27.7)	10 (16.7)	
>400	52 (40.0)	43 (71.7)	

Agatston score is shown as mean±SD, categorical calciumscores are shown as frequency (%). MACE comprises: nonfatal MI, revascularization and all-cause death. Ischemia was defined as SDS≥2.

imaging session. This DL method has recently been validated for a wide range of chest CT modalities (e.g. lung cancer screening CT, breast cancer CT and CT scans derived for radiotherapy planning) [12]. This method uses non-ECG-triggered CT images obtained for perfusion imaging, as a result no adaptations to the regular MPI are needed and no additional time is required to obtain ECG-triggered images. Most important advantage is that by using the non-ECG-triggered images the effective radiation dose remains the same. The aforementioned validation study showed both an excellent correlation between the DL derived CAC scores and manual CAC scores, and also correct classification of patients to their risk categories [12]. We therefore assume that implementation of this DL method to automatically determine CAC scores on ^{82}Rb-PET/CT images could have immediate clinical consequences.

In our cohort the prevalence of an abnormal ^{82}Rb-PET/CT result gradually increased by CAC score (*P* for trend <0.001). Since CAC is seen as marker to determine the extent of coronary sclerosis, this finding seems logical, as more coronary sclerosis translates into higher risk for future events. This finding is consistent with previous studies [8,9,26]. However, the extent of coronary sclerosis, e.g. a high CAC score is not the same as obstructive stenosis, e.g. stress-induced ischemia [27]. Normal ^{82}Rb-PET/CT results were found in 62% of the patients with high (≥400) CAC scores. Our results are in line with existing literature and confirm the poor correlation between CAC scores and flow-limiting obstructions [8,28,29]. In addition, a discrepancy between CAC scores and ^{82}Rb-PET/CT results was also found at the other end of the spectrum. Low CAC but abnormal ^{82}Rb-PET/CT was found in 12% of the patients. It has been suggested, and it is very likely that this is caused by noncalcified obstructive lesions [9]. Despite these discrepancies, CAC scores were independently associated with MACE in this study cohort.

Cox proportional hazard regression analysis showed that patients with high CAC scores had a 2.26 times higher risk of MACE compared to patients with a low CAC score. This association was found to be irrespective of known cardiovascular risk factors and the presence of ischemia on MPI. Several other studies show the same result, in both PET and

Table 3
MACE stratified by ischemia and CAC.

	No ischemia/low CAC *n=394*	No ischemia/high CAC *n=159*	Ischemia/low CAC *n=99*	Ischemia/high CAC *n=95*
MACE	**24 (6.2%)**	**32 (20.2%)**	**17 (17.1%)**	**42 (44.2%)**
All cause death	16 (4.1%)	20 (12.6%)	4 (4.0%)	3 (3.2%)
Myocardial infarction	3 (0.8%)	6 (3.8%)	3 (3.0%)	12 (12.6%)
Revascularization	5 (1.3%)	6 (3.8%)	10 (10.1%)	27 (28.4%)

MACE = Major cardiovascular event. Ischemia was defined as SDS≥2. CAC = Coronary artery calcium scores. Low ≤400, high = ≥400.

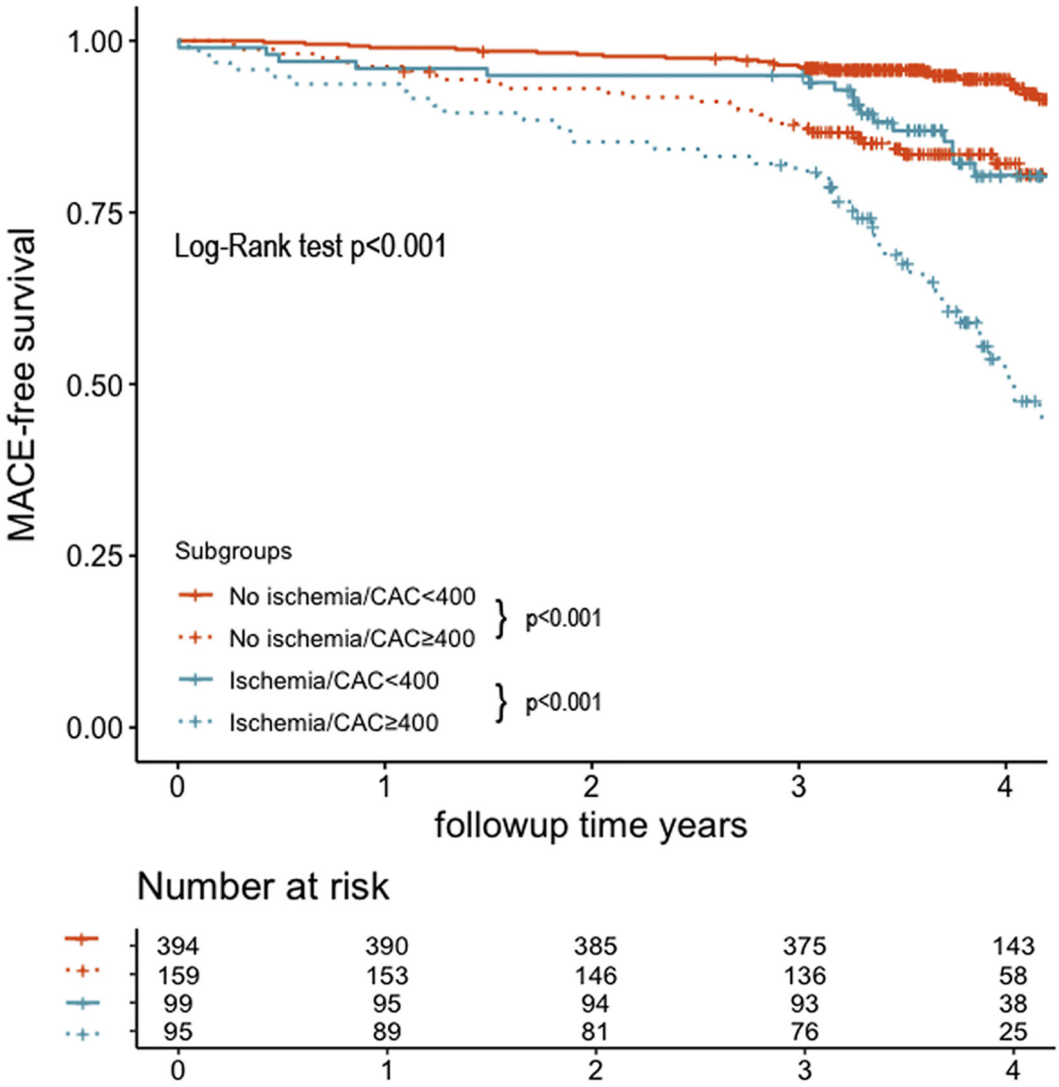

Fig. 3. MACE free survival curves according to MPI result and CAC score. Patients were divided in four groups according to both MPI results and CAC scores. *P* value for comparisons among subgroups were adjusted according to the Bonferroni-Holm correction.

Table 4
Unadjusted and adjusted Cox proportional regression analysis for MACE.

	Univariable		Multivariable*	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.03 (1.01–1.05)	0.002	1.03 (1.00–1.05)	0.046
Male sex	2.34 (1.58–3.48)	<0.001	1.85 (1.21–2.81)	0.007
BMI	1.01 (0.98–1.05)	0.463	–	
Hypertension	1.40 (0.94–2.08)	0.095	–	
Hypercholesterolemia	0.95 (0.66–1.37)	0.780	–	
Diabetes Mellitus	1.17 (0.75–1.82)	0.498	–	
Smoking	1.30 (0.85–2.01)	0.228	–	
Family history CAD	1.16 (0.76–1.75)	0.494	–	
Known CAD	2.77 (1.69–4.53)	<0.001	–	
Ischemia	3.19 (2.21–4.60)	<0.001	2.14 (1.45–3.17)	<0.001
CAC≥400	3.49 (2.39–5.10)	<0.001	2.26 (1.48–3.46)	<0.001

CAD = Coronary Artery Disease, CAC = Coronary Artery Calcium, MACE comprises: non-fatal MI, revascularization and all-cause death, ischemia was defined as SDS≥2. *Adjusted for age, sex, history of CAD and cardiovascular risk factors.

SPECT perfusion imaging, as well as asymptomatic and symptomatic patients [8,9,29,30]. In contrast, Rozanski found that high CAC scores did not predict future MACE in patients with normal MPI results [31]. This might be due to the low risk profile of the study cohort and/or short follow-up time in this cohort. After internal validation to correct for optimism and overfitting, the effect of the addition of the automated CAC score to a model with MPI data (and clinical covariates) on risk stratification was assessed. We found a significant overall NRI as a result of a significant NRI for patient without MACE. In total 19.8% of patients without MACE were correctly reclassified into a lower risk category with the addition of the automated CAC score. The greatest advantage of the reclassification was seen in the lower risk categories. This could be useful in clinical practice as it identifies patients that would not qualify for additional therapy and/or invasive CAG. The use of risk categories is however always arbitrary, a larger validation study is warranted to further elaborate this.

The results of our study strengthen the evidence of the complementary value of both functional and anatomical testing. With this DL method CAC scores can be obtained automatically without additional radiation exposure for the patient due to additional ECG-triggered CT scanning. The difference between the determination of the anatomical burden with CAC scores and functional testing could also be seen in the different components of MACE. Revascularization was mainly driven by ischemia on MPI (37 out of 48), and on the other hand 18 out of 24 patients suffering from a myocardial infarction showed high

CAC scores. Previous studies have shown that the incremental predictive ability of a high CAC score can help identify patients with normal MPI PET/CT but obstructive CAD as previously shown [9,32,33]. Also, in patients with ischemia there is a substantial difference in cumulative event rates between those with high and low CAC scores (57.6% vs. 23.4%). Our subanalysis without revascularization still revealed a significant difference in event rate in patients with ischemia between high and low CAC scores. Identification of patients with ischemia and high CAC scores might therefore lead to more aggressive treatment regimes, which potentially could reduce future events. Moreover, considering the significant NRI specifically for patients without MACE, it could also lead to more accurate identification of patients with a lower risk for future MACE. Our proposed combined assessment of a single imaging test could therefore improve clinical management by making a more accurate assessment of a patients' risk for future events than ischemia detection alone. This could lead to more efficient use of our healthcare system.

Although our results reflect regular care in a large hospital in the Netherlands it remains a single center, observational study. Considering its observational nature, it remains unclear if CAC score results would change clinical decision making. Future studies are needed for this. The proposed DL method is easily applicable, although only available with a purchased license. Lastly, the results of this study are only applicable to patients without a history of percutaneous intervention since our DL method is currently not able to distinguish between a coronary stent and calcium.

5. Conclusion

Automated CAC scores derived together with MPI in one single test are, irrespective of the presence of ischemia, associated with MACE in patients with suspected CAD. With the use of a DL algorithm CAC scores can be reliably obtained on non-ECG-triggered images. There is no additional radiation exposure for the patient and no manual scoring for the physician needed to obtain this automated CAC score. We therefore propose this single assessment DL method of calculating the CAC score to improve cardiovascular risk stratification in patients suspected of CAD undergoing MPI.

Data availability

Due to the rules and regulations the datasets generated and analyzed are not online available, however to encourage transparency and reproducibility they will be available from the corresponding author on reasonable request.

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Author statement

All of the authors take full responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Credit authorship contribution statement

Mirthe Dekker: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Project administration. **Farahnaz Waissi:** Methodology, Validation, Data curation, Writing - review & editing, Project administration. **Ingrid E.M. Bank:** Software, Investigation, Data curation, Writing - review & editing, Project administration. **Ivana Isgum:** Software, Investigation, Writing - review & editing. **Asbjørn M. Scholtens:** Software, Writing - review & editing. **Birgitta K. Velthuis:** Software, Writing - review & editing. Gerard Pasterkamp: Resources, Writing - review & editing, Funding acquisition. **Robbert J. de Winter:** Resources, Writing - review & editing, Supervision, Funding acquisition. **Arend Mosterd:** Investigation, Resources, Writing - review & editing, Project administration, Funding acquisition. **Leo Timmers:** Conceptualization, Resources, Writing - review & editing, Supervision, Funding acquisition. **Dominique P.V. de Kleijn:** Conceptualization, Resources, Writing - review & editing, Supervision, Funding acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.12.079.

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