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Journal of Cardiovascular Computed Tomography xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.elsevier.com/locate/jcct

Research paper

Standardized reporting systems for computed tomography coronary angiography and calcium scoring: A real-world validation of CAD-RADS and CAC-DRS in patients with stable chest pain

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ARTICLE INFO

Keywords:
Computed tomography
Computed tomography coronary angiography
Chest pain
Angina
Standardized reporting

ABSTRACT

Objectives: To assess the prognostic implications of standardized reporting systems for coronary computed tomography angiography (CCTA) and coronary artery calcium scores (CACS) in patients with stable chest pain.
Background: The Coronary Artery Disease Reporting And Data System (CAD-RADS) and Coronary Artery Calcium – Data and Reporting System (CAC-DRS) aim to improve communication of CACS and CCTA results, but its influence on prognostication is unknown.
Methods: Images from 1769 patients who underwent CCTA as part of the Scottish Computed Tomography of the HEART (SCOT-HEART) multi-center randomized controlled trial were assessed. CACS were classified as CAC-DRS 0 to 3 based on Agatston scores. CCTA were classified as CAD-RADS 0 to 5 based on the most clinically relevant finding per patient. The primary outcome was the five-year events of fatal and non-fatal myocardial infarction.
Results: Patients had a mean age of 58 ± 10 years and 56% were male. CAC-DRS 0, 1, 2 and 3 occurred in 642 (36%), 510 (29%), 239 (14%) and 379 (21%) patients respectively. CAD-RADS 0, 1, 2, 3, 4A, 4B and 5 occurred in 622 (35%), 327 (18%), 211 (12%), 165 (9%), 221 (12%), 42 (2%) and 181 (10%) patients respectively. Patients classified as CAC-DRS 3 were at an increased risk of fatal or non-fatal myocardial infarction compared to CAC-DRS 0 patients (hazard ratio (HR) 9.41; 95% confidence interval (CI) 3.24, 27.31; $p < 0.001$). Patients with higher CAD-RADS categories were at an increased risk of fatal or non-fatal myocardial infarction, with patients classified as CAD-RADS 4B at the highest risk compared to CAD-RADS 0 patients (HR 19.14; 95% CI 4.28, 85.53; $p < 0.001$).
Conclusion: Patients with higher CAC-DRS and CAD-RADS scores were at increased risk of subsequent fatal and non-fatal myocardial infarction. This confirms that the classification provides additional prognostic discrimination for future coronary heart disease events.

1. Introduction

Standardized reporting systems aim to improve the communication of results to referring physicians and provide consistent reporting, in order to aid quality assurance, education, research and peer-review. Recently standardized reporting systems have been developed for

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https://doi.org/10.1016/j.jcct.2019.07.010
Received 22 April 2019; Received in revised form 9 July 2019; Accepted 24 July 2019

Abbreviations list

CCTA	coronary computed tomography angiography
CACS	coronary artery calcium scoring
CAD-RADS	Coronary Artery Disease – Reporting and Data System
SCOT-HEART	Scottish COmputed Tomography of the HEART
CAC-DRS	Coronary Artery Calcium – Data and Reporting System
CT	computed tomography
HR	Hazard ratio
CI	Confidence interval

coronary computed tomography angiography (CCTA) and coronary artery calcium scoring (CACS).[1,2] However, their clinical relevance for prognostication is currently unknown.

The Coronary Artery Disease – Reporting And Data System (CAD-RADS) classifies patients based on the highest grade of coronary artery stenosis on CCTA, ranging from a score of zero for normal coronary arteries to 5 for patients with at least one occluded coronary artery (Table 1). The CAD-RADS system also includes additional modifiers for the presence of vulnerable plaque (V), grafts (G) and stents (S). The Coronary Artery Calcium – Data and Reporting System (CAC-DRS) classifies patients based on either visual or quantitative assessment of coronary artery calcification (Table 1). These scoring systems provide a simple method to indicate the overall severity of disease to the referring physician. Alongside disease severity, they also provide standardized recommendations for subsequent management and investigation for each category.[1,2]

The Scottish COmputed Tomography of the HEART (SCOT-HEART) trial is a large prospective multi-center randomized controlled trial that assessed the use of CCTA in patients with suspected angina due to coronary heart disease.[3] It showed that management based on CCTA improves diagnostic certainty and reduced the rate of coronary heart disease death and non-fatal myocardial infarction.[4,5] This post-hoc analysis of the SCOT-HEART trial aimed to assess the distribution of CAD-RADS and CAC-DRS groups within the SCOT-HEART population and to assess subsequent clinical outcomes.

2. Methods

2.1. Study design

The SCOT-HEART trial was a multicenter randomized controlled trial investigating the use of CCTA in patients with suspected angina due to coronary artery disease.[3] The primary results of the SCOT-HEART study have been published previously.[4–6]

2.2. Participants

In the SCOT-HEART study, 4146 patients attending cardiology outpatient clinics with stable chest pain were randomized to standard care or standard care plus CCTA. Of these participants, 2073 were randomized to the intervention arm, and 1778 of these subsequently underwent non-contrast electrocardiogram-gated computed tomography (CT) for calcium scoring and CCTA as described previously.[3,4] Cardiovascular risk was calculated using the ASSIGN (Assessing cardiovascular risk using SIGN guidelines) cardiovascular risk score as previously described.[7]

2.3. CAC-DRS reporting system

In the SCOT-HEART trial, coronary artery calcium score was assessed using the Agatston scoring system as described previously.[3,8] In the current study, each participant was assigned a CAC-DRS category[2] based on their previously calculated Agatston score (Table 1).

2.4. CAD-RADS reporting system

As the classification of the CAD-RADS system differed from the assessment of CCTA in the SCOT-HEART trial, all CCTA were reviewed and recategorized according to CAD-RADS[1] based on the most severe stenosis (Table 1). The CAD-RADS V modifier was assigned to patients with one or more plaques with two or more high-risk features, including low attenuation plaque (< 30 Hounsfield Units), positive remodelling, spotty calcification or the “napkin ring” sign.[1]

2.5. Outcomes

Outcome information was obtained in March 2018 from the electronic Data Research and Innovation Service (eDRIS) of the National Health Service (NHS) Scotland and confirmed by review of the patient health records where required.[5] The primary event for this sub-study was the occurrence of coronary heart disease death or non-fatal myocardial infarction.

2.6. Statistical analysis

Statistical analysis was performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Quantitative data are presented as mean and standard deviation or, if not normally distributed, as median and interquartile range. Statistical significance was assessed using Student t-test, Mann-Whitney *U* test, analysis of variance, Chi-square test or Fisher's exact test as appropriate. Hazard ratios (HR) and 95% confidence intervals (CI) are presented. Regression analysis was performed to assess the effect of cardiovascular risk factors on CAC-DRS and CAD-RADS scores. Variables which were statistically significant on univariate analysis were included in multivariate analysis. Outcome data were analyzed using Cox proportional hazards regression and presented graphically using cumulative incidence plots. Due to small number of events, CAD-RADS categories 2 and 3, and 4 and 5 were combined. A statistically significant difference was defined as a two-sided P value < 0.05.

3. Results

3.1. Patient demographics

Of the 1778 who underwent CT, there were 1769 CT images which were of suitable image quality for analysis. Patients had a mean age of 58 ± 10 years and 56% were male (Table 2). The primary event of

Table 1
Summary of the CAC-DRS and CAD-RADS systems.[1,2]

CAC-DRS	Agatston score
CAC-DRS 0	0
CAC-DRS 1	1–99
CAC-DRS 2	100–299
CAC-DRS 3	≥300

CAD-RADS	Degree of coronary stenosis	
CAD-RADS 0	0%	No plaque or stenosis
CAD-RADS 1	1–24%	Minimal stenosis or plaque with no stenosis
CAD-RADS 2	25–49%	Mild stenosis
CAD-RADS 3	50–69%	Moderate stenosis
CAD-RADS 4 A	70–99%	Severe stenosis
CAD-RADS 4 B	Left main stem > 50% or 3 vessels ≥70%	Severe stenosis
CAD-RADS 5	100%	Total occlusion

Table 2
Demographic information for CAC-DRS subgroups.

		All Participants	CAC-DRS			
			0	1	2	3
Number		1769	642 (36)	509 (29)	239 (14)	379 (21)
Male		997 (56)	250 (39)	276 (54)	162 (68)	309 (82) *
Age		58 ± 10	53 ± 10	58 ± 9	61 ± 8	64 ± 7 *
Body mass index (kg/m^2)		30 ± 6	30 ± 6	30 ± 6	29 ± 4	30 ± 5
Atrial fibrillation		34 (2)	12 (2)	8 (2)	4 (2)	10 (3)
Previous coronary heart disease		178 (10)	21 (3)	28 (6)	32 (13)	97 (26) *
Previous cerebrovascular disease		79 (4)	16 (2)	22 (4)	15 (6)	26 (7) *
Previous peripheral vascular disease		31 (2)	6 (1)	8 (2)	4 (2)	13 (3)
Smoking status	Current smoker	330 (19)	127 (20)	99 (19)	55 (23)	49 (13) *
	Ex-smoker	593 (34)	164 (26)	168 (33)	82 (34)	179 (47) *
	Non-smoker	845 (48)	350 (55)	242 (48)	102 (43)	151 (40) *
Hypertension		608 (35)	153 (24)	175 (35)	85 (36)	195 (52) *
Diabetes		196 (11)	44 (7)	63 (12)	26 (11)	63 (17) *
Family history		765 (44)	279 (44)	230 (45)	104 (44)	152 (40)
Total cholesterol (mg/dL)		192 ± 73	196 ± 68	197 ± 72	189 ± 80	180 ± 74 *
Anginal symptoms	Typical angina	654 (37)	148 (23)	185 (36)	96 (40)	225 (59) *
	Atypical angina	432 (24)	178 (28)	117 (23)	70 (29)	67 (18) *
	Non-anginal	683 (39)	316 (49)	207 (41)	73 (31)	87 (23) *
ASSIGN cardiovascular risk score		18 ± 11	12 ± 9	19 ± 11	22 ± 11	24 ± 11 *

Number and (percentage). *, $p < 0.05$.

coronary heart disease death or non-fatal myocardial infarction occurred in 41 patients (2.3%) over a median follow-up of 4.7 years (interquartile range [IQR], 4.0 to 5.7).

3.2. CAC-DRS

The median CAC score was 21 Agatston units [Interquartile range (IQR) 0, 230] and the most frequent classifications were CAC-DRS 0 (36%) or 1 (29%) (Table 2). Patients with higher CAC-DRS classifications were more likely to be older male ex-smokers, and have typical angina, a higher cardiovascular risk score, hypertension, diabetes, a slightly lower total cholesterol, and a history of previous coronary artery or cerebrovascular disease (Table 2). In the multivariate model, age, gender, smoking status, hypertension, history of previous coronary heart disease, chest pain symptoms and cardiovascular risk score were independent predictors of a higher CAC-DRS classification.

3.3. CAD-RADS

The most frequent CAD-RADS classification was 0 (normal coronary arteries) occurring in 622 patients (35%, Table 3). Of the 642 patients who were CAC-DRS 0, there were 112 (17%) who were categorised as CAD-RADS 1 or above. Patients with higher CAD-RADS classification were more likely to be older male non-smokers and have typical angina, previous coronary heart disease, hypertension, diabetes and a higher cardiovascular risk score. In the multivariate model, age, gender, smoking status, chest pain symptoms, previous history of coronary heart disease and cardiovascular risk score remained independent predictors of a higher CAD-RADS classification. CADRADS V was identified in 201 patients (11%) and was more frequent in patients with a higher CAD-RADS score (Fig. 1; $P < 0.001$).

3.4. Medications and revascularisation

Prescription of preventative medications at 6 weeks and increased

Table 3
Demographic information for CAD-RADS subgroups.

		CAD-RADS						
		0	1	2	3	4A	4B	5
Number		622 (35)	327 (18)	211 (12)	165 (9)	221 (12)	42 (2)	181 (10)
Male		252 (41)	173 (53)	126 (60)	105 (64)	160 (72)	32 (76)	149 (82)*
Age		53 ± 10	58 ± 8	60 ± 9	61 ± 8	61 ± 8	62 ± 8	62 ± 8 *
Body mass index (kg/m^2)		30 ± 6	29 ± 5	29 ± 5	30 ± 5	29 ± 5	30 ± 5	30 ± 5
Atrial fibrillation		12 (2)	5 (2)	3 (1)	5 (3)	6 (3)	1 (2)	2 (1)
Previous coronary heart disease		18 (3)	16 (5)	34 (16)	23 (14)	30 (14)	10 (24)	47 (26)*
Previous cerebrovascular disease		15 (2)	15 (5)	13 (6)	11 (7)	17 (8)	1 (2)	7 (4)
Previous peripheral vascular disease		7 (1)	4 (1)	4 (2)	2 (1)	6 (3)	4 (10)	4 (2)
Smoking status	Current smoker	112 (18)	58 (18)	47 (22)	27 (16)	45 (20)	8 (19)	33 (18) *
	Ex-smoker	168 (27)	108 (33)	84 (40)	71 (43)	77 (35)	21 (50)	64 (35) *
	Non-smoker	341 (55)	161 (49)	80 (38)	67 (41)	99 (45)	13 (31)	84 (46) *
Hypertension		155 (25)	111 (34)	69 (33)	74 (45)	104 (48)	16 (39)	79 (44)*
Diabetes		51 (8)	43 (13)	21 (10)	22 (13)	23 (11)	3 (7)	32 (18)*
Family history		273 (44)	148 (45)	92 (44)	66 (41)	101 (46)	21 (50)	64 (36)
Total cholesterol (mg/dL)		194 ± 67	196 ± 73	178 ± 83	192 ± 67	189 ± 75	195 ± 73	199 ± 77
Anginal symptoms	Typical angina	152 (24)	87 (27)	66 (31)	61 (37)	131 (59)	24 (57)	133 (73) *
	Atypical angina	163 (26)	89 (27)	59 (28)	42 (25)	46 (21)	9 (21)	24 (13) *
	Non-anginal	307 (49)	151 (46)	86 (41)	62 (38)	44 (20)	9 (21)	24 (13)*
ASSIGN cardiovascular risk score		12.4 ± 8.7	18.7 ± 11.1	19.7 ± 10.8	20.5 ± 10.1	22.8 ± 10.7	21.2 ± 10.4	24.3 ± 11.6 *

Number and (percentage). *, $p < 0.05$.

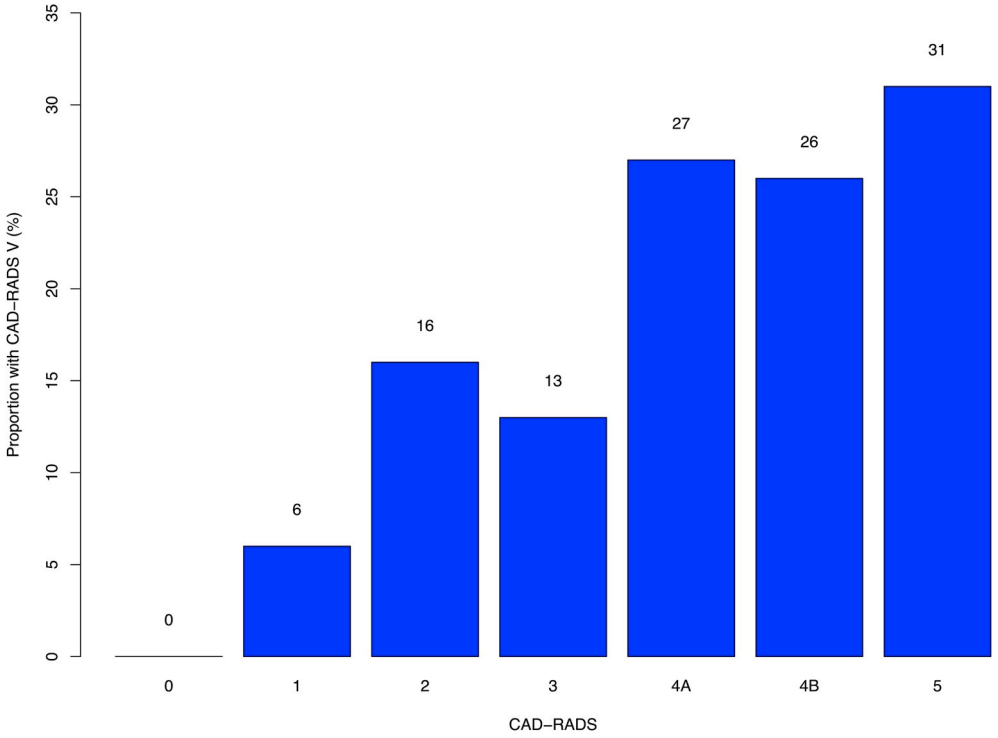

Fig. 1. Prevalence of CAD-RADS V classification in patients with different CAD-RADS categories.

use of coronary revascularisation was associated with higher CAC-DRS and CAD-RADS classification groups ($p < 0.001$ for both, Table 4, Fig. 2). When comparing patients with a CAD-RADS classification of 4 or 5 to patients to those with CAD-RADS classification of 1, the odds ratio for preventative medication use and coronary revascularisation were 7.06 (95% CI, 4.42 to 11.70, $p < 0.001$) and 42.15 (95% CI, 20.98 to 100.48, $p < 0.001$) respectively.

3.5. Clinical outcomes

Patients in the highest CAC-DRS category were at an increased risk of coronary heart disease death or non-fatal myocardial infarction compared to those with CAC-DRS 0 (Table 4, Fig. 3). Similarly, patients with a higher CAD-RADS classification were at an increased risk of coronary heart disease death or non-fatal myocardial infarction (Table 4, Fig. 4). Patients in CAD-RADS group 4B were at the highest risk (Hazard ratio (HR) 19.14 (95% CI 4.28, 85.53), $p = 0.0001$), but

Table 4
Medication use, revascularisation and subsequent outcomes in (A) CAC-DRS and (B) CAD-RADS subgroups.

CAC-DRS				
CAC-DRS	**Preventative medications at 6 weeks**	**Revascularisation**	**CHD death or non-fatal myocardial infarction[a]**	
			N (%)	**Hazard ratio[c]**
0	282 (44%)	7 (1%)	4 (1%)	–
1	370 (73%)	45 (9%)	10 (2%)	3.15 (0.99, 10.06) p = 0.052
2	211 (88%)	53 (22%)	5 (2%)	3.34 (0.90, 12.43) p = 0.073
3	352 (93%)	145 (38%)	22 (6%)	9.41 (3.24, 27.31) p < 0.0001

CAD-RADS				
CAD-RADS	**Preventative medications at 6 weeks**	**Revascularisation**	**CHD death or non-fatal myocardial infarction[b]**	
			N (%)	**Hazard ratio[c]**
0	243 (39%)	0	3 (1%)	–
1	236 (72%)	7 (2%)	7 (2%)	4.57 (1.18, 17.66) p = 0.03
2	170 (81%)	13 (6%)	4 (2%)	4.08 (0.91, 18.21) p = 0.07
3	145 (88%)	17 (10%)	7 (4%)	9.06 (2.34, 35.05) p = 0.001
4A	209 (95%)	94 (43%)	8 (4%)	7.66 (2.03, 28.85) p = 0.003
4B	41 (98%)	19 (45%)	4 (10%)	19.14 (4.28, 85.53) p = 0.0001
5	171 (94%)	100 (55%)	8 (4%)	9.22 (2.44, 34.74) p = 0.001

[a] Compared to patients with CAC-DRS 0.
[b] Compared to patients with CAD-RADS 0.
[c] Hazard ratio and 95% confidence interval. Number (percentage).

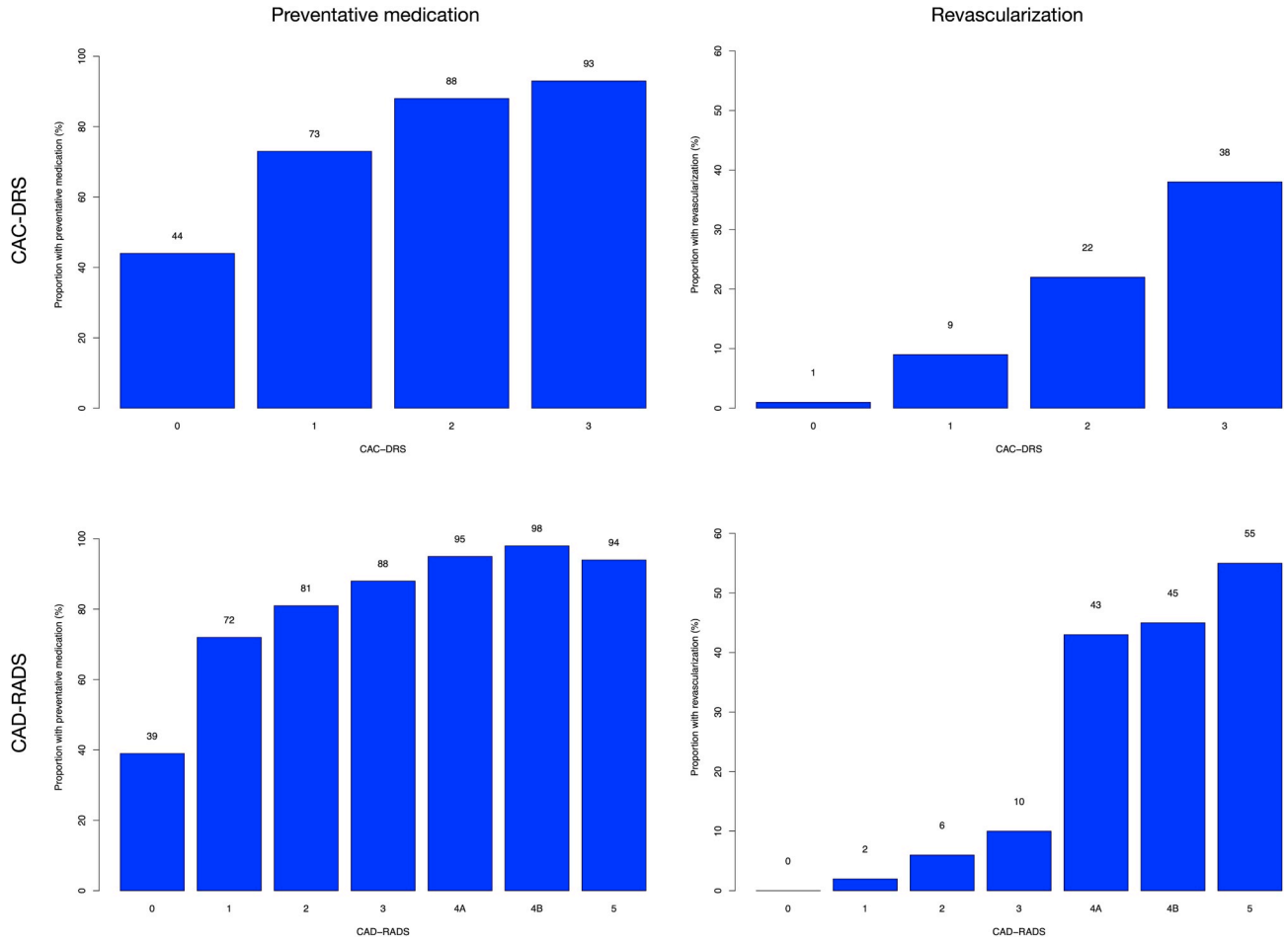

Fig. 2. Use of preventative medication at 6 weeks and revascularisation in patients in different CAC-DRS and CAD-RADS categories.

there was overlap between CAD-RADS categories 3 to 5 (Supplementary Fig. 1). We did not identify any difference in the rate of coronary heart disease death or non-fatal myocardial infarction in patients with or without the CAD-RADS V modifier (HR 1.59 (95% CI 0.70, 3.58), p = 0.266; Fig. 5).

4. Discussion

CAC-DRS and CAD-RADS stratify patients across the range of coronary artery disease, management and subsequent outcomes, with some overlap between the groups in terms of 5-year outcomes. Patients with low CAC-DRS or CAD-RADS scores have a very small, but not zero, risk of subsequent cardiac events. In contrast, those in the highest CAC-DRS and CAD-RADS categories were greater than 9 times more likely to suffer coronary heart disease death or non-fatal myocardial infarction than those with the lowest score.

CAC-DRS and CAD-RADS both follow a tradition of reporting and data systems used to classify the probability of cancer based on imaging findings.[9–13] These systems aim to improve the communication of results to clinicians, to provide recommendations for further management and to enhance research and audit. CAC-DRS and CAD-RADS mark a departure from the use of these systems in cancer imaging and applies the same structured reporting system to coronary artery disease. In classifying disease based on the most severe stenosis, CAD-RADS is also different to other CCTA scoring systems which quantified disease across the entire coronary tree.[14] In our study both CAC-DRS and CAD-RADS successfully identify patients in the lowest risk groups, but there was overlap in terms of management and outcomes in the other groups.

Multiple studies have shown the prognostic value of coronary artery calcification and its additive value to traditional risk factors for predicting the presence of coronary artery disease or subsequent cardiac events.[15–20] In the PROMISE study, a cut-off of 400 Agatston units identified patients with increased risk of cardiovascular death or myocardial infarction with an adjusted hazard ratio of 1.92 (95% CI 0.84, 4.39).[21] Similarly in the SCOT-HEART study, increased coronary artery calcium score was associated with an increased risk of coronary heart disease death or non-fatal myocardial infarction.[22] The CAC-DRS classification uses an upper limit of 300 Agatston units, potentially underestimating the increased risk of even higher coronary artery calcium score. Similar to previous studies, patients with no coronary artery calcification were are at a lower, but not absent, risk of cardiac events.[21,23,24] Indeed, CCTA identified at-risk patients with plaque disease but a calcium score of zero. Thus, coronary artery calcification alone may lack sufficient sensitivity for the diagnosis of patients with suspected angina due to coronary heart disease.

Patients classified as CAD-RADS 4B were at the highest risk of subsequent events. These patients had left main stem stenosis > 50% or 3 vessel disease ≥70%. This is in keeping with other studies which have shown that the presence of obstructive coronary artery disease is associated with a poorer prognosis.[25–27] In the CONFIRM registry (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) increasing CAD-RADS scores were associated with an increased risk of death or myocardial infarction up to a hazard ratio of 6.09 (95% CI 4.34 to 8.54) for patients with CAD-RADS 5. However, CAD-RADS classifications based on a single stenosis may merely be a surrogate marker of overall plaque burden. Indeed, it must be remembered that most myocardial infarctions occur in segments without previous obstructive coronary artery disease.[28–30] Moreover,

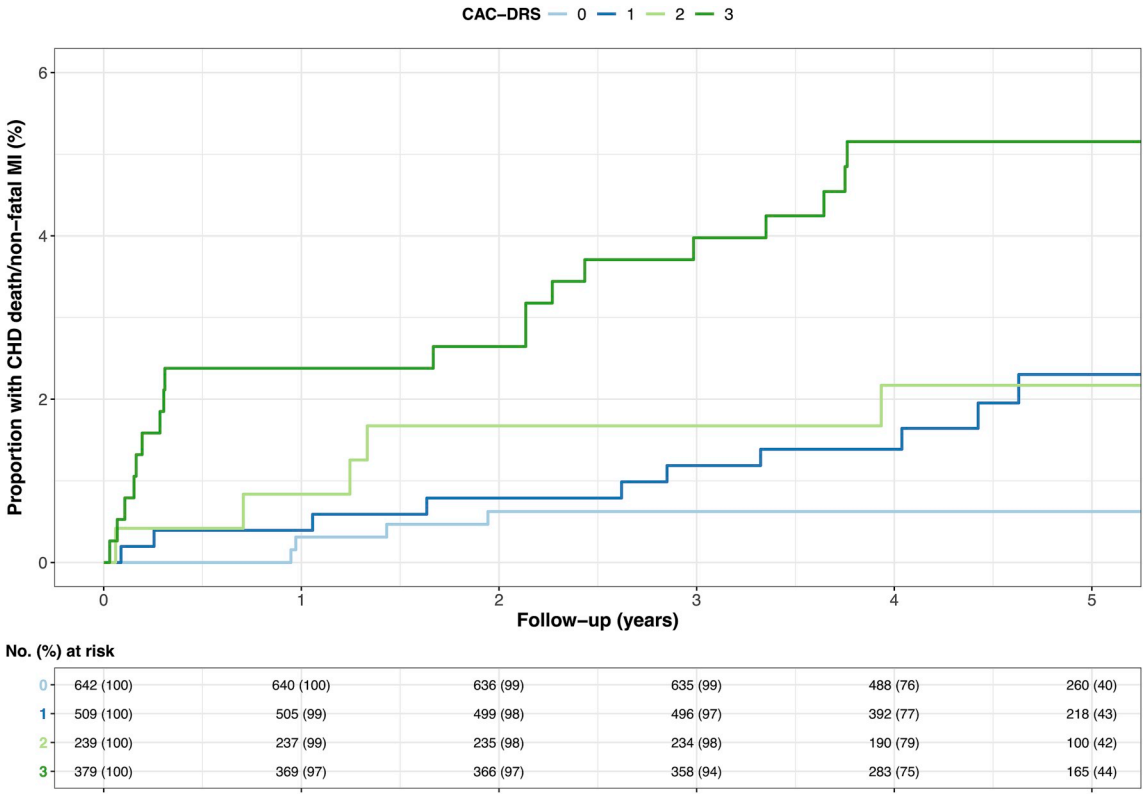

Fig. 3. Cumulative incidence curve of coronary heart disease (CHD) death or non-fatal myocardial infarction (MI) for patients with different CAC-DRS classifications.

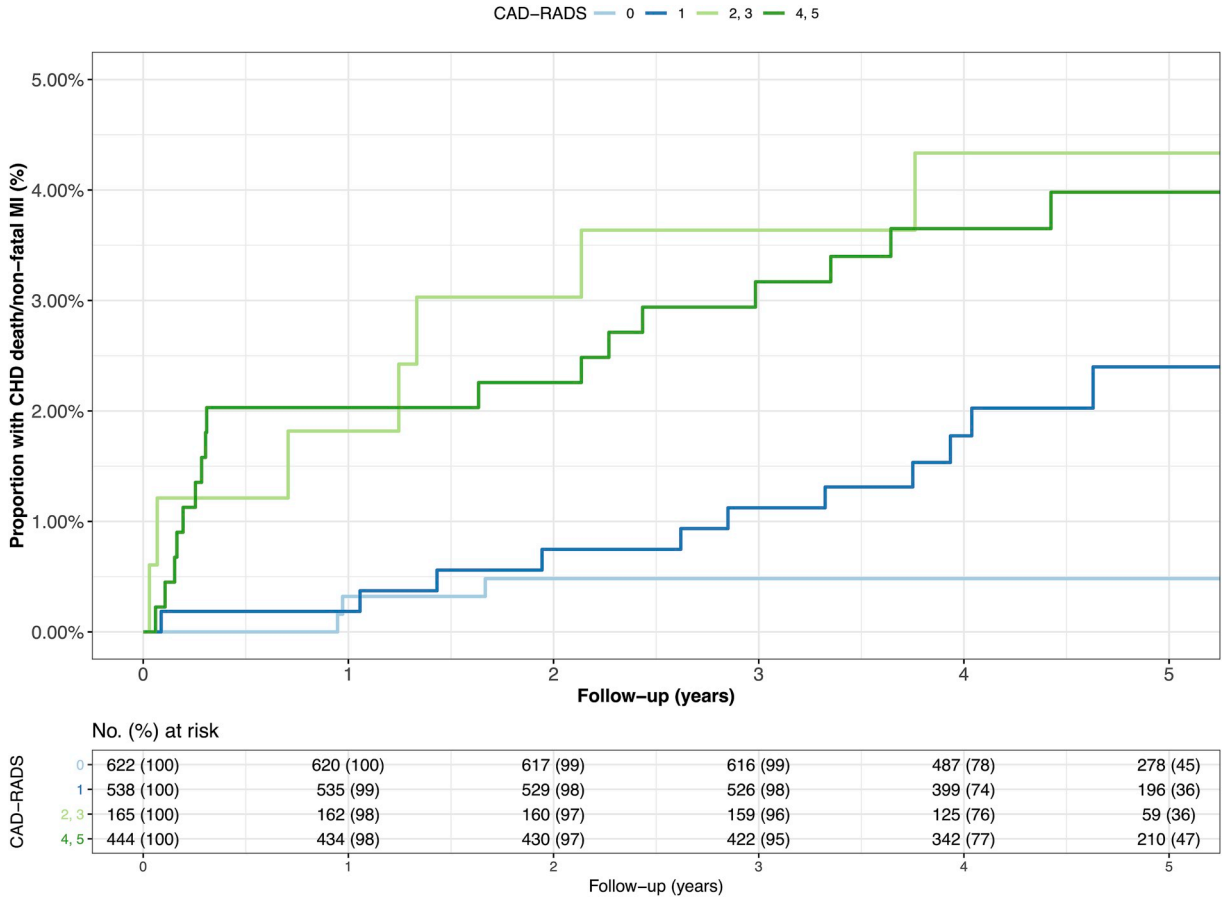

Fig. 4. Cumulative incidence curve of coronary heart disease (CHD) death or non-fatal myocardial infarction (MI) with different CAD-RADS classifications.

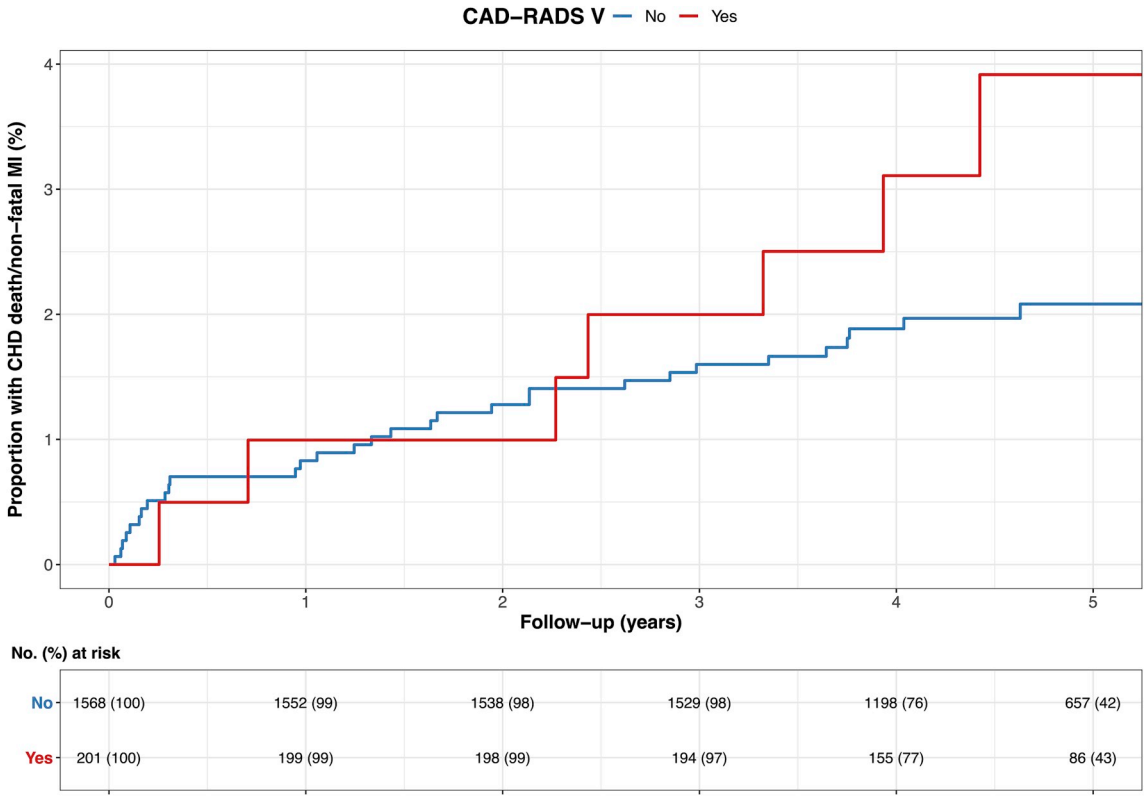

Fig. 5. Kaplan-Meier curve of coronary heart disease (CHD) death or non-fatal myocardial infarction (MI) for patients with or without CAD-RADS V classification.

patients with borderline obstructive disease in our study (CAD-RADS 3, 50–69%) had event rates that were similar to those with critical or occluded vessels. This is consistent with previous historical data demonstrating that 5-year myocardial infarction rates plateau above coronary stenoses of > 50%.[31] This finding may be because these CAD-RADS 3 patients had a heavy burden of atherosclerotic plaque despite the absence of obstructive disease, or because underlying characteristics of their plaque or phenotype puts them at a greater risk of subsequent coronary events. The factors contributing to myocardial infarction in patients without pre-existing obstructive coronary artery disease warrants further investigation. In addition, this highlights that there are subgroups of patients with non-obstructive coronary artery disease who are at increased risk of cardiac events, and who may benefit from more aggressive therapy.

The CAD-RADS V modifier was applied to 11% of patients in this study, similar to the rate of high risk plaques identified in other studies.[32] Interestingly, we did not identify an increased risk associated with the CAD-RADS V modifier, despite other definitions of adverse plaque being associated with an increased risk in the SCOT-HEART population.[22] In particular, the inclusion of spotty calcification in the CAD-RADS V classification reduces the specificity of this modifier. The definition of high risk plaque varies between studies.[22,32,33] Using the CAD-RADS definition of adverse plaque retrospectively did not identify patients who subsequently experienced adverse events. However, an alternative definition, using only the presence of positive remodelling or low attenuation plaque, identified patients at increased risk of coronary heart disease death or non-fatal myocardial infarction in the SCOT-HEART population.[22] An additional issue for the clinical use of the CAD-RADS V classification is the considerable observer variability in the classification of potentially "vulnerable" plaques.[34] Inter-observer reproducibility of the CAD-RADS system was found to be excellent, apart from the CAD-RADS V modifier which demonstrated only fair agreement.[34] Therefore, the CAD-RADS V modifier must be used with caution and that an alternative definition should be considered. Further standardization with quantitative assessment may provide a more reliable definition.

The application of a system that originally was used to qualify a cancer diagnosis to coronary artery disease does have some limitations.[35] First, the results of the CT scan are summarized with a single classification based on the most severe disease in a single vessel. This has the potential to underestimate the severity of multi-vessel disease, especially when there is a large burden of non-obstructive disease. More nuanced findings on CCTA also have the potential to be missed if only the CAD-RADS classification is communicated to the referrer. In particular, the increased risk of subsequent fatal or non-fatal myocardial infarction in a subset of CAD-RADS 3 patients (50–69% stenosis) must be remembered and appropriately investigated and treated. The CAD-RADS classification should therefore be considered in combination with the overall scan report and its conclusions.

The main limitation of this study is that the CAD-RADS system was applied retrospectively to the SCOT-HEART dataset. To date, the prospective use of this classification system has not been assessed. Similarly, no prospective data are available on management strategies based on the identification of vulnerable plaque features. Nevertheless, this study provides an interesting insight into the way in which CAC-DRS and CAD-RADS classify a population with suspected angina due to coronary artery disease and the potential outcomes in each group of patients. In addition, the number of events that have occurred in this low to intermediate risk population is small, particularly when split between the subgroups. This precludes comparisons between every

subgroup and necessitated combining some of the CAD-RADS groups for analysis.

This study shows that the CAC-DRS and CAD-RADS can stratify patients undergoing non-invasive imaging, but that there is some overlap between groups in terms of the 5 years outcomes, and that the vulnerable plaque modifier does not add additional prognostic value in this cohort. Similar to other reporting and data systems, CAC-DRS and CAD-RADS will need to continue to evolve in the light of new evidence.Acknowledgements

This trial was funded by The Chief Scientist Office of the Scottish Government Health and Social Care Directorates (CZH/4/588), with supplementary awards from Edinburgh and Lothian's Health Foundation Trust and the Heart Diseases Research Fund. DEN (CH/09/002, RE/13/3/30183) and MCW (FS/11/014) are supported by the British Heart Foundation. MCW is supported by The Chief Scientist Office of the Scottish Government Health (PCL/17/04). DEN is the recipient of a Wellcome Trust Senior Investigator Award (WT103782AIA). EvB is supported by the Scottish Imaging Network: A Platform of Scientific Excellence (SINAPSE). MRD is supported by the British Heart Foundation (FS/14/78/31020) and the Sir Jules Thorn Biomedical Research Award 2015 (15/JTA). The Royal Bank of Scotland supported the provision of 320-multidetector CT for NHS Lothian and the University of Edinburgh. The Edinburgh Imaging facility QMRI (Edinburgh) is supported by the National Health Service Research Scotland (NRS) through National Health Service Lothian Health Board. The Clinical Research Facility Glasgow and Clinical Research Facility Tayside are supported by National Health Service Research Scotland (NRS).

Conflicts of interest

MCW has performed consultancy for GE Healthcare. RC has a research grant from GE Healthcare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2019.07.010.

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