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Characteristics of conventional high-risk coronary plaques and a novel CT defined thin-cap fibroatheroma in patients undergoing CCTA with stable chest pain

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ABSTRACT

Background: Coronary computed tomography angiography (CCTA) can identify high-risk coronary plaque types. However, the inter-observer variability for high-risk plaque features, including low attenuation plaque (LAP), positive remodelling (PR), and the Napkin-Ring sign (NRS), may reduce their utility, especially amongst less experienced readers.

Methodology: In a prospective study, we compared the prevalence, location and inter-observer variability of both conventional CT-defined high-risk plaques with a novel index based on quantifying the ratio of necrotic core to fibrous plaque using individualised X-ray attenuation cut-offs (the CT-defined thin-cap fibroatheroma - CT-TCFA) in 100 patients followed-up for 7 years.

Results: In total, 346 plaques were identified in all patients. Seventy-two (21%) of all plaques were classified by conventional CT parameters as high-risk (either NRS or PR and LAP combined), and 43 (12%) of plaques were considered high-risk using the novel CT-TCFA definition of (Necrotic Core/fibrous plaque ratio of >0.9). The majority (80%) of the high-risk plaques (LAP&PR, NRS and CT-TCFA) were located in the proximal and mid-LAD and RCA. The kappa co-efficient of inter-observer variability (*k*) for NRS was 0.4 and for PR and LAP combined 0.4. While the kappa co-efficient of inter-observer variability (k) for the new CT-TCFA definition was 0.7. During follow-up, patients with either conventional high-risk plaques or CT-TCFAs were significantly more likely to have MACE (Major adverse cardiovascular events) compared to patients without coronary plaques (p value 0.03 & 0.03, respectively).

Conclusion: The novel CT-TCFA is associated with MACE and has improved inter-observer variability compared with current CT-defined high-risk plaques.

1. Introduction

Coronary computed tomography angiography (CCTA) is a validated diagnostic imaging modality to investigate patients with suspected coronary artery disease (CAD).[1] In addition to its ability to identify luminal stenosis, CCTA allows plaque visualisation, which is not available during routine invasive coronary angiography (ICA) without intravascular imaging.[2–4] High-risk plaque (HRP) features on CCTA, including low-attenuation plaque (LAP), positive remodelling (PR) and the Napkin ring sign (NRS), have been previously recognised as

Abbreviations: CCTA, coronary computed tomography angiography; CT-TCFA, computed tomography defined thin cap fibroatheroma; LAP, low attenuation plaque; MACE, major adverse cardiovascular events; NRS, napkin-ring sign; PR, positive remodelling.

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potentially valuable in identifying patients at increased risk of cardiovascular events.[5,6] However, the potential utility of these features may be limited in routine practice by inter-observer variability, particularly amongst less experienced CCTA practitioners.[7]

Histologically, high-risk plaques (i.e. potentially rupture-prone) typically have large lipid or necrotic cores separated from the coronary arterial lumen by a thin membrane cap.[8,9] Advances in image quality and software tools mean quantitative assessment of coronary plaque components is now feasible.[10,11] We have previously described histologically validated 'plaque map' analysis using CCTA to identify different plaque constituent volumes using X-ray attenuation cut-offs derived from the relationship of plaque to luminal contrast attenuation that automatically adjusts for inter-patient variation in contrast intensity.[11,12] A novel vulnerability index using this method to calculate a necrotic core/fibrous plaque ratio has been proposed with a cut-off of >0.9 identifying plaques analogous to Virtual Histology IVUS (VH-IVUS) defined thin-cap fibroatheroma (TCFA), giving a potential new high-risk plaque identifiable on CCTA, the "CT-TCFA".

This study aims to investigate the prevalence, location and inter-observer variability of both traditional CT-defined high-risk plaques and the new CT-TCFA amongst a cohort of patients who presented with stable chest pain and demonstrate their significance on cardiovascular outcomes.

2. Methods

2.1. Patients

Following Research Ethical Committee approval and informed consent, we undertook a prospective, observational cohort study at Royal Papworth Hospital on 100 stable chest pain patients thought to have a high likelihood of coronary artery disease. They were recruited from outpatient chest pain assessment clinics and underwent CCTA. Patients with conditions that preclude CTCA (previous reaction to intravenous contrast, serum creatinine >1.7 mg/dL) or compromise the image quality (atrial fibrillation) were excluded. Following the CCTA, all patients with a diagnosis of coronary artery disease underwent routine clinical treatment including medical therapy and risk factor modification. In keeping with clinical guidelines at the time, patient management was not further influenced by the presence or absence of high-risk plaques features. All patients were followed up with a structured interview via telephone and postal data collection in the subsequent seven years following recruitment. The primary endpoint MACE (Major adverse cardiovascular events) was the composite of all-cause mortality and non-fatal myocardial infarction (MI).

2.2. CCTA acquisition

Patients underwent a retrospectively-gated CT with ECG-dependent tube current modulation using a Somatom Definition 64-slice dual-source system (Siemens Medical Systems, Forchheim, Germany) with the following scan parameters: pitch 0.20–0.48, collimation 32 × 0.6 mm, tube voltage 120 kV and tube current 360 mA. In addition, intravenous contrast was injected in a triphasic protocol following a 20 mL timing bolus to assess circulation time. Images were reconstructed with a slice width of 0.75 mm, increment 0.5 mm, and a medium smooth convolution kernel (B26). Patients with a heart rate > 70 beats/min received metoprolol intravenously, and all patients received 0.6 mg of sublingual Nitroglycerin.

2.3. CCTA qualitative and quantitative plaque analysis

We performed a per-plaque analysis to study the prevalence and location of CCTA-identified high-risk plaque features using the currently accepted definitions in stable coronary disease. We also examined the relationship between those plaque definitions and quantitative plaque metrics, including plaque burden, necrotic core and fibrous plaque volumes and percentages. All CCTA analysis was performed by a level 3 trained operator with >5 years of experience.

Coronary arteries were divided into 18 segments according to the Society of Cardiovascular Computer Tomography modified classification[13] and analysed for the presence of atherosclerotic plaque disease if >1.5 mm in diameter as measured on CCTA. A coronary plaque was defined as a tissue structure of >1 mm within the vessel wall that could be discriminated from surrounding pericardial tissue, epicardial fat, and the vessel lumen itself. The severity of luminal-diameter stenosis was divided visually into non-obstructive plaques (<50% luminal stenosis) and obstructive plaques (>50% luminal stenosis) based on quantitative stenosis analysis on CCTA. Multi-vessel disease was defined as obstructive lesions in >1 coronary artery (2-vessel and 3-vessel CAD).

All plaque was initially classified into calcified plaque - a plaque with a CT attenuation of ≥130 Hounsfield units (HU) on a non-contrast image, or non-calcified plaque (<130 HU on a non-contrast image) - a plaque with lower attenuation compared with the contrast-enhanced vessel lumen.

Every plaque containing non-calcified elements was then further analysed for any of the following high-risk plaque features (Fig. 1A & 1B):

1. Positive remodelling (PR) – (ratio of vessel diameter at lesion site to reference vessel >1.1).[5]
2. Low attenuation plaque (LAP) – focal area of plaque <30 Hounsfield units {HU}.[5]
3. Napkin ring sign (NRS) – central area of low attenuation surrounded by higher attenuation rim <130HU.[6]

Plaques were classified by CCTA as high-risk if they had either PR and LAP combined or the NRS, as these are the plaques most strongly associated with future acute coronary syndrome (ACS) risk in prospective studies.[6,14,15]

Plaque quantification was performed with Vitrea (Vital Images, US.) utilising semi-automated segmentation with manual correction of vessel contours if required. Total plaque volume, defined as the entire volume of a coronary plaque, including calcified and non-calcified plaque, was reported in mm^3. Coronary plaque burden was calculated as [cross-sectional vessel area − cross-sectional lumen area] / cross-sectional vessel area. The software separates plaques into constituent parts, assigning each plaque voxel depending on its attenuation to create a colour-coded Plaque Map allowing visualisation of the plaque components. To create patient specific plaque maps the mean attenuation (HU) of luminal contrast for each plaque was calculated by measuring luminal attenuation proximal and distal to each plaque. The attenuation cut-offs for each plaque component were calculated according to ratios of luminal contrast and plaque attenuation (necrotic core <0.197, fibrous plaque 0.197–0.470, calcified plaque >1.295) derived using the histologically validated method described in detail previously.[11,12] This sets attenuation thresholds for plaque components individualised to each patient and allows the volumes of the necrotic core, fibrous plaque, and calcified plaque to be calculated. Plaques with a necrotic core/fibrous plaque ratio (NC/Fib) >0.9 were classified as CT-TCFA (Fig. 2). This technique can be used on any software where the attenuation thresholds for quantifying plaque can be altered.

We then determined the frequency, location and patient characteristics associated with these different plaque types. Patients were divided into groups according to the presence of any high-risk plaques and the rate of MACE events that occurred were subsequently recorded. In order to identify the inter-observer variability of the different high-risk plaque features and types in a real-world setting, 40 plaques were re-analysed independently by a level 2 trained operator with <5 years of experience.

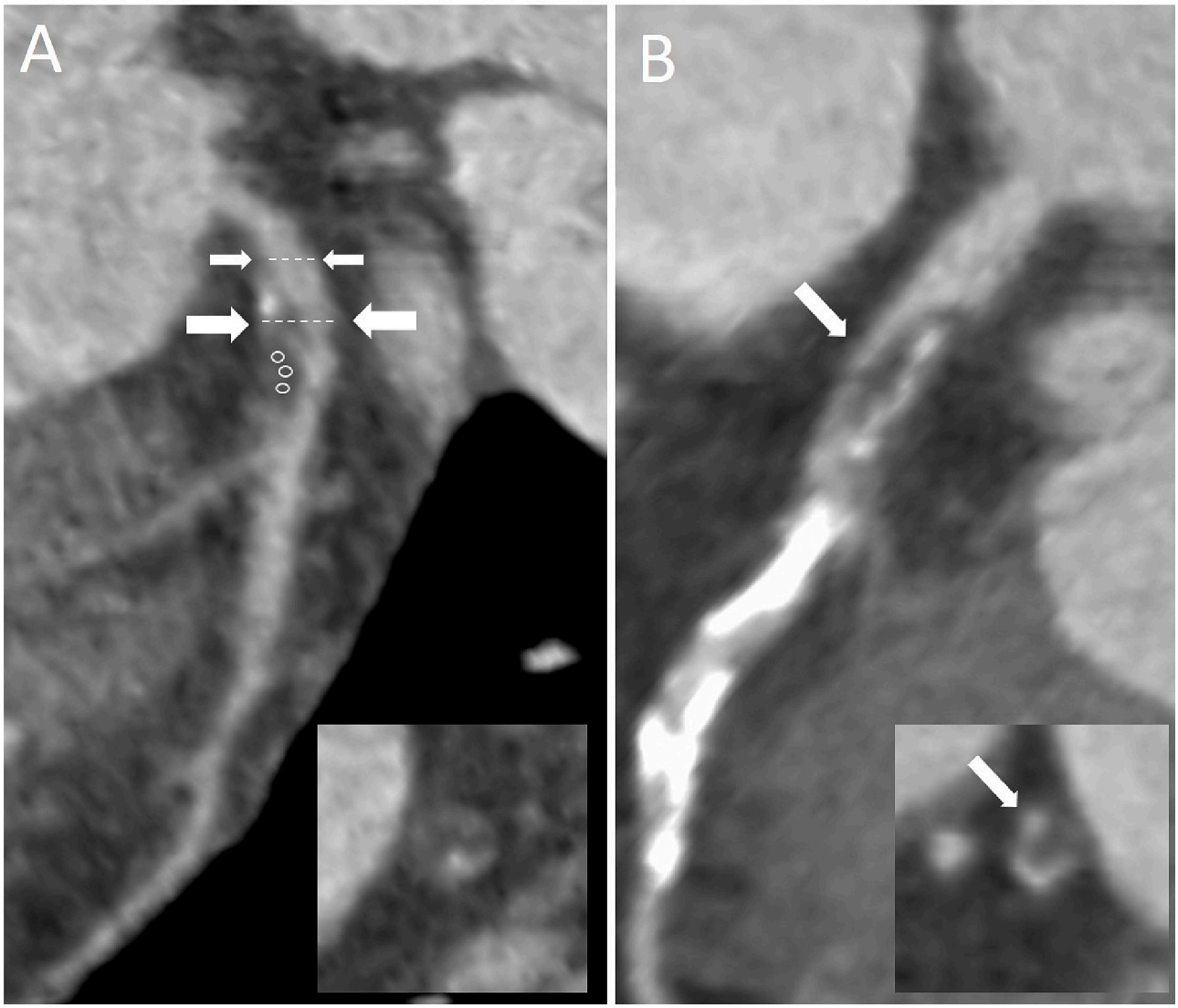

Fig. 1. (A) An atherosclerotic plaque showing positive remodelling (white arrows) and low attenuation plaque (white circles) in the proximal left anterior descending artery on CCTA. (B) An atherosclerotic plaque showing a Napkin ring sign in the right coronary artery.

2.4. Statistical analysis

Categorical variables are presented as numbers (%), and continuous variables as mean ± standard deviation. The chi-square test was used for the comparison of categorical variables. Between-group comparisons were made using the independent-samples *t*-test. Inter-observer variability was expressed as a kappa coefficient (k). Event rates were expressed as Kaplan–Meier curves and compared by log-rank tests. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics version 26 software.

3. Results

3.1. Prevalence and characteristics of different CT-defined high-risk plaque types

After CCTA examination, 3 patients were discovered to have had previous coronary artery bypass grafting; another 2 patients had poor CT images for plaque analysis. A further 8 patients were lost to long-term follow-up, giving a final study population of 87 patients (patient demographics are shown in Table 1).

The total number of plaques present in all 87 patients was 346, of which 244 (71%) contained only calcified plaque. The remainder 102 (29%) plaques contained non-calcified elements. Of the 346 plaques, Forty-one plaques (12%) were obstructive (luminal stenosis >50%). Ninety-three plaques (27%) exhibited at least one conventional high-risk CCTA feature (LAP, PR or NRS). The most frequent feature was LAP, which was present in 87 (25%) plaques, while there were 64 (18%) plaques with PR and 46 (13%) plaques with NRS. The kappa co-efficient of inter-observer variability (*k*) for PR was 0.7, and LAP 0.3. There were 59 plaques with LAP and PR combined. Seventy-two (21%) of all plaques were classified by conventional CT parameters as high-risk (either NRS or PR and LAP combined), and 80 (23%) of plaques were considered high-risk using either conventional parameters or the new CT-TCFA definition. The kappa co-efficient of inter-observer variability (*k*) for NRS was 0.4 and for PR and LAP combined 0.4. Using the novel CT-TCFA definition of (NC/fib ratio of >0.9) led to 43 (12%) of plaques being classified as high-risk. The kappa co-efficient of inter-observer variability (*k*) for CT-TCFA was 0.7.

Plaque map quantification of constituent plaque volumes of the three high-risk plaque types (LAP&PR, NRS and CT-TCFA) are shown in Table 2. Compared with non-high-risk plaques, we found that all 3 high-risk plaques types had greater NC volumes and percentages than non-high-risk ones (p-values <0.001). In addition, the percentage of

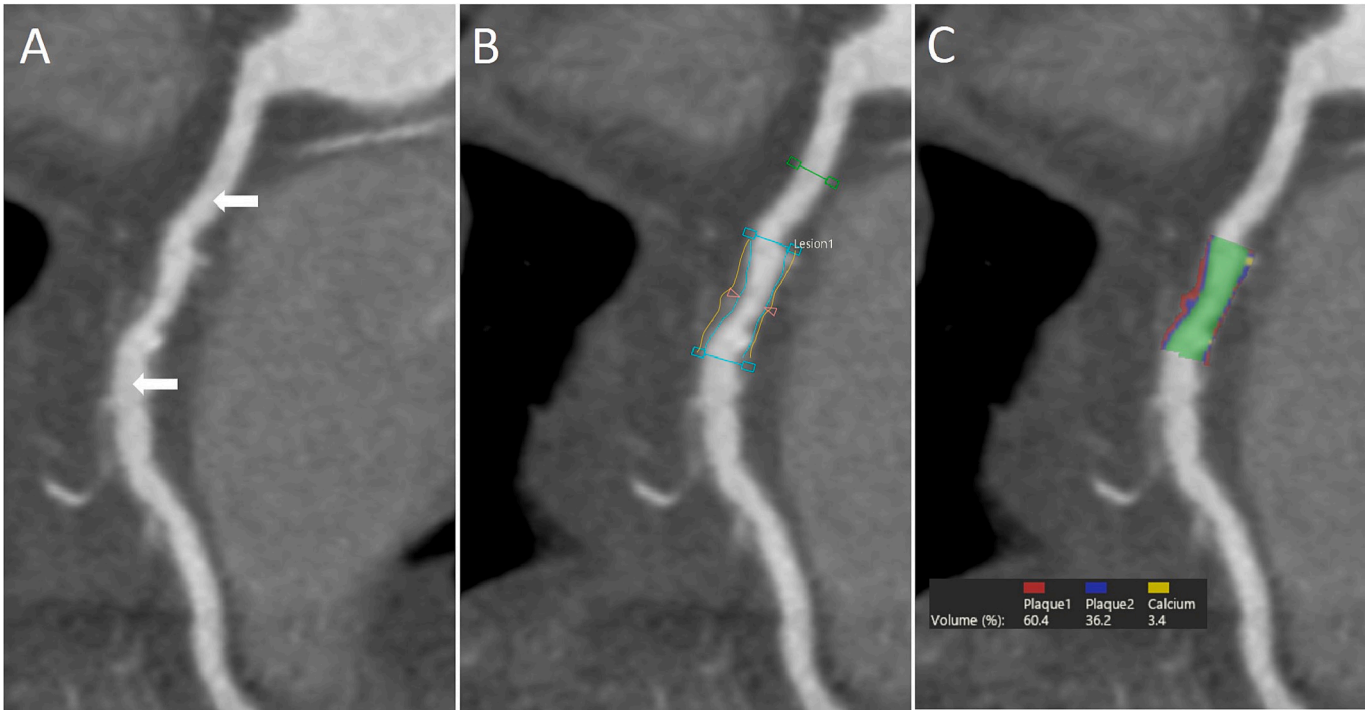

Fig. 2. Defining a CT-TCFA (necrotic core/fibrous plaque ratio > 0.9). (A) Measurement of luminal contrast attenuation proximal and distal to plaque (white arrows). (B) Creation of vessel and lumen borders. (C) Quantification of plaque constituent volumes (red = necrotic core, blue = fibrous plaque, yellow = calcified plaque) using attenuation cut-offs for each plaque component calculated according to ratios of luminal contrast and plaque attenuation.

Table 1
Baseline patient characteristics.

Patient demographics	(n = 87)
Male	58 (67%)
Age (years)	63 ± 13
Hypertension (mmHg)	54 (62%)
Diabetes	11 (13%)
Current smoker	6 (7%)
BMI, (kg/m^2)	30 ± 6
Hyperlipidemia (TC > 4 or LDL >2 mmol/L)	28 (32%)
Family history of CVD	39 (45%)
Multivessel disease	11 (13%)
Calcium score (Agatston units)	596 ± 1109

BMI: body mass index, CVD: cardio-vascular disease.

calcified plaque was lower in all 3 high-risk types when compared to the non-high-risk ones (p-values <0.001). Finally, luminal stenosis >50% was significantly more frequent in all 3 high-risk plaque types than in the non-high-risk plaques.

We compared the characteristics of the patients (41/87–46%) who had at least one conventional (NRS or LAP & PR) high-risk plaque or novel defined CT-TCFA (NC/fib >0.9) and those without. We found those patients with high-risk plaques were more likely to have hyperlipidaemia (p-value =0.01), greater chances of multi-vessel CAD (p-value =0.002), and higher coronary artery calcium scores (p-value =0.005). All other variables in the two groups were comparable (Table 3).

There was considerable overlap of plaques between all three definitions of high-risk plaque. Eight (19%) and 10 (23%) CT-TCFA (plaques with NC/fib ratio > 0.9) overlapped with the high-risk plaques showing NRS and LAP & PR, respectively. Seventeen plaques met the definition of all 3 high-risk plaques (Fig. 3).CT-TCFA wasn't present in twenty-one plaques with NRS and 32 plaques with LAP & PR. The characteristics of the conventionally defined high-risk plaques without CT-TCFA are shown in supplemental table 1. In plaques with NRS, comparing CT-TCFA vs. no CT-CTFA there was no difference in plaque burden (66% ± 9 vs. 67% ± 12, p = 0.4) or luminal stenosis >50% (64% vs. 71%, p = 0.5) but they had more necrotic core (46% ± 10 vs. 28% ± 8, p < 0.001)

Table 2
Quantitative analysis for each CCTA high-risk plaque feature vs non-high-risk ones.

	Non-high-risk plaques (23)	Low attenuation and positive remodelling plaques (59)	p value	Napkin ring plaques (46)	p value	CT TCFA (43)	p value
NC volume, mm^3	40 ± 25	83 ± 61	<0.001	93 ± 63	<0.001	91 ± 62	<0.001
NC %	24 ± 8	37 ± 12	<0.001	38 ± 13	<0.001	46 ± 11	<0.001
Fibrous plaque volume, mm^3	63 ± 36	97 ± 71	0.01	106 ± 71	0.004	75 ± 49	0.1
Fibrous plaque, %	40 ± 9	42 ± 10	0.2	41 ± 10	0.2	37 ± 8	0.09
Ca volume, mm^3	71.5 ± 58	76 ± 136	0.4	76 ± 131	0.4	36 ± 44	0.007
Ca %	36 ± 14	21 + 18	<0.001	21 ± 18	<0.001	17 ± 15	<0.001
NC/Fib ratio	0.6 ± 0.2	0.9 ± 0.3	<0.001	1 ± 0.3	<0.001	N/A	
NC/Fib > 0.9	1 (4%)	27 (46%)	<0.001	25 (54%)	0.04	N/A	
Plaque burden %	58 ± 17	62 ± 10	0.06	66 ± 10	0.006	62 ± 11	0.1
Luminal stenosis > 50%	3 (13%)	26 (44%)	0.006	31 (67%)	<0.001	20 (46.5%)	0.007

Values are n (%) or mean ± SD.

Table 3
Patient characteristics in relation to high-risk plaques.

	Patients with high-risk plaques (41)	All other patients (46)	p value
Male	30 (73%)	28 (61%)	0.2
Age (years)	64 ± 10	64 ± 13	0.4
Hypertension (mmHg)	27 (66%)	27 (59%)	0.5
Diabetes	7 (17%)	4 (9%)	0.3
Current smoker	4 (10%)	2 (4%)	0.4
BMI, (kg/m^2)	29 ± 5	30 ± 6	0.3
Hyperlipidemia (TC > 5 or LDL > 3 mmol/L)	11 (27%)	2 (4%)	0.01
Family history of CVD	17 (41%)	22 (48%)	0.5
Multivessel disease	10 (24%)	1 (2%)	0.002
Calcium score (Agatston units)	970 ± 1345	310 ± 793	0.005

Values are n (%) or mean ± SD.
BMI = body mass index, CAD = coronary artery disease.

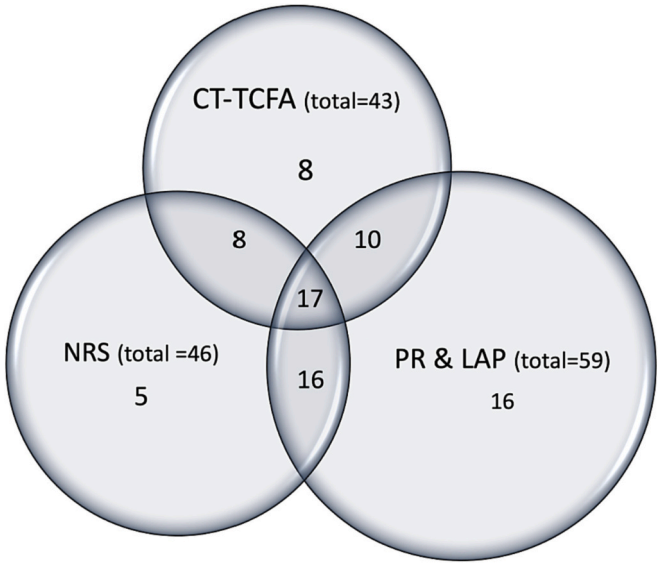

Fig. 3. NRS and PR&LAP plaques overlapping with CT-TCFA.
CT-TCFA = computed tomography defined Thin-cap fibroatheroma, NRS = Napkin ring sign, PR = Positive remodelling, and LAP = Low attenuation plaque.

and less calcified plaque (16% ± 16 vs. 27% ± 18, p = 0.02). This was similar for plaques with LAP and PR comparing CT-TCFA vs. no CT-CTFA showed no difference in plaque burden (60% ± 9 vs. 64% ± 11, p = 0.09) or luminal stenosis >50% (41% vs. 47%, p = 0.7), more necrotic core (47% ± 8 vs. 30% ± 10, p < 0.001) and less calcified plaque (14% ± 12 vs. 27% ± 20, p = 0.006.

3.2. Location and long-term clinical outcomes of CT defined high-risk plaques

Overall, 1566 coronary segments were examined in all 87 patients. A total of 36 segments were excluded due to poor imaging quality, leaving 1530 segments (98%) for evaluation. All segments with a diameter > 1.5 mm were analysed for the presence coronary atherosclerotic plaque. Fig. 4 shows the distribution of all the plaques amongst the coronary segments.

Most plaques were found in the left anterior descending (LAD) artery (156 plaques – 45%), while the left main stem had 20 (6%) plaques, the right coronary artery (RCA) had 97 (28%) plaques, and left circumflex (LCx) had 69 (20%) plaques. The majority of the plaques (228–66%) were clustered in the proximal or mid coronary segments, while the remaining (118–34%) were found in either distal vessels or side branches. The majority (80%) of the high-risk plaques (LAP&PR, NRS and CT-TCFA) were located in the proximal LAD, mid-LAD, proximal RCA and mid-RCA.

4. Plaque-based analysis of CCTA findings associated with MACE

Survival was examined after a mean follow-up period of 7 ± 0.8 years. Out of the total 87 patients followed up, MACE occurred in 17 patients (19%), comprising death in 10 patients and ACS in 7 patients. Eighteen patients had no coronary plaque on CCTA and they had no MACE events in the subsequent 7 years. Forty-six patients had no CT evidence of vulnerable plaque (neither conventional or CT-CTFA and MACE occurred in 6 (13%) of those patients. In the 39 patients who had conventional high-risk plaque (LAP&PR or NRS) MACE occurred in 10 (26%) patients. Twenty-seven patients had CT-CTFA with a MACE event occurring in 6 (22%). Compared to patients with no coronary plaque, those with conventional CT-defined high-risk plaques (LAP&PR and NRS) were significantly more likely to be associated with MACE (Fig. 5A). A similar Kaplan-Meier curve with a significant difference in MACE events was found comparing no coronary plaques to the presence of the new proposed CT-TCFA (Fig. 5B). In contrast, there was no significant difference in MACE events between patients with no coronary plaque and non-high-risk plaques (Fig. 5A).

5. Discussion

In this study, we used CCTA in a cohort of stable patients with a high suspicion of CAD to examine the characteristics, prevalence and location of both conventionally defined high-risk plaque and a new potential CT defined high-risk plaque – the CT-TCFA. CT-TCFA is determined using colour-coded plaque map analysis to identify different plaque characteristics using the X-ray attenuation ratio of the plaque and the luminal contrast. This has been validated against post-mortem histology and can discriminate fibrous tissue, necrotic core and calcification with minimal overlap.[11] We found that conventional CT-defined high-risk plaque and CT-TCFA were clustered in the proximal coronary arteries. It is possible some bias is present in this finding as given the spatial resolution of CTCA the smaller (<1.5 mm diameter) distal arteries could not be analysed. However this distribution pattern matched previous findings from invasive angiography and post-mortem studies of the location of plaques deemed responsible for myocardial infarctions.[16,17] We also found that these high-risk plaques occurred more commonly in patients with hyperlipidemia. This mirrors pathological studies which have demonstrated an association between the incidence of TCFA in patients dying suddenly from acute MI and hyperlipidemia.[17]

The clinical importance of conventional high-risk plaque features, particularly the presence of LAP&PR and NRS, is well established.[5,6] In addition, quantitative plaque measures such as total plaque volume, non-calcified plaque volume and volume of low attenuation plaque may also provide further prognostic information.[18–21] In a subgroup of the ICONIC study, CT-defined necrotic core and fibrofatty plaque volumes significantly correlated with future cardiac events independent from lesion stenosis diameter.[22] We found that conventional CCTA-defined high-risk plaque had higher percentages of necrotic core and lower percentages of calcified plaque, in keeping with previous findings showing constituent plaque volumes correlate with high-risk plaque features.[23] The most powerful predictor of cardiac risk may be a combination of adverse plaque characteristics, including quantitative measures of plaque burden and high-risk features.[24] In addition to predicting future events, CT assessment of high-risk plaque improves the diagnosis of ACS in patients with acute chest pain who otherwise had no ECG or enzymatic evidence of ischemia.[25] Furthermore, when correlated against coronary lesions with positive Fractional Flow Reserve (FFR), high-risk CCTA plaque characteristics improved the identification of coronary lesions that cause ischemia.[26]

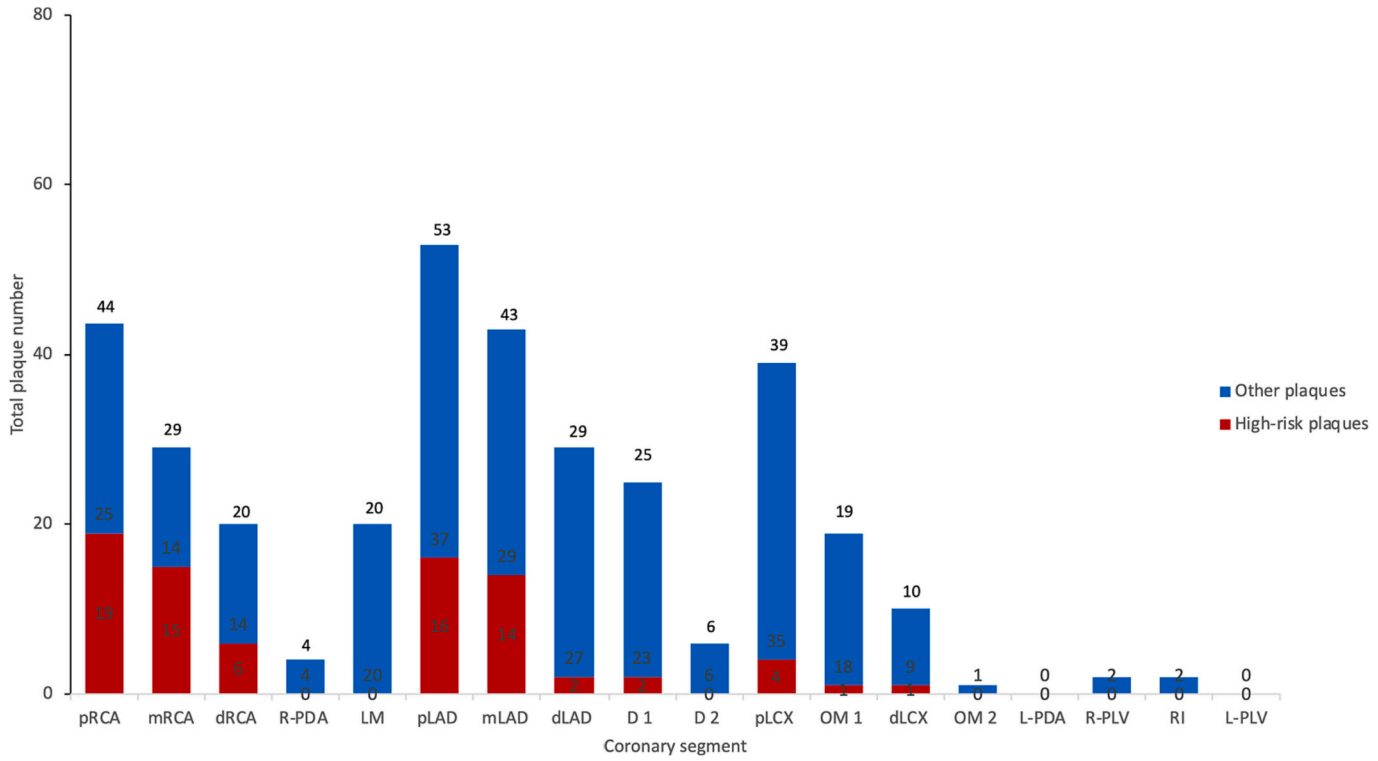

Fig. 4. Distribution of atherosclerotic plaques in Coronary Artery Trees. Most of the high-risk plaques were clustered in the proximal sites of vessels.
P = proximal, m = mid, d = distal, RCA = right coronary artery, R-PDA = right posterior descending artery, LM = left main, LAD = left anterior descending, D = diagonal, LCX = left circumflex, OM = obtuse marginal, L-PDA = left posterior descending artery, R-PLV = right posterior left ventricular, RI = ramus intermedius, and L-PLV = left posterior left ventricular.

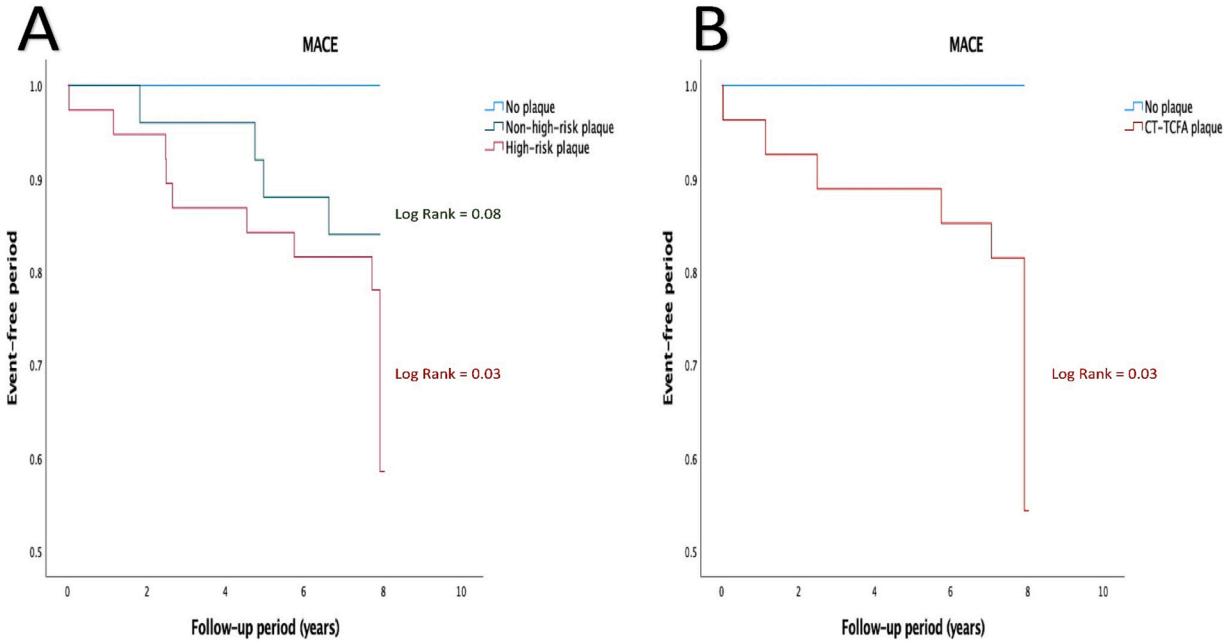

Fig. 5. Kaplan-Meier Curves for MACE events in: (A) patients with conventionally defined high-risk plaques vs non-high-risk plaques and no plaques, (B) patients with CT-TCFAs vs no plaques on CCTA.

It is now recommended that high-risk plaque features should be routinely reported.[27] However, there are concerns that the subjective nature of these features raises issues with inter-observer variability.[7,28] In our study, the kappa co-efficient of inter-observer variability (k) for the conventional high-risk plaques of NRS was 0.4 and for LAP combined PR 0.4. In contrast, the CT-TCFA is based on plaque volumes calculated in a semi-automated fashion, and the early career reader and the expert reader demonstrated a strong concordance ($k = 0.7$).

We found significant morphological overlap between both the conventional high-risk plaques (LAP&PR and NRS) and the newly

introduced 'plaque map' (CT-TCFA), with 51/80 high-risk plaques meeting more than one definition. Some conventional high-risk plaques were not classified as CT-TCFA after plaque map analysis. This was not affected by overall plaque burden or luminal stenosis. Conventional high-risk plaques that met the criteria for CT-TCFA did have higher percentage necrotic core, this is not surprising given a necrotic core/fibrous plaque ratio > 0.9 is the criteria used to define CT-TCFA. Interestingly high-risk plaques were more likely to be classified as CT-TCFA in plaques with less calcification. Possible explanations for this include that partial volume effects from heavily calcified lesions may affect the attenuation of adjacent plaque components limiting the use of plaque map quantitative plaque volume analysis. Another possibility is that in plaques with high calcium burden the partial volume artefact may affect the identification of LAP, PR and NRS.

In this study, over the 7 year follow up period we found the rate of MACE for patients with conventional high-risk plaques (26%) and CT-CTFA (22%) was similar to that of conventional high-risk plaque found in a previous study (23%) undergoing mid-term (4 year) follow up.[14] While our study was relatively small, the Kaplan-Meier curves showed similar survival from MACE over an extended follow up period for conventional high-risk plaque and CT-CTFA. This combined with the fact that there was considerable overlap of plaques within these definitions means that CT-CTFA is likely identifying a broadly similar group of patients with atherosclerotic coronary disease to conventional high-risk plaques, but with the potential advantage of lower inter-observer variability. Interestingly, patients with no high-risk plaques were initially free of MACE for 18 months but did not have an identical course to patients with no plaques and subsequently began having MACE events. This may be as some MACE events are caused by plaques other than TCFAs (plaque erosions and calcified nodules).[8] Another possibility is that given the dynamic nature of coronary plaque,[29] some non-high-risk plaque may have progressed to a more high-risk phenotype over the time course of the study. Given this, overall atherosclerotic disease burden remains a determinant of coronary artery risk assessment and the focus should not be on individual plaque features alone.[30] It is possible that in the future, risk assessment will be further enhanced by radiomics - enhanced image analysis of large amounts of quantitative information from digital imaging not distinguishable to the human eye.[31] Further validation is required before clinical use but preliminary research has shown radiomics-based machine learning analysis can improve the discriminatory power of coronary CT angiography in the identification of advanced atherosclerotic lesions.[32]

6. Limitations

This study has a number of limitations that should be acknowledged. Firstly, due to spatial resolution constraints, CT is not able to directly identify TCFA. The CT-TCFA definition is based on a high CT-defined percentage of necrotic core to fibrous plaque mirroring that is found in histological TCFA.[8] This has previously been used in vivo, comparing favourably with Virtual Histology Intravascular Ultrasound (VH-IVUS).[12] However, further validation using different CT scanner vendors and software analysis systems would improve the generalizability of the CT-TCFA. Secondly, this is a single-centre study with a relatively low sample size which precluded further survival analysis between potentially vulnerable plaques (either with the traditional high-risk signs or CT-TCFA) and stable ones. Further studies with larger sample sizes evaluating the utility of CT-TCFA are required.

Thirdly, the study was conducted in patients with a high prevalence of coronary artery disease. This resulted in a large number of calcified plaques which considering the partial volume effects of calcium may have affected analysis of non-calcified plaque components. In addition, there was a relatively high percentage of plaques (27%) exhibiting high-risk CCTA features so these findings may not applicable to other lower risk populations. Fourthly, it is possible that patients with ongoing angina despite optimal medical therapy may have undergone elective revascularisation during the study period. This information was not recorded so any effect on the outcomes of the study is unknown. Finally, the plaque-map analysis approach requires the evaluation of contrast intensity and creation of individual plaque/contrast ratios for each patient which can time consuming and automation of this process is required for widespread use.

7. Conclusions

Our study introduces a potentially new CT-defined high-risk plaque based on a vulnerability index of necrotic core to fibrous plaque. It has improved inter-observer variability compared with current CT-defined high-risk plaques, so it may be more suitable for widespread use - particularly amongst less experienced operators for identifying atherosclerotic plaque composition that improves risk stratification for potential future cardiac events.

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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Appendix A. Supplementary data

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