Original Article

Quantitative plaque characterisation and association with acute coronary syndrome on medium to long term follow up: insights from computed tomography coronary angiography

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Background: Computed tomography coronary angiography (CTCA) is an established imaging modality widely used for diagnosing coronary artery stenosis with expanding potential for comprehensive assessment of coronary artery disease (CAD). Lesion-based analyses of high-risk plaques (HRP) on CTCA may aid further in prognostication presenting with stable chest pain. We conduct qualitative and quantitative assessments to identify HRPs that are associated with acute coronary syndrome (ACS) on a medium to long term follow-up.

Methods: Retrospective cohort study of patients who underwent CTCA for suspected CAD. Obstructive stenosis (OS) is defined as ≥50% and the presence of HRP and its constituents: positive-remodelling (PR), low-attenuation-plaque (LAP; <56 HU), very-low-attenuation-plaque (vLAP; <30 HU) and spotty-calcification (SC) were recorded. A cross-sectional quantitative analysis of HRP was performed at the site of minimum-luminal-area (MLA). The primary endpoint was fatal or non-fatal ACS on follow-up.

Results: A total of 1,257 patients were included (mean age 61±14 years old and 51% male) with a median follow-up of 7.24 years (interquartile range 5.5 to 7.7 years). The occurrence of ACS was significantly higher in HRP (+) patients compared to HRP (–) patients and patients with no plaques (20.5% *vs.* 1.6% *vs.* 0.4%, log-rank test P<0.001). ACS was more frequent in HRP (+)/OS (+) patients (20.7%) compared to HRP (+)/OS (–) patients (8.6%), HRP (–)/OS (+) patients (1.8%) and HRP (–)/OS (–) patients (1.0%). OS, cross-sectional plaque area (PA) and the presence of vLAP identified those HRP lesions that were more likely to cause future ACS. Cross-sectional LAP area (<56 HU) in HRP lesions added incremental prognostic value to OS in predicting ACS (P=0.008).

Conclusions: The presence of OS and the LAP area at the site of MLA identify the HRP lesions that have the greatest association with development of future ACS.

Keywords: Coronary artery disease (CAD); high-risk plaque (HRP); acute coronary syndrome (ACS); computed tomography coronary angiography (CTCA)

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Introduction

Acute coronary syndrome (ACS) is a major public health issue (1,2). It can be the initial manifestation in many patients with coronary artery disease (CAD) causing significant mortality and morbidity. Despite our improved understanding of the disease process and management, appropriate risk stratification is lacking. Early identification of at-risk patients and the development of preventative strategies is much needed. Although, in-vivo identification of the rupture-prone plaque is possible with intracoronary imaging techniques and a wealth of data is available in patients for secondary prevention, their utility in patients with stable chest pain is limited (3-5). Computed tomography coronary angiography (CTCA) is a non-invasive test that, in addition to the diagnosis of luminal stenosis, it also can assess the degree of atherosclerotic plaque burden and plaque composition (6,7). Studies have shown the association between ACS with CTCA derived high-risk plaque (HRP) features of positive remodelling (PR), low attenuation plaque (LAP) and spotty calcification (SC). However, the occurrence of ACS remains infrequent in these high-risk patients (8,9).

Further differentiation of the HRP lesions that are associated with future ACS on CTCA is needed for the optimisation of risk stratification in stable patients. There have been very few studies that have assessed the incremental benefit of quantitative plaque analysis in patients with HRP (10). Specifically, lesion-based analyses of HRP on CTCA that includes assessment of plaque burden, plaque area, LAP area, minimal luminal diameter (MLD) and minimal luminal area (MLA) may aid further in prognostication. The limitation of comprehensive quantitative plaque analysis is that it is time consuming and expert dependent. Hence, we focused only on cross-sectional quantitative analysis at the site of MLA to assess whether it can serve as a surrogate for comprehensive plaque analysis. Through qualitative and quantitative analysis of HRP, we sought to identify those HRP that have the greatest association with future ACS on medium to long-term follow-up. We present the following article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-763/rc).

Methods

Of the 1,735 eligible patients with follow-up data that underwent CTCA at a major tertiary referral hospital (Monash Health, Melbourne, Australia) from January 2008 to March 2013, 103 patients with prior coronary artery bypass graft (CABG) surgery, 84 patients with previous ACS or percutaneous coronary intervention (PCI), 29 patients with poor CTCA image quality, 128 patients with early revascularisation (<3 months between CTCA and PCI), 134 deaths from non-cardiac causes were excluded. We conducted retrospective cohort study on the remaining 1,257 patients were followed up until 30th November 2017 for the development of ACS (*Figure 1A*). Prior to their CTCA, each patients completed a structured questionnaire which captured demographic details such as age, height, weight, symptoms, and cardiovascular risk factors. Follow-up information on patient outcomes was obtained by assessment of hospital medical records, detailed structured questionnaires sent by mail/email, or by telephone contact if the questionnaire was not returned. Records from the registry of birth and deaths were also obtained. All reported events were verified by hospital records and adjudicated by two cardiologists in consensus. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional Human Research and Ethics Committee of Monash Health approved the study (HREC reference number HREC/13115L/MonH) and individual consent for this retrospective analysis was waived.

The primary endpoint of this study was major adverse cardiovascular events (MACE) defined by a composite of cardiac death and ACS (myocardial infarction and unstable angina). Cardiac death was defined as any death caused by acute myocardial infarction. ACS was defined as per the basis of the fourth universal definition of myocardial infarction and the Canadian Cardiovascular Society grading of angina pectoris that included presentation with typical sounding chest pain associated with troponin elevation with or without ECG changes (11,12). In the event of no troponin rise, chest pain that was Canadian Cardiovascular Society class 3 or 4 was considered significant (13). Determination of the culprit vessel was done by a combination of electrocardiographic and invasive coronary angiographic findings. Cardiologist (A Lin) who was

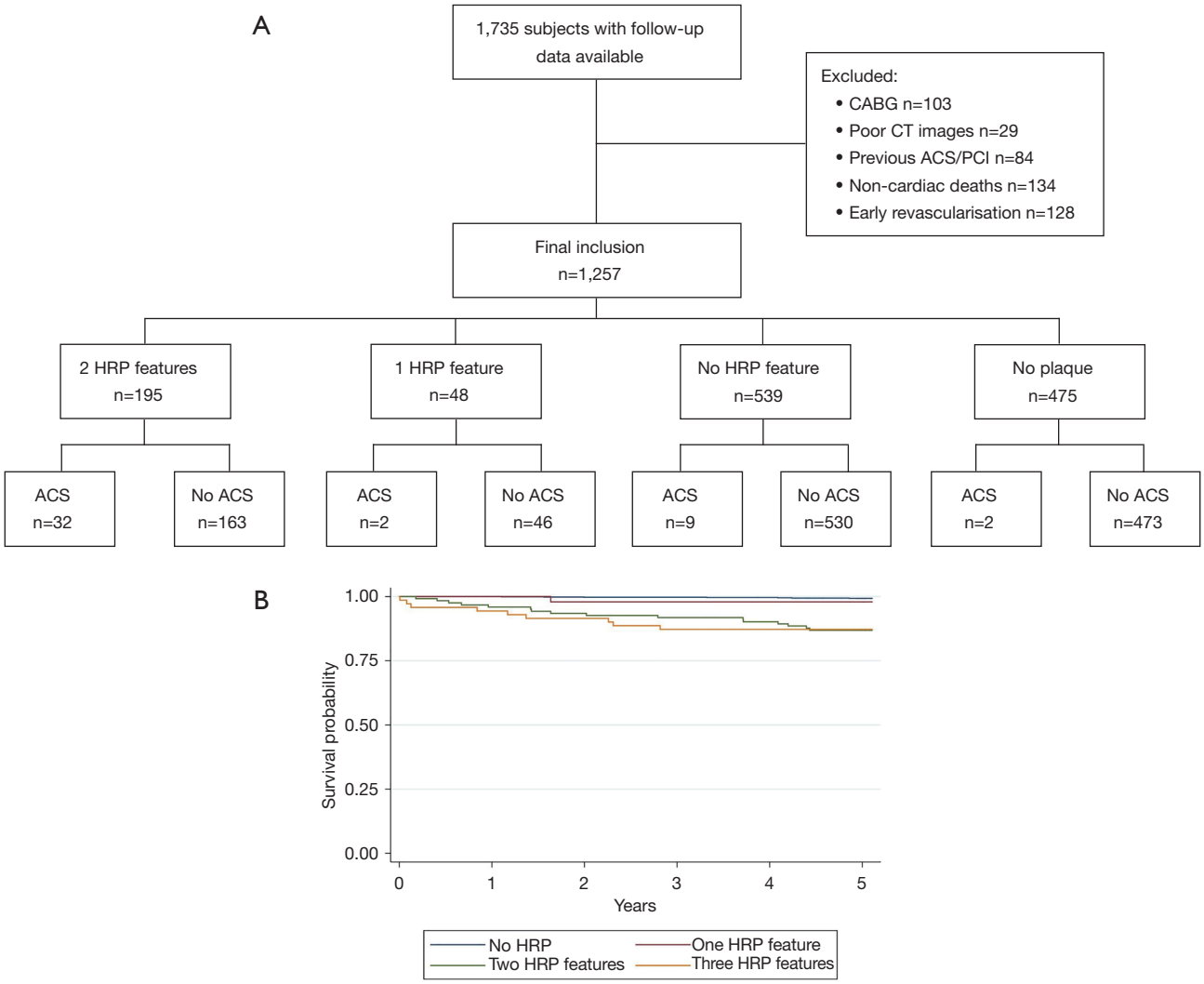

Figure 1 Number of acute coronary events in patients based on the number of HRP features (A) and Kaplan-Meier curve of patients stratified according to the numbers of HRP features (B). HRP, high-risk plaque; ACS, acute coronary syndrome; CABG; coronary artery bypass grafts; CT, computed tomography; PCI, percutaneous coronary intervention.

blinded to the CTCA findings independently adjudicated all the events.

CTCA

Patients underwent cardiac CT assessment using a 320-row detector CT scanner (Aquilion One Vision, Toshiba Medical Systems Corporation, Tokyo, Japan). All patients received sublingual nitroglycerine (unless clinically contraindicated), and additional beta-blockers were administered to achieve a pre-scan heart rate of <60 beats/min in accordance with Society of Cardiovascular Computed Tomography guidelines (8,14). The studies were performed according to established guidelines and departmental protocols at the time of the scan.

CTCA analysis

Data was transferred to an external workstation (Vitrea®, version 6.0; Vital Images, Minnetonka, Minnesota) for further analysis. Two level-III experienced readers (DW and RKM) who were blinded to the patient's clinical information evaluated all the scans. In the event of disagreement, a joint reading was performed, and a consensus decision was

reached. Studies were interpreted according to current guidelines using a 16-segment model (15). Each coronary segment >2 mm in diameter was analysed for the presence of plaque and the diameter stenosis of each lesion was visually graded and categorised as follows: no stenosis (0%), minimal (<25%), mild (25–49%), moderate (50–69%), severe (70–99%), occluded (100%) (16). Obstructive disease was defined as stenosis >50%. Plaque composition was classified as non-calcified, calcified, or mixed.

The measurement of total coronary atherosclerotic plaque burden was performed using the segmental involvement score (SIS) and segmental stenosis score (SSS). SIS was calculated as the total number of coronary segments with plaque, irrespective of the degree of luminal stenosis within each segment (range, 0 to 16). SSS was calculated by grading each coronary segment based on stenosis severity, as having no plaque to severe stenosis (range, 0 to 3), followed by the summation of the scores of all 16 individual segments to yield a total score (range, 0 to 48).

HRP characteristics

Binary evaluation of HRP characteristics included low attenuation plaque (LAP), spotty calcification and positive remodelling. LAP was defined as plaques with <56 Hounsfield unit (HU), and plaques with <30 HU were defined as very low attenuation plaques (vLAP) (17). Spotty calcification was defined when calcification was <3 mm in size. Positive remodelling was defined as remodelling index ≥1.1 (8). The napkin-ring sign on CTCA is another previously described HRP feature but was not included in this analysis due to its infrequent occurrence in our study.

Quantitative plaque analysis

Quantitative plaque analysis was performed on all plaques with HRP features using attenuation-based-automated SurePlaque (Vitrea 6, version 3.0; Vital Images and Toshiba Medical Systems) software with appropriate manual correction. Total plaque volume was calculated summating all the plaque areas in an analysed segment. Total LAP volume was then quantified for each plaque with HRP features. Cross-sectional quantitative analysis was performed at the site of MLA in all HRP lesions and assessed parameters included plaque area (PA), plaque burden (PB), minimal luminal area (MLA), minimal luminal diameter (MLD) and plaque composition using predefined HU thresholds: very low attenuation plaque (<30 HU), low attenuation plaque (<56 HU), fibrofatty (56 to 130 HU), fibrous (131 to 350 HU), and calcified plaque (≥350 HU) (18-20).

The cross-sectional LAP areas were classified according to tertiles of low, mid and high LAP areas. Each of these groups was further divided based on the presence or absence of obstructive stenosis (OS) into OS (–) or OS (+) groups. There were six group comprising: OS (–)/low LAP, OS (+)/low LAP, OS (–)/mid LAP, OS (+)/mid LAP, OS (–)/high LAP and OS (+)/high LAP.

Statistical analysis

Categorical data are presented as raw numbers and percentages and compared with the chi-square test. Continuous data are displayed as mean ± standard deviation if data were normally distributed, or medians (interquartile range) for non-normal data and compared with *t*-tests or Mann-Whitney tests as appropriate. Kaplan-Meier plots were constructed, and the log-rank test was used to assess the differences in equality of curves. Univariable Cox proportional hazard regression models were performed to assess clinically relevant variables on the outcome of interest. Variables of clinical relevance or with a P<0.20 on univariate assessment were considered for the multivariable model. Final multivariable covariates included gender, hypercholesterolemia, smoking, presence of vulnerable plaques and obesity. Conditional proportional hazards assumptions were visually inspected by plotting Schoenfield residuals. The incremental prognostic value of including assessment of low attenuation plaque values and OS >50% was compared by Harrell's c-statistic. A 2-sided P value of <0.05 was considered statistically significant. Statistical analysis was performed using Stata MP/14 (StataCorp, College Station, Texas, USA). Data is reported according to the number of data points available.

Results

Study population and clinical characteristics

Included in the study were 1,254 patients (mean age 60.9±13.7, 50.9% were male) with a median follow-up period of 7.24 years (interquartile range 5.53 to 7.7 years). Of these, 583 (46%) patients had hypertension, 581 (46%) had hyperlipidaemia, 138 (10.9%) had diabetes mellitus, 128 (10.2%) patients were active smokers, and 152 (12.1%) patients were obese. On comparison of the traditional risk factors, only smoking was associated with ACS (*Table 1*).

Table 1 Patient characteristics

Characteristics	Overall (n=1,257)	ACS (n=45)	No ACS (n=1,212)	P
Age (years), mean ± SD	60.9±13.7	59.9±11.7	61±13.8	0.86
Male gender	638 (50.9%)	29 (64%)	610 (51%)	0.41
Hypertension	583 (46%)	23 (51%)	560 (45%)	0.76
Hypercholesterolemia	581 (46%)	18 (40%)	563 (45%)	0.05
Diabetes mellitus	139 (11.1%)	8 (18%)	131 (11%)	0.39
Current smoker	128 (10.2%)	9 (20%)	119 (10%)	0.03
Ex-smoker	223 (18%)	8 (18%)	215 (18%)	0.84
Family history of IHD	536 (43.3%)	19 (42%)	517 (43%)	0.42
Obesity (BMI >30 kg/m^2)	152 (12.1%)	7 (16%)	145 (13%)	0.16

ACS, acute coronary syndrome; BMI, body mass index; IHD, ischemic heart disease.

CTCA results

Of 1,257 patients, 209 (16.6%) patients had a ≥50% stenotic lesion in at least 1 coronary artery, only 17 (0.6%) patients had severe stenosis (≥70%) and 475 (37.8%) patients had no coronary atherosclerosis. There were 243 (19.3%) patients who had HRP with at least one high-risk feature and 106 (8.4%) patients had HRP with OS. On comparison of the traditional risk factors, only diabetes mellitus and smoking were associated with the presence of HRP. There were 195 HRP (+) patients with ≥2 features (plaques with ≥2 of PR, LAP and SC), 48 HRP (+) patients with 1 feature (either PR, LAP or SC), 539 HRP (–) patients had plaques with no HRP features and 475 patients had no plaques. The intraobserver and interobserver assessment of HRP was highly reproducible with excellent intraclass coefficient of 0.92 and 0.91 respectively.

Patient-level analysis

Of the 1,257 patients, 45 (3.6%) patients had ACS during the follow-up. Three patients had ACS related death, 34 (2.7%) patients had myocardial infarction and 8 (0.6%) patients had unstable angina. Culprit lesion precursors were identified by both invasive coronary angiography (ICA) and CTCA in 42 (93%) patients and were not known in three patients who died of acute myocardial infarction. The culprit lesion was found in 21 left anterior descending arteries, 3 left circumflex arteries and 19 right coronary arteries.

Plaque composition and stenosis severity: association with ACS

Of the 45 patients who had ACS, 34 patients had HRP while 11 patients had no HRP. During follow-up, 32 (16.4%) of 195 patients with HRP (+) patients with ≥2 features developed ACS (*Figure 1B*). In comparison, 2 (4.1%) of 48 HRP (+) patients with one HRP feature, 9 (1.6%) of the 539 HRP (–) patients and 11 (0.01%) of the 1,014 patients without HRP developed ACS (*Figures 1A,2A*).

Compared to 9 HRP (+) patients who had ACS, none of the HRP (–) patients developed ACS within the first year of follow-up. From year one to year five of the follow-up duration, HRP (+) patients had more events compared to HRP (–) patients (1–2 years: 6 *vs.* 3 patients; 2–3 years: 5 *vs.* 0 patient; 3–4 years: 2 *vs.* 1 patient; 4–5 years: 4 *vs.* 3 patients; >5 years: 8 *vs.* 4 patients).

Overall, ACS occurred in 24 (11.1%) of 217 OS (+) patients compared to 21 (2%) of 1,040 OS (–) patients. When the relationship between HRP and OS was assessed, ACS was more frequent in HRP that caused OS with 22 (20.7%) of 106 patients developing ACS. In comparison, 12 (8.6%) of 139 HRP (+)/OS (–) patients, 2 (1.8%) of 111 HRP (–)/OS (+) patients and 9 (1.0%) of 901 HRP (–)/OS (–) patients developed ACS (*Figure 2A,2B*).

Predictive value of plaque characteristics

The presence of HRP was associated with ACS (HR 14.5, 95% CI: 7.3–28.6; P<0.001) as were its constituents PR

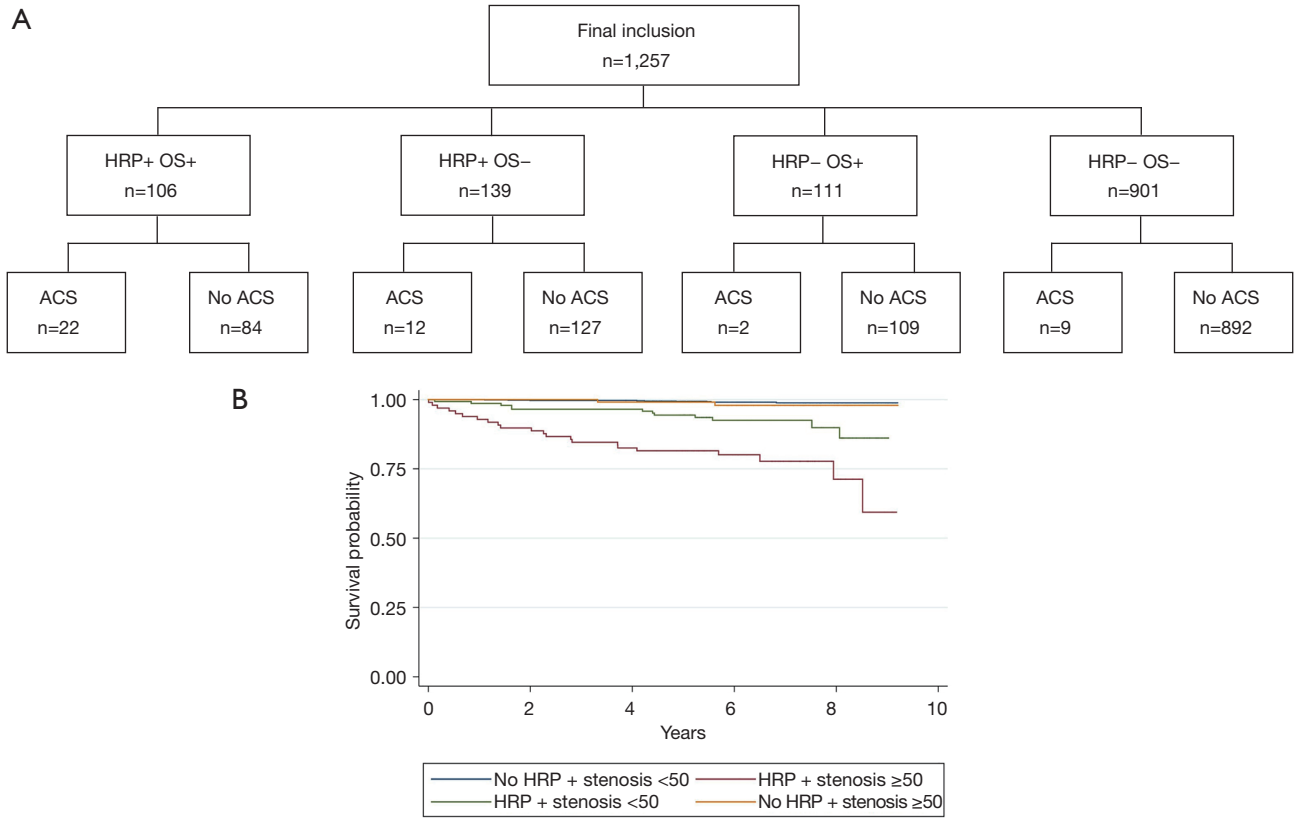

Figure 2 Occurrence of ACS based on the presence of OS (>50%) and HRP features on CTCA (A) and Kaplan-Meier curve of patient based on the presence of OS (>50%) and HRP features (B). ACS, acute coronary syndrome; OS, obstructive stenosis; HRP, high-risk plaque; CTCA, computed tomography coronary angiography.

(HR 14.5, 95% CI: 7.3–28.7; P<0.001), SC (HR 5.4, 95% CI: 3–9.9; P<0.001) and vLAP (HR 16.7, 95% CI: 9.1–30.5; P<0.001). The presence of ≥2 HRP features (HR 14.4, 95% CI: 7.46–26.44; P<0.001), OS ≥50% (HR 6.3, 95% CI: 3.5–11.4; P<0.001) and plaques with any HRP features and OS (HR 10.3, 95% CI: 5–21.2; P<0.001) were associated with ACS.

On multivariate Cox regression analysis of variables comprising sex, hyperlipidaemia, smoking, diabetes mellitus, obesity, and presence of at least one HRP feature, only the presence of HRP was an independent predictor of ACS (HR 14.99, 95% CI: 7.47–30.06, P<0.001). The occurrence of ACS was significantly higher in HRP (+) patients compared to HRP (–) patients and patients with no plaques (20.5% *vs.* 1.6% *vs.* 0.4%, log-rank test P<0.001). OS ≥50% was not a predictor of ACS on multivariate analysis (P=0.43).

Survival analysis

On survival analysis of patients with events limited to five years of follow-up, the time interval between the CTCA and event was shorter in HRP (+) patients [HR 3.34 (1.16–9.63), P=0.03; Kaplan Meier log-rank 0.02]. The comparison of proportion of surviving between HRP (+) patients to HRP (–) patients annually was 73% and 100%; 56% and 82%; 41% and 82%; 35% and 82%; 24% and 64% respectively for up to 5 years follow-up (*Table 2*).

Cross-sectional lesion level analysis: assessment of ACS predictors among plaques with HRP features

Among 234 HRP (+) patients with at least one HRP feature, there were 310 HRP lesions. There were 11 patients with 3 HRP lesions, 44 patients had 2 HRP lesions and 188

Table 2 Survival analysis in only patients with events limited to 5-year follow-up: comparing proportion surviving at annual time point

Year	HRP absent, %	HRP present, %
0	100	100
1	100	73
2	82	56
3	82	41
4	82	35
5	64	24

HRP: HR 3.34 (1.16–9.63), P=0.03, Kaplan-Meier log-rank 0.02. HRP, high-risk plaque.

patients had 1 HRP lesion. PR was a feature in all HRP lesions while LAP was present in 161 lesions. OS was present in 128 lesions (41.2%). The mean SIS score was 3.6±0.9 and the mean SSS score was 6.1±4.32.

During follow-up, ACS developed in 34 HRPs (10.9%). LAP was the most common determinant of ACS in a HRP with 28 (17.3%) of 161 HRPs with LAP developing ACS. In comparison 7 (4.6%) of 149 HRPs without LAP developed ACS. The development of ACS was more frequent in HRP (+)/OS (+) lesions with ACS occurring in 22 (17%) of 128 lesions compared to the ACS occurring in 13 (7.1%) of 182 HRP (+)/OS (–) lesions. In addition, patients with HRP (+)/OS (+) presented earlier with ACS (mean duration of 2.6 years) compared to those with HRP (+)/OS (–) (mean duration of 3.75 years).

On quantitative plaque analysis of HRPs, OS, cross-sectional PA (HR 1.08, 95% CI: 1.02–1.14; P=0.007) and the presence of vLAP (HR 3.77, 95% CI: 1.64–8.67; P=0.002) identified those HRP lesions that were more likely to cause future ACS. The lesions that lead to ACS had larger mean LAP [56] area (2.9±1.9 *vs.* 2.1±2.1 mm^3, P=0.04) and PA (13.9±5.9 *vs.* 11.2±4.9 mm^3, P=0.005) compared to the lesions that did not lead to ACS. Lesions with ≥50% stenosis (HR 2.46, 95% CI: 1.23–4.91; P=0.01) but not MLA (P=0.61) or MLD (P=0.73) was associated with ACS. Total plaque length (P=0.78), total plaque burden (P=0.58) and in addition, the measures of total atherosclerotic plaque burden such as SIS (P=0.11) and SSS (P=0.09) were also not associated with ACS.

In the 11 HRP (–) patients who developed ACS during follow-up, all culprit lesions were identified. On the assessment of CTCA, only 2 patients had stenosis ≥50%, 4 lesions had <25% stenosis, 3 culprit lesions had 25–49% stenosis and 2 culprit lesions had no plaque. The mean SIS and SSS in these patients were 2.9 and 5.1.

Obstructive disease and LAP area

On comparison of the HRPs at cross sectional lesion level using OS (–)/low LAP as reference, only the lesions with OS (+)/mid LAP (HR 4.08, 95% CI: 1.06–15.79; P=0.04) and OS (+)/high LAP (HR 5.68, 95% CI: 1.59–20.2; P=0.007) were associated with ACS.

Predictive value of HRP and OS of ACS

The predictive value of each quantitative plaque characteristic of ACS during follow-up was evaluated by ROC analysis. The AUC for OS (+) was 0.64 and LAP area was 0.65. The predictive value increased to AUC of 0.71 when OS and LAP area were combined. On comparison of AUC, this was statistically significant when compared to OS alone (P=0.008).

Discussion

We investigated the predictors of ACS in a population with stable CAD undergoing CTCA on a medium to long term follow-up and the salient findings of our study are (I) CTCA derived HRP is an independent predictor of future ACS beyond traditional cardiovascular risk factors; (II) absence of HRP features was associated with event-free survival at one year and reduced annual risk compared to those with HRP features up to 5 years of follow-up; (III) ACS occurred early and more frequently in HRP lesions that caused OS and cross-sectional LAP area added further incremental prognostic value in predicting ACS; (IV) presence of vLAP identified HRP that were associated with ACS; and (V) absence of HRP was associated with low rates of ACS irrespective of the presence of OS.

The event rate in our study is in line with what is expected in a population free of prior revascularisation and prior documented ACS. We excluded patients who underwent early revascularisation and focused on only type I myocardial infarction and cardiac deaths. Of note, 82% of ACS events in our study were due to myocardial infarction as compared to <5% in previous studies (10,21). As quantitative plaque analysis on CTCA is time-consuming and reader dependent, we employed only cross-sectional

quantitative plaque analysis at the site of MLA, which appears to act as a surrogate for the entire plaque analysis. It was observed that LAP area quantification just at the site of MLA which could be easily performed in a short period at the time of CT reporting, gave the same prognostic information compared to the entire plaque LAP volume quantification that was done in previous studies (17).

Additionally, just the presence of very low attenuation plaque (<30 HU) was also predictive of ACS. The definition of LAP as <30 HU was validated against IVUS on old generation CT scanners with tube voltage of 135 kV (22). As plaque density is affected by lumen contrast density and tube voltage, more contemporary CT studies have used <56 HU for LAP definition (19). Considerable overlap exists between LAP and fibrous plaque and a recent histopathological validation study observed that vLAP (<30 HU) had high specificity and positive predictive value but had low sensitivity and probably represents the true necrotic core. In comparison higher cut off values such as 56 HU were sensitive with higher negative predictive value but had low specificity and represent fibrofatty components of LAP (20).

We observed that the degree of stenosis in a lesion with HRP features is associated with ACS [(22 (20.7%) of 106 HRP (+)/OS (+) patients *vs.* 12 (8.6%) of 136 HRP (+)/OS (–) patients]. Stenosis severity itself was not as important as only 1.8% of HRP (–)/OS (+) patients developed ACS, similar to the observation made in the PROSPECT study where events rarely occurred from non-fibroatheromas regardless of stenosis severity. ACS was more frequent in OS (+)/mid or high LAP and those with vLAP. SIS and SSS were not predictive. These observations suggest that the underlying plaque composition determines whether stenosis severity becomes a prognostic indicator. In addition, there is evidence to suggest that culprit lesions are more likely to be obstructive before an event with silent plaque rupture and healing contributing to accelerated plaque growth in the days leading up to an event (23-26). A sub study from COURAGE trial also found an association between stenosis >50% and future AMI (27). Pathological studies have demonstrated that ruptured plaques demonstrated layering from multiple healed plaque ruptures suggesting that silent plaque ruptures and healing may contribute to rapid plaque growth in HRP prior to an event (26).

Consistent with previous studies, we observed that compared to HRP (+) patients, HRP (–) patients had a lower event rate up to 5 years of follow-up and a 100% event-free survival rate up to 1 year (28-30). None of the traditional risk factors apart from the presence of HRP features were predictive of ACS. The presence of HRP identifies a cohort of patients who have a higher risk of ACS and the prognostic importance of HRP is now recognised and is reflected in the recommendation on CTCA reporting (16). Our findings suggest that in HRP lesions that caused OS with large PA and low attenuation plaque allowed us to further identify the lesions that are at higher risk of future ACS.

Despite the known increased risk, the event rate even among patients with HRP is overall low and current guidelines do not recommend treatment or management of CTCA identified HRPs (31). Selecting the HRP (+) patients who are at greatest risk of future ACS for future trials aimed at intense medical or other preventative therapies with the assessment of progress through serial imaging or monitoring for events may be the way forward.

Chronic vascular inflammation plays a primary role in atherogenesis and plaque vulnerability (32). Proteomic and transcriptomic analyses of vulnerable plaques demonstrates an increased amounts of activated macrophages and differentiated subsets of T cells, which in turn produce various proinflammatory and chemotactic cytokines (33). This has been supported by imaging studies using invasive intracoronary techniques (34,35) and positron emission tomography (36,37). The vascular wall and the surrounding adipose tissue interacts in a complex and likely bidirectional manner (38,39). Adipose tissue is detected within the window of –190 to –30 HU (40,41) and experimental animal studies have shown lower HU to be associated with more lipid-dense AT (42). Vascular inflammation inhibits lipid accumulation in pericoronary adipose tissue (PCAT) and can be detected on routine CTCA as an increase in CT attenuation of PCAT surrounding the proximal right coronary artery (43). A post hoc analysis of the CRISP-CT study has demonstrated incremental improvement in predicting cardiac mortality of high PCAT attenuation over the presence of HRP (44). Future studies are needed to integrate these novel CT imaging biomarkers into a single risk profile to guide personalised treatment strategies.

Limitations

This was a single centre retrospective study. Treatment information following CTCA and compliance to medications was not known. Patients included were investigated for chest pain and there may have also been some referral bias. Several aspects may have influenced

our results: firstly, patients with incomplete datasets were excluded from the study, which may have led to information bias. Secondly, patients with significant baseline plaque burden who underwent early revascularisation were excluded from the study. Thirdly, patients needing late revascularisation due to progression of the disease without ACS were excluded. Lastly, assessment of luminal stenosis may have been over-estimated in calcified lesions and under-estimated in non-calcified lesions.

Conclusions

CTCA identified HRP is an independent predictor of future ACS beyond traditional cardiovascular risk factors with all the HRP features of PR, LAP, SC being associated with an increased risk. The HRP lesions with obstructive (>50%) stenosis and large LAP area have the greatest association with future ACS. The cross-sectional LAP area at the site of MLA can potentially serve as a surrogate for entire plaque LAP volume quantification. Stenosis severity alone in the absence of HRP feature was not associated with future ACS.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-763/rc

Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-763/dss

Peer Review File: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-763/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-763/coif). DW serves as an unpaid editorial board member of Cardiovascular Diagnosis and Therapy from February 2021 to January 2023, and DW received honoraria for lectures from Eli-Lilly, Pfizer and Boehringer. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Monash Health Human Ethics Committee (HREC reference number HREC/13115L/MonH), and individual consent for this retrospective analysis was waived.

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