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**ORIGINAL PAPER**

# Quantitative coronary plaque analysis predicts high-risk plaque morphology on coronary computed tomography angiography: results from the ROMICAT II trial

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**Abstract** Semi-automated software can provide quantitative assessment of atherosclerotic plaques on coronary CT angiography (CTA). The relationship between established qualitative high-risk plaque features and quantitative plaque measurements has not been studied. We analyzed the association between quantitative plaque measurements and qualitative high-risk plaque features on coronary CTA. We included 260 patients with plaque who underwent coronary CTA in the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) II trial. Quantitative plaque assessment and qualitative plaque characterization were performed on a per coronary segment basis. Quantitative coronary plaque measurements included plaque volume, plaque burden, remodeling index, and diameter stenosis. In qualitative analysis, high-risk plaque was present if positive remodeling, low CT attenuation plaque, napkin-ring sign or spotty calcium were detected. Univariable and multivariable logistic regression analyses were performed to assess the association between quantitative and qualitative high-risk plaque assessment. Among 888 segments with coronary plaque, high-risk plaque was present in 391 (44.0%) segments by qualitative analysis. In quantitative analysis, segments with high-risk plaque had higher total plaque volume, low CT attenuation plaque volume, plaque burden and remodeling index. Quantitatively assessed low CT attenuation plaque volume (odds ratio 1.12 per 1 $mm^3$, 95% CI 1.04–1.21), positive remodeling (odds ratio 1.25 per 0.1, 95% CI 1.10–1.41) and plaque burden (odds ratio 1.53 per 0.1, 95% CI 1.08–2.16) were associated with high-risk plaque. Quantitative coronary plaque characteristics (low CT attenuation plaque volume, positive remodeling and plaque burden) measured by semi-automated software correlated with qualitative assessment of high-risk plaque features.

**Keywords** Coronary CT angiography · High-risk coronary plaque · Coronary atherosclerosis · Quantitative assessment

Dr Liu and Dr Maurovich-Horvat have contributed equally to this work.

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

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## Introduction

Patients with coronary artery disease (CAD) may not experience any symptoms before developing acute coronary syndrome (ACS) or sudden cardiac death. In majority of cases ACS develops at the site of previously non-stenotic plaque with high-risk features that ruptures with subsequent thrombosis rather than at the site with a stable plaque and luminal narrowing [1–3]. Therefore, the early identification of patients with high-risk plaques is of utmost importance to allow for early medical therapy. The ultimate goal is to reduce the mortality and morbidity of CAD through improved cardiovascular risk stratification [4, 5].

The histological features of the culprit plaques in ACS include large necrotic core, higher macrophage count, positive remodeling, speckled calcium and thin fibrous cap [3, 6]. Similar morphological features (positive remodeling, larger plaque area, spotty calcification and large necrotic core) were observed with intravascular imaging in culprit lesions of patients with ACS [7].

Coronary CT angiography (CTA) is a non-invasive modality that allows the simultaneous visualization of the coronary artery wall and lumen. Furthermore, coronary CTA can detect high-risk plaque features associated with the presence of acute coronary syndrome and with the future cardiovascular events in qualitative analysis (e.g. positive remodeling, low CT attenuation plaque spotty calcification, napkin-ring sign and spotty calcium) [8, 9]. More recently, advances in image quality and quantitative software tools for plaque quantification allowed establishing plaque volume and burden as predictors of major cardiovascular events [10, 11]. The quantitative plaque assessment is now sufficiently reproducible [12] and the utility of automated quantitative plaque analysis tools are currently under investigation [13, 14]. However, the relationship between established qualitative high-risk plaque features and quantitative plaque metrics has not been studied.

Therefore, the aim of study was to perform quantitative assessment of coronary plaque on coronary CTA using an automated software tool in the setting of multicenter clinical trial. Furthermore, we sought to investigate the association of quantitative plaque metrics with well-established qualitative high-risk plaque features.

## Materials and methods

### Patient population

This is a secondary analysis of the prospective multi-center Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) II trial (ClinicalTrials.gov ID: NCT01084239). Our study cohort consisted of subjects who were randomized to the coronary CTA arm of the trial (Fig. 1). A detailed description of the patient selection was previously published [15]. In summary, between April 2010 and January 2012, 501 patients with low to intermediate risk who presented to the emergency departments (ED) of nine hospitals in the United States with a clinical suspicion for acute coronary syndrome (ACS) were enrolled and randomized to either coronary CTA or standard of care. All study participants provided written consent for participation in ROMICAT II. This study has been approved by the local institutional review board.

### Coronary CTA imaging protocol

Coronary CTA (retrospectively ECG-gated or prospectively ECG-triggered scan) was acquired using 64-slice multidetector-row CT (MDCT) or more advanced scanner models [16]. The study sites used the scanners from three vendors (Siemens, General Electric and Toshiba) and different scanner generations (64-slice, 128-slice, 256-slice, and dual source scanners). Images were transferred to a central core laboratory for analysis.
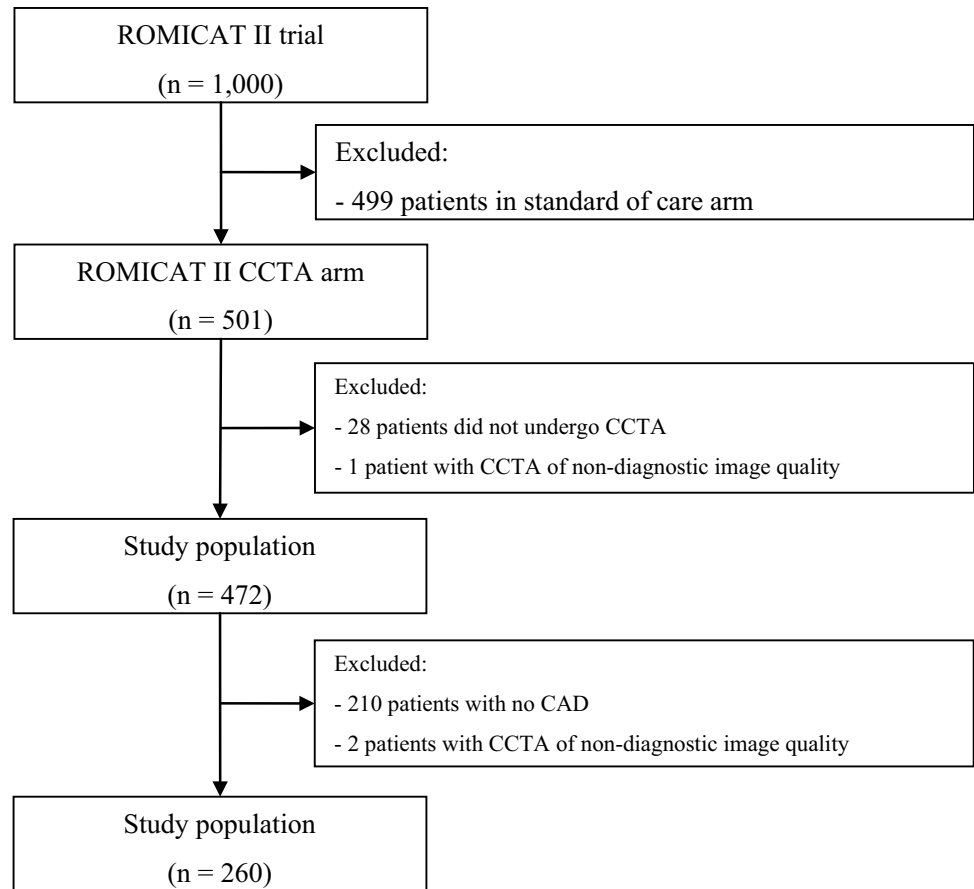
### Qualitative coronary CTA analysis

The coronary CTA analysis was performed per coronary segment using the model of the Society of Cardiovascular Computed Tomography [17, 18]. Coronary CTA datasets were equally divided among three readers in a random fashion (MF, SBP, TL), who performed qualitative plaque characterization. All readers had at least 5 years of experience and a level III training in coronary CTA.

The degree of diameter stenosis was graded by visual estimation as either significant stenosis ($\geq$50%), or no significant stenosis (<50%) in each coronary segment. If coronary plaque was present, qualitative plaque characterization was performed to note the presence of four high-risk plaque features: positive remodeling (remodeling index > 1.1), low CT attenuation (presence of non-calcified plaque with CT attenuation <30 HU), napkin-ring sign (presence of a central area of low CT attenuation that is in contact with the lumen and a ring-like higher attenuation plaque tissue surrounding this central area) and spotty calcium (size of calcium: <3 mm diameter, length < 1.5 of vessel diameter, width < 2/3 of vessel diameter) [8].

### Quantitative coronary CTA analyses

Quantitative coronary CTA analysis was performed in scans with coronary plaque using a validated software tool (QAngio CT Research Edition version 2.0, Medis medical imaging systems b.v, Leiden, the Netherlands) [19, 20]. Four readers (MF, SBP, MTL, PMH), each with at least 5 years

**Fig. 1** Inclusion and exclusion criteria

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                    │     ROMICAT II trial     │
                    │       (n = 1,000)        │
                    └─────────────────────────┘
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                              │   ┌──────────────────────────────────┐
                              │   │ Excluded:                        │
                              │   │ - 499 patients in standard of    │
                              │   │   care arm                       │
                              │   └──────────────────────────────────┘
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                    ┌─────────────────────────┐
                    │  ROMICAT II CCTA arm     │
                    │       (n = 501)          │
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                              │   ┌──────────────────────────────────┐
                              │   │ Excluded:                        │
                              │   │ - 28 patients did not undergo    │
                              │   │   CCTA                           │
                              │   │ - 1 patient with CCTA of non-    │
                              │   │   diagnostic image quality       │
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                    │    Study population      │
                    │       (n = 472)          │
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                              │   │ Excluded:                        │
                              │   │ - 210 patients with no CAD       │
                              │   │ - 2 patients with CCTA of non-   │
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                    │    Study population      │
                    │       (n = 260)          │
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of experience and level III training in coronary CTA performed the quantitative plaque measurements. Each of the four readers individually performed the quantitative plaque measurements in equally divided and randomly assigned coronary CTA studies. Further, all four readers analyzed 20 randomly selected coronary CTA datasets to determine interobserver agreement.

The segmentation of the luminal and outer coronary artery wall boundaries was performed automatically with manual adjustment (Fig. 2). Quantitative plaque measurement was only conducted in coronary segments with coronary plaques. The readers selected proximal and distal reference sites at normal or nearly normal vessel locations adjacent to the plaque. The final results of the quantitative measurements were reported per coronary segment using the model of the Society of Cardiovascular Computed Tomography [18]. If multiple plaques were found in one coronary segment, quantitative measurements from all plaques were summed for such segment. Lumen diameter stenosis, total plaque volume, volumes of plaque with CT attenuation with <30 and <60 HU, plaque burden and remodeling index were obtained using the automated software tool. The coronary plaque burden was calculated as the percentage of plaque area from the cross-sectional vessel area at the site of

minimal luminal area. The remodeling index was calculated as the outer vessel wall area at the site of the minimal luminal area divided by the vessel area defined by the vessel wall reference at that location. The vessel wall reference provides the estimate of the normal tapering of the coronary artery between the proximal and distal reference segment. We defined positive remodeling as the remodeling index >1.1. The diameter stenosis was calculated as the minimal luminal diameter divided by the mean of the luminal diameters of the proximal and distal reference sites.

**Statistical analysis**

All statistical analyses were performed using Stata 13.1 (StataCorp LP, College Station, Texas). Continuous data are presented as mean ± standard deviation or median with interquartile range. Categorical variables are presented as absolute and relative frequencies. Intraclass correlation coefficient (ICC) was calculated by the use of a two-way random-effects model and was used to evaluate interobserver agreement among four readers. Comparisons between groups were performed using univariable multilevel mixed-effects logistic regression models that account for the group structure (i.e. multiple segments per patient) and thus possible
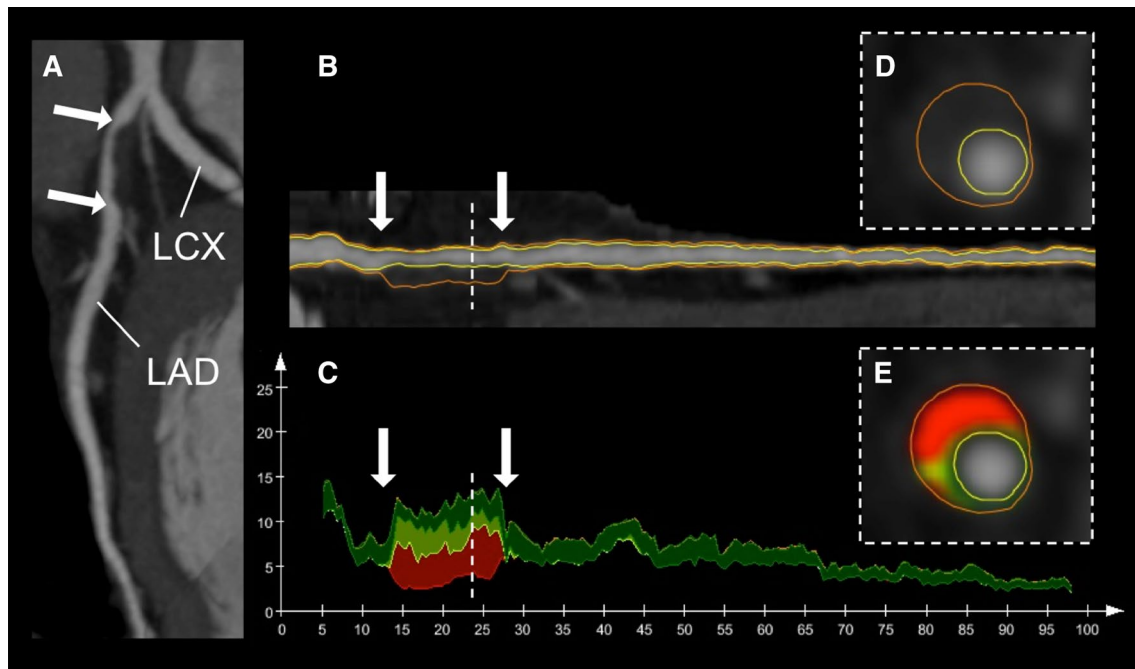
**Fig. 2** Curved multi-planar reconstruction of the LAD (**a**). A non-calcified, positively remodeled plaque with a low CT attenuation is visible in the proximal segment of the LAD indicated by *white arrows*. The segmentation of the luminal and outer vessel boundaries (*yellow and orange lines*) was performed automatically with manual adjustment (**b**). The graph illustrates the distribution of various plaque CT attenuation values, *Y axis* plaque cross-sectional area, *X axis* distance from the left coronary ostium (**c**). Cross-sectional image of the plaque at the position indicated by *white dashed lines* (*panel* **d**), the *panel* **e** shows the same cross-section with color overlay based on CT numbers, *red*: low-attenuation non-calcified plaque (≤30 HU), *light and dark green*: high-attenuation non-calcified plaque (30–120 HU). (*LAD left* anterior descending artery, *LCX left* circumflex coronary artery)

autocorrelation effects in the data. We used the same regression method performing univariable (i.e. unadjusted odds ratios) and multivariable analyses (i.e. adjusted odds ratios) to determine the association between qualitative and quantitative high-risk plaque characteristics. Two-sided p value of <0.05 was considered significant.

## Results

### Study population

From 501 patients randomized to the coronary CTA arm, 473 patients successfully underwent coronary CTA. Reasons for not undergoing a coronary CTA included: patient declined coronary CTA (n=9), safety concerns (n=5), unavailability of coronary CTA (n=5), or technical difficulties (n=9). One patient was excluded from further analysis due to non-diagnostic image quality in all coronary segments. Total of 472 patients were included in the qualitative plaque analysis, and 470 patients in the quantitative plaque assessment (two patients were excluded due to insufficient image quality for quantitative assessment) (Fig. 1). Patients with coronary artery plaque (n=260) were included for further

quantitative plaque analysis (mean age 56.1 ± 7.8 years, 62.7% men), Table 1. Quantitiative plaque asssessment was feasible in all patients with coronary plaque. At the segment level, we excluded only 2.8% (108 out of 3804) of coronary segments with insufficient image quality for quantitative analysis.

### Qualitative plaque characteristics

Coronary artery disease defined as the presence of any coronary plaque was detected in 260 patients. Of these

**Table 1** Clinical characteristics of study patients

|  | Patients (n = 260) |
| --- | --- |
| Age (years), mean ± SD | 56.1 ± 7.8 |
| Men, n (%) | 163 (62.7) |
| Cardiovascular risk factors, n (%) |  |
| Hypertension | 157 (60.4) |
| Diabetes mellitus | 53 (20.4) |
| Dyslipidemia | 142 (54.6) |
| Former or current smoker | 145 (55.8) |
| Family history of premature CAD | 65 (25.0) |

patients, 45 (17.3%) had obstructive CAD, defined as ≥50% stenosis, and 215 (82.7%) had non-obstructive CAD, with a stenosis of 1–49%. Calcified plaques were present in 216 (83.1%) and non-calcified plaques in 197 (75.8%) patients. At least one high-risk plaque feature was present in 166 (63.8%) patients. The most common high-risk plaque feature was spotty calcium, which was present in 151 (58.1%) patients. Positive remodeling was present in 55 (21.2%), low HU plaque was present in 39 (15.0%), and napkin-ring sign was present in 26 (10.0%) patients, Table 2. In total, coronary plaque was found in 888 coronary segments. Among them, 82 segments had positive remodeling, 53 segments had low CT attenuation plaque, 35 segments had napkin-ring sign and 347 segments had spotty calcification.

## Quantitative plaque measurements

We quantitatively analyzed coronary plaques in 888 coronary segments (number of segments with multiple plaques n = 66/3804). The median lumen diameter stenosis of these segments was 0.11 (IQR 0.05–0.23). The median total plaque volume was 36.0 mm$^3$ (IQR 17.8–75.2). The median plaque burden was 0.45 (IQR 0.38–0.53). The median low CT attenuation plaque volume was 0.17 mm$^3$ (IQR 0.00–1.07) for <30 HU and 0.90 mm$^3$ (IQR 0.14–3.57) for <60 HU. The median remodeling index was 1.02 (IQR 0.92–1.15).

**Table 2** Coronary computed tomography angiography characteristics of patients with coronary atherosclerotic plaque (qualitative data)

|  | Patients (n = 260) |
| --- | --- |
| Coronary artery disease category, n (%) |  |
| No CAD | 0 (0.0) |
| Non-obstructive CAD (1–49% stenosis) | 215 (82.7) |
| Significant CAD (≥50% stenosis) | 45 (17.3) |
| Coronary plaque category, n (%) |  |
| No plaque | 0 (0.0) |
| Calcified plaque | 216 (83.1) |
| Non-calcified plaque | 197 (75.8) |
| High-risk plaque category, n (%) |  |
| Any high-risk plaque | 166 (63.9) |
| Positive remodeling | 55 (21.2) |
| Low HU plaque | 39 (15.0) |
| Napkin-ring sign | 26 (10.0) |
| Spotty calcium | 151 (58.1) |

*CAD* coronary artery disease, *HU* Hounsfield unit

## Interobserver variability of quantitative coronary plaque analysis

We observed good to very good interobserver agreement among four readers for the quantitative measurements of volume of plaque with <30 HU (ICC 0.80, 95% CI 0.74–0.86), volume of plaque with <60 HU (ICC 0.87, 95% CI 0.82–0.91), positive remodeling (ICC 0.69, 95% CI 0.60–0.77), and plaque length (ICC 0.98, 95% CI 0.98–0.99).

## Association of quantitative plaque measurements with high-risk plaque features

Out of the 888 coronary segments containing any plaque 391 segments showed at least one high-risk plaque feature, whereas 497 segments contained no high-risk plaque feature. Coronary segments with high-risk plaque features of positive remodeling, low CT attenuation plaque and napkin-ring sign demonstrated higher diameter stenosis, larger low CT attenuation plaque volume, larger maximum plaque burden and increased remodeling index as compared to segments without any high-risk plaque feature (Table 3). Notably, there was no difference in diameter stenosis (median 0.10 vs. 0.12, p = 0.823), total plaque volume (median 32 mm$^3$ vs. 36 mm$^3$, p = 0.678) and plaque burden (median 0.53 vs. 0.57, p = 0.107) in segments with spotty calcium vs. without any high-risk plaque feature.

In univariable analyses, we used the quantitative plaque metrics as independent variables and the presence of any high-risk plaque feature (positive remodeling, low CT attenuation plaque and napkin-ring sign—we excluded spotty calcium as there was no significant association of quantitative plaque characteristics and the presence of spotty calcium) as dependent variable. We found that total plaque volume, low CT attenuation plaque (<30 and <60 HU) volume, plaque burden and remodeling index were strongly associated with the presence of any high-risk plaque feature (Table 4). In multivariable analysis low CT attenuation (<30 HU) plaque volume (odds ratio = 1.12, 95% CI 1.04–1.21, p = 0.03), plaque burden (odds ratio = 1.53, 95% CI 1.08–2.16, p = 0.017) and remodeling index (odds ratio = 1.25, 95% CI 1.10–1.41, p < 0.001) continued to demonstrate an association with the presence of any high-risk plaque feature. Similar results were found when using low CT attenuation plaque volume of <60 HU.

## Discussion

We demonstrated an association between quantitative coronary plaque measurements and the presence of high-risk coronary plaque features (positive remodeling, low CT attenuation plaque and napkin-ring sign) identified by experienced

**Table 3** Association between quantitative coronary plaque measurements and individual high-risk plaque features (analyses performed per coronary segment, p values for the comparison to segments with no high-risk plaque)

| | Segments without HRP (N=497) | Napkin-ring sign (N=35) | p | Positive remodeling (N=82) | p | LAP (N=53) | p | Spotty calcium (N=347) | p |
|---|---|---|---|---|---|---|---|---|---|
| Diameter stenosis | 0.12 (0.05–0.23) | 0.33 (0.10–0.54) | <0.001 | 0.20 (0.10–0.39) | <0.001 | 0.22 (0.10–0.46) | <0.001 | 0.10 (0.05–0.22) | 0.823 |
| Plaque volume | 36.1 (18.9–70.0) | 134.3 (52.6–178.0) | 0.001 | 95.7 (39.9–149.2) | <0.001 | 94.6 (36.7–149.2) | 0.001 | 32.3 (16.3–77.8) | 0.678 |
| LAP volume (<30 HU) (mm$^3$) | 0.17 (0.00–0.98) | 3.69 (0.49–8.14) | <0.001 | 1.72 (0.25–6.23) | <0.001 | 2.30 (0.42–6.46) | <0.001 | 0.16 (0.00–1.03) | 0.662 |
| LAP volume (<60 HU) (mm$^3$) | 0.85 (0.13–2.93) | 12.34 (3.25–26.53) | <0.001 | 5.56 (1.81–17.48) | <0.001 | 8.04 (2.84–20.10) | <0.001 | 0.83 (0.13–3.58) | 0.456 |
| Plaque burden | 0.57 (0.48–0.68) | 0.79 (0.67–0.93) | <0.001 | 0.72 (0.58–0.88) | <0.001 | 0.74 (0.58–0.90) | <0.001 | 0.53 (0.44–0.67) | 0.107 |
| Plaque burden > 0.7; n (%) | 104 (20.9) | 25 (71.4) | <0.001 | 44 (53.7) | <0.001 | 33 (62.3) | <0.001 | 79 (22.8) | 0.593 |
| Remodeling index | 1.00 (0.89–1.13) | 1.20 (1.04–1.36) | <0.001 | 1.18 (1.03–1.37) | <0.001 | 1.20 (1.04–1.42) | <0.001 | 1.04 (0.94–1.15) | 0.014 |
| Remodeling index > 1.1; n (%) | 150 (30.2) | 23 (65.7) | <0.001 | 52 (63.4) | <0.001 | 33 (62.3) | <0.001 | 129 (37.2) | 0.099 |

*HRP* high-risk plaque, *LAP* low CT attenuation plaque, *HU* Hounsfield unit

**Table 4** Unadjusted and adjusted associations between quantitative coronary CTA measurements and the presence of any high-risk plaque feature (positive remodeling, low CT attenuation plaque and napkin-ring sign)

| Independent variables | Unadjusted OR (95% CI) | p value | Model 1 Adjusted OR (95% CI) | p value | Model 2 Adjusted OR (95% CI) | p value |
|---|---|---|---|---|---|---|
| Total plaque volume[†] | 1.01 (1.01–1.01) | <0.001 | 1.00 (1.00–1.01) | 0.148 | 1.00 (1.00–1.01) | 0.626 |
| LAP volume (<30 HU)[†] | 1.21 (1.13–1.29) | <0.001 | 1.12 (1.04–1.21) | 0.003 | | |
| LAP volume (<60 HU)[†] | 1.11 (1.08–1.15) | <0.001 | | | 1.08 (1.03–1.12) | <0.001 |
| Plaque burden* | 1.83 (1.51–2.21) | <0.001 | 1.53 (1.08–2.16) | 0.017 | 1.53 (1.08–2.16) | 0.016 |
| Remodeling index* | 1.38 (1.23–1.55) | <0.001 | 1.25 (1.10–1.41) | <0.001 | 1.23 (1.08–1.39) | 0.001 |
| Diameter stenosis* | 1.41 (1.23–1.61) | <0.001 | 0.96 (0.74–1.25) | 0.770 | 0.94 (0.73–1.23) | 0.667 |

*LAP* low CT attenuation plaque, *HU* Hounsfield unit, *OR* odds ratio, *CI* confidence interval

*Per 0.10 increase

[†]Per 1 mm$^3$ increase

readers in patients who presented in the ED with suspected ACS. The analysis was feasible in the majority of coronary CTA scans that were acquired in the setting of multicenter clinical trial and various CT scanner use.

The histologic features of coronary plaques found in culprit lesions of sudden cardiac death victims included large overall plaque size and large necrotic core, higher macrophage count, positive remodeling, speckled calcium, and thin fibrous cap [3]. Similar morphologic features (plaque rupture, thrombus, positive remodeling, larger plaque area, spotty calcium, and large necrotic core) were observed with intravascular imaging techniques when examining culprit

lesions of ACS [7, 21]. High-risk plaque features can be also detected in ACS patients by non-invasive coronary CTA imaging. Coronary plaque features such as positive remodeling, low CT attenuation plaque, napkin-ring sign, and spotty calcium were more often seen in culprit lesions of ACS as compared to lesions causing stable angina pectoris [10, 22, 23]. Furthermore, the presence of high-risk plaque features assessed either by qualitative or quantitative assessment was associated with increased risk of future major cardiovascular events [9, 24, 25].

The association between coronary plaque characteristics assessed by coronary CTA and histologic plaque

composition was assessed by multiple ex vivo investigations [26, 27]. Early studies using 16-multidetector row CT demonstrated that coronary CTA provides an accurate and reproducible method for the quantitative assessment of total plaque and calcified plaque areas. Subsequently, an ex vivo investigation using state-of-the-art scanner and reconstruction technique showed that qualitative assessment of the attenuation pattern of non-calcified plaques in coronary CTA significantly improves the diagnostic accuracy for the detection of high risk plaques as defined by histology. The authors showed that in experimental conditions the napkin-ring sign had an excellent specificity to identify advanced lesions (98.9%, 95% CI 97.6–100%) [26]. Seifarth et al. investigated the histological correlates of the napkin-ring sign and concluded that the detection of this specific plaque attenuation pattern in coronary CTA was independently linked to the size of the necrotic/lipid core, the size of the plaque and the vessel area as measured in histology [27].

Coronary CTA is a unique non-invasive imaging modality with the ability to assess all main coronary arteries and total coronary plaque burden. The accuracy of coronary CTA plaque quantification was successfully validated against grey scale intravascular ultrasound (IVUS) and virtual histology-IVUS (VH-IVUS). Boogers et al. demonstrated that automated quantification of coronary plaque in coronary CTA correlated well with IVUS-derived measurements of lumen area stenosis and plaque burden [28]. Studies using VH-IVUS as a reference standard demonstrated that coronary CTA allows for an accurate and reproducible quantification of coronary plaque burden and plaque volume [29, 30]. In addition, these studies showed that non-calcified plaque components with high CT numbers (>30 HU) correlated with fibrous plaque tissue whereas plaques with low CT numbers (<30 HU) correlated with necrotic core and fibro-fatty plaque components as assessed by VH-IVUS [30]. In line with these observations Marwan et al. demonstrated that lipid-rich plaques have a higher percentage of pixels with low HU values compared with plaques of predominantly fibrous components by using intraplaque pixel CT number histogram analysis [31]. Moreover, in vivo studies utilizing optical coherence tomography as the reference standard to identify thin-cap fibroatheromas demonstrated that high-risk plaques have lower CT numbers as compared to stable lesions (35–45 vs. 62–79 HU; P < 0.001) [32].

Previous studies have assessed associations between both quantitative and qualitative high-risk plaque features as detected by coronary CTA in comparison with intravascular ultrasound (IVUS), optical coherence tomography (OCT) and histology. The direct comparison between qualitative and quantitative coronary CTA assessment of high risk plaque has not been studied. Our study provides support for the feasibility of automated plaque assessment in the evaluation of patients with CAD. We demonstrated that quantitative measures of coronary plaque (low CT attenuation plaque volume, positive remodeling and plaque burden) are associated with high-risk plaque as determined by a simple quantitative plaque assessment. These results were achieved in the setting of a multicenter, multivendor trial with contemporary clinical practice equipment and image quality. Only a small fraction of coronary CTA scans had an image quality precluding qualitative and quantitative plaque analysis. This observation provides evidence that both types of analyses are feasible in the current clinical practice. However, quantitative analysis requires specialized software and additional time for analysis. We previously showed in the identical population that the evaluation of high-risk plaque from both qualitative and quantitative assessment is predictive of ACS independently of stenosis and clinical risk [8, 33].

Quantitative plaque assessment has a possible value in a few areas of the clinical practice. The implementation of quantitative plaque assessment may improve interobserver variability as has been demonstrated in previous studies. The use of automated software for quantitative plaque evaluation may improve the accessibility of high-risk plaque assessment for readers with less extensive training and experience. The use of automated software will eventually decrease the time needed for analysis and will allow for more efficient implementation of the high-risk plaque assessment in the clinical practice. Our findings suggest that automated plaque quantification might be a robust proxy to qualitative plaque assessment performed by experienced readers.

High-risk plaques detected in qualitative analysis are predictors of both acute and future cardiovascular events [10, 25]. Similarly, quantitative plaque measurements can also serve as a marker of increased risk of future cardiovascular events [19]. A recently published study showed that total plaque volume and total non-calcified plaque volume as assessed with the semiautomatic plaque quantification tool on coronary CTA had an incremental value to predict future ACS events over traditional cardiovascular risk factors and CT features of vulnerable plaques (calcium score, stenosis severity and number of segments with NCP) [19]. In a prospective study, Kristensen et al. demonstrated that the volume of non-obstructive NCP as measured with automated plaque assessment tools is a strong and independent predictor of cardiovascular events in patients with nonSTsegment elevation myocardial infarction who underwent coronary CTA prior to invasive coronary angiography and percutaneous coronary intervention [26]. Notably, neither calcium score, nor calcified plaque volume were associated with an increased risk of major cardiovascular events [26]. Thus, the quantitative plaque assessment provides valuable tool both to identify patient with ACS and provide personalized prediction of cardiovascular risk.

## Limitations

We restricted our analysis to four most established high-risk plaque features (positive remodeling, low CT attenuation plaque, napkin-ring sign, and spotty calcium). There is a clear overlap between some of the quantitative features and qualitative features (e.g. positive remodeling, low CT attenuation and napkin-ring sign). Our definition of high risk plaque in quantitative measurements is arbitrary and depends highly on our patient population. Larger clinical trials may be needed to investigate the clinical utility of such quantitative measurements and determine appropriate thresholds associated with increased risk. Our observations were made in the population of patients with suspected ACS and thus the generalizability to populations with stable chest pain may be limited.

## Conclusions

Quantitative coronary plaque characteristics (low CT attenuation plaque volume, positive remodeling and plaque burden) measured by automated software correlate with qualitative assessment of high-risk plaque features. The use of automated software may improve feasibility of high-risk risk plaque detection in research applications (ACS detection, plaque progression, prognostication of future major cardiovascular events) and clinical practice.

**Compliance with ethical standards**

**Conflict of interest**   Dr. Hoffman receives grant support from Siemens Medical Solutions and Heart Flow Inc. and consultant/advisory board support from Heart Flow Inc. Pieter Kitslaar is an employee of Medis medical imaging systems B.V. Other authors declares that he/she has no conflict of interest.

**Ethical approval**   All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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