Non-Calcified Coronary Artery Plaque on Coronary CT Angiogram

Subjects: Cardiac & Cardiovascular Systems

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Coronary artery disease (CAD) is associated with increased mortality and morbidity and remains a great healthcare concern. Early detection of coronary artery plaque before its progression to calcification can allow early interventions towards regression. This will eventually translate into a lower incidence of future cardiovascular (CV) events. Dedicated and focused outcome-based research is highly indicated in this area to assess if there is utility of coronary computed tomography angiography (CCTA) in symptomatic and asymptomatic patients with zero or minimum coronary artery calcium score of zero (CACS). CCTA can be performed with minimal possible radiation exposure.

cardiac CT calcium score | coronary computed tomography | angiography

1. Introduction

Coronary artery disease is widely established as a leading cause of mortality in developed countries [1]. Assessment of calcium on non-contrast computed tomography (CT) scans is a well-recognized traditional approach for predicting cardiovascular (CV) outcomes in asymptomatic individuals [2]. Interestingly, a number of new technological advancements and innovations in non-invasive imaging can further delineate patients with high risk for future major cardiovascular events (MACE). One of these promising advances is the ability to distinguish coronary artery plaques through non-invasive approaches, which include non-invasive coronary CT angiography (CCTA).

The most recent ACC/AHA guidelines for chest pain assessment have mentioned the importance of coronary CTA as one of the first-line tests to evaluate obstructive coronary artery stenosis [3][4]. Regardless of the magnitude of coronary artery stenosis identified by CCTA, the overall plaque burden has been linked to poor prognosis in multiple prior reports [5][6][7][8]. In addition, SCCT guidelines on CCTA interpretation recommend visual plaque quantification in the CAD RADS reporting scheme [9]. High-risk plaque (HRP) on CCTA includes positive remodeling (PR), napkin ring lesions, spotty calcification, and low-attenuation non-calcified plaque (LAP) with a HU < 30 [10][11][12].

With prominent advances in plaque quantification and characterization on CCTA using artificial intelligence/machine learning-based algorithms or pipelines, the inter-observe, intra-observer, and inter-scanner variations in reporting plaque quantification can be minimized. This will facilitate more population-based research in

symptomatic and asymptomatic individuals to understand the importance of the presence, distribution, and characteristics of plaque on coronary CTA in predicting future cardiovascular outcomes.

2. Prevalence and Significance of Non-Calcified Coronary Artery Plaque on Coronary Computed Tomography Angiogram

2.1. Non-Calcified Plaque (NCP) Detected by CCTA in Symptomatic Patients

Hausleiter et al. analyzed 161 patients and noncalcified coronary plaques were found in 48 (29.8%). Among these, 38 (23.6%) also had coronary calcifications, while noncalcified plaques as the sole manifestation of CAD were observed in 10 (6.2%) patients. Patients with noncalcified plaques exhibited higher total cholesterol, LDL, and CRP levels, along with a trend toward increased diabetes mellitus. Most noncalcified plaques resulted in lumen narrowing of less than 50%. In the remaining 113 patients, CAD was ruled out in 53 (32.9%), while 60 (37.3%) had calcifications without noncalcified plaque [13]. Nance Jr et al. evaluated 458 patients at low-to-intermediate risk for CAD presenting with chest pain. During a 13-month median follow up, the presence of plaque was associated with higher adverse outcomes, the Hazard ratios (HRs) of mixed vs. NC vs. calcified plaque were 86.96 vs. 58.06 vs. 32.94; all with *p*-values < 0.05, respectively [14]. In their population, patients with isolated NCP had a significantly higher likelihood of adverse cardiac events of 5% (hazard ratio 151.77, $p < 0.01$).

In a post hoc analysis of 1769 patients with stable chest pain from the SCOT-HEART cohort, Williams et al. examined the presence of adverse plaque (positive remodeling and LAP) and its association with outcomes at 5 years. Unsurprisingly, the primary events encompassing fatal and non-fatal myocardial infarction (MI) were higher in the presence of LAP compared to other plaque types (HR: 1.6, 95% CI: 1.1–2.34, $p = 0.014$). Also, more events were noted in patients with adverse plaque despite having CACS < 100 AU with a HR of 3.38 (CI 1.13 to 10.08, $p = 0.03$). The 41 patients with fatal or nonfatal MI at follow-up had significantly higher LAP burden of 7.5% [4.8–9.2] versus 4.1% [0–6.8] in patients without events (HR of 1.6; 95% CI = 1.1–2.3, $p < 0.001$). The overall presence of LAP burden of >4% increased the likelihood of MACE by five times in this population [15].

2.2. Non-Calcified Plaque (NCP) Detected by CCTA in Asymptomatic Patients

Multiple studies have observed NCP prevalence in asymptomatic patients. Rodriguez et al. examined 202 patients [16] at low-to-intermediate risk for CAD. Male sex was associated with a higher total plaque index compared to women (42.06 mm^2 ± 9.22 vs. 34.33 mm^2 ± 8.35; $p < 0.001$). Similarly, patients with elevated LDL level (β = 0.04 mm^2/mg/dL; $p = 0.02$), elevated systolic blood pressure (β = 0.80 mm^2/10 mm Hg; $p = 0.03$), and DM (β = 4.47 mm^2; $p = 0.03$) were found to have a significantly higher NCP. Nezarat et al. [17], in patients younger than 40 years old, noted both calcified plaque as well as NCP to be elevated in DM patients as compared to non-diabetics (19% vs. 58%; $p < 0.001$). Despite a CACS of 0, patients with DM had a higher prevalence of NCP (46%, $p < 0.0001$). On quantitative plaque assessment, all volumes in the NCP type were threefold higher in the presence of DM.

Jin et al. evaluated the characteristics and predictors of subclinical coronary atherosclerosis and cardiac events in 914 asymptomatic young adults. NCP was the most common type of plaque in asymptomatic young adults and was identified in 6.9% of the population. Forty-six subjects (5.3%) had a CACS of 0 and seventeen (42.5%) had CACS > 0. Multivariate analysis revealed a HR of 2.2 for subclinical coronary atherosclerosis and 49.17% of them for NCP [18].

2.3. Comparison of CCTA Non-Calcified Plaque (NCP) with IVUS-VH

Obaid et al. assessed the accuracy of CCTA in evaluating plaque components in 57 patients with histologic correlation from 8 postmortem coronary arteries. CT contrast attenuation plaque maps were created in 108 plaques and these maps correlated remarkably with IVUS in regard to plaque composition. In addition, a strong correlation was noted between the two modalities in regard to calculation of necrotic core and total plaque volume. The diagnostic accuracy of CCTA to IVUS-VH was 83% versus 92% for calcified plaque, 80% versus 65% for necrotic core, and 80% versus 79% for fibroatheroma [19]. The CCTA accuracy was similar to IVUS in evaluating plaque fibroatheroma and had superior detection for the fibrotic core (80% vs. 79% and 80% vs. 65%), respectively. However, the IVUS has a better ability to detect calcified plaque and thin-cap fibroatheroma (TCFA) [20].

Carrascosa et al. evaluated 40 patients with CCTA, and compared to IVUS, which was heralded as the gold standard for accuracy evaluation, the total number of plaques was 276. About 99% of them were classified by the CCTA precisely as calcified plaque versus NCP, while 82% of the NCP was subdivided accurately into fibrous and soft plaque [21] using a cut-off value of 88 HU on CCTA. Schepis et al. evaluated the reproducibility of NCP volume measurement by DSCT in comparison to IVUS. This study included 70 patients with 100 individual NCPs (1 to 3 plaques per patient). The difference in the NCP volume by CT measurement between different observers and the variation in the same observer reading was reported to be 6 ± 5% and 11 ± 7%, respectively. The CT mean plaque volume 89 ± 66 mm was comparable to IVUS 90 ± 73 mm with a mean difference between both modalities of 1 ± 34 mm. Bland–Altman agreement between the two modalities was modest, i.e., −67 to +65 mm [19].

3. Summary

There is an emerging interest in the assessment of plaques identified by CCTA in both symptomatic and asymptomatic patients. CCTA is being increasingly utilized after subsequent incorporation into the new ACC/AHA guidelines as one of the premier first-line tests in symptomatic patients alongside other traditional stress-testing modalities [3]. Another key reason is the increased availability of artificial intelligence (AI) pipelines based on CCTA plaque algorithms that are now being validated and integrated in the clinical setting. However, CCTA is currently not recommended by both the ACC/AHA and European guidelines in asymptomatic patients [3].

Coronary artery calcium score is performed on non-contrast CT images in asymptomatic patients. However, contrast-enhanced CT scans of coronary arteries with their increased spatial resolution allows plaque assessment regardless of type. Non-calcified plaques (NCPs) are considered precursor lesions for calcified plaque. If attempts

are made to identify NCP regression at any early age, a reduction in prevalence of CAD can be achieved along with accompanying reductions in morbidity and mortality [19][22].

Although high-risk plaque features have been defined on CCTA, and plaque characterization has been compared with IVUS-VH on autopsied coronary arteries, there is variation in plaque burden assessment noted on CT with some degree of inter-vendor and inter- and intra-observer variations. This is more a significant issue when the vessel wall is counted as plaque in patients with isolated NCP. However, with augmented AI based plaque analysis, significant improvement is anticipated. Of note, despite the high prevalence of NCP, a reduced occurrence of obstructive CAD is being identified in patients with isolated NCP as compared to calcified plaque [16][23]. On another note, few studies have examined outcomes in regard to MACE in these patients with soft plaque. A limitation of CT is the inability to identify thin-cap fibroatheroma due to limits with resolution. Thus, reliable classification of NCP into vulnerable and stable plaque based on CT density assessment cannot be performed. Despite these concerns, CCTA has a bright future in regard to its potential in risk stratification of individuals with zero CACS and prediction of cardiac events based on plaque characterization. Population-based CCTA studies like MESA and the recent Miami heart study have significantly expanded our understanding of plaque prevalence and its relationship with obstructive CAD. As this population continues to be examined and explored, our knowledge regarding plaque constituency or relationships with ethnicity, familial/genetic tendencies, and risk factor profiles will improve in years to come. One of the ongoing studies addressing this question is the CONFIRM 2 trial. Plaque that is not calcified on the CT scans can be regressed with treatment and confirmed with follow-up imaging. The clinical utility of this strategy has yet to be established. In a meta-analysis by Andelius et al., patients were subdivided into three cohorts which encompassed intense statin therapy, moderate statin therapy, and a control group. The intensive statin group had a higher reduction in the total plaque volume as well as mean volume. The control group, on the other hand, showed significant increases in total plaque as well as mean plaque volume [24].

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