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Implications of serial coronary computed tomography angiography in the evaluation of coronary plaque progression

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Purpose of review

The purpose is to review the use of coronary computed tomography (CT) angiography to assess coronary plaque burden/progression and to discuss about recent clinical trials that have utilized this imaging modality to study the effect of new pharmacotherapies on plaque burden/progression.

Recent findings

There are numerous clinical trials that have utilized coronary CT angiography to demonstrate the potential benefits of statins, apixaban, rivaroxaban, aged garlic extract, biologic agents, and omega-3 fatty acids to reduce coronary plaque progression. Coronary CT angiography can identify high-risk plaques and can also quantify total plaque burden, both of which are independent risk factors to predict major adverse cardiac events.

Summary

Coronary heart disease remains one of the leading cause of mortality in the world. Utilizing coronary CT angiography, it is possible to identify rupture-prone plaques and also to quantify the total plaque burden. New pharmacotherapies that have the potential to reduce plaque progression have been used in clinical trials and these trials have utilized coronary CT angiography to track coronary atheroma progression. In future, we will see frequent utilization of coronary CT angiography to track coronary atheroma.

Keywords

coronary calcifications, coronary CT angiography, coronary plaque progression, vulnerable plaque

INTRODUCTION

Early identification of high risk coronary plaques is crucial to prevent acute coronary syndromes. As such, many imaging modalities have been developed which identify such plaques. Coronary computed tomography (CT) angiography (CCTA) is one of such modalities which is increasingly been used recently as it is noninvasive and easy to perform even in the outpatient settings. CCTA can also assess plaque burden and plaque progression. Utilizing this ability of CCTA, numerous clinical trials have been conducted to assess the effect of new pharmacotherapies on coronary plaque progression. In this review, we will discuss recent studies that have utilized CCTA to track coronary plaque progression (Table 1).

FORMATION OF CORONARY PLAQUE

Vascular calcifications, as first described by Rudolph Virchow in 1858 [1], have an important role in the pathophysiology of atherosclerosis. Atherosclerosis

begins with deposition of lipoproteins in the sub-endothelial matrix followed by the migration of monocytes [2]. The monocytes convert to macrophage and start phagocytosis of the lipoproteins [3]. The lipoprotein-cholesterol complex gets oxidized which then cause death of lipid-laden macrophages (foam cells) [4]. The abnormal apoptosis of these foam cells releases toxic material leading to activation of T cells and triggering further inflammation [5]. This is followed by the migration and proliferation of smooth muscle cells into the intima which secrete collagenous material leading to the

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KEY POINTS

- Vulnerable coronary plaques and total plaque burden can both predict adverse cardiac events.
- CCTA is useful imaging modality to identify vulnerable plaques and to track coronary plaque progression.
- Numerous clinical trials have been conducted that have utilized serial CCTA to study the effect of new pharmacotherapies on coronary plaque progression.

formation of fibrous cap. In high-risk lesions, the lipid pools become confluent and grow into necrotic cores. Further deposition of the hyaluronan and versican in the necrotic core along with macrophage infiltration convert the lesion into fibroatheroma [6]. Angiogenesis happens in the growing lesion with the help of vascular endothelial growth factor [7], placental growth factor [8], and oncostatin M [9], making the lesions more unstable. If the fibrous cap is thick, the plaque becomes stable. Myocardial infarction is mostly associated with thin-cap fibroatheroma (TCFA) which can either fracture or can have superficial erosion of the intima, both processes can either lead to healing of the lesion or formation of thrombi based on the coronary hemodynamics and individual's thrombotic state [10]. Necrotic core of the atheroma serves as an initiation site for calcifications. Injured macrophages and vascular smooth muscle cells release extracellular vesicles which serve as sites for deposition of amorphous calcium phosphate or more crystalline hydroxyapatite [11–13]. The balance of procalcification factors and inhibitors determines whether calcification occurs and whether microcalcification (unstable plaque) converts to macrocalcification (stable plaque) [14^{***}].

Table 1. Effect of drug therapy on rate of coronary plaque progression (refer to text)

Drug	Rate of plaque progression on serial computed tomographies
Statins	Reduction
Testosterone	Increase (Harm)
Aged garlic extract	Reduction
Xarelto	Reduction
Eliquis	Reduction
^a EPA/DHA	Reduction
Cilostazol	Reduction
Biologic agents	Reduction

Note: The summary table is original and not adapted from other publications.
^aEPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

PLAQUE CHARACTERIZATION BASED ON CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Coronary plaques are classified differently in different clinical trials depending on the research question of interest. One way to classify is based on the amount of calcium: noncalcified, partially calcified, or calcified [15]. Noncalcified plaques are further classified into fibrous, fibrofatty, or low attenuation based on Hounsfield unit. Noncalcified plaques can also be classified as homogenous or heterogenous in attenuation pattern [16]. Heterogenous plaques can be divided into with and without Napkin-ring sign (NRS). NRS plaques are low attenuation in the center because of the large lipid-rich necrotic core which makes them rupture-prone [17]. Microcalcifications in these plaques further destabilize them [18]. Current CCTA can't detect microcalcifications because of low spatial resolution (0.4–0.6 mm). High-risk calcification that can be detected on CCTA is 'spotty' calcification which is a CCTA marker of histological microcalcifications defined as less than 3 mm of calcified plaque and more than 130 Hounsfield unit density surrounded by noncalcified plaque [19]. The term 'positive remodeling' refers to high-risk plaque (HRP) with large lipid core which tends to grow outwards and not usually causing luminal narrowing.

Instead of looking into individual HRP features, many clinical trials have utilized the concept of quantifying the total plaque burden in the affected arteries. Percentage atheroma volume (PAV) from CCTA can adequately assess total atherosclerotic plaque burden in patients with hemodynamically significant coronary artery disease $PAV = ((\text{total atheroma volume} / \text{total vessel volume}) \times 100)$.

'THE VULNERABLE PLAQUE' VERSUS 'PLAQUE BURDEN' FOR RISK ASSESSMENT

The vulnerable plaque is a TCFA, characterized by large lipid or necrotic core and surrounded by thin fibrous cap. These HRPs, when they rupture, may not necessarily cause clinical syndromes. Interestingly, an advanced atheroma most likely had undergone repeated episodes of rupture and healing [20]. Multiple rupture and healing process lead to subsequent lumen narrowing. Thin-cap fibroatheroma can transition to thick-cap fibroatheroma within a 12-month interval, secondary to rupture and healing without causing any clinical events [21]. If many HRPs rupture over different time period, very few of them will lead to clinical events. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial showed that,

in patients with stable coronary artery disease, percutaneous intervention (PCI) did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy [22]. The possible explanation of the outcome of COURAGE trial is that PCI fixes one lesion whereas medical management stabilizes total plaque burden in the entire coronary vasculature. Therefore, for accurate risk assessment, total plaque burden plays important role rather than individual plaque characteristics. CCTA, thus, has a tremendous potential in future clinical trials, not just that it identifies HRPs but also because of its ability to assess and track total plaque burden.

Numerous clinical trials have used CCTA to track the coronary plaque progression and looked for any adverse clinical outcomes. Papadopoulou *et al.* [23] performed CCTA in 32 patients with acute coronary syndromes (ACSs) who underwent PCI and tracked the plaque progression after 39 months. They found patients with clinical events have larger normalized total atheroma volume (TAVnorm) at baseline and TAVnorm progressed over time [23]. Motoyama *et al.* [24] performed CCTA to evaluate HRP and significant stenosis (>70%) in 3158 patients with suspected or known Coronary Artery Disease. They also performed serial CCTA in 449 patients and tracked the plaque progression during the mean follow-up of 3.9 years. They found CCTA-verified HRP and plaque progression detected by serial CCTA were independent predictors of ACS [24].

The SCOT-HEART (Scottish Computed Tomography of the Heart) was a multicenter randomized controlled trial where 4146 patients with stable chest pain were randomly assigned to CCTA (2073 patients) or to standard care alone (2073 patients) [25[■]]. In the posthoc analysis of the SCOT-HEART study, Williams *et al.* [26[■]] found that coronary heart disease death or nonfatal myocardial infarction was 3 times more frequent in patients with adverse plaque (4.1 versus 1.4%; $P < 0.001$; hazard ratio [HR]: 3.01; 95% confidence interval [CI]: 1.61–5.63; $P = 0.001$) and was twice as frequent in those with obstructive disease. Patients with both obstructive disease and adverse plaque had the highest event rate, with a 10-fold increase in coronary heart disease death or nonfatal myocardial infarction compared with patients with normal coronary arteries (HR: 11.50; 95% CI: 3.39–39.04; $P < 0.001$) [26[■]]. Another study by Gu *et al.* [27] looked not just only for association of atherosclerosis and adverse clinical outcome but also for gender difference in the progression of atherosclerosis. The study enrolled 1046 patients with suspected coronary artery disease who underwent serial CCTA and were followed up for mean of 4.9 years. Compared with women, men

had significantly higher progression of severe proximal plaque score (SPPS), segment stenosis score (SSS), and segment involvement score (6.6 versus 3.5%, 28.0 versus 18.3%, 26.6 versus 16.8%, respectively, all $P < 0.005$). There was a strong association between the progression of SPPS as well as SSS and major adverse cardiac events (MACE), for both genders [27].

THERAPEUTIC MEASURES TO DECREASE PLAQUE PROGRESSION

Statins are known to have mortality benefits if initiated immediately after acute myocardial infarction [28]. Statins lower low-density lipoproteins and also stabilize the plaques. Andelius *et al.* [29] conducted a systematic literature review and meta-analysis to examine the effect of statin therapy on different plaque volumes assessed by serial CCTA. The study found intensive statin therapy reduced total plaque volume (TPV) by -20.87 [95% CI -31.17 , -10.56 ; $P < 0.001$] μl , whereas moderate statin therapy reduced it by -1.67 (95% CI: -9.99 , 6.65 ; $P = 0.69$) μl . In contrast, TPV increased significantly in controls by 14.96 (95% CI 5.28 , 24.64 ; $P = 0.002$) μl [29]. The PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) study was a prospective study consisting of a registry of consecutive patients without history of coronary artery disease who underwent serial coronary computed tomography angiography at an interscan interval of at least 2 years. There was a slower rate of PAV progression in lesions of statin-taking patients compared with lesions in statin-naïve patients. Statins were associated with a 21% reduction in annualized total PAV progression above the median and 35% reduction in HRP development [30[■]]. There were several articles published on the basis of the data of PARADIGM study. One article raised an interesting argument. From prior studies, we know that progression of coronary artery calcium predicts all-cause mortality [31]. Conversely, statins, which markedly reduce MACE risk, increase coronary ACS. The article, based on PARADIGM study data, showed that in the nonstatin group, coronary ACS increase was positively associated with both noncalcified and calcified plaque volume increase. However, in the statin-taking group, coronary ACS increase was positively associated with calcified plaque volume change but was negatively associated with noncalcified plaque volume change [32].

As CCTA provided an easy and accurate way to evaluate for progression of coronary plaques, numerous studies have tried pharmacotherapies, other than statins, to see if they reduce plaque

progression and reduce events. An observational study by Shin *et al.* [33] included patients who underwent serial CCTA with a scan period of more than 2 years. Patients with LDL-Cholesterol (LDL-C) below 70 mg/dl displayed a significant attenuation in plaque progression as compared with those with follow-up LDL-C levels at least 70 mg/dl [33]. Budoff *et al.* did a randomized study to see if testosterone treatment of older men with low testosterone slows progression of noncalcified coronary artery plaque volume. Among 138 patients (73 receiving testosterone treatment and 65 receiving placebo), testosterone treatment compared with placebo was associated with a significantly greater increase in noncalcified plaque volume from baseline to 12 months as detected by CCTA [34[■]]. Another study by Matsumoto *et al.* [35] enrolled 55 patients with metabolic syndrome who were prospectively assigned to consume 2400 mg aged garlic extract per day (27 patients) or placebo (28 patients) orally. Both groups underwent CCTA at baseline and follow-up 354 plus-minus 41 days apart. The % low attenuated plaque change was significantly reduced in the aged garlic extract group compared with the placebo group ($-1.5 \pm 2.3\%$ compared with $0.2 \pm 2.0\%$, $P=0.0049$) [35]. Lee *et al.* [36] did a randomized trial to evaluate whether rivaroxaban compared with warfarin slowed the progression in coronary plaque volumes using CCTA in patients with nonvalvular atrial fibrillation. One hundred twenty patients were enrolled and were followed for 52 weeks. The changes in absolute and normalized fibrous plaque volume were greater in warfarin group compared with rivaroxaban group ($P=0.035$) [36]. A similar randomized controlled trial study with apixaban also demonstrated less plaque progression as compared with the warfarin group [37]. Alfaddagh *et al.* [38[■]] randomized 218 patients with stable coronary artery disease on statins to high-dose eicosapentaenoic acid and docosahexaenoic acid (3.36 g daily) or no omega-3 for 30 months. Coronary plaque volume was measured by coronary computed tomographic angiography and plasma omega-3 fatty acid levels were measured. Plasma omega-3 fatty acid index at least 4% prevented progression of fibrous, noncalcified, calcified and total plaque in nondiabetic patients whereas those in the lowest quartile ($<3.43\%$) had significant progression of fibrous, calcified and total plaque [38[■]]. Another study by Lee *et al.* [39[■]] (ESCAPE study) randomized 100 people with diabetes who had mild to moderate coronary atherosclerosis, assessed by CCTA, to either 200 mg/day cilostazol or 100 mg/day aspirin ($n=50$ each group). After 12 months of treatment, coronary artery stenosis decreased in the cilostazol group but remained unchanged in the

aspirin group. In the cilostazol group, the noncalcified portion of plaques decreased significantly whereas it did not change significantly in the aspirin group [39[■]].

BIOLOGIC AGENTS IN THE PREVENTION OF ACCELERATED ATHEROSCLEROSIS

Psoriasis is associated with accelerated risk of myocardial infarction [40]. Lerman *et al.* [41[■]] compared total coronary plaque burden and noncalcified coronary plaque burden (NCB) and HRP prevalence between patients with psoriasis ($n=105$), patients with hyperlipidemia eligible for statin therapy, and healthy volunteers without psoriasis ($n=25$). Compared with healthy volunteers, patients with psoriasis had increased total coronary plaque burden (1.22 ± 0.31 versus 1.04 ± 0.22 , $P=0.001$), NCB (1.18 ± 0.33 versus 1.03 ± 0.21 , $P=0.004$), and HRP prevalence beyond traditional risk (odds ratio, 6.0; 95% confidence interval, 1.1–31.7; $P=0.03$) [41[■]]. Severe psoriasis is treated with biologic therapy. Elnabawi *et al.* [42[■]] did an observational study and showed favorable modulation in coronary artery plaque disease indices by CCTA in severe psoriatic patients treated with commonly used biological classes of drugs: anti-Tumor Necrosis Factor, anti-IL (Interleukin)12/23, and anti-IL17, compared with those not treated with biologic therapy. Another study enrolled 28 patients with severe psoriasis initiating biological therapy and 28 matched controls not receiving systemic therapy, and the coronary plaque and stenosis were evaluated by serial CCTA. After a 13-months follow-up, the severity of luminal narrowing in the diseased segments was unchanged in the intervention group (Wilcoxon $W=76$, $n=483$, $P=0.39$) but increased at follow-up in the control group (Wilcoxon $W=281$, $n=414$, $P=0.02$) [43]. These findings support the idea that inflammatory pathways of psoriasis share similarities with the mechanisms identified in atherosclerosis and that immunomodulation with the help of biologic agents can reduce coronary atherosclerosis.

SOME ONGOING CLINICAL TRIALS UTILIZING CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY TO ASSESS CORONARY PLAQUE BURDEN

HIV remains one of the high-risk factors for atherosclerosis [44] and it is important to track the progression of coronary atherosclerosis in HIV patients. The Multicenter AIDS Cohort Study Quantitative Coronary Plaque Progression Study is a large prospective multicenter study quantifying progression

of coronary plaque among HIV-infected compared with uninfected men, assessed by serial CCTA [45[■]]. Another ongoing randomized, placebo-controlled EVAPORATE study will evaluate the effects of icosapent ethyl 4g/day on atherosclerotic plaque in a North American population of statin-treated patients with coronary atherosclerosis, triglyceride levels of 200–499 mg/dl, and low-density lipoprotein cholesterol levels of 40–115 mg/dl [46[■]].

Future Directions

Current sample sizes for serial CT angiography trials are in the range of 50–140 for various studies, depending upon the effect size that is anticipated. Machine learning will undoubtedly play a role in improving computer-aided detection of the plaque using an automated method [46[■]]. As these edge detection algorithms improve, reproducibility of disease will be improved, allowing for smaller sample sizes and greater precision.

CONCLUSION

Identification of vulnerable coronary plaques and more importantly tracking the plaque burden and plaque progression is crucial to prevent adverse cardiac events. Computed tomographic angiography has emerged as an important noninvasive modality to track coronary plaque progression. There are also new studies that have highlighted the utility of hybrid PET/CT and PET/MRI with ¹⁸F-NaF to detect vulnerable plaques [47[■]], but future studies will define their utility in cardiovascular trials. In future, we will see more and more use of computed tomographic angiography in research and clinical practice that will help us in therapeutic decision-making.

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Conflicts of interest

There are no conflicts of interest.

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