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Coronary Artery Disease Progression: Insights from Cardiac CT

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Abstract

Plaque progression is a multi-faceted process characterized by the incidence, extent, stenosis, burden, morphology, and vulnerability of plaque, which may ultimately result in myocardial infarction or death. For years, intravenous ultrasound (IVUS) has been the primary modality to study progression. However, it is invasive and impractical for screening or monitoring. While coronary artery calcium scoring (CAC) has been widely studied as a non-invasive method to measure plaque progression, it is limited to visualization of stenosis and non-calcified plaque. Coronary computed tomographic angiography (CCTA) allows for visualization of the severity of stenosis, plaque burden, plaque morphology, and ability to differentiate between plaque types. Furthermore, certain CCTA plaque features are useful in identifying vulnerable plaque including low attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign. This review covers multiple aspects of plaque progression-- its pathophysiology, clinical implications, and use of novel non-invasive technology for the assessment of plaque progression over time.

Introduction

Coronary artery disease a major public health issue that is increasing worldwide, and over the years there has been an improved understanding of the progression of coronary plaques leading to cardiovascular events. The term "plaque progression" refers to the evolution of atherosclerotic lesions from early, reversible stages triggered by endothelial dysfunction to the larger advanced plaques associated with coronary artery disease that can be visualized on imaging. Plaque progression is a multi-faceted process characterized by the incidence, extent, stenosis, burden, morphology, and vulnerability of plaque, and ultimately may result in myocardial infarction or death. For the past few decades, the invasive method of intravenous ultrasound (IVUS) has been the primary "gold standard" modality used to study plaque progression, and was widely used in large studies investigating risk factors leading to increased progression as well as direct effects of drug therapies on different components of plaque. Coronary artery tomographic angiography (CCTA) has been increasingly used non-invasive imaging modality to investigate coronary artery disease (CAD) as it can provide information on presence, extent, stenosis severity , burden, morphology, as well as characteristics of coronary plaque, and promising new software has been developed to automate plaque quantification from CCTA imaging making it a more efficient process. The current review summarizes the potential utility of CCTA in assessing plaque progression.

MECHANISM OF PLAQUE PROGRESSION

Plaque progression occurs as a result of multifactorial interactions between the vascular endothelium, various biomarkers, and is affected by the morphology of the plaque itself. Much of our knowledge of atherosclerotic lesions stems from the AHA definitions and six histological classifications [1-3], which are important to understanding the mechanism of plaque progression, especially the incidence of plaque. Lesions at initial stages are known as the fatty streak, where macrophages gather within smooth muscle cells and the proteoglycan- rich intima of the blood vessel. This stage appears to be reversible with little tendency to

progress. The stage at which plaque has a tendency to progress is observed in intermediate lesions characterized by pools of extracellular lipid [4].

More advanced lesions develop when the pools of extracellular lipid become larger confluent cores, and thick layers of fibrous connective tissue may eventually form in the lesions. At this stage, plaque is visualizable by invasive or non-invasive modalities. The lipid cores can develop into plaque rupture associated with myocardial infarction or sudden death [5], or may also develop into a fibroatheroma or calcified plaque, considered to be healed plaques. A large amount of the lipid cores are associated not only with developing plaque rupture but also plaque stenosis progression. In a previous pathology study, repeated silent plaque ruptures resulted in progression of stenosis severity and was frequently seen in males who experienced sudden cardiac death [6]. This suggests that visualization of coronary plaque may be beneficial in the management of patients with suspected CAD to predict future MI or sudden cardiac death.

Plaques may also develop additional features such as hematomas, hemorrhage, or thrombotic deposits, making them more prone to instability. ACS is often caused by thrombi which arise from ruptured, eroded or calcified plaques, with calcified nodules having the least association [7,8]. Plaque hemorrhages are associated with plaque rupture and there has been evidence of significantly greater prior hemorrhage in vulnerable plaques [8]. Interestingly, lesions also appeared to progress and regress; in a study by Kubo et al [9] examining natural history of coronary plaque visualized by IVUS, it was found that plaques with pathological intimal thickening, thin-capped fibroatheromas (TCFA), and thick-capped fibroatheromas showed significantly more plaque progression compared with fibrous and fibrocalcific plaque. Of interest, of the plaques characterized as thin-capped fibroatheromas (TCFA), which are thought to be particularly prone to rupture, 75% actually "healed" during a 12-month follow-up, while in that time new TCFAs also developed. In this regard, plaque potentially changes its morphology over time and these morphological changes can be risk factors of future myocardial infarction.

PLAQUE PROGRESSION RISK FACTORS

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Many studies have confirmed the association of CAD risk factors with plaque progression by quantifying progression of atheroma volume, particularly through large, pooled IVUS studies. Females were found to have lower plaque burden compared to men, despite the fact that women were more likely to have a history of hypertension, higher BMI, LDL, HDL, triglycerides, CRP, and blood pressures [10]. Patients with diabetes were found to have greater percent atheroma volume and total atheroma volume, as well as a higher rate of progression [11]. Patients with metabolic syndrome seem to have accelerated progression of plaque and less atheroma regression, though it is debatable whether disease progression is driven by the individual risk factors themselves versus the syndrome [12].

While plaque burden is an important measure of progression, degree of stenosis as well as histological classification of thin-capped fibroatheromas are also factors affecting progression to cardiovascular events. Stone et al. [13] found in a prospective study of patients who had 3-vessel angiography and IVUS after PCI that lesions associated with recurrent events were more likely to be characterized by plaque burden of 70% or greater, have a minimal luminal area of 4.0 mm^2 or less, or to be thin-cap fibroatheromas. Lesions that were not fibroatheromas rarely resulted in major adverse cardiovascular events, regardless of plaque burden or minimal luminal area. The lesions responsible for follow-up events were actually angiographically mild at baseline with mean diameter stenosis of 32.3 ± 20.6%. DeFilippis et al used data from Multi-Ethnic Study of Atherosclerosis (MESA) to investigate the correlation of the widely used Framingham Risk Score (FRS) and Reynolds Risk Scores (RRS) with incidence and progression of CAC [14]. The study found that though both RRS and FRS were significantly associated with progression of subclinical atherosclerosis measured by CAC, discordance in risk category classification (>10% or <10% risk) between FRS and RRS occurred in 13.7% participants, and RRS provided additional predictive power more consistently. This study suggests that beyond the traditional risk factors that have been linked to cardiovascular disease, it may be important to identify patients with high risk plaque features that can lead to clinically significant cardiovascular events.

CLINICAL POTENTIAL IN ASSESSING PLAQUE PROGRESSION (natural history, drug efficacy, prognosis)

Invasive Plaque Assessment Methods

IVUS and OCT studies

IVUS has emerged as the gold standard for in-vivo vessel wall imaging, and many studies have used IVUS to quantify and characterize plaque progression. With IVUS, one can obtain a cross-sectional view of the artery, showing distinct layers of the vessel including the adventitia, media, intima, and the lumen. The technique, Virtual Histology (VH) is useful for quantifying changes in plaque volume, accurate measurement of plaque areas and remodeling [15]. Spectral analysis of radiofrequency ultrasound signals can be used to discriminate between various plaque types and study plaque composition [16].

In recent years, multiple large prospective atherosclerosis progression/regression trials have been done with IVUS, including CAMELOT [17], REVERSAL [18], ACTIVATE [19], ASTEROID [20], ILLUSTRATE [21], PERISCOPE [22], and STRADIVARIUS [23]. These trials investigated the effects of various therapies on progression of plaque, and furthermore, many pooled analyses have used these studies to investigate the effects of various risk factors on the rate of plaque progression, development, and composition.

Optical coherence tomography (OCT) is an emerging method to assess plaque with some possible advantages over IVUS – however, to date it appears that there are not yet any large prospective atherosclerosis trials done using the technique. It is a high resolution imaging modality and uses light waves to probe the vessel, offering a better delineation of the border between the lumen and the vessel wall [24]. The resolution of OCT is about 10-fold higher than IVUS, but it has a lower depth of tissue penetration [25]. For assessment of invasive treatments such as stenting, optical coherence tomography may become preferred over IVUS, since IVUS has limited ability to identify vessel erosion, dissection, thrombus, and stent strut coverage [26]. However, the procedure is more difficult to perform because of the need to remove blood from the coronary artery in order to visualize the vessel. Although OCT is an emerging, promising imaging

technology for assessing plaque, its usefulness in clinical applications and research compared to IVUS remains to be seen.

Non-invasive Plaque Assessment Methods

CAC and CCTA Studies

While IVUS has been widely used for plaque imaging and OCT is a promising new method, the invasive nature of these modalities makes them impractical for screening, risk-stratification, or monitoring. Among non-invasive methods of measuring plaque progression, there are two main approaches, coronary artery calcium (CAC) scoring and CCTA. CAC scoring uses non-contrast CT findings to generate a score that has been shown to correlate with increased cardiovascular risk, and has been mainly used in assessing the extent and burden of coronary calcium plaque. Since the extent and burden of CAC is strongly associated with the overall coronary atherosclerotic burden [27], CAC has been considered as a marker of CAD and associated with future cardiovascular events. Despite a simple and easily measured scoring, CAC is limited to visualization of plaque stenosis severity as well as non-calcified plaque. In contrast with this limited utility of CAC scanning to evaluate coronary atherosclerosis, given the high resolution 3D nature of coronary CT, providing information about anatomical CAD, CCTA permits visualization of the extent, severity of stenosis, and burden of coronary plaque, and plaque morphology including both calcified and non-calcified plaque. Additionally, some plaque features on coronary CT have been reported to be associated with vulnerable plaque.

CAC Studies

Coronary artery calcification (CAC) scanning has been widely used for the risk stratification among asymptomatic subjects [28,29]. Recently, progression of coronary artery calcium has been extensively studied as a predictor of natural history of atherosclerosis, as well as its correlation with prognosis. CAC of zero has been considered as a low cardiovascular events during an inter-mediate term observation [30]. One potential underlying mechanism of this long-term warranty period of CAC 0 may be that patients without any CAC are

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less likely to have plaque progression over time. Min et al. [31] examined the different time of CAC progression among patients with or without CAC and explored that a mean time of conversion from no CAC to CAC>0 was approximately 5 years among those with CAC 0, whereas a mean time of CAC progression among those with CAC>0 was 1.9 years of follow-up. In addition, baseline CAC score was the strongest predictor of CAC progression over time, following other risk factors including smoking and diabetes. This study indicated that plaque burden by CAC scanning was associated with plaque progression over time. Another study also reported the similar results. Erbel et al. developed a mathematical model to predict CAC progression based on a study featuring a cohort of 3481 participants with baseline and 5-year CT follow-ups [32]. The study divided males and females into categories based on their percentile of CAC distribution and graphed the CAC score by age for each category and found that the graphs of the baseline and 5-year curves were nearly indistinguishable. Based on this result, they tested the hypothesis that the progression of CAC over time follows a predictable exponential curvature once the calcification process has begun. The model showed good agreement between observed and predicted values, demonstrating that CAC progression is nearly inevitable, and cardiovascular risk factors had only a limited influence.

With respect to the relation of plaque progression to prognosis, Budoff et al. [33] found that CAC progression was associated with all-cause mortality, even when adjusting for cardiovascular disease risk factors. In the study of 4609 asymptomatic patients, among patients with scores >30, assessing for progression of CAC added additional information regarding future prognostic risk. Subsequently, Budoff et al. [34] using data from the MESA study demonstrated that progression of CAC is associated with increased risk for future myocardial infarction and fatal coronary heart disease (CHD). For patients with a baseline CAC of zero, any increase in CAC was associated with 1.4-1.5 x greater risks for CHD. Annual CAC increases ≥ 100 units were associated with 2-3x greater risks for total and hard CHD events, with an annual total CHD event rate of 3-6% per year.

While CAC of 0 has a very high negative predictive value in ruling out a >50% coronary stenosis [35], CAC does not display the presence and burden of non-calcified– plaque and may underestimate the risk among patients at a high risk such as those with symptoms, known CAD, or suspected CAD.

In a study comparing the relation between plaque characteristics as assessed by CAC, CCTA, and VH IVUS, Van Velzen et al evaluated atherosclerotic plaques in 53 patients with acute coronary syndrome (ACS) and 59 patients with stable CAD using the three methods [36]. Though patients with a zero calcium score have been shown to have a low rate of cardiac events, this study demonstrated that in patients with ACS, despite a calcium score of zero, the presence of substantial plaque burden could not be excluded. Among patients with a calcium score of zero, those with ACS had a higher number of plaques on CT angiography than those with stable CAD, furthermore, on VH-IVUS a higher degree of high-risk plaque features including thin-cap fibroatheromas and necrotic cores were noted. Therefore, the limitation of CAC to visualizing only plaque stenosis severity and non-calcified plaque can overlook vulnerable plaque in certain populations.

CCTA Studies

Though CCTA allows visualization of the severity of stenosis, plaque burden, and plaque morphology of both calcified and non-calcified plaque, one limitation is that it cannot reliably identify the high risk thin-capped fibroatheromas due to spatial resolution. However, there are certain CCTA plaque features are have been proven useful for identifying vulnerable plaque, including low attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign [37,38]. Overall, CCTA has excellent diagnostic accuracy for detection of coronary plaques – compared to IVUS, it derives similar plaque areas and volumes, as well as percent stenosis, though it appears that CCTA may slightly overestimate the lumen area [39], which is thought to be due to partial volume effects leading to overestimation of brighter structures. In regards to characterization of plaques, when comparing CCTA with IVUS findings, CCTA showed excellent ability to differentiate between type of plaques - there are highly significant differences in plaque densities on CCTA among soft, fibrous, calcified plaque, and lumen areas compared to IVUS characterizations by echogenicity [40]. Also, recent technology can provide low radiation dose for CCTA with approximately <1-3mSv [41,42]. These advantages of CCTA allow us to investigate natural history of CAD or the effect of medicine using serial CCTA that may be more safe and reasonable method when compared to IVUS.

Multiple studies have been done using CCTA to investigate various aspects of plaque progression. Lehman et al. examined the progression of coronary plaque using serial CCTA [43] in a study of 69 patients with acute chest pain. In this study, the coronary plaque burden measured by semi-automated CT software significantly increased in 2 years and was associated with clinical risk factors. Papadopoulou et al. also demonstrated the natural history of coronary plaque on CCTA among 32 patients with known CAD [44]. In this study, the total coronary plaque burden was measured at baseline and follow-up, and plaque progression/regression of total plaque burden was observed during a median of 39 months using serial CCTA. Of interest, the results from CCTA fit the regression line illustrated by numerous previous studies examining the relation between mean LDL-C level and plaque progression/regression on IVUS, indicating the potential of serial CCTA to evaluate plaque progression as a substitute for IVUS. Ito et al. [45] evaluated various variables associated with plaque progression (defined as increased stenosis severity or ratio of positive remodeling index at follow-up to baseline ≥1.1) in patients who underwent serial CCTA. In the study of 148 patients, they found that only LDL cholesterol (≥ 100 mg/dL) at follow-up was associated with plaque progression, and there was no specific finding predictive of plaque progression based on the baseline characteristics of patients. The findings suggest the importance of control of LDL cholesterol and the potential of serial CCTA for guiding medical intervention, risk factor modification, dietary modification among patients who have poor control of their risk factors based on CCTA findings before they develop CAD symptoms or cardiovascular events. With respect to the relation of plaque morphology to plaque progression, out of 36 progressive lesions, they demonstrated that 9 plaques (25%) considered "high-risk" (evidence of positive remodeling, or low attenuation plaque) at baseline remained high-risk at follow-up. Of interest, 9 plaques additionally developed high-risk plaque at follow-up from other types of plaque and/or no plaques at baseline. This study suggests that in clinical settings where IVUS is unavailable, CCTA can identify plaque progression (either the progression of coronary stenosis or the development of plaque to vulnerable plaque) and may suggest changes in medical management in patients with uncontrolled risk factors.

Potential plaque assessment by semi-automated CCTA Software

As mentioned before, CCTA has the benefit of being able to quantify both calcified and non-calcified plaque, and is competent in the assessment of the presence, severity and type of coronary plaque by visual assessment. However, a major limitation to date is that the process of quantifying plaque by volumetric assessment has required manually tracing contours, a time-consuming process. Recently, plaque software has been developed to semi-automate this process so that it requires only a fraction of the time of manual delineation. These novel semi-automated softwares have shown the good correlation of coronary plaque volume compared to that assessed by IVUS to date.

AUTOPLAQ (APQ; Cedars-Sinai Medical Center, Los Angeles, CA) is one such software tool developed to quantify both calcified and noncalcified plaque using CCTA [46]. Dey et al [47] evaluated the accuracy of APQ compared to IVUS. In this study, the IVUS plaque area was manually traced, and coronary CT angiography plaque areas were manually traced as well as analyzed by the automated software. Automated processing was found to greatly speed up plaque quantification: processing times ranged from 15-35 minutes for manual IVUS, 5-15 minutes for manual, to less than 20 seconds for automated plaque segmentation and quantification. There was no significant difference between the plaque volumes calculated from IVUS compared to APQ, and the difference in plaque volume manually quantified from CT was not significantly different from APQ either. In fact, APQ quantification had smaller absolute differences from the IVUS results than CT manual quantification. APQ has also been shown to have reliable interscan reproducibility of quantitative plaque measurements. Schuhbaeck et al. evaluated total plaque volume, volume of calcified and non-calcified plaque, and maximal remodeling index in CTAs done twice in consecutive patients, and using APQ there were no significant differences in any of the measurements between scans [48].

QAngio (Medis, Netherland) is another software developed for automated plaque quantification (Figure 1), and its accuracy has also been compared to IVUS. In a study designed to demonstrate the accuracy of the automated quantification of plaque on cardiac CT, Boogers et al used a unique algorithm to co-register CT and IVUS datasets using anatomical markers, allowing for slice-by-slice comparison of each location along the transverse axis of the coronary arteries. This study compared the percent lumen area stenosis, plaque

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burden, and degree of remodeling at the level of minimal lumen area in IVUS and CT, as well as the mean plaque burden for the whole coronary plaque using both methods [49]. The lumen area stenosis was found to be correlated with plaque burden at the level of the minimal lumen area as well as mean plaque burden. However, the minimal lesion area was significantly underestimated, while lumen area stenosis was significantly overestimated by the automated method on CT compared with IVUS. In terms of coronary plaque remodeling, there was a moderate correlation between the two methods.

The development of automated plaque software should theoretically reduce inter-observer differences on plaque assessment compared to manual methods, and several studies have addressed the issue of reproducibility of the results. In the study by Papadopoulou, it was noted that both intra- and inter-observer differences for lumen and vessel areas were small [44]. Papadopoulou et al. published an additional study [50] addressing the reproducibility of inter- and intra-observer measurements, and found that both inter-and intra-observer relative differences for lumen, vessel, plaque area, and plaque burden were small and insignificant. The compositional measurements of plaque attenuation values, however, was more variable, especially the percentage of low attenuation plaque which had a relatively high inter-observer variability of 12%. This could be a potentially limiting factor, as low attenuation plaque is perhaps the most clinically relevant component in longitudinal CCTA studies.

Regardless of these limitations, semi-automated software has allowed CCTA to be used in investigating the natural history of coronary atherosclerosis. In the aforementioned study by Papadopoulou et al, they investigated plaque progression through CTA scans by quantifying changes in plaque burden, lumen dimensions, and arterial remodeling over time. Blackmon et al [51] also performed a study to evaluate the accuracy and effect on interreader reproducibility of a different automated postprocessing software algorithm for volumetric measurement of noncalcified lesions. The study not only found excellent correlation between expert manual measurements and the automated plaque volumetry, there was improved interreader correlation for volume measurements using the plaque analysis algorithm.

With development of automated software, one of the most time-consuming steps of reading CCTA scans can be made more efficient and more reproducible, which may encourage more widespread use.

Relationship of medical therapy to serial plaque assessment

As noted earlier, IVUS has been used for the evaluation of medical effect for coronary plaque volume or vulnerability in many previous studies. However, invasive modalities may not be practical for routine plaque assessments.

With respect to the use of CAC in assessing therapeutic interventions, though statins have been shown to reduce cardiovascular events across many patient populations, many studies to date have not shown significant reduction in CAC progression. In a study by Houslay et al. [52] a subset of patients with calcific stenosis and coronary artery calcification who were part of the SALTIRE (Scottish Aortic Stenosis Lipid Lowering Therapy, Impact on Regression) trial were randomly assigned to either atorvastatin 80 mg or a matched placebo. While the atorvastatin reduced serum LDL and CRP levels compared to the placebo, the statin did not have a major effect on the rate of coronary artery calcification. Schmermund et al. [53] analyzed progression of CAC volume scores in trial of patients who were assigned to receive either 80 mg or 10 mg of atorvastatin daily over a year, and while the LDL level was significantly reduced in the group receiving the higher dose statin, the intensive statin therapy did not lower CAC progression compared to the standard statin therapy. The St. Francis Heart Study [54] which assigned patients to taking atorvastatin 20 mg daily with antioxidants vitamin C and E versus matching placebos also found that the treatment of statins with antioxidants failed to have an effect on progression of CAC. A more recent study by Saremi et al [55] in the Veterans Affairs Diabetes Trial (VADT) found that progression of CAC was actually higher in patients who used statins more frequently. These seemingly paradoxical results are likely due to that fact that statins stabilize plaque by reducing non-calcified plaque burden, resulting in increased CAC density and higher CAC scores. This suggests a potential limitation of the use of CAC for the evaluation of medical effect. In contrast, with the ability to classify plaque composition, CCTA has also been a natural choice to investigate changes in plaque composition in patients on lipid-lowering therapies, which can be altered within only three weeks of intensive stain therapy [56].

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Several studies using CCTA have demonstrated the ability of statins to reduce non-calcified plaque burden. Our group previously [57] evaluated 100 patients who had CTA for evaluation of CAD, and found that the total progression was significantly reduced among statin users, with significantly reduced progression of non-calcified plaque volume and low attenuation plaque volume, with no significant changes in calcified plaque. Burgstahler et al. [58] reported findings from the New AGE II Pilot Study of 46 men with established coronary artery disease after a year of 20 mg of atorvastatin that showed significant reduction of noncalcified plaque burden, however no reduction in total plaque burden or coronary calcium score on follow-up. Inoue et al. [59] used CTA to assess the effect of fluvastatin treatment on 24 patients who received the statin after a baseline scan versus 8 subjects who refused treatment, and reported a significantly greater plaque volume change in statin versus control group that was due mostly to a reduction in low attenuation plaque, with no significant difference in lumen volume and remodeling index between the two groups. Thus, the ability of CCTA to classify plaque composition provides an advantage over CAC, which can only quantify calcified plaque.

Conclusion

We suggest that plaque progression- change in morphology, extent, severity, burden and rupture—is an important markers in assessing future CVD risk, and CCTA may be used a substitute for IVUS for this purpose in the future.

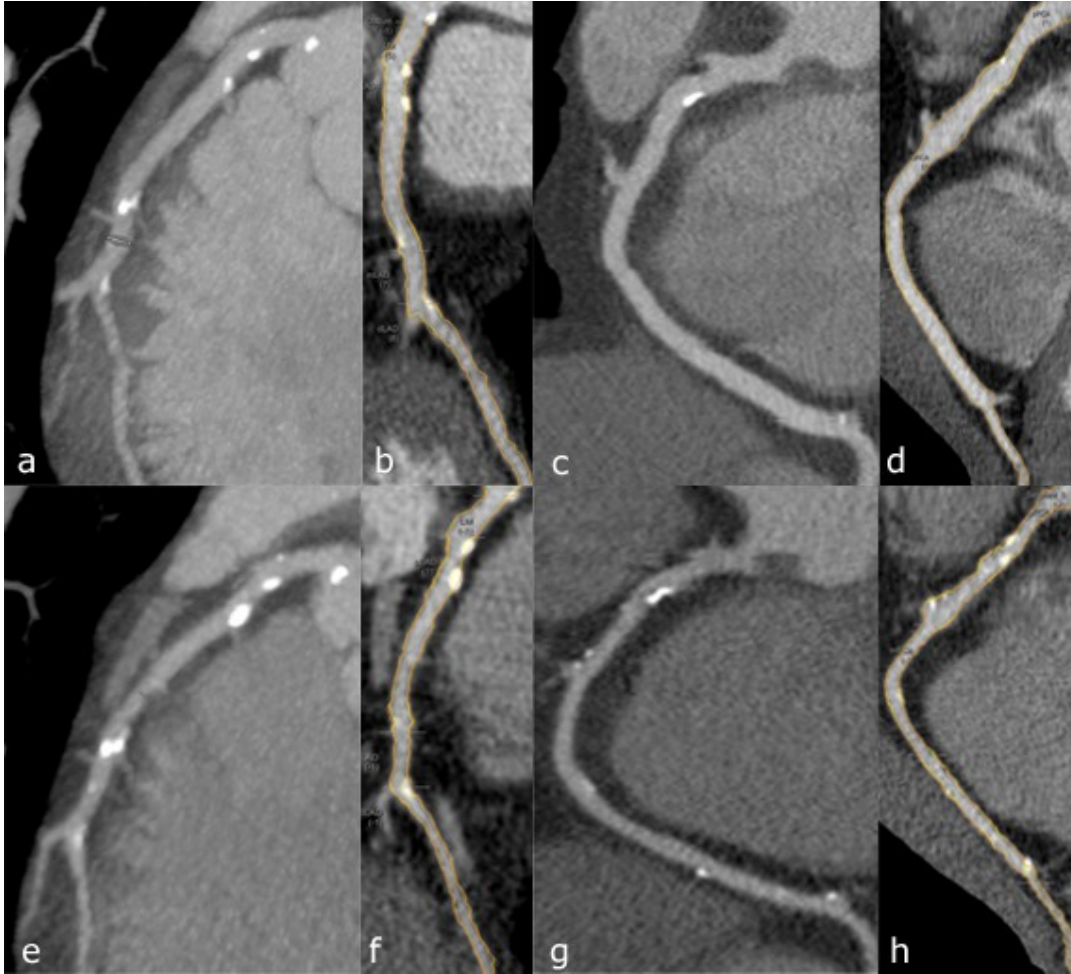**Figure 1. Sample of a patient with plaque progression over time.**

Figure Legend

Figures 1 Sample of a patient with plaque progression overtime

The figure shows the progression on total plaque volume among a patient who underwent serial CCTA at baseline and follow-up of 5 years from the first scan. For visual assessment, curved multiplanar reformat images show that there were diffuse CAD on LAD (a) and RCA (c) at baseline. At 5 years from the baseline, the patient had more developed CAD on LAD (e) and RCA (g). We measured the total plaque volume combined LAD and RCA at baseline (b and d) and at follow-up (f and h) using semi-automated software (QAngio, Medis, Netherland). Changes shown in images represent an increase in percent aggregate plaque volume of 6% to 13% over five years.

Abbreviations: LAD- Left anterior descending artery, RCA- right coronary artery.

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- Of major importance **

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