Chapter

# Changes in Atherosclerotic Plaque Composition with Anti-Lipid Therapy as Detected by Coronary Computed Tomography Angiography

*Drew Thomas, Darma Marcelin and Shone Almeida*

## Abstract

Lipid management remains the mainstay of cardiovascular disease prevention. Drugs that target cholesterol reduction, such as HMG-CoA reductase inhibitors (statins) and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have shown significant mortality and morbidity benefit. Predominantly targeting low-density lipoprotein (LDL). These drugs have been indicated to reduce lipid composition and plaque proliferation. Total plaque burden and composition can now be assessed with noninvasive advanced cardiac imaging modalities. This chapter will address the components of atherosclerotic plaque as identified with coronary computed tomography angiography (CCTA) and review in detail the changes in plaque characteristics that may be responsible for reduction in cardiac events. These changes in plaque composition may help guide future management of cardiovascular disease, serving as an imaging biomarker for better risk stratification. Readers will gain a deeper understanding of plaque morphology with direct clinical applicability as well as an understanding of how noninvasive imaging can be utilized to assess plaque composition.

**Keywords:** coronary computed tomography angiography (CCTA), statin, PCSK9, low density lipoprotein (LDL), atherosclerotic plaque

## 1. Introduction

Cardiovascular disease (CVD) has remained the leading cause of death in the United States in 2018 [1]. Atherosclerosis is the leading factor in causing cardiovascular death. The main factors that drive atherosclerosis are LDL cholesterol, hypertension, diabetes, and smoking [2]. Currently the United Stated Preventive Services Task Force recommends screening everyone who are at risk for coronary artery disease, all men over age 35 and all women over age 45. For risk stratification a ten year atherosclerotic risk score can be calculated to help decide if treatment should be started [3]. Treatment options can be aided by cardiac imaging. Cardiac imaging is mainly performed via intravascular ultrasound (IVUS), optical coherence tomography (OCT), and coronary computed tomography angiography (CCTA).

This development has made plaque characterization possible. Categories of plaque are placed into 4 broad categories: low-attenuating, fibrofatty, fibrocalcified, and densely calcified plaque [4].

## 2. Pathophysiology of atherosclerosis

The coronary arteries are composed of three layers: tunica intima, tunica media, and tunica adventitia. The tunica intima is the innermost lining inside these vessels, which is further composed of three layers of the endothelium. Simple squamous cells make up the innermost layer, which functions as a barrier that allows blood to flow smoothly. Any break in any part of the endothelial lining exposes blood to the subendothelial layer, starting the clotting mechanism. The tunica media is the middle layer of the vessels, composed of layers of smooth muscle cells. The tunica adventitia is the outer connective tissue layer supporting the vessel itself formed of loose connective tissue, vessels, and nerves [1]. When the initial fatty streaks or plaque precursors grow, it is usually outward, meaning there is not an initial direct effect on the blood flow or size of the lumen [5]. Lesions progress when the intima's smooth muscle cells begin to divide and secrete extracellular matrix molecules, such as collagen [6]. Other smooth muscle cells will penetrate the intima from the media, where they will join the other muscle cells in forming a fibrous cap overlying the lipid core. When there is a persistence of risk factors such as high LDL levels, the lipid core continues to grow in this manner.

The major lipoprotein classes include chylomicrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins, low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Larger in size and more triglyceride-rich lipoproteins are the less dense. Protein molecules, known as apolipoproteins (apo) on these particles' surface, guide the lipoproteins' interaction with tissues, cells, and different organs. LDL receptors bind to apo-B, the predominant apoprotein in LDL, and apo-E found on VLDL and some HDL particles. This receptor-mediated uptake delivers circulating cholesterol to the liver and other tissues. Apo-B may contribute to LDL's atherogenicity by promoting Apo-B particle entrapment within the arterial wall. Apo A-I, the predominant apoprotein in HDL, aids antiatherogenic efflux of cholesterol from peripheral tissues [6].

The different type of plaque morphology includes foam cell-rich matrix (obtained from fatty streaks), collagen-rich matrix (from sclerotic plaques), collagen-poor matrix without cholesterol crystals (from fibrolipid plaques), atheromatous core with abundant cholesterol crystals (from atheromatous plaques), and segments of normal intima derived from human aortas at necropsy. Atheromatous cores are associated with the most significant platelet deposition and largest thrombus formation than other components of atherosclerotic lesions. Therefore, we are led to believe that atherosclerotic plaques with larger atheromatous cores are more prone to cause acute coronary events because of their greater thrombogenicity after rupture [7].

Studies have also shown that aggressively lowering LDL cholesterol alters the composition of coronary atheromas. Lowering LDL cholesterol decreases the size of the lipid core, stabilizing the plaque by decreasing the lipid core and increasing the ratio of fibrous tissue to atheroma. This stabilizes the plaque by increasing the calcification of the plaque, reducing likelihood of plaque rupture [6]. There is an increase in fibrous tissue and calcified tissue within the atheroma replacing the lipid core. Therefore, calcification increases with aggressive lipid-lowering therapies like statins.

Noninvasive imaging modalities such optical coherence tomography (OCT), intravascular ultrasound (IVUS), and coronary computed tomography angiography (CCTA) have the ability to characterize plaque based on the above pathophysiology and define high risk features that in turn increase risk of cardiovascular events [8].

## 3. Plaque characterization by noninvasive imaging

Coronary artery calcium scoring and coronary artery calcification assessment are among the most emerging noninvasive coronary artery imaging applications. Initially, calcifications on chest radiography and ex vivo histology were used to discuss the relationship between coronary calcification and obstructive coronary artery diseases. The coronary artery calcium (CAC) scan consists of a non-contrast, electrocardiogram gated computed tomography of the heart. It is obtained during a short period of held inspiration. Once the image is obtained, the arterial calcium is defined using Hounsfield units. A density of greater than 130 Hounsfield units across an area of at least 1 mm is considered significant. Atherosclerotic calcification is reported either by volume or mass in Agatston units (AU), a semi-quantitative measure that further incorporates aspects of calcium density and distribution [9].

Progression of coronary calcium scores have a direct impact on clinical coronary events. One of the largest cohorts, the Multi-Ethnic Study of Atherosclerosis (MESA), followed over 5,600 patients. Participants received initial CAC scans and were followed for a median duration of 7.6 years, and then received follow up CAC. The change in calcium score was measured between initial and follow up was correlated with coronary artery events. Endpoints included myocardial infarction, angina followed by revascularization, resuscitated cardiac arrest, and cardiac death. Patients with non-zero CAC score at baseline were more likely to be older, male, diabetic, previous smoker and be on lipid lowering medication or hypertensive medication. Eighty-four percent of patients with a zero CAC score at baseline remained at zero on follow up. Patients with calcium score increases greater than 100 had a two to three-fold greater risk for the cardiac endpoints. Patients with 15–29% annual increase in CAC had an increased risk (hazard ratio: 1.6) for cardiac events compared to those with less than five percent progression annually. The study concluded that CAC scores correlate with clinical events including MI and cardiac death [10].

Computed tomography can characterize plaque morphology based upon Hounsfield Units, identifying high risk plaque. Plaque morphology on CCTA is characterized as low-attenuating plaque, fibrofatty, fibrocalcified and densely calcified. High risk or vulnerable plaque features include low-attenuating, spotty calcification and positive remodeling. Compared with intravascular ultrasound,, CCTA has shown high sensitivity and specificity in evaluating plaque morphology [4].

A large study published in the Journal of American College of Cardiology by Motoyama et al. established CCTA characterization of plaque morphology and the clinical implications. The study stratified patients into different morphological groups. Low attenuated plaque was defined as less than 30 Hounsfield Units. This was correlated with previous studies using intravascular ultrasound showing a sensitivity of 91% and specificity of 100%. %. Intermediate attenuated plaque was defined 30 HU to 150 HU and calcified plaque was defined as greater than 150 HU. Remodeling was the other factor in this study (positive, negative, or none). Coronary artery positive remodeling was defined as when the size of the lumen is increased by 10% more in the region of the plaque than in a reference segment

proximal to the plaque. This large study showed that when a subject has both positive remodeling and low attenuated plaque they are at high risk for having an acute coronary syndrome in the next two years. Twenty two percent of subjects with both low attenuated plaque and positive remodeling had acute coronary syndrome within the next two years compared to less than one half of one percent of the subjects with neither positive remodeling nor low attenuated plaque [11].

Several trials have demonstrated that use of statin therapy has shown benefit in primary prevention of coronary artery disease and secondary prevention of coronary artery disease. Statins have become the standard of care in coronary artery disease and are in all major anti lipid and coronary artery disease guidelines. Statins offer several benefits. Directly, they reduce hepatic cholesterol synthesis but several pleiotropic effects have been defined, including reduction in inflammation, cholesterol egress from the vasculature and plaque stabilization as described. There are many different areas of research being performed on various potential beneficial effects of statin therapy including beneficial effect on vascular tone by the upregulation of nitric oxide, reducing platelet aggregation and having antithrombotic properties, and anti-inflammatory properties including reduction in oxidative stress [4].

## 4. Changes in atherosclerotic plaque composition with lipid lowering therapies

### 4.1 Statins

Cardiovascular disease (CVD) has remained the leading cause of death in the United States in 2018 [9]. One of the main targets in the biosynthesis of cholesterol is inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA). Reduction in low density lipoprotein (LDL) cholesterol and then therefore reduction in morbidity and mortality has been achieved in several trials including Scandinavian Simvastatin Survival Study and West of Scotland Prevention Study [4].

Computed tomography can characterize plaque morphology based upon Hounsfield Units. This can identify at risk plaque. Plaque morphology on CCTA is identified as low-attenuating, fibrofatty, fibrocalcified, and densely calcified. At risk or vulnerable plaque is low-attenuating plaque. Intravascular ultrasound is the gold standard in characterizing plaque, however CCTA has shown high sensitivity and specificity in evaluating plaque morphology [10].

A large study published in the Journal of American College of Cardiology by Motoyama et al. established CCTA characterization of plaque morphology and the clinical implications. The study stratified patients into different morphological groups. Low attenuated plaque was defined as less than 30 Hounsfield Units. This was correlated with previous studies using intravascular ultrasound showing a sensitivity of 91% and specificity of 100%. %. Intermediate attenuated plaque was defined 30 HU to 150 HU and calcified plaque was defined as greater than 150 HU. Remodeling was the other factor in this study (positive, negative, or none). Coronary artery positive remodeling was defined as when the size of the lumen is increased by 10% more in the region of the plaque than in a reference segment proximal to the plaque. Therefore, a subject could have both low attenuated plaque and positive remodeling, either low attenuated plaque or positive remodeling, or neither low attenuated plaque nor positive remodeling. This large study showed that when a subject has both positive remodeling and low attenuated plaque they are at high risk for having an acute coronary syndrome in the next two years.

Twenty two percent of subjects with both low attenuated plaque and positive remodeling had acute coronary syndrome within the next two years compared to less than one half of one percent of the subjects with neither positive remodeling nor low attenuated plaque Several trials have demonstrated that use of statin therapy, HMG-CoA reductase inhibition, has shown benefit in primary prevention of coronary artery disease and secondary prevention of coronary artery disease. Statins have become the standard of care in coronary artery disease and are in all major anti lipid and coronary artery disease guidelines. They also have mortality benefits as well. Statins work in the pathway of cholesterol synthesis. This occurs in the hepatocytes. This results in upregulation of hepatic LDL receptors and reduces serum LDL. This causes reduction in LDL deposition on atherosclerotic plaque on coronary arteries and other arteries for that matter. Statins also have reduction in the inflammatory cascade as well. Overall there is stabilization of atherosclerotic plaque due to statin therapy. There are several trials including Rosuvastatin to Prevent Vascular Events in Men and Women With Elevated C-Reactive Protein (JUPITER), Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes (MIRACL), and Heart Outcomes Prevention Evaluation (HOPE-3) that all show reduction in C-Reactive Protein (CRP). This also could aid in reduction of coronary events but is still controversial at this point. There are many different areas of research being performed on various potential beneficial effects of statin therapy including beneficial effect on vascular tone by the upregulation of nitric oxide, reducing platelet aggregation and having antithrombotic properties, and anti-inflammatory properties including reduction in oxidative stress [10] Atherosclerotic plaque can regress. Plaque regression occurs when there is removal of lipids and necrotic material from the plaques, endothelial repair occurs, and smooth muscle proliferation stops. This can occur by several different mechanisms: high density lipoprotein cholesterol, destruction of foam cells and macrophages, and restoration of endothelium. Statin therapy has been studied in the process of atherosclerotic plaque reduction. Meta-analysis of eight trials comparing statin with placebo showed that in 919 patients with 461 patients in the statin arm and 458 patients in the placebo group that there was a statistically significant mean difference in coronary atheroma volume between the two groups. -3.573 (95% CI -4.46 to −2.68; $P < 0.01$). Plaque characterization was similar in both groups. Intravascular ultrasound was used in the studies [12].

Coronary CTA has allowed physicians to directly visualize atherosclerotic plaque characterization and volume. This allows identification of features of vulnerable plaque including positive remodeling and low attenuating plaque, altering clinical management [4]. One early study on the effects of statin therapy via coronary CTA by Zeb et al. evaluated one hundred patients who underwent coronary CTA without known history of coronary artery disease. Patients underwent plaque characterization as low attenuation plaque (LAP as less than 30 Hounsfield units), non-calcified plaque (NCP) and calcified plaque and volumetric quantification among a statin versus non-statin arm. This was a retrospective observational study in attempts to evaluate the plaque volume and characteristics over time. At mean follow up of 406 days the total plaque volume was reduced in the statin arm compared to the non-statin arm (−33.3 $mm^3$ +/− 90.5 vs. 31 $mm^3$ +/− 84.5, $p = 0.0006$). Non calcified plaque volume was significantly reduced in the statin therapy arm as well (−47.7 $mm^3$ +/− 71.9 vs. 13.8 $mm^3$ +/− 76.6, $p < 0.001$). Low attenuated plaque volume was shown to have significantly reduced progression (−12.2 $mm^3$ +/− 19.2 vs. 5.9 $mm^3$ +/− 23.1, $p < 0.0001$). There was a non-significant trend toward increased production of calcified plaque volume. Mean plaque volume difference was statistically significant for both low attenuated plaque and non-calcified plaque (−18.1, 95% Cl: −26.4, −9.8 for LAP; −101.7, 95% Cl: −162.1, −41.4 for NCP; $p < 0.001$).

The authors concluded that statin therapy lowers the progression of LAP and NCP plaque in comparison with non-statin therapy [13].

Another landmark trial using CT derived plaque characterization was the Paradigm study (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography. This multinational, observational prospective study evaluated serial coronary CTA's at a greater than two-year interval. With 654 enrolled patients, the majority of patients were on statin therapy (408 vs. 246). All patients had baseline coronary CTA's, followed for greater than two years, and then had subsequent coronary CTA. In the statin arm initial low density lipoprotein (LDL) cholesterol was on average 114 and reduced to 94.5 at follow up. The non-statin arm had an initial average LDL of 111 and follow up LDL of 104. The plaque was characterized into calcified and non-calcified plaque including: fibrous, fibro-fatty, and lipid rich. The authors demonstrated that an increase in coronary artery calcium score was associated with the increase in plaque volume in both the statin and non-statin groups. In the non-statin arm coronary artery calcium score was associated with increase in calcified and non- calcified plaque volume increase [B (95% CI): 1.579 (1.150–2.009) and 0.369 (0.123–0.614), respectively, all $P < 0.05$). In the statin arm there was a statistically significant increase in coronary artery calcium score associated with increased calcified plaque volume [B (95% CI): 0.756 (0.552–0.961), $P < 0.001$]. Non calcified plaque volume decreased [B (95% CI): −0.194 (−0.364 to −0.023), $P = 0.026$). Fibrous plaque volume also decreased as well [B (95% CI): −0.304 (−0.535 to −0.073), $P = 0.010$]. The fibro fatty and lipid rich plaque volume also decreased but was not statistically significant. In the non-statin arm, the increase in coronary calcium score reflects the increased atherosclerotic burden including calcified and non-calcified plaque. The statin arm increase in coronary calcium score only is correlated with calcified plaque. Therefore, in the statin arm, while the calcified plaque increased the fibrous and overall, non-calcified plaque decreased. With statin therapy, the ratio of plaque composition shifts to more stable, lower risk morphology, specifically calcified and fibrocalcified types [14].

Another variable of coronary atherosclerosis is the fibrous cap. A thin fibrous cap can also be a sign of vulnerability, increasing risk for plaque rupture and presenting with acute coronary syndrome [15]. The EASY-FIT study (Effect Of Atorvastatin Therapy On Fibrous Cap Thickness In Coronary Atherosclerotic Plaque As Assessed By Optical Coherence Tomography) assessed the differences between Atorvastatin 5 mg and Atorvastatin 20 mg on the fibrous cap using optical coherence tomography. The EASY-FIT study enrolled 70 patients with unstable angina pectoris who had untreated hyperlipidemia. These patients were previously treated with successful percutaneous coronary intervention (PCI). The OCT that was performed looked at a nonculprit lesion in the coronary artery. Patients were placed in either an Atorvastatin 20 mg/day arm or a 5 mg/day arm with OCT at baseline and at 12-month follow-up. Thin-cap fibroatheroma was defined as plaque having minimal fibrous cap thickness of <65 micrometers and thick cap was defined as fibrous cap thickness > 65 micrometers. The fibrous cap thickness increased significantly in both groups. In the Atorvastatin 20 mg/day vs. 5 mg/day the increase was (69% [IQR: 25% - 104%] vs. 17% [IQR: −1% to 34%] $p < 0.001$. The minimal lumen area did not change at follow up for either group. There was a negative correlation between the fibrous cap thickness and the serum LDL but no correlation between total serum cholesterol, triglycerides, or glycosylated hemoglobin. This study suggests that high to moderate intensity statin might be superior in providing benefit in plaque stabilization compared to low intensity Atorvastatin in secondary prevention in the setting of unstable angina [16].

## 5. Effects of EPA on atherosclerotic plaque via CCTA

There is limited evidence about the effects of eicosapentaenoic acid (EPA) on atherosclerotic plaque. The mechanism of action of these omega 3 fatty acids occurs several ways: reducing inflammation, plaque volume, membrane stabilization as well as triglyceride reduction. There is some evidence that EPA might have an effect on atherosclerotic plaque volume and characterization. The Evaporate trial (Effect of icosapent ethyl on progression of coronary atherosclerosis) was a multicenter, randomized, double-blinded, placebo-controlled trial with intention to treat analysis which evaluated patients with known coronary artery disease and hypertriglyceridemia already on statin therapy. Patients in the EPA arm were given four grams of EPA daily and their plaque progression was measured by CCTA. They had CCTA scans at baseline, 9 months and 18 months. The primary end point was the change in low attenuated plaque volume seen on CCTA. Low attenuated plaque volume was significantly reduced in the EPA arm of the study at 18 month follow up vs. placebo (−0.3 +/− 1.5 vs. 0.9 +/− 1.7 $mm^3$, P = 0.006). Other parameters EPA arm vs. placebo arm respectively: total plaque (−9% vs. 11% P = 0.002), total non-calcified plaque (−19% vs. 9%, P = 0.0005), fibrofatty (−34% vs. 32%, P = 0.0002), fibrous (−20% vs. 1%, P = 0.003), and calcified plaque (−1% vs. 15%, P = 0.053). Dense calcium did not show significant difference between the two groups. Interestingly there was no significant difference in total cholesterol, LDL, HDL or triglycerides compared to baseline. The study concluded that EPA was associated with plaque regression, specifically the low attenuation, higher risk plaque, compared to statin therapy alone [17].

Of critical importance is whether the change in plaque composition with addition of EPA translates into a reduction in cardiovascular events. The REDUCE-IT trial (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) is a randomized, double blinded, placebo controlled trial comparing EPA (4 g total) to placebo. Over eight thousand patients were enrolled and followed for an average of 5 years. In this trial enrollment only occurred for age 45 and older with cardiovascular disease or were age 50 or older with diabetes and at least one other cardiovascular risk factor. Requirements also included: fasting triglyceride level of 150–499 mg/dL, LDL cholesterol level of 41–100 mg/dL, and on the same statin dose for at least four weeks. The primary end point was composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in time to event analysis. Secondary end points included: key secondary efficacy end point, composite of cardiovascular death or nonfatal MI, fatal or nonfatal MI, emergency or urgent revascularization, cardiovascular death, hospitalization for unstable angina, fatal or nonfatal stroke, death from any cause, non-fatal MI or non-fatal stroke. The primary end-point occurred in 17.2% of patients in the icosapent ethyl arm compared to 22% in the placebo arm (hazard ratio, 0.75; 95% confidence interval, 0.68 to 0.83; P < 0.001), absolute between group difference of 4.8% (95% CI, 3.1 to 6.5). The number needed to treat in order to avoid one primary end point was 21 over a 5 year follow up. Key secondary end points occurred in 11.2% of patients in the icosapent ethyl arm compared to 14.8% in the placebo arm (hazard ratio, 0.74, 95% CI, 0.65 to 0.83; P < 0.001) with absolute between group difference of 3.6% (95% CI, 2.1 to 5.0). The number needed to treat to avoid one key secondary end point was 28 (95% CI, 20 to 47) in a 5 year follow up. For individual primary and secondary end points icosapent ethyl arm vs. placebo arm respectably: rate of cardiovascular death (4.3% vs. 5.2%; 0.80; 95% CI, 0.66 to 0.98; P = 0.03), death from any cause (6.7% vs. 7.6%, 0.87; 95% CI, 0.74 to 1.02). All primary and secondary end points significantly statistically favored

the icosapent ethyl arm compared to placebo except for death from any cause. The study authors concluded that in patients 45 years and older with hypertriglyceridemia receiving statin therapy, cardiovascular risk including cardiovascular death was lowered with icosapent ethyl therapy than with placebo [18].

## 6. Effects of PCSK9 inhibitors on atherosclerotic plaque via CCTA

Statin therapy has been the standard for the reduction of LDL cholesterol for fifty plus years. However, there is still cardiovascular risk even after high dose statin therapy. To reduce this risk more medications have been developed and implemented. One class is the Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Studies have shown that PCSK9 inhibitors reduce LDL cholesterol and reduce clinical events. An initial study looking at plaque via intravascular ultrasound called the Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) showed that there was decrease in percent atheroma volume after 76 weeks with PCSK9 therapy in addition to statin therapy. The primary end point of percent atheroma volume did not decrease in the placebo group but did decrease in the evolucumab group (0.05% vs. 0.95%). The between group difference is −1.0% (95% CI, −1.8% to −0.64%) $P < 0.001$ [19].

In this next trial coronary calcium score was mainly used in combination with coronary CTA to evaluate plaque production in three groups: statin, statin plus PCSK9 inhibitor, and no therapy. This study was a retrospective study to evaluate if PCSK9 inhibitors could reduce the plaque burden that is already present in patients. This was performed by evaluating the association between PCSK9 inhibitor therapy and coronary calcium score via CCTA. Baseline characteristics of the 120 patients that were retrospectively enrolled in this study showed that 53% of patients had calcium score of zero, 47% of patients had coronary calcium score of greater than zero. Twelve and a half percent had severe coronary artery calcification with scores >400 AU's. A correlation was observed between coronary calcium score and lipid lowering therapy ($P < 0.0001$) without correlation between any other traditional risk factor for coronary artery disease including hemoglobin A1c levels, blood pressure, and lipid levels. Scores increased with age ($P = 0.048$) particularly age greater than sixty years old. Coronary artery calcium score was higher in the statin and statin plus PCSK9 group mainly because they had higher diagnosed coronary artery disease and therefore required lipid lowering therapy. Calcium score was measured annually. The progression in the statin monotherapy group was 29.7% and 14.3% in the PCSK9 inhibitor group ($P < 0.01$). There is a clear association between the lower plaque production via coronary calcium score due to PCSK9 therapy. This is a low powered study with a low patient enrollment. There were several limitations including being an open label design, short study duration, all participants were Japanese, and difference in statin dose. More studies need to be performed to include a longer term, double blinded, prospective study. However, in this initial study coronary artery calcium score was reduced from 29.7% in the statin group and 14.3% in the statin plus PCSK9 group. Plaque progression might be prevented by additional therapy with PCSK9 inhibitor therapy [20]. This study can set the stage for future studies using coronary CTA to follow the atherosclerotic plaque with PCSK9 inhibitor therapy. Characteristics of atherosclerotic plaque should also be reviewed in future studies.

Patients with certain comorbidities in addition to coronary artery disease are at higher risk for further acute coronary syndrome events. One comorbidity being diabetes mellitus. The American Diabetes Association is also interested in reducing cardiovascular risk for their subset of patients. In the 457-P: One-Year

Administration of Anti-PCSK9 Antibody Is Enough to Stabilize Vulnerable Coronary Plaques in Diabetic Patients, which Are Resistant to Intensive Statin Therapy trial they attempted to review the efficacy of PCSK9 therapy. As previously described low attenuating plaque is categorized as vulnerable plaque and is associated with increased risk of acute coronary syndrome. In this study 142 patients with type two diabetes mellitus, asymptomatic coronary artery disease with vulnerable coronary plaques, on intensive statin therapy for two years were evaluated by coronary CTA to evaluate the plaque. PCSK9 inhibitors were given for a one-year duration. There was a 74% decrease in LDL cholesterol. Importantly an improvement of vulnerable plaque was seen. This was measured by Housfield Units (HU). As explained previously vulnerable plaque or low attenuating plaque have a Housfield Unit of less than 50. There was a rise in plaque HU (43.2 +/− 12.0 HU at baseline to 128.5 +/− 52.3 HU, $p < 0.0001$ after one year of PCSK9 therapy). This infers stabilization of vulnerable plaque in the setting of diabetic patients on intensive statin therapy with vulnerable plaque seen on CCTA. The conclusion was drawn that a one- year administration of PCSK9 inhibitor therapy produced significant stabilization of vulnerable plaque in patients with asymptomatic coronary artery disease who are resistant to intensive statin therapy [21].

Overall there is very minimal data in this category. This is an area for future studies. Many studies are currently being performed in this area and will continue to explore this area of research. Plaque progression, plaque volume, plaque characterization can all be assessed via coronary CTA. This gives cardiologists advantages in treatment options and more informed discussion with patients. Further research in this area is needed.

## 7. Future directions

There are several areas for future research. One is epicardial fat and pericoronary fat. For example, in the trial Epicardial adipose tissue and pericoronary fat thickness measured with 64-mutidetector computed tomography: potential predictors of the severity of coronary artery disease they looked at epicardial and pericoronary fat to see if there was association between the amount of fat thickness to the severity of coronary artery disease. This showed that there was in increase in fat thickness in patients with obstructive coronary artery disease [22]. This research is in the beginning stages and much further research can be done.

A new software has been developed called Cleerly software that uses artificial intelligence to quantify coronary artery stenosis and plaque composition at the vessel and lesion level in order to track it over time. This is another clinical tool that is taking an invasive procedure like a coronary artery catheterization and making it noninvasive and easily accessible to patient and physician on an online platform. This helps clinicians determine the best treatment approach for each individualized patient. This is a very small part of a bigger overarching vision of precision medicine.

## 8. Conclusion

Atherosclerosis is an evolving field with an explosion of data coming recently of various subsets which include different imaging modalities, plaque characterization, and treatment options. This has allowed the medical field to delve into the pathophysiology of atherosclerotic plaque formation, how to properly image this plaque, and proper ways to treat this plaque in order to lower clinical events and

mortality. The coronary CTA has allowed us to look at the morphology of atherosclerotic plaque and to be able to track the plaques over time on various treatments including statin therapy which is the gold standard, icosapent ethyl therapy, and the newest treatment of PCSK9 inhibitors. Many trials as discussed above have shown the effects of various medications on atherosclerotic plaque over time and how it correlates to the morphology of the plaque and how this correlates clinically. The morphology change from a high risk plaque to a low risk plaque with a higher calcification is one of the key discoveries that coronary CTA allowed us to see. The non- invasive approach of this modality is clearly the future of following atherosclerosis in patients on lipid lowering therapy. Future research needs to be performed on the effects PCSK9 inhibitors on atherosclerotic plaque via coronary CTA as well as continued trials connecting clinical events and mortality to lipid lowering therapy via coronary CTA.

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## References

[1] Xu J. Mortality in the United States, 2018 [Internet]. Cdc.gov. 2020 [cited 30 December 2020]. Available from: https://www.cdc.gov/nchs/data/databriefs/db355-h.pdf

[2] Atherosclerosis | NHLBI, NIH [Internet]. Nhlbi.nih.gov. 2021 [cited 29 January 2021]. Available from: https://www.nhlbi.nih.gov/health-topics/atherosclerosis

[3] Morris B. What are the USPSTF recommendations for lipid screening? [Internet]. Medscape.com. 2021 [cited 29 January 2021]. Available from: https://www.medscape.com/answers/2074115-193300/what-are-the-uspstf-recommendations-for-lipid-screening

[4] Almeida S, Budoff M. Effect of statins on atherosclerotic plaque. Trends in Cardiovascular Medicine. 2019;29(8):451-455.

[5] Shang T, Yavagal D. Application of acute stroke imaging: Selecting patients for revascularization therapy. Neurology. 2012;79(Issue 13, Supplement 1):S86-S94.

[6] Libby P. Atlas of Atherosclerosis | Harrison's Principles of Internal Medicine, 20e | AccessMedicine | McGraw-Hill Medical [Internet]. Accessmedicine.mhmedical.com. 2021 [cited 7 January 2021]. Available from: https://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=192509277

[7] Fernández-Ortiz A, Badimon J, Falk E, Fuster V, Meyer B, Mailhac A et al. Characterization of the relative thrombogenicity of atherosclerotic plaque components: Implications for consequences of plaque rupture. Journal of the American College of Cardiology. 1994;23(7):1562-1569.

[8] He C, Wang J, Yin Y, Li Z. Automated classification of coronary plaque calcification in OCT pullbacks with 3D deep neural networks. Journal of Biomedical Optics. 2020;25(09).

[9] Adamson P, Newby D. Non-invasive imaging of the coronary arteries. European Heart Journal. 2018;40(29):2444-2454.

[10] Budoff M, Young R, Lopez V, Kronmal R, Nasir K, Blumenthal R et al. Progression of Coronary Calcium and Incident Coronary Heart Disease Events. Journal of the American College of Cardiology. 2013;61(12):1231-1239.

[11] Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T et al. Computed Tomographic Angiography Characteristics of Atherosclerotic Plaques Subsequently Resulting in Acute Coronary Syndrome. Journal of the American College of Cardiology. 2009;54(1):49-57.

[12] Ling G, Kalanuria, Nyquist. The prevention and regression of atherosclerotic plaques: emerging treatments. Vascular Health and Risk Management. 2012;:549.

[13] Zeb I, Li D, Nasir K, Malpeso J, Batool A, Flores F et al. Effect of statin treatment on coronary plaque progression – A serial coronary CT angiography study. Atherosclerosis. 2013;231(2):198-204.

[14] Lee S, Sung J, Andreini D, Budoff M, Cademartiri F, Chinnaiyan K et al. Differential association between the progression of coronary artery calcium score and coronary plaque volume progression according to statins: the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging (PARADIGM) study. European Heart Journal - Cardiovascular Imaging. 2019;20(11):1307-1314.

[15] Fujimoto J, Pitris C, Boppart S, Brezinski M. Optical Coherence Tomography: An Emerging Technology for Biomedical Imaging and Optical Biopsy. Neoplasia. 2000;2(1-2):9-25.

[16] Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S et al. Effect of Atorvastatin Therapy on Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by Optical Coherence Tomography. Journal of the American College of Cardiology. 2014;64(21):2207-2217.

[17] Budoff M, Bhatt D, Kinninger A, Lakshmanan S, Muhlestein J, Le V et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. European Heart Journal. 2020;41(40):3925-3932.

[18] Bhatt D, Steg P, Miller M, Brinton E, Jacobson T, Ketchum S et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. New England Journal of Medicine. 2019;380(1):11-22.

[19] Nicholls S, Puri R, Anderson T, Ballantyne C, Cho L, Kastelein J et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients. JAMA. 2016;316(22):2373.

[20] Ikegami Y, Inoue I, Inoue K, Shinoda Y, Iida S, Goto S et al. The annual rate of coronary artery calcification with combination therapy with a PCSK9 inhibitor and a statin is lower than that with statin monotherapy. npj Aging and Mechanisms of Disease. 2018;4(1).

[21] HIRAI A, FUJIMURA K, HIRAI K, KONDO S, SHIRAKAMI A, SAKAI T et al. 457-P: One-Year Administration of Anti-PCSK9 Antibody Is Enough to Stabilize Vulnerable Coronary Plaques in Diabetic Patients, which Are Resistant to Intensive Statin Therapy. Diabetes. 2019;68(Supplement 1):457-P.

[22] Demircelik M, Yilmaz O, Gurel O, Selcoki Y, Atar I, Bozkurt A et al. Epicardial adipose tissue and pericoronary fat thickness measured with 64-multidetector computed tomography: potential predictors of the severity of coronary artery disease. Clinics. 2014;69(6):388-392.