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Prognostic Value of Serial Coronary CT Angiography in Atherosclerotic Plaque Modification: What have we learnt?

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Abstract

Purpose of review—To provide an update and to outline the status of coronary computer tomography angiography (CCTA) in evaluation of coronary plaques and discuss the relevance of serial CCTA in guiding cardiovascular risk stratification and anti- atherosclerotic medical therapy.

Recent Findings—Coronary CTA is now the imaging modality of choice in monitoring changes in coronary plaque. It has been used in innumerable clinical trials which have demonstrated the benefits of several therapeutic agents and has excellent correlation with previously used invasive imaging modalities. It is safe, fast, less cumbersome, and a cost-effective testing method compared to other invasive imaging modalities for coronary plaque analysis.

Summary—The emergence of a noninvasive imaging modality such as CCTA, now permits quantification not only of plaque burden but also allows for further distinction of plaque components and identification of vulnerable plaques. Application of these findings continues to extend the prospect of coronary CTA in evaluation and management of atherosclerotic coronary artery disease (CAD) in clinical practice. In the future artificial intelligence and machine learning will play a significant role in plaque analysis allowing for high accuracy and reproducibility which will lead to a substantial increase in the utilization of coronary CTA.

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Author Contributions

Dr. Matthew Budoff conceived of the article idea. All authors were involved in literature search. The first draft of the manuscript was written by Venkat S. Manubolu, and all authors assisted with edits of the manuscript. All authors read and approved the final manuscript.

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Keywords

Coronary plaque; Coronary CT Angiography; Atherosclerosis; Plaque progression; High risk plaque; Serial CTA

Introduction

Cardiovascular disease, principally ischemic heart disease continues to be the most common cause of death worldwide, despite major advances in the field of cardiology[1]. Atherosclerosis is an insidious process that remains latent for a prolonged period before the development of clinical cardiovascular disease (CVD). Cardiovascular disease represents the late stages of the disease process and involves the establishment of complex atherosclerotic lesions. Various noninvasive and invasive imaging modalities have allowed detection of early and subclinical atherosclerosis. In recent years, advances in cardiovascular imaging have provided invaluable insights into the development of plaque and the evolution of coronary artery disease. Coronary computed tomography angiography (CCTA) is especially effective in the quantitative and qualitative assessment of plaque. Furthermore, CCTA has been validated as a non-invasive imaging modality for characterization of high-risk plaque features such as low attenuation plaque (LAP), positive remodeling (PR), napkin ring sign (NRS) and spotty calcification. The plaque phenotypes are clinically relevant as vulnerable plaques are thought to have a high propensity to rupture and lead to acute coronary syndrome. Current evidence supports the hypothesis that total plaque burden along with high-risk plaque features are associated with future cardiovascular events and unfavorable clinical outcomes[2-5].

For several years we have known that people with stenosis on angiography are at high risk for having cardiovascular events, hence, in certain clinical situations we treat these patients with percutaneous coronary intervention to avoid adverse outcomes. This is undoubtedly the treatment of choice in acute coronary syndromes. However, in the stable coronary heart disease (SCHD) population with significant coronary stenosis, revascularization with optimal medical therapy compared to optimal medical therapy alone has not shown improvement in overall clinical outcomes. Evidence from landmark randomized controlled trials such as COURAGE, BARI 2D and ISCHEMIA demonstrated that revascularization improved symptoms but did not reduce the risk of death, myocardial infarction, or other major cardiovascular events[6-8]. This raises the question of whether it is the degree of luminal stenosis or the extent of plaque burden which places these patients at higher risk of future cardiovascular events. Existing evidence on the atherosclerotic process suggests that plaque burden along with plaque characteristics are the primary driving factors and are more important in predicting future cardiovascular events [5, 9, 10].

Technological leaps in cardiovascular imaging, have enhanced our understanding of the pathophysiology of coronary atherosclerosis. Although, historically important intravascular plaque assessment will inevitably underestimate plaque burden. Furthermore, invasive serial imaging is inconvenient and not clinically indicated in all patients undergoing cardiac catherization. Conversely, CCTA is a non-invasive technique that can provide a significant

wealth of information with accuracy and greater reproducibility. It is also easy and safe to perform serial imaging in patients considered to have high risk plaques for follow up of vulnerable lesions and to monitor the effects of medical therapy using CCTA.

The objective of this review is to discuss the current position of CCTA in evaluation of atherosclerotic plaque and utilization of serial CCTA as a prognostic tool in assessing the progression and/or regression of atheroma. We will discuss several notable cardiovascular outcome trials and clinical trials that have utilized CCTA for monitoring the effect of anti-atherosclerotic medical therapy.

Understanding Coronary Plaque Morphology and High-Risk Features

To date, advancement in CCTA technology has made it feasible to identify coronary stenosis and define plaque characteristics on cardiac CT. Several features of CT imaging, including excellent spatial resolution (0.3-0.6mm), temporal resolution (80ms), cardiac volume coverage, slice thickness and reconstruction algorithms have enabled us to capture high quality images[11]. Improvements in CCTA image quality have allowed for reliable and accurate characterization of plaques. Plaque can be classified based on dense calcium component, high-risk features known as vulnerable plaques or American heart association histopathology classification system[12]. Based on dense calcium component, plaques are classified into calcified, partially calcified and noncalcified plaques. Noncalcified plaque is further classified into low attenuation plaque (LAP), fibrous or fibrofatty plaque based on Hounsfield unit (HU) attenuation thresholds. High risk plaques (HRP) have been identified on CCTA to demonstrate features such as LAP, positive remodeling (PR), spotty calcification and the napkin ring sign (NRS). Furthermore, recent advances have allowed machine learning and AI, to identify and distinguish between thick and thin cap fibrous atheromas using CCTA data. The latter plaques are also prone to rupture and can be considered vulnerable.

In 1987, Glagov et. al. described the process of arterial remodeling in response to atherosclerosis[13]. They noted that the human coronary arteries enlarge in response to plaque formation and suggested that functionally important luminal stenosis is delayed until the plaque occupies 40 percent of the internal elastic lamina area. At this point there is a decline in luminal area with increasing plaque, the transition from compensatory enlargement to ultimate obstruction. Severe luminal stenosis leading to ischemia happens primarily in the late stages of the atherosclerosis disease process. During this process some of the plaques may rupture leading to MI. Postmortem studies of patients who died suddenly reported that 75% cross sectional vascular area narrowing has been seen in 70% of ruptured plaques[14]. This explains the phenomenon of plaque progression for weeks to months before it ruptures and results in an event. In a prospective Japanese study, patients were evaluated by four serial invasive coronary angiograms over a one-year period. A subset of patients in this study demonstrated a rapid increase in the extent of luminal stenosis between two angiograms (i.e. plaque progression). More than 70% of individuals in this group sustained an acute coronary event. Conversely, those with gradual increase in luminal stenosis across all four angiograms developed stable angina symptoms and the remaining patients with no change in luminal stenosis had an uneventful course. All

three groups had similar nonobstructive disease at baseline and were treated similarly with appropriate medical therapy[15]. This illustrates the importance of rapid plaque progression in increasing likelihood of plaque rupture and MI.

While it is well established that vulnerable plaques are responsible for most MIs, not all plaques with such features lead to an acute event. In the postmortem study mentioned previously[14], one of the major differences between the ruptured plaques and high risk plaques that did not rupture (with similar histological features as ruptured plaque except for intact fibrous caps) was larger size of the ruptured plaques. These observed changes suggest that a high-risk plaque must evolve to possess a larger plaque burden and necrotic volume before plaque rupture. These findings are supported by a study that employed CCTA in patients with established or suspected CAD[16]. This study evaluated 1059 patients who underwent CCTA. Atherosclerotic lesions were analyzed for presence of two high risk features: PR and LAP. The remodeling index, plaque, LAP areas and volume were evaluated. 22% of these patients with high-risk plaques developed acute events in 2 years. Evaluation of segments resulting in ACS demonstrated significantly larger remodeling index, total plaque volume and LAP volume compared with segments not resulting in ACS. Subsequently in a serial CCTA study involving 449 patients with stable CAD and high-risk plaque features, plaque progression over time carried a 28-fold higher likelihood of an acute coronary event, whereas plaques that did not demonstrate progression in the interval between the two CCTA studies remained free from acute events[17]. From these observations it is evident that plaque progression is inevitable and an important step between subclinical atherosclerosis and acute coronary events. This provides us with a window of opportunity, to identify atherosclerosis early and limiting plaque progression may reduce the likelihood of plaque rupture and myocardial infarction.

Traditionally the concept of plaque risk is understood only as the change in the degree of luminal stenosis. This however is an oversimplification. Intravascular ultrasound (IVUS) and CCTA have established that the presence of a thin fibrous cap, necrotic core volume and positive remodeling are strong predictors of cardiovascular events. CCTA studies have now demonstrated that high risk plaque features are better described in quantitative terms, because their quantitative measures influence their prognostic contribution to ischemia and future events[18]. Taking all these factors into consideration, plaque progression and regression should be assessed in terms of increase risk (degree of vulnerability) or decrease risk (plaque stabilization) of rupture rather than percent luminal stenosis alone. Increased necrotic core volume, fibrous cap thinning, and positive remodeling are considered progression and decreased necrotic core volume, increased thickness of fibrous cap and calcification of cap is considered regression.

Utility of serial CCTA: Its role in plaque characterization and modification

As our understanding of plaque histology and phenotype has improved, interest has risen in the ability of CCTA to identify particular at-risk plaque structures. In addition, CCTA presents a new opportunity for noninvasive measurement of total coronary plaque burden that has not been previously available. Prospective ECG gating, post processing techniques and several other innovations in the field of CCTA have focused on improving the clarity

and quality of scans to compensate for decreased scan radiation. This has enabled the reduction in average radiation dose to 1.0 – 3.0 mSv and even allows for submillisevert scans. Owing to these current advancements, CCTA has emerged as a key noninvasive method of assessing cardiovascular risk by evaluating coronary stenosis and plaque burden. Moreover, serial CCTA allows for tracking of the atherosclerosis process which in turn can guide treatment options that can potentially improve outcomes. Therefore, CCTA has been increasingly used in numerous research studies and clinical trials to assess plaque modification. CCTA has also been used in early phases of drug development and safety assessment.

Large prospective trials like PROMISE and SCOT- HEART suggests that high risk plaque is independently associated with major adverse cardiovascular events (MACE). Results from a secondary analysis of the PROMISE trial that studied 4415 symptomatic patients with suspected CAD indicated that presence of high-risk plaque (eg, positive remodeling, low CT attenuation or napkin ring sign) found on CCTA was independently associated with a future MACE at a median follow up period of 2 years. HRP was associated with higher MACE rate (6.4% vs 2.4%; HR, 2.73;95% CI,1.89-3.93) in younger patients, women and in patients with nonobstructive coronary artery disease[19]. Subsequently similar results were observed in SCOT-HEART trial. The SCOT-HEART randomized trial studied 4146 patients with stable angina referred to cardiology clinics. These participants were evaluated with CCTA in addition to standard care and compared to standard care alone. They found that participants in the CCTA group had lower rates of the composite endpoint of death from coronary heart disease (CHD) or nonfatal myocardial infarction (MI) at median follow up period of 4.8 years [20].There was a 41% reduction in primary clinical end point of death from coronary heart disease or nonfatal MI in CCTA group compared to standard care group (2.3% vs 3.9%, P=0.004). This benefit was primary driven by a reduction in non-fatal MI. Subsequently a post hoc analysis of the SCOT HEART trial involving 1,769 patients, found that patients with adverse plaque characteristics had a higher cardiovascular risk score and higher calcium score. CHD death or non-fatal myocardial infarction was 3 times more frequent in patients with adverse plaque compared to those without (4.1% vs 1.4%; P<0.001; HR:3.01; P=0.001)[21]. In addition, patients with obstructive disease and adverse plaque had a 10-fold increase in rate of CHD death or non-fatal MI at 5 years. There are several plausible reasons that may explain these findings. Notably, there were a greater proportion of patients in the CCTA group that were initiated on preventive medications compared to standard care. This trial added additional information on how CCTA can inform clinical decision making with the goal of better targeting which patients would benefit from preventive care.

Summary of Clinical Trials

Serial CCTA use has been prominent in evaluating the anti-atherosclerosis hypothesis of several therapeutic agents. Now we will discuss the latest CCTA trials and studies that evaluated efficacy and safety of medical therapy (Table 1).

Statins

Over the last 2 decades, the use of statins to lower lipid levels has consistently demonstrated a reduction in cardiovascular events in multiple large clinical outcome trials[22, 23].

Many studies used CCTA to evaluate the effects of statin therapy on plaque burden. In the PARADIGM study, changes in atherosclerotic plaques were quantitatively analyzed using serial CCTA at an interval of 2 years [24]. In this group of patients without clinical CAD, statin treated patients demonstrated reduced plaque volume progression, greater plaque calcification and lower likelihood of developing high risk plaque features. These findings are consistent with prior invasive imaging trials.

Specifically, a reduction in plasma low-density lipoprotein cholesterol (LDL-C) by way of statin therapy, has been shown to reduce both non-calcified plaque and MACE. Otaki et.al. used serial CCTA to retrospectively evaluate the effect of LDL-C on plaque characteristics. 531 patients who underwent serial CCTA at least 1 year apart were evaluated for changes in plaque burden between scans[25]. The decrease in LDL-C group was noted to have a reduction in total plaque (TP), total non-calcified plaque (NCP), LAP, medium low attenuation plaque (MLAP) and medium attenuation plaque (MAP) volume at follow up compared to baseline (p <0.05 for all plaque types). Conversely, those who did not have a decrease in LDL-C had an increase in TP, total NCP and MAP volumes (p<0.01 for all plaque types). The largest reduction was seen in NCP volume between the groups. In both groups calcified plaque (CP) volume was increased and no change was seen in percent diameter stenosis, contrast density difference and remodeling index between baseline and follow up. This was the first study to use serial CCTA to evaluate the various components of NCP in response to LDL-C reduction. Further prospective, randomized studies are needed to evaluate these conclusions and determine the effect of statins on plaque composition.

It is well known that people with HIV have an increased risk of coronary atherosclerosis and cardiovascular events. The pathophysiology of HIV-associated CV disease is poorly understood. Current knowledge suggests that immune activation, inflammation, and platelet reactivity may be heightened in HIV which contributes to the increased risk of atherosclerosis. The REPRIEVE mechanistic sub-study was a prospective, double blind randomized controlled trial that coenrolled 800 participants with the aim of determining the prevalence and composition of CAD in HIV infected individuals as well as assessing of the effect of pitavastatin on the composition of non-calcified plaque and the progression of plaque volume[26]. Participants were randomized to receive pitavastatin vs placebo and underwent serial CCTA along with biomarkers of inflammation and immune activation at baseline and after 2 years of follow up. Published data to date show that plaque was seen on 49% of participants. Though luminal obstruction (at least 50% obstruction) was rare (3%), vulnerable plaque was seen in 23% of participants. 35% of participants had CAC greater than 0. This is the first large scale study using CCTA to assess plaque burden in HIV infected individuals. It provides substantial baseline data on the degree of plaque burden and inflammatory markers most closely associated with plaque among this population. REPRIEVE and associated sub-studies are ongoing to assess the role of statin therapy on non-calcified plaque.

Colchicine

Inflammation is known to play a key role in atherosclerosis, plaque formation and plaque instability in ACS. Colchicine, due to its anti-inflammatory properties, has been a proposed therapy to reduce inflammation in the coronary vasculature. A prospective 2018 study used serial CCTA over a 12-month period to evaluate the effect of colchicine 0.5mg/day on coronary plaque morphology in patients with ACS events in the preceding month[27]. The control population was recruited from cardiology clinic at the same institution. LAP volume was significantly lower the in the colchicine group compared to controls (mean 15.9 mm^3 [−40.9%] vs. 6.6 mm^3 [−17.0%]; p = 0.008). HsCRP was also significantly lower in the colchicine group compared to controls (mean 1.10 mg/l [−37.3%] vs. 0.38 mg/l [−14.6%]; p < 0.001). These differences remained significant after multivariate linear regression. No significant change was seen in total atheroma volume or LDL levels between the groups. Notably, a strong linear association (p<0.001) and strong correlation (r=0.578) was seen between change in LAP volume and hsCRP. These data emphasize the key role that inflammation plays in the atherosclerotic process and indicate that inflammation may be an important modifiable risk factor in the prevention of CAD.

Cilostazol

Cilostazol, an anti-platelet agent has been hypothesized to decrease the progression of atherosclerosis. It functions by inhibiting phosphodiesterase-3 which in turn leads to inhibition of platelet aggregation and thrombus formation. The ESCAPE trial was a prospective randomized controlled trial that compared the effect of Cilostazol 200mg once daily with aspirin 81mg once daily on CAD in patients with type 2 diabetes mellitus and with mild to moderate CAD over a 12-month period[28]. CCTA and CAC calculations were used to assess coronary artery atherosclerosis. This study found that those in the cilostazol group had decreased coronary artery stenosis (44.0 ± 2.1% to 40.4 ± 2.5%) compared to those in the aspirin group. Additionally, the amount of non-calcified plaque decreased in the cilostazol group (20.6 ± 3.0 to 17.3 ± 3mm^3) compared to the aspirin group (15.2 ± 2.5 to 16.6 ± 2.9mm^3). Though differences were seen between these groups, the changes did not reach statistical significance. Anti-platelet factors may remain a potential target for the prevention of atherosclerosis in the diabetic population, however, to date no further trials have re-evaluated the use of cilostazol in the primary prevention of atherosclerosis.

Direct oral anticoagulants

Recent studies have suggested that direct oral anticoagulants (DOACs) may play a significant role in reducing vascular calcification[29]. The mechanism by which this occurs is not yet fully understood, however, one mechanism hypothesizes that thrombin activates pro-inflammatory receptors thereby increasing atherogenesis and calcification in endothelial cells. Additionally, the effects of thrombin on inflammatory receptors may cause smooth muscle migration and proliferation, a recognized key step in atherosclerosis. In a 2018 study of 303 patients who underwent CCTA for atrial fibrillation ablation planning were enrolled into three groups; warfarin users, DOAC users and a control group who was not on anticoagulation therapy[30]. CCTA was used to compare coronary plaque burden between these groups. Results showed that the warfarin treated group had a significantly greater

overall coronary plaque burden (p=0.008) and a higher prevalence of high-risk plaque (p<0.0001) compared to those who used DOACs and the control group. No difference in overall plaque burden was observed between the DOAC and control groups, however the DOAC group had a lower prevalence of high-risk plaque compared to the control group (LAP (p=0.014) and napkin-ring sign (p=0.029)).

In a prospective randomized trial, 66 patients with non-valvular atrial fibrillation were randomized to receive warfarin or apixaban and underwent CCTA assessment at baseline and at 52 weeks[31]. The primary outcome was to examine the rate of change in coronary artery calcification between the groups. Secondary outcomes included examination of the quantitative changes of various plaque types and volumes. Similar to previous studies, the warfarin group had higher plaque progression compared to the apixaban group, especially in calcified plaque. After adjustment for traditional CV risk factors and plaque volume, those in the warfarin group had a significant increase in TPV (p=0.03), LAP (p=0.02) progression and in calcified plaque (p=0.005). Though the exact mechanism by which DOACs work to modify atherosclerosis is not clearly understood, these studies suggest that DOACs positively modify atherosclerotic risk.

Biologic agents

The use of biologic agents has become a mainstay in the treatment of various autoimmune disease and inflammatory conditions. Previous studies have suggested that those with severe psoriasis and chronic inflammation have an increased risk of MI. Elnabawi et.al. conducted a prospective observational trial in 2019 comparing the phenotypes of coronary plaque between patients with psoriasis receiving biologic therapy compared those not on biologic therapy[32]. 290 participants with psoriasis were recruited for this study, all of whom were naïve to biologic treatment. At one year follow up there was a 5% reduction in total coronary plaque burden in those receiving biologic therapy p=0.009. This was primarily due to a reduction in non-calcified plaque p=0.005. There was also a significant reduction in the fibrofatty burden p=0.004 and necrotic burden p=0.03. No significant difference was seen in the fibrous plaque burden. Conversely, no significant change in total plaque burden, NCP burden, or fibrous burden were seen at the one year following in the non-biologic group. Between the groups the reduction in NCP burden at one year was significantly lower in the biologic treated group compared with the non-biologic group p=0.03 both before and after adjustment for traditional cardiovascular risk factors. This study demonstrated a positive effect of biologic agents on plaque burden, particularly on inflammatory driven plaque phenotypes. Most recently Choi et.al conducted a prospective observational study in 2020 assessing the modifications of lipid rich necrotic core (LRNC) in plaques in response to biologic therapy in patients with psoriasis[33]. LRNC is the histopathologic equivalent to LAP seen on CCTA and is predictive of future cardiovascular events. Modifications in LRNC can therefore be used as a correlate for risk of MACE. This study found that at one-year, participants receiving biologic therapy had a reduction in LRNC p=0.28 compared to those who did not receive biologic therapy p=0.06. The change between groups was also significant before (p=0.004) and after adjustment for traditional CV risk factors and psoriasis severity (p=0.033). Similar to previous studies, this study provided encouraging results as to a modifiable risk factor of CVD in patients with psoriasis.

Similar studies assessing the role of biologic agents on coronary plaque in patients with rheumatoid arthritis (RA) have also been conducted. Karpouzas et.al. conducted a observational cohort study to evaluate the effect of biologic agents on CVD in patients with RA[34]. They found that biologic disease modifying anti-rheumatic arthritis (DMARD) agent use was associated with lower long term CVD risk (OR 0.15 [95% CI 0.04–0.60]). This effect was primarily seen in those with NCP or LAP at baseline. Plaque progression analysis demonstrated that DMARD use was associated with the transition of non-calcified plaque to mixed/calcified plaque (OR 4.00[95%CI 1.05-15.32]) and was also associated with a lower likelihood of new plaque formation (OR 0.40 [95% CI 0.17-0.93]) in patient without mixed/calcified plaque. Notably, the use of biologic DMARD agents also predicted LAP loss (p=0.042). Like studies in patients with psoriasis, the use of biologic agents in patients with RA have shown promising results in terms of favorable plaque modification.

Aged Garlic Extract

Aged garlic extract (AGE) has been shown to have numerous cardiovascular risk modifying effects including lowering blood pressure, total cholesterol and low-density lipoprotein (LDL), decreasing LDL oxidation and oxidative damages, decreasing platelet aggregation and directly suppressing atherosclerosis[35-37]. A recent prospective study also evaluated the effect of AGE on coronary plaque volume using CCTA in patient with diabetes mellitus (DM). This prospective study assigned patients to receive 2,400mg AGE/day (37 patients) or placebo (29 patients) and serial CT was performed at baseline at follow up 1 year later. Similar to previous studies, the AGE group had a statistically significant regression in normalized LAP [median and standard deviation (SD) −0.2 (18.8) vs. 2.5 (69.3); p=0.0415, compared with the placebo group. No differences were observed in TP, fibrous, or fibro fatty plaque volumes between the AGE and placebo groups[38]. These results support previous data regarding cardio-protective benefits of AGE, suggesting that one mechanism of action is through the reduction in LAP.

Omega-3-fatty acids

Over the past decade many trials have investigated the role of omega 3-fatty acids in atherosclerosis[39-42]. Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and icosapent ethyl are all various omega 3- fatty acids that have been showed to have beneficial effects on atherosclerosis and the prevention of CHD. Recently, two landmark trials, REDUCE-IT and EVAPORATE were conducted to investigate the benefits of icosapent ethyl (IPE). The REDUCE-IT trial, conducted in 2019, was a multicenter, randomized, double-blind, placebo-controlled trial that randomized 8,179 participants on statin therapy with fasting triglyceride levels of 135-499 mg/dL to receive IPE 2g twice daily for a total of 4g or placebo[43]. Participants were followed for a median of 4.9 years. The primary endpoint of this study was composite of CVD, nonfatal MI, non-fatal stroke, coronary revascularization or unstable angina. Over the follow up period, the primary endpoint occurred in 17.2% of patients in IPE group compared to 22% in the placebo group (hazard ratio (HR) 0.75%, 95% CI 0.68-0.83; p<0.001). Notably, the primary composite endpoint of MACE was 25% lower in the IPE group compared to placebo. Specifically results showed a 20% reduction in CV death, a 31% reduction in myocardial infarction (MI), and a 35% reduction in urgent or emergent coronary revascularization with IPE. In 2020,

the EVAPORATE trial, a multi-center, randomized, double-blind, placebo-controlled trial of 80 patients, further evaluated the effect of 4g of IPE per day compared to placebo on coronary plaque progression using serial CCTA[39]. CCTA was conducted at baseline, at 9 months and at the conclusion of 18 months. The primary endpoint of this study was progression of LAP volume over 18 months. Analysis was also conducted to look at progression of other plaque types including total plaque, NCP, fibrofatty plaque, fibrous plaque and calcified plaque. The most common plaque type expressed in both groups was fibrous plaque. LAP was conversely the least common plaque type in both groups. After multivariate regression adjusting for typical cardiovascular risk factors, the change in LAP volume was statically lower in the in the IPE group compared with placebo (−0.3 ± 1.5 vs 0.9 ± 1.7mm^3; p= 0.006). Total plaque, total NCP, fibrofatty plaque, fibrous plaque were all also significantly lower in the IPE group compared to the control group. Dense calcified plaque, however, was not statically different between groups. Together the REDUCE- IT trial and the EVAPORATE trial clearly demonstrate a benefit of IPE in patients with residual hypertriglyceridemia despite maximal statin therapy. These data provide novel insights into the mechanism of omega 3-fatty acids and atherosclerosis.

PCSK9 Inhibitors

In recent years, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have gained popularity in the field of cardiology. PCSK9 functions by transporting the hepatic LDL receptor to lysosomes where it is destroyed thus increasing levels of circulating LDL-C. PCSK9 may also play a role in vascular inflammation and atherosclerosis independent of hepatic LDL receptors. Evolocumab is a fully human monoclonal antibody that targets PCSK9 thereby lowering circulating LDL levels. Hirai et.al. conducted a retrospective study comparing individuals given 140mg evolocumab every 2 weeks compared to controls in order to investigate the effects of evolocumab on vulnerable coronary plaques and to identify factors associated with plaque stability and size using serial CCTA at baseline and at 6 months after therapy[44]. All patients were also being treated with statin therapy. Vulnerable plaques were defined as those with low attenuation and positive remodeling on CCTA. In the evolocumab group, the stability of vulnerable coronary plaques as determine by increasing attenuation, was significant increased from 39.1 ± 8.1 HU at baseline to 84.9 ± 31.4 HU after six months (p < 0.001). Additionally, the evolocumab group also had a significant decrease in size of vulnerable coronary plaques after six months (p < 0.001) and a significant decrease in stenosis at vulnerable coronary plaque sites from 27.0 ± 10.4% at baseline to 21.2 ± 9.8% after six months (p < 0.001). No change between baseline and six months was seen in these parameters in the control group. Larger phase 3 clinical trials assessing the effect on evolocumab (PCSK9 Inhibitor) on coronary plaque volume and plaque composition using CCTA and positron emission tomography (PET) are currently underway.

DISCO (Dietary Intervention to Stop Coronary Atherosclerosis)

Dietary and lifestyle modifications are the cornerstone of prevention of CAD. There is limited direct evidence appraising the influence of diet and exercise on coronary plaque burden and plaque composition. The DISCO- CT trial evaluated the effect of lifestyle changes on plaque progression. In this study Henzel et al. recruited 92 patients with

nonobstructive CAD (2 segments with atheroma <70% stenosis on baseline CCTA) and randomized them to optimal medical therapy (OMT) versus OMT plus DASH (Dietary Approach to Stop Hypertension) diet and physical activity[45]. Patients underwent CCTA at baseline and at an average of 67±14 weeks later. They showed that there was a reduction in NCP volume in both the experimental and the control arm and there was a significant difference in the reduction of NCP volume between the groups (p=0.04). However, there was no change in TPV or percent atheroma volume between the groups. This is the first randomized trial to use CCTA to demonstrate the mechanistic effects of lifestyle changes on plaque progression. Conducting outcome trials assessing lifestyle interventions is extremely difficult and long-term follow up is cumbersome. Therefore, use of CCTA imaging endpoints serves as a substitute and a less expensive approach for evaluating the effectiveness of lifestyle interventions. The findings of this trial are consistent with primary prevention of cardiovascular disease with the Mediterranean diet outcome trial that has shown to reduce major adverse cardiovascular events (myocardial infarction and stroke).

Conclusion

Built upon extensive knowledge derived from innumerable clinical trials, CCTA is a well validated noninvasive imaging modality for assessment of CAD.[46, 47] Several other paramount clinical trials are on the horizon, such as, SCOT HEART-2, STOP, EPIC HIV study and a trial evaluating the effect of evolocumab on coronary artery plaque volume and composition[48]. Numerous other clinical trials will enhance our knowledge on plaque progression and provide mechanistic insights into the effect of medical therapy on plaque evolution. Future studies will also strengthen the evidence on plaque modification and determine the clinical utility of quantitative and qualitative plaque analysis. Introduction of machine learning and continuous advancements in imaging techniques in addition to radiation dose reduction strategies will enable widespread use of CCTA. Over the next decade we can foresee CCTA being used routinely in clinical practice to guide medical therapy and in the management of coronary artery disease.

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Table 1.

CCTA studies for characterization and tracking of coronary plaque.

Study Therapy (Year)	Study population	Number of participants	Follow up serial CT	Summary of Findings
Statins (2018)	Suspected or Known CAD	1,255	≥ 24 months	Slower progression of total PAV. Rapid progression of calcified PAV. Lower incidence of HRP features.
Colchicine (2018)	Post-Acute coronary syndrome.	80	≥ 12 months	Greater reduction in LAP volume. No change in TAV, DCP and NCP volume.
Cilostazol, ESCAPE (2019)	Diabetes & Subclinical atherosclerosis	100	≥ 12 months	Greater reduction in NCP. No change in TP or CP volume.
Apixaban (2019)	Non-Valvular Atrial Fibrillation	66	≥ 12 months	Lower total, LAP and calcified plaque progression. No change in NCP, fibrous or fibrofatty plaque.
Biologics (TNF α, IL-12/23 and IL-17 inhibitors) (2019)	Psoriasis	290	≥ 12 months	Reduction in necrotic core and NCP burden. No change in fibrous plaque burden.
Biologics (TNF α, IL-12/23 and IL-17 inhibitors) (2020)	Psoriasis	209	≥ 12 months	Reduction in LRNC.
Biologics (TNF inhibitors) (2020)	Rheumatoid Arthritis	150	≥78 months	Stabilization of NCP. Lower likelihood of new plaque formation.
Aged Garlic Extract (2020)	Diabetes Mellitus.	80	≥ 12 months	Higher percentage reduction in LAP. No difference in TP, fibrous or fibrofatty plaque volumes.
Icosapent ethyl (IPE), Evaporate (2020)	Known CAD, elevated TGs	80	≥18 months	Reduction in LAP, fibrous, fibrofatty, NCP and TP volume. No change in DCP volume.
Evolocumab (2020)	Known CAD on statin therapy	98	≥ 6 months	Increased stability of vulnerable plaques. Decrease in size of vulnerable plaques.
DASH diet and Exercise, DISCO (2021)	Nonobstructive CAD	92	≥ 12 months	Greater reduction in Noncalcified plaque. No change in TP or PAV.

Abbreviations: TP-Total plaque; NCP- Noncalcified plaque; CP-Calcified plaque; DCPV-Dense calcified plaque; LAP- Low attenuation plaque; LRNC-Lipid rich necrotic core; PAV-Percent atheroma volume; TAV-Total atheroma volume; HRP- High risk plaque.