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Invited review

Should CT replace IVUS for evaluation of CAD in large-scale clinical trials: Effects of medical therapy on atherosclerotic plaque

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A B S T R A C T

Clinical trials assessing the effect of medical therapies on atherosclerotic plaques have hitherto employed invasive imaging techniques such as intravascular ultrasound (IVUS). This has limited the study population to high-risk patients in whom invasive coronary angiography is indicated; moreover, IVUS typically is performed utilizing a target lesion-based analysis. Recently, comprehensive quantitative analysis of all atherosclerotic plaques in the complete coronary artery network has become possible through the use of coronary computed tomography angiography (CCTA). Excellent inter-observer and inter-scan reproducibility of CCTA has been reported. Several studies have already tested the applicability of CCTA-measured plaque volume changes as an imaging surrogate endpoint in clinical trials and have found positive results. Further, substantial evidence supports the use of CCTA as a novel imaging surrogate that can accurately assess the changes in plaque characteristics according to medical treatment. In this review, we summarize current evidences that support the use of CCTA as a novel imaging surrogate that can replace IVUS in evaluating the results of treatment. We also attempt to determine whether the technological advances in CCTA will extend its application beyond use as a diagnostic method in clinical practice to use in large-scale clinical trials.

1. Introduction

Intracoronary imaging techniques, including intravascular ultrasound (IVUS), have been established as the gold standard surrogate for determining the clinically relevant progression of atherosclerosis.[1,2] The introduction of this imaging technique, with its specific endpoints, has enabled the evaluation of novel cardiovascular therapies in smaller sample sizes within a shorter period than that when the traditional clinical endpoints such as mortality or myocardial infarction have been used.[3] Therefore, several large-scale clinical trials assessing the temporal changes in coronary atherosclerotic plaques in response to novel treatments have made use of this invasive technique.[4–6] However, the target populations in these studies were limited to patients who were at higher risk and in whom invasive coronary angiography was indicated. This made evaluating the effect of these drugs in lower risk groups – which account for a majority of the disease population – difficult despite the fact that the importance of primary prevention is increasingly emphasized.[7–9]

For the past two decades, remarkable advances have been made in both acquisition and post-processing techniques related to computed tomography (CT).[10] The wide availability and accessibility of CT compared to that of invasive coronary imaging has rapidly led to CT – both coronary artery calcium scan and coronary computed tomography angiography (CCTA) – becoming one of the most widely used imaging modalities to evaluate patients in cardiology clinical practice. The association between CT findings and clinical outcomes has repeatedly been proven[11–14]; this has convinced members of several cardiology expert societies to incorporate CT in their recent guidelines on the assessment of coronary artery disease (CAD), cardiovascular risk stratification, and management of blood cholesterol levels.[7,8,15–17] These guidelines mostly consider only the coronary artery calcium scan or the utility of CCTA in qualitative categorical assessment of luminal stenosis. However, the utility of CCTA in evaluating quantitative compositional changes in coronary atherosclerosis has made it possible to widen the scope of its use as an alternative imaging surrogate.[18]

In this review, we summarize current evidences that support the use of CCTA as a novel imaging surrogate that can replace IVUS in evaluating the response to treatment. We also attempt to determine whether the technological advances in CCTA will extend its application beyond use as a diagnostic method in clinical practice to use in large-scale clinical trials (Fig. 1).

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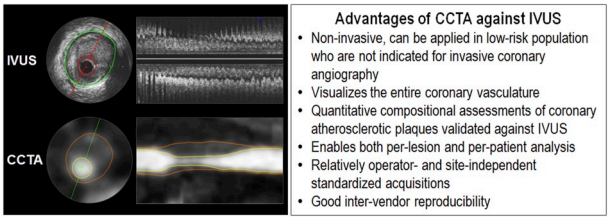

Fig. 1. Summary of the comparison between intravascular ultrasound (IVUS) and coronary computed tomography angiography (CCTA) – (Left panel) same lesion scanned with IVUS (upper) and CCTA (lower) (Right panel) advantages of CCTA against IVUS.

2. IVUS as the current gold standard imaging surrogate endpoints in cardiovascular trials

For an imaging method to be used as a surrogate endpoint for clinical trials, the results of the imaging tests need to be linked with the treatment effectiveness as well as the clinical outcomes. A direct association between the burden and progression of coronary atherosclerosis assessed using IVUS and adverse clinical outcomes have been observed.[19,20] Previous studies have further identified the characteristics of individual plaques that are prone to be the direct cause of adverse events including attenuated plaque, spotty calcification, and remodeling,[21–24] and also have found that there is a wide range of inter-individual difference in the response to medical treatment including statins.[20,25] Other invasive atherosclerosis imaging techniques also have enabled the detection of high-risk features such as thin-cap fibroatheroma, macrophages and microvessels by optical coherence tomography and lipid core burden by near-infrared spectroscopy, and have demonstrated associations between future adverse events with these features.[26–29]

As a result, therapeutic strategies directly targeting the regression of coronary artery plaque volume or reducing the so-called high-risk plaque features defined by intracoronary imaging have been proposed. On the basis of these supporting observations, the change in plaque burden – usually the percent atheroma volume – measured by serial IVUS has become the gold standard imaging surrogate endpoint for evaluating the results of novel therapeutics for CAD.[4,30]

However, IVUS has limitations as a surrogate endpoint for cardiovascular trials. Owing to the invasive nature of IVUS, the study population in previous studies has been skewed toward high-risk patients in whom invasive coronary angiography is clinically indicated.[4,30,31] Hence, the effect of novel therapies and the natural history of CAD were mostly assessed in patients at relatively high risk or patients with advanced CAD. Because of this, the remaining patients at earlier stages of coronary atherosclerosis or lower-risk populations, who account for a much larger portion of the total disease population, are not fully evaluated. Resource constraints, including relatively high costs and the need for trained interventionists for performing the procedure and interpreting the findings have also limited patient recruitment and successful follow-ups without the patients dropping out from clinical trials to date.[32]

In addition, owing to the practical limitations of intravascular imaging in the extent of the coronary vasculature that can be interrogated, catheter-based invasive intracoronary imaging cannot assess severely stenotic, calcified, or tortuous lesions through which catheters cannot pass.[2,32] Some reports state that intracoronary imaging may only be able to assess ~50%–75% of all plaques – although the most clinically important plaques in the proximal and mid segments are readily imaged.[33] Consequently, IVUS studies usually followed plaque volume changes only in a specific target lesion located in one of the three major vessels per patient, instead of evaluating the entire coronary bed. This results in only partial sampling of the total coronary plaque burden in any given patient and makes it difficult to determine the potential inter-lesion correlation between coronary plaques.[2,34,35]

As coronary atherosclerosis is a dynamic disease that can involve concurrent development and regression of plaques within a patient, this "partial sampling" of the coronary tree, which allows only per-lesion based assessments, possibly weakens the link between IVUS-based plaque volume changes and the clinical outcomes. Although some serial IVUS studies employed the 3-vessel IVUS approach to overcome this limitation,[19,36,37] this method requires additional time and wiring and exposes patients to subsequent risks of procedural complications.[32,38]

These limitations of IVUS mostly originate from its invasiveness and the observations that contemporary patients with stable chest pain are at a lower risk than previously reported; therefore, the introduction of a novel non-invasive imaging technique that can quantitatively assess temporal changes in individual lesions in the entire coronary tree of a patient is the need of the hour.[39]

3. Ability of CCTA to assess coronary plaques in the current era

The clinical relevance of the correlation between the findings from coronary plaque images and clinical outcomes and the efficacy of using imaging surrogate endpoints for cardiovascular clinical trials has already been proven by using IVUS. Therefore, the greatest, and possibly only, barrier remaining for CCTA to be an alternative imaging surrogate endpoint replacing IVUS is its accuracy and reliability in quantitative assessment of individual plaque burden and plaque characteristics. The ability of CCTA with 64 or more detector rows in the quantitative assessment of coronary atherosclerosis has been intensely validated and is currently actively evolving.

3.1. Validation studies against IVUS – quantitative compositional assessment

The diagnostic performance and accuracy of CCTA versus quantitative coronary angiography in the qualitative assessment of luminal diameter stenosis have been proven in several early studies.[10,40] More recent studies have widened the applicability of CCTA, into the quantitative assessment of atherosclerotic plaques and the measurement of plaque volume.

The dose reduction systems in modern scanners determine the energy delivered by CCTA by the patient's biometrics to minimize the radiation exposure.[41] This difference in the type of energy can cause variations in the Hounsfield Unit range detected on the plaque components and a difficulty in lumen evaluation especially in patients with extensive coronary calcification.[42] In this regard, the accuracy and reproducibility of CCTA has been directly compared against those of IVUS in the quantitative analysis of atherosclerotic plaques in numerous studies including patients with various extent of plaque burden.[18,43–48] The primary results have been promising; CCTA appears to be highly sensitive for the detection of any plaque and measurement of luminal area, stenosis severity, plaque volume, and plaque area in a quantitative manner.[49–51]

In addition to the total coronary atherosclerotic burden, the constituents of plaques and some of their characteristic features have been identified as markers of adverse outcomes.[19,24] Further, several drugs, especially statins, have been shown to induce changes in plaque characteristics and plaque components.[4,21] Thus, quantification of compositional changes and identification of high-risk plaque features is a key element for an imaging modality to be used in clinical trials that assess temporal changes reflecting drug effects. These changes in coronary atherosclerotic plaque compositions and high-risk plaque features could previously be tracked only with invasive imaging, but it can now be accurately tracked using CCTA.[18] When validated against IVUS with respect to the current reference standards for the measurement of coronary artery plaque volume, CCTA correctly assessed the composition and characteristics of coronary atherosclerotic plaques.[49,50,52] Histologic studies also found that CCTA can identify these so-called

high-risk plaque features.[53,54]

3.2. Reproducibility and reliability of CCTA in serial quantitative assessment of coronary atherosclerosis

The state-of-the-art current-generation CT scanners with advanced iterative reconstruction and rapid acquisition speeds have markedly improved the reproducibility of CCTA.[47,55–57] The development and improvements in the plaque assessment software have also contributed to improving the accuracy by enabling adoptive thresholds to identify plaque components, correcting the influence of luminal contrast densities on plaque attenuation values, and improving the detection of soft plaques.[58,59] In one study, the observer variability was lower than the serial changes in plaque burden, which is the most common endpoint in IVUS progression/regression studies.[60] Although these plaque assessment software require excellent and good CCTA image quality and could contain incorrect extractions which require manual corrections, novel approaches including machine learning algorithm are being developed to improve the applicability of these techniques.[61,62] These findings suggest that CCTA data analysis using fully or semi-automated software can detect changes in atherosclerotic plaque size and volumes beyond the observer bias, and hence provides the opportunity for CCTA to be used as a surrogate imaging endpoint for future clinical trials that assess responses to treatment.

4. Advantages of using CCTA-measured changes as surrogate end points

4.1. The standardization of image acquisition and interpretation

The technical aspects of CCTA are highly standardized with clearly established acquisition protocols based on the available guidelines from the Society of Cardiovascular Computed Tomography for performing the procedure, data acquisition, interpreting the results, and reporting data.[63–65] As compared with invasive coronary imaging, which requires highly trained operators[64]; this ability of CCTA to enable operator- and site-independent standardized acquisitions makes it an excellent imaging modality to serve as a surrogate imaging endpoint in clinical trials.

4.2. Inter-vendor reproducibility

Studies also have reported the inter-vendor and inter-scan reproducibility of quantitative measurements of coronary plaque volumes using standardized fully or semi-automated software.[66–68] Intraobserver interscan correlations of the total, calcified plaque and non-calcified plaque volumes were excellent with r value ranging 0.93 to 0.97, with interobserver interscan correlations ranging 0.81 to 0.96.[66] The consistency in quantitative reporting regardless of the scanner variety expands the site eligibility for participation in a clinical trial, and can increase patient recruitment. Further, when local reporting is not feasible in multicenter clinical trials, images can be readily exported in the Digital Imaging and Communications in Medicine (DICOM) format and transferred to the core laboratories for validated imaging analysis.[64]

4.3. Assessment of the whole coronary tree of a patient

CAD is a dynamic disease that involves the whole coronary vasculature; multiple plaques in different stages can coexist in a single patient – where one plaque is stabilizing whereas another is just developing.[35,69] Therefore, it is debatable whether serial measurement of plaque burden in a single segment or lesion of one coronary artery reasonably reflects the approximation of plaque progression in all coronary beds, making it difficult to estimate the clinical outcome.[2]

In this regard, CT offers optimal opportunity by simultaneously visualizing the entire coronary tree and enabling assessment of all coronary plaques in a patient, unlike invasive coronary imaging which requires wiring of each coronary artery.[64] Furthermore, CCTA can provide reconstructed images in any plane without compromising their spatial resolution. This ability of CCTA to enable both per-lesion and per-patient level analysis concurrently is one of its major advantages that can overcome the partial sampling problem of IVUS. The non-invasiveness of CCTA also enables enrollment of patients at a lower risk in whom invasive imaging is not indicated and makes scheduled follow-ups easier, lowering the concerns regarding patient drop-out. Although this quantification of the entire coronary tree using currently available commercial software could be a time-consuming process and requires highly experienced interpreters in patients with high plaque burdens, the global quantification of plaque burden showed incremental value in predicting rapid plaque progression and clinical outcomes when added to the conventional semi-quantitative and qualitative approaches.[70] CCTA also enables the identification of vulnerable plaques in patients without inducible ischemia.[71]

5. Potential for use of CCTA in large-scale clinical trials or registries

Recent CCTA studies have demonstrated the feasibility and possibility of use of CCTA in future large-scale clinical trials. The representative CCTA registry is the CONFIRM (COronaryCTAngiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter).[72] Except for the requirement that CCTA must be performed using a scanner with ≥64-detector row, the restrictions and exclusion criteria about type of scanner or contrast used were kept to a minimum to facilitate the recruitment of sites and patients; moreover, CCTA interpretation was performed at each site. As a result, more than 27,000 patients were enrolled at 12 cluster sites in 6 countries. To the best of our knowledge, this registry represents the first prospective international multicenter database to relate CCTA-measured severity of CAD to mortality and the independent prognostic value of CCTA results.[12]

More recently, the PROMISE (PROspective Multicenter Imaging Study for Evaluation of chest pain) and SCOT-HEART (Scottish COmputed Tomography of the HEART) trials, which are the two largest and most comprehensive known cardiovascular imaging outcome trials have been published, each comprising more than 10,000 patients.[73,74] Both studies tried to incorporate CCTA into the diagnostic strategies and clinical decision-making process for stable CAD patients; moreover, both studies successfully enrolled a sufficient number of patients so as to enable statistically meaningful primary endpoints.[75] CCTA was found to be a useful and readily accessible clinical tool in both studies. Although all three studies have mainly employed semi-quantitative and qualitative analysis of CCTA, they prove the applicability and readability of CCTA in large-scale clinical trials.

Further, the SCOT-HEART study also revealed the direct association between coronary artery plaque characteristics and adverse outcomes.[76] Patients with both obstructive disease and high-risk plaque features had a 10-fold increase in the event rate of coronary heart disease death or nonfatal myocardial infarction compared with patients with normal coronary arteries. Further, the specific plaque characteristics including positive remodeling and low-attenuation plaque were the most helpful in predicting future cardiac events. Recent ICONIC (Incident COroNary Syndromes Identified by Computed Tomography) study, a nested case-control study within a cohort of 25,251 patients undergoing CCTA, employed quantitative CCTA assessment method and found low-attenuation plaque, spotty calcification, and fibro-fatty and necrotic-core plaque volumes to be independent predictors of acute coronary syndrome.[77] This direct association between plaque composition and long-term coronary events has been never assessed by IVUS studies in large populations of CAD patients and once again confirms the advantage of comprehensive CCTA analysis.[76,77]

Apart from the usefulness of CCTA in diagnostic strategies, earlier studies with relative small study populations have demonstrated the

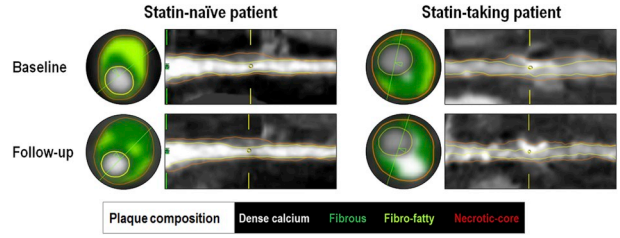

Fig. 2. Representative figure of the temporal changes in the lesions in patients with and without statin treatment assessed by coronary computed tomography angiography. The lesion in statin-taking patient showed progression of calcification while lesions in statin-naïve patients not.[81]

changes in percent atheroma volume after statin treatment, as measured using serial CCTA.[78–80] The temporal changes in plaque characteristics and the disease burden were successfully traced in these studies, which have also described the feasibility of using comprehensive quantitative analysis of serial CCTA for assessing the progression and regression of coronary atherosclerosis.[78–80]

More recently, prospective observational studies involving large numbers of patients have extended the feasibility of CCTA to the evaluation of response to medical treatment.[81,82] Consistent with the prior findings of invasive studies, strict control of low-density lipoprotein levels significantly attenuated the progression of plaque volume.[82] Further, the use of statins induced alterations in both characteristics and constituents of atherosclerotic plaques when more than 3,000 plaques in 1,255 patients were serially assessed (Fig. 2).[81] These observations, which are in accordance with the results of previous IVUS studies, support the possibility of applying CCTA in large-scale clinical trials to assess the quantitative changes in a per-lesion as well as a per-patient manner.

6. Current limitations and issues to be further addressed

There are some limitations of CCTA that need to be further addressed for it to be an image surrogate endpoint that could completely replace IVUS. First, the threshold for meaningful plaque volume change assessed using serial quantitative CCTA needs to be defined, considering the fact that statistical significance can often be reached even if the reported changes are within the sampling error. The direct histological validation of plaque components identified by CCTA using Hounsfield Unit cut-offs is also warranted. Second, although the inter-vendor reproducibility of the quantitative compositional plaque volume analysis has shown promising results, the reproducibility between 64-row scanners with filtered back-projection filters and newer scanners with iterative reconstruction algorithms of all generations is not yet sufficiently evaluated. Radiation and safety regarding the use of iodine contrast are also challenges that can prevent the widespread use of CCTA. The spatial resolution of CCTA is still somewhat lower than that of invasive intracoronary imaging. Lastly, the time-consuming process of comprehensive quantitative analysis of CCTA using currently available commercial software could also be a limitation to the use of CCTA in large-scale clinical trials, especially when targeting patients with high plaque burden. Future semi-automated methods for plaque analysis that utilize machine learning are promising.

However, as the rapid evolvement of the technical aspects is currently ongoing, the future seems bright for CCTA to be an alternative to IVUS that is more accessible, safe, and provides a reliable surrogate endpoint. With the introduction of new vendors, including dual-source CTs and novel postprocessing techniques, along with the support of artificial intelligence in image interpretation, CCTA could usher in a new era of imaging clinical trials.[83–86]

7. Conclusion

At present, CCTA offers a comprehensive, accurate, and reproducible quantitative assessment of the whole network of coronary arteries, which was hitherto only available with intracoronary imaging modalities. As CCTA can be used for a wider range of patient groups, including the low-risk population, and is readily accessible owing to its non-invasiveness, CCTA-based quantitative analysis of coronary atherosclerosis could function as a novel imaging surrogate endpoint that could replace IVUS.

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