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Review article

What is the clinical role of non-invasive atherosclerosis imaging?

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A B S T R A C T

Non-invasive atherosclerosis findings have been demonstrated to provide incremental diagnostic and predictive values for ischemia, acute coronary syndrome, and cardiovascular outcomes. The challenge is to translate research findings to a clinical role. Here, we review the current utility of atherosclerotic imaging and the incremental value of plaque imaging. We also evaluate future clinical and research implications for three patient populations: asymptomatic prevention, stable chest pain, and acute chest pain.

1. Introduction

Coronary artery disease remains the leading cause of death in the United States, and the majority of deaths are not preceded by coronary symptoms.[1] Coronary computed tomographic angiography (CCTA) demonstrates a high negative predictive value for the evaluation of luminal obstruction.[2] However, as the majority of myocardial infarctions are preceded by non-obstructive plaques, increasing attention has turned to evaluation of atherosclerosis anatomy. This includes non-obstructive plaque, plaque composition, and adverse plaque features (also known as atherosclerotic plaque characterstics, APCs).[3-5] (see Figs. 1 and 2)

As proof of concept, invasively determined APCs that correlated with high risk histopathologic features in sudden coronary death predicted future culprit lesions in the PROSPECT trial.[6] However, non-invasive techniques such as CCTA would improve the generalizability and applicability of atherosclerosis imaging. In this review, we will discuss the clinical role of non-invasive atherosclerosis imaging by CCTA and outline potential knowledge gaps for future investigation.

Some desirable clinical goals with coronary atherosclerosis imaging include prognostication, decision making for preventive medical therapy, and decision making for referral to invasive angiography. We will review these goals in the context of three major patient groups (Table 1): asymptomatic patients for consideration of preventive therapy, stable patients suspected of coronary artery disease,and acute chest pain patients.

2. Atherosclerosis imaging in prevention

Preventive medical therapy for coronary artery disease has been prescribed using clinical risk scores and targeting high-risk groups with sufficiently elevated risk equivalents, such as diabetics and elderly. The population-based approach has been favored over the use of tools such as coronary artery calcium (CAC) to individualize patient risk stratification. New evidence and guidelines over the last year have brought this approach strongly into question. Aspirin for primary prevention demonstrated no overall benefit in the ASCEND and ARRIVE trials for diabetics and older adults respectively, and the 2018 ACC/AHA guidelines for lipid-lowering preventive therapy added an increased role for risk enhancers such as CAC.[7–9]

Currently, the guideline-recommended clinical role of atherosclerosis imaging in primary prevention is in the use of CAC as a risk enhancer to reclassify borderline and intermediate risk patients.[9] CAC scoring has consistently demonstrated incremental prognostic value over Framingham Risk Score and individual risk factors, most notably in the MESA study, an NHLBI-sponsored population-based cohort of 6814 patients.[10] Importantly, a CAC score of 0 demonstrates a 10 year event rate of 1.1–1.7%, and the absence of CAD reclassifies 41% of statin recommended candidates as not eligible for statin therapy.[11,12] The MESA, Dallas Heart and Heinz-Nixdorf Recall Study were used to develop a summary risk score for CAC and risk factors for shared decision-making.[13]

Additional CAC evaluation besides Agatston score may enhance risk prediction. CAC plaque features offer prognostic value above score alone. CAC density, defined as CAC score divided by CAC volume, was observed by Criqui et al. in the MESA cohort to be inversely associated

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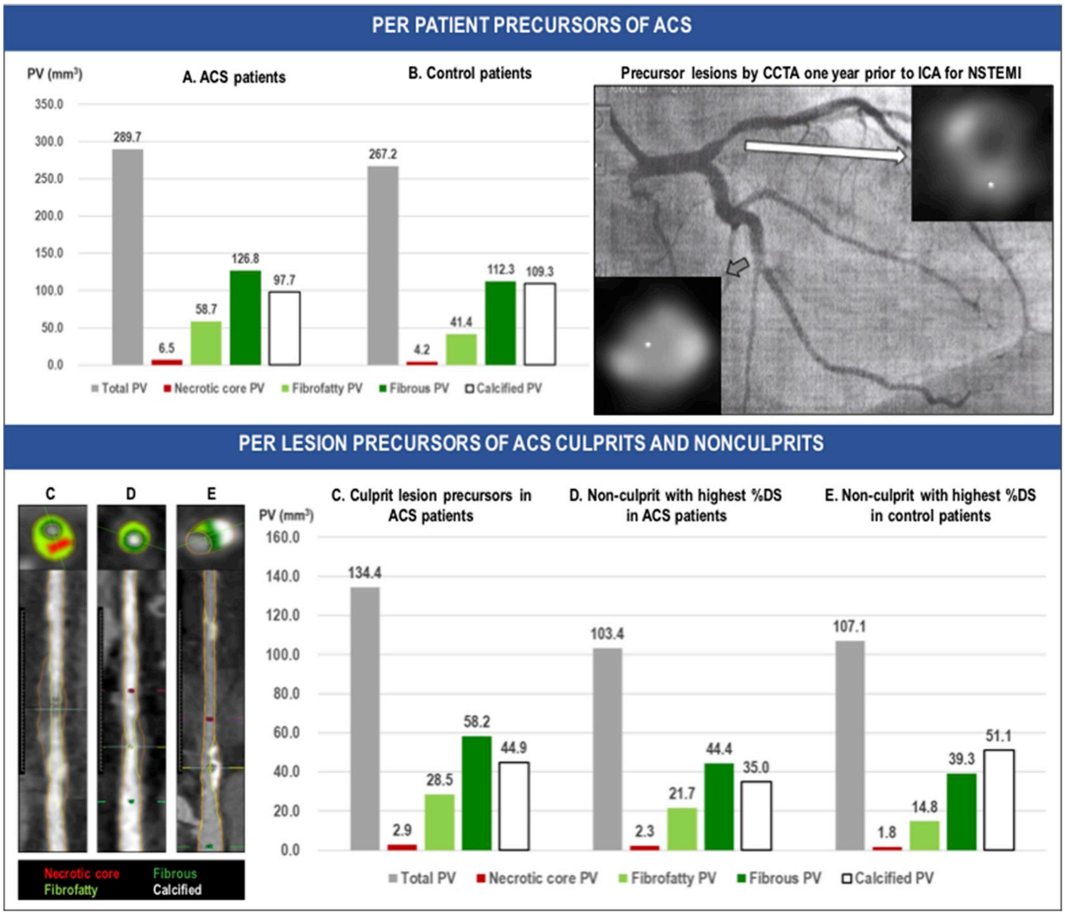

Fig. 1. Precursors of ACS and controls as identified by CCTA. A. Adjudicated first ACS cases with CCTA measurements (n = 234) of a nested case-control cohort of 25,251 patients undergoing CCTA exhibit elevated fibro-fatty and necrotic core volumes (65.2 ± 95.4 mm3); 34.6% exhibit diameter stenosis ≥50% and 52.1% exhibit high-risk plaque. **B**. Non-event controls propensity matched by demographics, risk factors, and number of obstructive vessels by CCTA exhibit lesser fibro-fatty and necrotic core volumes (45.6 ± 68.8, multivariate adjusted p = 0.008) with no difference in calcified or total plaque volumes (p = NS for all); %DS and HRP are significantly decreased in control patients ($p < 0.05$ for all). **Inset image**. A 67-year old man with NSTEMI. One year previously he underwent CCTA for typical angina, demonstrating nonobstructive CAD. ICA was performed during the NSTEMI, with PCI of the LAD (white arrow) that was adjudicated as the culprit lesion by EKG findings. The baseline CCTA precursor lesion to which the culprit was aligned exhibited 41%DS (asterisk indicates lumen in cross-section), HRP with PR, LAP, SC, and high cross-sectional plaque burden. The second OM (gray arrow) also appeared diseased at the time of the NSTEMI, but did not undergo PCI. The baseline CCTA precursor lesion to which the OM was aligned exhibited 13%DS (asterisk indicates lumen in cross-section) with PR but no other features of HRP. Compared to the OM precursor lesion, the LAD precursor lesion demonstrated longer lesion length, higher plaque volume, and a lower percentage of calcified plaque. **C**. Culprit lesion precursors exhibit elevated fibro-fatty and necrotic core volumes (31.32 ± 55.5 mm3). **D**. Within-patient controls, using the non-culprit with the highest baseline %DS, exhibit lesser total plaque and necrotic core volumes ($p < 0.05$ for both). **E**. Between-patient controls, using the lesion with the highest %DS in the control patient, exhibit lesser non-calcified plaque components (p = 0.04), but no decrease in calcified plaque volume (p = NS). ACS, acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary computed tomographic angiography; %DS, percent diameter stenosis; EKG, electrocardiogram; HRP, high-risk plaque; ICA, invasive coronary angiography; LAD, left anterior descending artery; LAP, low-attenuation plaque; NRS, napkin-ring sign; NS, nonsignificant; NSTEMI, non-ST elevation myocardial infarction; OM, obtuse marginal; PR, positive remodeling; SC, spotty calcification. (Adapted with permission from JACC Imaging).

with risk independent of CAC volume.[14] Blaha et al. observed among the same patients that multivessel CAC adds significantly to CAC for prediction of CHD and CVD events.[15] Sex-specific interpretation of atherosclerosis imaging may also be important. Among 63215 asymptomatic patients in the multicenter CAC consortium, CAC density was not independently predictive of CV mortality in women (p = 0.51), but was in men ($p < 0.001$).[16] Within CAC subgroups, women had fewer calcified lesions and vessels, but greater lesion size and plaque density compared to men. Detectable CAC was associated with 1.3-fold higher hazard for CV death among women compared to men ($p < 0.001$).

The role of serial CAC is not welldefined. Budoff et al. observed in the MESA cohort that elevated CAC progression is associated with an increased risk for future CHD events independent of baseline CAC, with an adjusted hazard ratio of 1.2 (1.0–1.9) for every 100 units annual change in CAC.[17] Lehmann et al. suggested a simpler approach with the Heinz Nixdorf Recall Study, demonstrating that the follow-up CAC on repeat scanning after 5 years was more predictive of MACE events and easier to interpret than CAC progression.[18] CAC progression is primarily useful in primary prevention patients not taking statins; patients taking statins have improved outcomes with paradoxically faster vascular calcification and decreased non-calcified plaque.[19,20] In the St. Francis Heart Study, statins reduced MACE events while increasing CAC score. Thus, statin prescription appears to decouple the link between calcification and outcomes, and CAC progression is not interpretable.

CCTA, which can visualize stenosis severity and non-calcified plaque, improves plaque imaging compared to CAC. Given the large body of primary prevention data and the historically lower radiation dose of CAC, CCTA is rated as inappropriate for primary prevention patients.[9,21] However, the incremental prognostic value of CCTA to CAC is apparent in certain subpopulations with intermediate CAC and in the elderly. For intermediate CAC, in the CONFIRM study, Cho et al. found that among 3217 asymptomatic individuals that CCTA stenosis

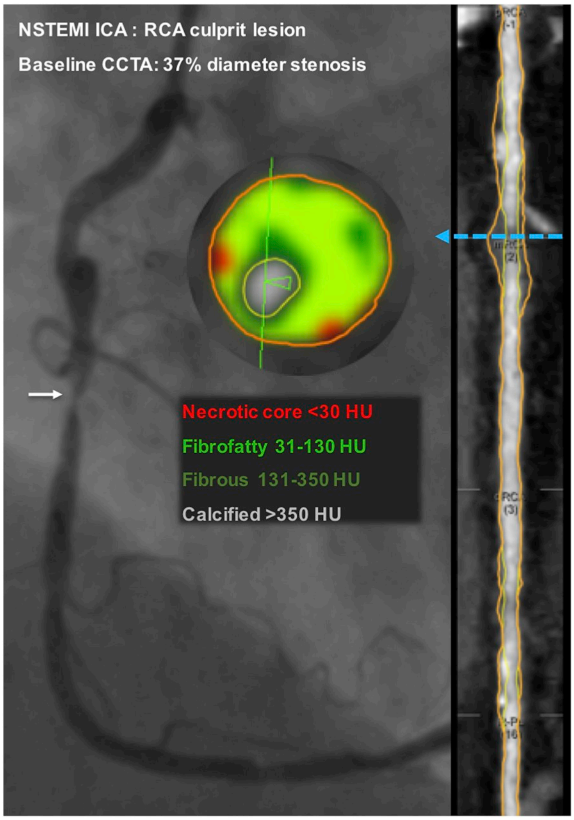

Fig. 2. 51 year old female smoker with atypical chest pain presenting to the ED. An initial troponin was normal with nonspecific EKG changes, and she underwent CCTA with multiple nonobstructive lesions with HRP. Later that day the repeat troponin became abnormal and she was referred for ICA, which revealed an RCA culprit lesion (white arrow) The CCTA precursor lesion to which the culprit was aligned exhibited 37%DS (blue arrow), HRP with PR and LAP, and no SC or NRS. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

severity provided incremental prognostic utility in individuals with CACS > 100, with an increment in area under the curve of 0.24 and NRI of 0.62 ($p < 0.001$ for all), but not among those with CACS ≤ 100 or > = 400.[22] For the elderly, Han et al. found that CCTA stenosis severity improved discrimination and reclassification beyond Framingham Risk Score and CAC only among patients in the highest tertile of age > 62. It may be that in age < 62, there are insufficient patients with CACS > 100 for significant information gain by CCTA.[23]

Additionally, CCTA allows visualization of noncalcified plaque characteristics associated with plaque rupture that cannot be observed with noncontrast CAC. Motoyama et al. initially defined atherosclerotic plaque characteristics (APCs) of unstable high-risk plaques (HRP) as positive remodeling (HU), noncalcified low-attenuation plaque (LAP) with Hounsfield unit < 30, and spotty calcification (SC).[24] Subsequently, in a single center cohort of 3158 patients, she observed that the presence of both PR and LAP in HRP predicted ACS independent of clinical risk factors and stenosis.[25] Maurovich-Horvat and colleagues additionally identified in histopathology the napkin-ring sign (NRS), which is relatively rare compare to the other APCs, correlates best to advanced fibroatheroma and strongly predicts MACE events.[26,27] Takamura et al. observed that in a consecutive cohort of 495 consecutive patients and only 9 cardiac events, the presence of PR or LAP was an independent predictor of cardiovascular events above CACS alone, with an NRI of 0.96 ($p < 0.007$).[28]

As newer scanning protocols lower CCTA radiation doses to approach those of CAC and newer tools are developed to automatically quantify non-calcified coronary plaque that may not be visualized by CAC, CCTA based atherosclerotic imaging may become more applicable to primary prevention. Future applications in primary prevention may include presence of CCTA-visualized nonobstructive plaque for risk reclassification and plaque quantification or APCs for risk prediction, or CAC to exclude low-risk older patients or diabetics that will gain insufficient benefit from aspirin. In addition, CCTA may be useful in younger patients with non-traditional risk factors and less calcification such as autoimmune disorders, gestational diabetes and preeclampsia, HIV or oncology treatment.

3. Atherosclerosis imaging in stable coronary disease

Currently, the primary clinical role of atherosclerosis imaging in stable coronary artery disease is in the use of luminal evaluation for decisions on referral to ICA, and to improve patient risk stratification for decisions on medical therapy. In the CONFIRM study, early revascularization reduces the 1-year mortality in high- and intermediate-risk, but not low-risk CAD, as determined by CCTA.[29] The severity and extent of any coronary plaque, whether obstructive or nonobstructive, is prognostically and therapeutically important. Improved preventive treatment in the CCTA arm of the SCOT-HEART trial, perhaps due to CCTA-visualized nonobstructive CAD and HRP, is attributed for the dramatic 41% reduction in 5 year MACE.[30]

The prognostic importance of HRP has been validated in several large studies of symptomatic patients, most notably in the SCOT-HEART and PROMISE randomized controlled trials. In the CCTA arm of the SCOT-HEART study, the presence of either PR or LAP increased MACE events threefold.[31] The SCOT-HEART investigators observed no incremental prognostic value for HRP or obstructive CAD above CACS in 1778 symptomatic patients.[31] Although, the CCTA was necessary to determine the primary study endpoint of angina diagnostic certainty.[31] In the CCTA arm of the PROMISE trial, high-risk plaque independently predicted MACE above and beyond ASCVD risk score and stenosis severity, particularly in patients with nonobstructive CAD.[32] This was also a stronger predictor in women and younger patients, who are more likely to exhibit nonobstructive disease.[32] Based upon this data, the Coronary Artery Disease – reporting and data system (CAD-RADS) consensus document recommends reporting of HRP inclusive of PR, LAP, SC, and NRS as a separate modifier independent of coronary artery disease severity.[33] Given the benefit of treatment for nonobstructive CAD and the particular prognostic importance of HRP in women with nonobstructive disease, it is all the more important to reduce sex disparities in treatment and prevention. In the PROMISE trial, even women with abnormal noninvasive tests were significantly less likely to receive downstream statins than men.[34]

HRP may identify features that promote plaque rupture, but non-HRP coronary plaque can lead to ACS events when HRP is obscured by calcium or other artifacts. This could be via non-rupture mechanisms of coronary thrombosis, such as plaque erosion and calcified nodule. Thus, investigators have found that simple qualitative characterization of plaque extent by the number of involved segments, or of composition as calcified, noncalcified, and mixed plaque, can be prognostically useful. Several scores incorporating qualitative plaque composition have observed the adverse effect of non-calcified and mixed plaque compared to calcified plaques, including the CONFIRM risk score and the CT-Leaman score.[35,36] Most recently, the Leiden risk score utilized the Leiden and CONFIRM cohorts to derive and validate a score inclusive of plaque extent, location, and composition.[37] They found improved discrimination when added to clinical risk factors (0.768 vs 0.742, $p = 0.001$) compared to the CADRADS classification of stenosis severity.[37] Furthermore, in the CONFIRM study, a machine learning score incorporating only the stenosis and plaque composition from a 16-segment coronary tree exhibited greater discrimination (AUC 0.771) than other scores including the Duke prognostic index, the segment stenosis score, and the CT-Leaman score (ranging from 0.685 to 0.701, $p < 0.001$ for all).[38]

Table 1
Future directions with plaque imaging in major clinical categories.

	Standard of care	Future directions with plaque imaging
Primary prevention	Agatston score as risk enhancer for ASCVD risk categories Individualized risk prediction with MESA CAC score	Improved scores for risk prediction incorporating novel CAC evaluation Risk prediction with CCTA
Stable CAD	Presence of obstructive CAD for referral to invasive coronary angiography Segment-based scores for risk assessment Presence of HRP for elevated risk	Treatment of nonobstructive coronary artery disease for risk reduction Precision risk prediction with quantitative and qualitative plaque evaluation
Acute chest pain	Absence of CAD for rapid discharge from ED	Normal hsTnI and low-risk nonobstructive, non-HRP CAD for rapid discharge from ED

Quantitative plaque imaging, a time-consuming research technique, can provide more valuable insights into stable coronary disease. Plaque burden is frequently quantified as plaque volume or as percent atheroma volume (PAV, defined as plaque volume/vessel volume congruent to the invasive vascular ultrasound literature, and also termed variously as mean plaque burden or aggregate plaque volume), and is associated with ischemia in vessel-specific ischemia.[39,40] Furthermore, the importance of individual plaque components was demonstrated in the ICONIC study, a nested case-control study within the CONFIRM cohort of 234 patients with downstream ACS compared to non-events propensity matched for CAD risk factors and CCTA-evaluated obstructive (> = 50%) CAD.[4] Over 65% of ACS patients had non-obstructive CAD at baseline, highlighting the importance of plaque evaluation, although maximal percent diameter stenosis severity was higher in cases than controls (Figure). ACS patients did not differ significantly from matched controls by total plaque, calcified, or fibrous plaque volume, but had significantly higher fibrofatty (58.7 ± 85.8 vs. 41.4 ± 62.2 mm^3, p = 0.009) and necrotic core volumes. An important measure from the PROSPECT study, the maximal cross-sectional plaque burden (defined as the plaque area over the vessel area), was also significantly higher in cases than controls (66.1 ± 25.8 vs. 56.5 ± 28.7, p < 0.001). On the other hand there was no significant difference in the mean plaque burden (also known as PAV, defined as the total plaque volume over the total vessel volume). ACS patients exhibited HRP more frequently than controls (52.1% vs 33.3%, p = 0.003), but a significant fraction of the precursor lesions did not exhibit HRP. This highlights a risk prediction gap that may improve with quantitative plaque evaluation.

Quantitative plaque evaluation also permits careful evaluation of plaque progression. In the PARADIGM multinational registry of 1335 patients who underwent serial CCTA >2 years apart, both baseline and annualized change in PAV significantly improved risk prediction for MACE.[41] Quantitative plaque evaluation also provides an explanation for the negative results of the St. Francis Heart Study. Lesions in the statin-exposed patients compared to statin-naïve patients exhibited a slower overall and noncalcified PAV progression, but faster calcified PAV progression (p < 0.001). In addition, statins were associated with a 35% reduction in HRP development.[3] As a corollary, in statin-naïve patients, CACS progression is positively associated with non-calcified plaque progression, but in statin-exposed patients, CACS progression is negatively associated with non-calcified plaque progression.[19] Thus, CCTA-visualized plaque progression of separate plaque components may be a promising tool for monitoring efficacy of therapy.[42]

In the future, APC and automated quantitative plaque imaging may be utilized to identify low-risk nonobstructive plaques that are below the risk-benefit threshold of medical therapy, and high-risk plaques (whether obstructive or not) that may exhibit ischemia and will benefit from revascularization. Serial plaque quantification may be useful in selected high-risk patients to monitor response to therapy and to reclassify risk.

4. Acute chest pain

Currently, CCTA has a class IIa, Level of Evidence B recommendation for acute chest pain with low-to-intermediate pretest likelihood of ACS and negative EKG and biomarkers.[43] CCTA exhibits a sensitivity of 95% and a specificity of 87% to detect ACS in patients with chest pain in the ED, and has been demonstrated to safely permit earlier discharge and time to diagnosis.[44] However, approximately one fifth of acute chest pain patients with ACS have nonobstructive coronary disease, so HRP is critically important for improved triage of ACS.[45]

In ROMICAT II, at least one high-risk plaque feature was present in 95% of patients with ACS and 30% without ACS (p < 0.001), and all nonobstructive ACS patients had at least one high-risk plaque. However, while approximately 2/3 of patients with ≥ 50% stenosis have ACS, only 1/5 of patients with any HRP features have ACS. Even the highest-risk HRP feature of napkin ring sign has a positive predictive value of <50%. Thus, acute chest pain patients with ≥ 50% stenoses or any high-risk plaque feature cannot be safely discharged, but should not be automatically sent to invasive coronary angiography. Plaque imaging should determine which patients should be observed for a longer duration, and ACS patients should be subsequently referred to ICA on clinical grounds. An algorithm incorporating CCTA stenosis severity and HRP with high-sensitivity cardiac troponin may safely exclude acute chest pain patients with low risk for ACS.[46] Furthermore, in a modeling exercise among acute chest pain patients eventually diagnosed as non-ACS, the presence or absence of nonobstructive CAD would result in reclassification of 14% patients for statin eligibility compare to ASCVD risk score.[47]

The time pressure for acute chest pain highlight some major challenges of plaque imaging and adoption in routine clinical practice. Plaque imaging requires excellent image quality and greater interpretation time. In addition, the interobserver variability of APCs may be a limiting feature; that of spotty calcification is quite low (kappa 0.28), while that of napkin-ring sign is quite high, at least in research cohorts (kappa 0.86)[26,48] In the future, automated plaque quantification or machine learning detection of high-risk features in ED patients may provide improved risk stratification for discharge and ICA referral.

5. Conclusions and future directions

Recent studies have highlighted the prognostic value of atherosclerosis plaque imaging with APCs and quantitative plaque composition, but trials that integrate atherosclerosis plaque imaging in therapeutic choices have not yet been performed. In current practice, we highlight the value of reporting CAC and CCTA findings according to current interpretation guidelines. For primary prevention, we emphasize the use of CAC findings as a risk enhancer for primary prevention. For stable CAD, we highlight the evaluation of HRP and qualitative CT scores in stable CAD, and the mortality benefit of medical therapy for nonobstructive CAD. For acute chest pain, we emphasize the importance of HRP evaluation in addition to stenosis severity, as the prevalence of nonobstructive CAD in ACS is not low.

In the future, important steps are needed to incorporate plaque imaging into clinical practice for maximal information gain. First, developments in automated plaque quantification, machine learning, and radiomic plaque features will reduce the time and interobserver variability of plaque evaluation. Second, incorporation of HRP and novel imaging markers into risk scores specific to asymptomatics, stable CAD and acute chest pain will allow risk-benefit analysis and shared decisionmaking. Third, trials that incorporate plaque evaluation into a treatment strategy will allow translation of imaging into action. Dramatic changes in the clinical role of atherosclerosis plaque imaging are on the horizon.

Conflicts of interest

The authors have no relevant conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2019.05.010.

References

1. Benjamin EJ, Muntner P, Alonso A, et al. American heart association council on E, prevention statistics C, stroke statistics S. Heart disease and stroke statistics-2019 update: a report from the American heart association. *Circulation.* 2019;139:e56–e66.
2. Mowatt G, Cook JA, Hillis GS, et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. *Heart.* 2008;94:1386–1393.
3. Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *JACC Cardiovasc Imaging.* 2018;11:1475–1484.
4. Chang HJ, Lin FY, Lee SE, et al. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol.* 2018;71:2511–2522.
5. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol.* 2009;54:49–57.
6. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med.* 2011;364:226–235.
7. Group ASC, Bowman L, Mafham M, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med.* 2018;379:1529–1539.
8. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2018;392:1036–1046.
9. Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. *Circulation.* 2018:CIR0000000000000625 2018.
10. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med.* 2008;358:1336–1345.
11. Hecht HS. Coronary artery calcium scanning: past, present, and future. *JACC Cardiovasc Imaging.* 2015;8:579–596.
12. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American college of cardiology/American heart association cholesterol management guidelines: MESA (Multi-Ethnic study of atherosclerosis) (vol 66, pg 1657, 2015). *J Am Coll Cardiol.* 2015;66 2686-2686.
13. McClelland RL, Jorgensen NW, Budoff M, et al. 10-Year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors derivation in the MESA (Multi-Ethnic study of atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) study and the DHS (Dallas heart study). *J Am Coll Cardiol.* 2015;66:1643–1653.
14. Criqui MH, Denenberg JO, Ix JH, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. *J Am Med Assoc.* 2014;311:271–278.
15. Blaha MJ, Budoff MJ, Tota-Maharaj R, et al. Improving the CAC score by addition of regional measures of calcium distribution: multi-ethnic study of atherosclerosis. *JACC Cardiovasc Imaging.* 2016;9:1407–1416.
16. Shaw LJ, Min JK, Nasir K, et al. Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC Consortium. *Eur Heart J.* 2018;39:3727–3735.
17. Budoff MJ, Young R, Lopez VA, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol.* 2013;61:1231–1239.
18. Lehmann N, Erbel R, Mahabadi AA, et al. Heinz Nixdorf Recall study I. Value of progression of coronary artery calcification for risk prediction of coronary and cardiovascular events: result of the HNR study (Heinz Nixdorf Recall). *Circulation.* 2018;137:665–679.
19. Lee SE, Sung JM, Andreini D, 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. *Eur Heart J Cardiovasc Imaging.* 2019. https://doi.org/10.1093/ehjci/jez022 jez022.
20. Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol.* 2005;46:166–172.
21. Taylor AJ, Cerqueira M, Hodgson JM, et al. Accf/scct/acr/aha/ase/asnc/nasci/scai/scmr 2010 appropriate use criteria for cardiac computed tomography a report of the American college of cardiology foundation appropriate use criteria task force, the society of cardiovascular computed tomography, the American college of radiology, the American heart association, the American society of echocardiography, the American society of nuclear cardiology, the north American society for cardiovascular imaging, the society for cardiovascular angiography and interventions, and the society for cardiovascular magnetic resonance. *J Am Coll Cardiol.* 2010;56:1864–1894.
22. Cho I, Chang HJ, BOH, et al. Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the COronary CT Angiography EvaluatioN for Clinical Outcomes InteRnational Multicenter (CONFIRM) study. *Eur Heart J.* 2015;36:501–508.
23. Han D, Hartaigh BO, Gransar H, et al. Incremental prognostic value of coronary computed tomography angiography over coronary calcium scoring for major adverse cardiac events in elderly asymptomatic individuals. *Eur Heart J Cardiovasc Imaging.* 2018;19:675–683.
24. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol.* 2007;50:319–326.
25. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol.* 2015;66:337–346.
26. Maurovich-Horvat P, Schlett CL, Alkadhi H, et al. The napkin-ring sign indicates advanced atherosclerotic lesions in coronary CT angiography. *JACC Cardiovasc Imaging.* 2012;5:1243–1252.
27. Feuchtner G, Kerber J, Burghard P, et al. The high-risk criteria low-attenuation plaque <60 HU and the napkin-ring sign are the most powerful predictors of MACE: a long-term follow-up study. *Eur Heart J Cardiovasc Imaging.* 2017;18:772–779.
28. Takamura K, Fujimoto S, Kondo T, et al. Incremental prognostic value of coronary computed tomography angiography: high-risk plaque characteristics in asymptomatic patients. *J Atheroscler Thromb.* 2017;24:1174–1185.
29. Schulman-Marcus J, Lin FY, Gransar H, et al. Coronary revascularization vs. medical therapy following coronary-computed tomographic angiography in patients with low-, intermediate- and high-risk coronary artery disease: results from the CONFIRM long-term registry. *Eur Heart J Cardiovasc Imaging.* 2017;18:841–848.
30. Newby DE, Adamson PD, Berry C, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med.* 2018;379:924–933.
31. Williams MC, Moss AJ, Dweck M, et al. Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-HEART study. *J Am Coll Cardiol.* 2019;73:291–301.
32. Ferencik M, Mayrhofer T, Bittner DO, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain a secondary analysis of the PROMISE randomized clinical trial. *Jama Cardiol.* 2018;3:144–152.
33. Cury RC, Abbara S, Achenbach S, et al. Coronary artery disease - reporting and data system (CAD-RADS): an expert consensus document of SCCT, ACR and NASCI: endorsed by the ACC. *JACC Cardiovasc Imaging.* 2016;9:1099–1113.
34. Pagidipati NJ, Coles A, Hemal K, et al. Sex differences in management and outcomes of patients with stable symptoms suggestive of coronary artery disease: insights from the PROMISE trial. *Am Heart J.* 2019;208:28–36.
35. Hadamitzky M, Achenbach S, Al-Mallah M, et al. Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (COronary CT Angiography EvaluatioN for Clinical Outcomes: an InteRnational Multicenter Registry). *J Am Coll Cardiol.* 2013;62:468–476.
36. Andreini D, Pontone G, Mushtaq S, et al. Long-term prognostic impact of CT-Leaman score in patients with non-obstructive CAD: results from the COronary CT Angiography EvaluatioN for clinical outcomes InteRnational multicenter (CONFIRM) study. *Int J Cardiol.* 2017;231:18–25.
37. van Rosendael AR, Shaw LJ, Xie JX, et al. Superior risk stratification with coronary computed tomography angiography using a comprehensive atherosclerotic risk score. *JACC Cardiovasc Imaging.* 2019 Jan 16. https://doi.org/10.1016/j.jcmg.2018.10.024 pii: S1936-878X(18)31036-2., [Epub ahead of print].
38. van Rosendael AR, Maliakal G, Kolli KK, et al. Maximization of the usage of coronary CTA derived plaque information using a machine learning based algorithm to improve risk stratification; insights from the CONFIRM registry. *J Cardiovasc Comput Tomogr.* 2018;12:204–209.
39. Nakazato R, Shalev A, Doh JH, et al. Aggregate plaque volume by coronary computed tomography angiography is superior and incremental to luminal narrowing for diagnosis of ischemic lesions of intermediate stenosis severity. *J Am Coll Cardiol.* 2013;62:460–467.
40. Driessen RS, Stuijfzand WJ, Raijmakers PG, et al. Effect of plaque burden and morphology on myocardial blood flow and fractional flow reserve. *J Am Coll Cardiol.* 2018;71:499–509.

41. Lee SE, Sung JM, Rizvi A, et al. Quantification of coronary atherosclerosis in the assessment of coronary artery disease. *Circ-Cardiovasc Imag.* 2018;11.
42. Lo J, Lu MT, Ihenachor EJ, et al. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet HIV*. 2015;2:e52–63.
43. Taylor. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography: a Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance (vol 122, pg e525, 2010). *Circulation.* 2010;122:E642–E643.
44. Samad Z, Hakeem A, Mahmood SS, et al. A meta-analysis and systematic review of computed tomography angiography as a diagnostic triage tool for patients with chest pain presenting to the emergency department. *J Nucl Cardiol.* 2012;19:364–376.
45. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain results from the ROMICAT-II trial. *J Am Coll Cardiol.* 2014;64:684–692.
46. Ferencik M, Liu T, Mayrhofer T, et al. Hs-troponin I followed by CT angiography improves acute coronary syndrome risk stratification accuracy and work-up in acute chest pain patients: results from ROMICAT II trial. *JACC Cardiovasc Imaging.* 2015;8:1272–1281.
47. Emami H, Takx RAP, Mayrhofer T, et al. Nonobstructive coronary artery disease by coronary CT angiography improves risk stratification and allocation of statin therapy. *Jacc-Cardiovasc Imag.* 2017;10:1031–1038.
48. de Knegt MC, Linde JJ, Fuchs A, et al. Reproducibility of coronary atherosclerotic plaque characteristics in populations with low, intermediate, and high prevalence of coronary artery disease by multidetector computer tomography: a guide to reliable visual coronary plaque assessments. *Int J Cardiovasc Imaging.* 2016;32:1555–1566.