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Emerging Role of Coronary Computed Tomography Angiography in Lipid-Lowering Therapy: a Bridge to Image-Guided Personalized Medicine

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Abstract

Purpose of Review To summarize the current status of coronary computed tomography angiography (CTA) in the assessment of coronary plaques and discuss the ability of serial coronary CTA to quantitatively measure changes in the plaque burden in response to lipid-lowering therapy.

Recent Findings Recent advances in coronary CTA have allowed identification of high-risk coronary features in acute coronary syndrome and measurement of changes in the coronary plaque burden with good reproducibility. Statin therapy may delay plaque progression and change some plaque features. However, the clinical relevance of quantitative changes in coronary plaques and the optimal methods to reduce the plaque burden remain unclear.

Summary Despite guideline-directed lipid-lowering therapy, adverse events still occur in substantial numbers of patients receiving statins. Coronary CTA is noninvasive and has high diagnostic performance in patients with coronary artery disease, making change in the plaque burden an applicable biomarker for individualized assessment of future risk.

Keywords Coronary artery disease · Coronary computed tomography angiography · Statin · Plaque · Lipid · Atherosclerosis

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Introduction

Cardiovascular disease is the leading cause of death and disability worldwide [1]. Lowering of the low-density lipoprotein cholesterol concentration with statins has been shown to decrease the incidence of primary and secondary cardiovascular events, possibly through the stabilization and regression of atherosclerotic plaques [2–4]. However, despite optimal guideline-directed medical therapy, many patients develop cardiovascular events in individual cases [5]. There is a need to identify further treatment that is suited to the individual and not only based on conventional atherosclerotic risk factors.

Considerable evidence from clinical trials using serial coronary intravascular ultrasound (IVUS) suggests that statin therapy can ameliorate the progression of coronary plaques and even induce disease regression [6, 7]. However, IVUS requires an invasive approach and is not suitable for patients with low to moderate cardiovascular risk. Recent advances in coronary computed tomography angiography (CTA) technology have allowed for the noninvasive assessment of coronary artery disease (CAD) with high diagnostic performance [8, 9]. Coronary CTA has emerged as a potential alternative to invasive angiography in many circumstances, facilitating evaluation of the degree of coronary stenosis and characterization of coronary plaques [10]. There is now increasing interest in and continuing debate on the potential role of coronary CTA as a noninvasive method for assessing CAD, identifying nonobstructive lesions with features of plaque vulnerability, defining the prognosis of low- to moderate-risk patients, and guiding therapeutic interventions. Direct visualization of disease progression or regression by serial coronary CTA has the potential to identify these patients and provide personalized risk assessment.

Accordingly, direct visualization of coronary plaques by coronary CTA has the potential to identify an individual patient's personal risks and evaluate progression or regression of plaque burden in individual cases (Fig. 1). In the present paper, we review the current status of coronary CTA in the qualitative and quantitative assessment of coronary plaques and discuss the ability of serial coronary CTA to quantitatively measure changes in the plaque burden in response to lipid-lowering therapy. Furthermore, considering adverse cardiovascular events still occur in a significant number of patients receiving statins, we discuss the role of coronary CTA as a biomarker for personalized risk assessment and therapy.

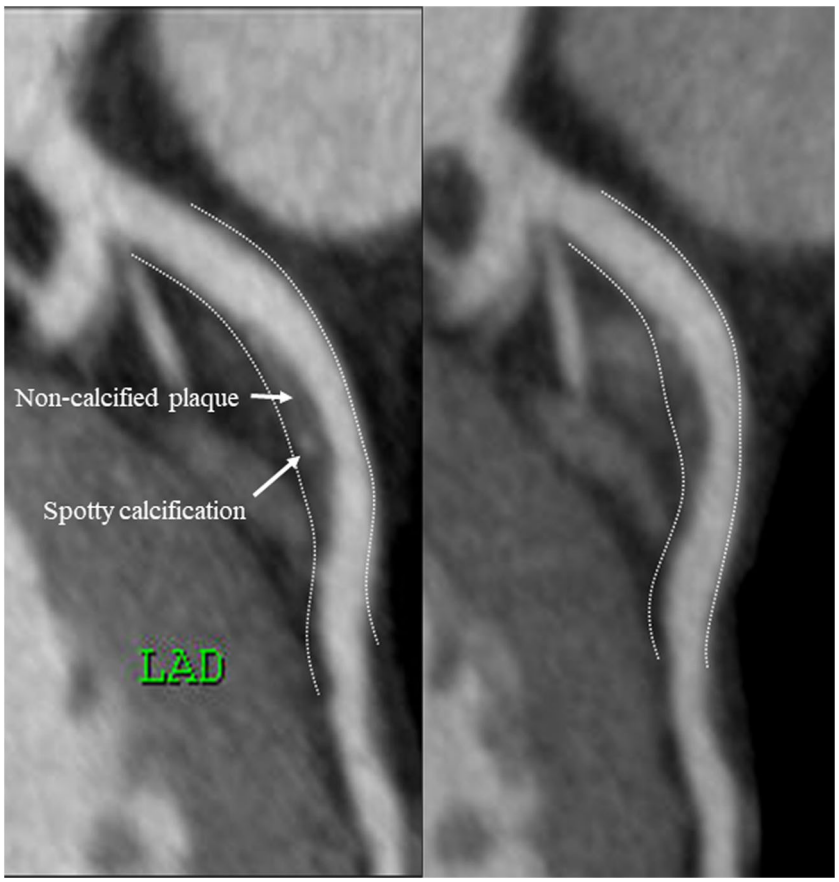

Fig. 1 A case of plaque regression by statin therapy with serial coronary computed tomography angiography (CTA) findings. **a** At baseline, coronary CTA shows a noncalcified plaque and spotty calcification in the mid-proximal left anterior descending artery (LAD). **b** One year after intensive statin therapy, spotty calcification was not found in the same area

Plaque Assessment by Coronary CTA

Significance of High-Risk Features of Coronary Plaques

A high-risk coronary artery plaque is considered to be at risk of becoming a culprit lesion that causes acute coronary syndrome, and high-risk patients with such plaque morphology may be directed toward more potent local and systemic approaches to preventive treatment. Invasive coronary angiography defines the vessel lumen with high quality, but it does not show the amount and composition of plaques. IVUS is one of the most widely used invasive imaging modalities for plaque evaluation and quantification [11]. In patients with high-risk plaques, IVUS can reliably assess the plaque burden, positive remodeling, and the presence of a necrotic core and calcifications [12, 13]. Coronary CTA also reportedly allows for evaluation of plaque characteristics [14]. The presence and size of the necrotic core, which is a key high-risk feature, can be assessed by grading the tissue in Hounsfield units (HU) [15].

Imaging by coronary CTA has been extensively compared with that by IVUS and became a reality after demonstration of a good correlation with virtual histology [16, 17]. Some plaque characteristics on coronary CTA have been implicated as signs of plaque vulnerability: low-attenuation plaques (< 30 HU), the napkin-ring sign (a low-attenuation core surrounded by a rim of relatively high attenuation), positive remodeling (remodeling index; lesion plaque area/reference area ratio of ≥ 1.1), and spotty calcifications (< 3 mm) [18, 19]. The recent CAD-RADS guideline of the Society of Cardiovascular Computed Tomography defines a vulnerable plaque as a plaque that clearly demonstrates two or more of these features by coronary CTA [20]. All of these plaque characteristics have been revealed as significant and independent predictors of cardiovascular events in multiple studies [21–23]. A study with a long-term follow-up (almost 100 months) confirmed lower cumulative hard cardiac event-free survival in patients with at least one coronary plaque with two or more high-risk characteristics when compared with patients with no lesion with more than one high-risk plaque characteristic (70% vs. 93%, respectively; log rank $p < 0.0001$) [24]. In the PROMISE study, adverse plaques (positive remodeling, low-attenuation plaques, or the napkin-ring sign) were associated with an increased risk of death, myocardial infarction, or hospitalization for unstable angina at 2 years (hazard ratio, 2.73; 95% confidence interval, 1.89–3.93) [25]. In the SCOT-HEART study, which comprised 1769 subjects with suspected CAD followed over a median duration of 4.7 years, showed that adverse coronary plaque characteristics (defined as positive remodeling or low-attenuation plaques) were significantly associated with the incidence of coronary heart disease or nonfatal myocardial infarction (hazard ratio, 3.01; 95% confidence interval, 1.61–5.63; $p = 0.001$) [26]. To date, only a few studies have focused on the impact of serial changes in plaque features on cardiovascular outcomes [25–27]. In a recent cohort study of 268 patients with stable angina, serial coronary CTA revealed that the progression of the lipid-rich plaque volume and total plaque volume were independent predictors of major adverse cardiac events (MACE) [25].

Several studies using invasive intracoronary imaging such as IVUS and optical coherence tomography revealed changes in plaque composition with a possible stabilizing effect of statin therapy [35–38]; however, the response of plaque components to statin therapy is still being debated. In previous studies, IVUS has shown normalization of the remodeling index at the lesion site [28], reduction in the fibro-fatty lesion content and necrotic core [29], increased calcification, and resolution of pathological intimal thickening lesions [30, 31]. In contrast, other studies have revealed no significant reduction of the necrotic core using IVUS after statin therapy [32, 33]. Coronary CTA may be considered an effective tool with which to determine plaque burden progression or response to medical therapies. Several studies have been performed to investigate the effect of statin treatment on the change in plaque components using serial coronary CTA examinations [34, 35]. A limitation of coronary CTA is the relatively poor soft tissue contrast, which makes it difficult to further subclassify noncalcified subcomponents (i.e., fibrous versus fatty components) based only on HU attenuation [36]. Whether the plaque volume and characteristics as measured by coronary CTA can be widely used in clinical practice requires more extensive prospective validation.

Quantitative Measurement of Coronary Plaque Burden

In the assessment of CAD, the quantification of coronary plaques by IVUS is a strong predictor of future events [37, 38]. It is an accepted surrogate marker for the effect of lipid-lowering therapy if measured with IVUS. Most clinical trials evaluated the change in the percent atheroma volume, which is the normalized quantity of plaque. The percent plaque volume changes linearly, but it is relatively weakly correlated with the post-treatment low-density lipoprotein cholesterol level [39]. A meta-analysis demonstrated that the reduction of the percent plaque volume is strongly associated with a lower incidence of myocardial infarction or revascularization as well as MACE. Thus, IVUS has been considered the clinical reference standard. However, IVUS characteristics are difficult to generalize because the results were derived from patients referred for cardiac catheterization, and such patients are an apparently high-risk population. Coronary CTA can also quantify the plaque burden. The noncalcified plaque burden by coronary CTA is associated with future cardiovascular events. In one study, the quantity of noncalcified plaque in nonobstructive lesions in a cohort of patients with non-ST

segment myocardial infarction was associated with recurrent acute coronary syndrome events in a multivariate analysis, while the coronary artery calcification (CAC) score and calcified plaque burden provided no additional predictive value [40]. Another cohort of 2748 patients without a history of CAD demonstrated that the total plaque volume as well as the noncalcified and low-density plaque volumes predicted cardiac death within 5 years of follow-up [41•].

To quantify the plaque burden with coronary CTA, the vessel wall boundaries must be delineated manually or automatically. Because manual assessment is labor-intensive and can be affected by reader experience, several commercial software tools for automated plaque assessment have been developed. The current fully automated coronary CTA-based plaque volume quantification technique shows an excellent correlation with IVUS [17, 42]. Coronary CTA with same-vendor follow-up has good scan–rescan reproducibility, suggesting a role of coronary CTA in monitoring the response of coronary artery plaques to therapy [26].

Change in Plaque Burden as Shown by Serial CTA

Previous studies have shown that coronary CTA can facilitate observation and quantification of the change in the plaque burden over time [25, 34, 35, 43–55] (Table 1). Similarly, in a small cohort of 32 patients, treatment with fluvastatin resulted in a reduction in plaque quantity and a decrease in the necrotic core volume in high-risk areas as evaluated by coronary CTA [34]. In a retrospective study of 100 patients with known CAD referred for coronary CTA, 60 patients treated with statins showed a reduction in the noncalcified plaque volume after approximately 1 year but no change in the calcified plaque volume [49]. A multicenter prospective observational study showed the change in the plaque volume in response to different statins. Patients with baseline mild noncalcified coronary plaque on coronary CTA were divided into two groups according to the statin protocol undertaken [intensive statin therapy ($n = 55$), moderate statin therapy ($n = 85$), and no statin therapy ($n = 66$)]. The study results confirmed that statin therapy can delay progression and even induce plaque regression of mild noncalcified coronary plaque. Another study also demonstrated that the low-attenuation plaque volume, total plaque volume, and percent plaque volume showed significant regression among patients undergoing intensive statin therapy compared with patients undergoing no statin therapy [50]. In a recent large prospective cohort of 1255 patients (474 statin-naïve and 781 statin-taking patients), statin-taking patients displayed a lower rate of overall percent atheroma volume progression than statin-naïve patients (1.76% vs. 2.04% per year, respectively; $p < 0.002$) [55]. Further, the annual incidence of new high-risk plaque features was lower in lesions among statin-taking patients (0.9% vs. 1.6% per year, respectively; $p < 0.001$). Limited data from prospective randomized trials regarding the effect of statin use on specific plaque components and the plaque burden are available to date. In a randomized trial utilizing serial coronary CTA in 37 human immunodeficiency virus-infected patients with a measured outcome of plaque regression [35], remarkable changes in plaque size were observed using coronary CTA (change of + 18.2% in the placebo group versus − 4.7% in the atorvastatin group for the lesion total plaque volume in 1 year). Notably, the noncalcified plaque regressed by 19.4% in the atorvastatin group. Another prospective randomized trial of 140 patients with acute myocardial infarction with a measured outcome of change in plaque components demonstrated that intensive lipid-lowering therapy had not decreased the necrotic core volume or fibro-fatty volume by the 12-month follow-up [54]. A recent meta-analysis confirmed that these initial studies using coronary CTA showed a greater decrease in the noncalcified plaque volume than the calcified plaque volume by intensive statin therapy [56•]. The ability of coronary CTA to quantify changes in coronary atherosclerosis over time in response to therapy has the potential to improve our understanding of the significance of plaque changes in each individual.

However, special resolution of coronary CTA is less than that of IVUS despite the use of the latest generation CT scanners. In addition, the reproducibility of coronary CTA was reported to be less than that of IVUS, especially when different CT vendors were used [25–27]. Therefore, clinical trial designed to evaluate plaque progression/regression by coronary CT needs a larger sample size than that by IVUS. In addition, based on the 2010 Appropriateness Use Criteria for Cardiac Computed Tomography, repeat CTA in asymptomatic patients with stable symptoms with prior CTA results is broadly considered inappropriate [57]. The potential issue of repeat CTA is radiation exposure. Although radiation exposure from coronary CTA has been considerably reduced by almost 80% over the last 10 years [58], it is still concerning, and routine serial coronary CTA to assess noncalcified plaques or track atherosclerosis or stenosis for monitoring the therapeutic efficacy of medical interventions should not be recommended in the present clinical situation.

Clinical Relevance of CAC Score

Cardiac CT can also provide information on the CAC score, which is strongly associated with cardiovascular events. A cohort study demonstrated that the combination of the CAC score with traditional risk factors significantly improved risk prediction over prior models [59•], and a CAC score of 0 is one of the best predictors of low cardiovascular risk [60]. Data from the Multi-Ethnic Study of Atherosclerosis (MESA),

Table 1 Serial coronary CTA studies quantifying the plaque burden

Authors	Design	Year	Population	Time interval (months)	n	Main findings
Burgstahler et al.	Prospective, observational	2007	Elevated CAD risk	16	27	Noncalcified plaque volume decreased by 24%
Schmid et al.	Retrospective, observational	2008	Suspected CAD	17	50	Annualized total plaque volume increased by 22%
Lehman et al.	Prospective, observational	2009	Chest pain	24	69	Noncalcified plaque volume increased (3.1% to 4.4%), but calcified plaque volume did not
Tardif et al.	Prospective, randomized	2010	ACS	6	191	Noncalcified plaque volume: placebo, 6% increase and VIA-2291, − 4.9% decrease
Inoue et al.	Prospective, observational	2010	Suspected CAD	12	32	Total plaque volume: − 17.2% by fluvastatin
Hoffmann et al.	Retrospective, observational	2010	Suspected CAD	25	63	Noncalcified plaque volume increased by 38%
Papadopoulou et al.	Prospective, observational	2012	ACS	39	32	Plaque volume increased by 6.7%
Zeb et al.	Retrospective, observational	2013	Suspected CAD	13	100	Noncalcified plaque volume: statin use, − 28.7% and non-statin use, + 10.0%
Lo et al.	Prospective, randomized	2015	HIV	12	37	Plaque volume: placebo, + 18.2% and atorvastatin, − 4.7%
Auscher et al.	Prospective, randomized	2015	AMI	12	140	Percent atheroma volume: intensive care, − 0.4% and usual care, − 0.6%. No decrease in necrotic core volume
Li et al.	Prospective, observational	2016	Plaque present on CTA	18	206	Intensive statin treatment and low-attenuation plaque decrease
Nakanishi et al.	Retrospective, observational	2016	Plaque present on CTA	41	142	Normalized total plaque volume: patients with DM, 52.8 mm^3 and patients without DM, 118.3 mm^3
Shin et al.	Retrospective, observational	2017	Plaque present on CTA	38	147	Association between LDL-C of < 70 mg/dl and slowed plaque progression
Tamarappoo et al.	Retrospective, observational	2018	Plaque present on CTA	42	116	Association between LDL-C reduction and noncalcified plaque regression
Lee et al.	Prospective, observational	2018	Suspected or known CAD	45	1255	Percent atheroma volume progression: statin-taking, 1.76% per year and statin-naïve, 2.04% per year
Gu et al.	Retrospective, observational	2018	Stable CAD	22	268	0.24% increase in total plaque burden: − 0.8% in no-MACE group and 6.6% in MACE group

CTA, computed tomography angiography; *LDL-C*, low-density lipoprotein cholesterol; *CAD*, coronary artery disease; *ACS*, acute coronary syndrome; *HIV*, human immunodeficiency virus; *AMI*, acute myocardial infarction; *CM*, diabetes mellitus; *MACE*, major adverse cardiac events

which involved 5600 men and women, demonstrated that patients with a CAC score of 0 are not likely to benefit from statin therapy because of the very low event rate [61]. The latest American College of Cardiology/American Heart Association (ACC/AHA) Clinical Practice Guidelines on the Management of Blood Cholesterol stated that in primary prevention, a CAC score of 0 is useful for reclassifying patients to a lower risk group, often allowing statin therapy to be withheld or postponed unless higher-risk conditions are present [62]. In contrast, individuals with a higher CAC score need more aggressive treatment for cardiovascular risk factors. In the 2018 ACC/AHA guidelines, a CAC score of > 100 or the 75th percentile for age and sex were considered high-risk factors, and statin therapy was recommended in individuals at intermediate ASCVD risk of 7.5% to 19.9% [63]. The CAC score itself can robustly identify individuals who might benefit from anti-atherosclerotic therapies.

CAC progression is also important for predicting future cardiovascular events. Several studies have consistently demonstrated that an increase in CAC is associated with a 4- to 7-fold increase in cardiovascular events, independent of the baseline CAC score, cardiovascular risk factors, and demographic variables [64–66]. However, the changes in CAC need to be interpreted with caution. Recent clinical studies

have focused on each component of the CAC score, including the calcified plaque area and calcium density. The presence of dense calcified plaque showed a significant association with a lower risk of cardiovascular events than the presence of calcified plaque with low CT density [67]. High-intensity statin treatment could consistently increase densely calcified plaques as shown in IVUS and CTA studies [68], suggesting that the traditional CAC score could potentially increase with statin therapy. Thus, the result of serial CAC score measurements should be interpreted according to the use of statins. Considering the lack of consistent evidence of the ability to regress in response to therapy, the performance of serial CAC score measurements currently seems to have a minimal role in evaluating the therapeutic response or change in atherosclerotic disease over time.

Limitations and Future Development of Coronary CTA for Personalized Lipid-Lowering Therapy

The current appropriate ACC/AHA criteria for detection and risk assessment of a stable CAD state that CAC measurement and coronary CTA may be appropriate in asymptomatic patients with high global risk [69]. Among asymptomatic individuals, diabetes mellitus (DM) may be a category in which coronary CTA could be useful for further risk stratification because patients with DM are at very high risk. Whether coronary CTA could be appropriate for cardiovascular risk assessment in asymptomatic patients with DM is currently undergoing active debate. A recent investigation showed the long-term prognostic value of coronary CTA in 591 asymptomatic patients with type 2 DM [70]. Approximately one-sixth of patients had obstructive CAD in the left main or proximal left anterior descending artery and high-risk lesions that were consistently associated with the majority of cardiac events during the 6-year follow-up [70]. In a cohort study, coronary CTA findings were incremental for the prediction of MACE in asymptomatic individuals with DM beyond conventional risk factors and the CAC score, allowing for improved risk stratification [71]. Another study of 517 consecutive asymptomatic patients demonstrated that the extent and severity of CAD as determined by coronary CTA independently predicted an increased risk of MACE beyond traditional risk factors [72]. These results suggest the possibility of using CTA to identify subgroups of patients with high-risk features and the potential for CTA to improve the prognosis through aggressive treatment such as lipid-lowering therapy in asymptomatic patients with DM. Meanwhile, the FACTOR-64 study, a randomized controlled trial that followed 900 asymptomatic patients with DM, demonstrated that screening these patients with coronary CTA did not reduce all-cause mortality and nonfatal myocardial infarction at 4 years versus optimal DM care [73]. Coronary CTA screening led to more aggressive risk factor modification in 70% of patients, including improvements in statin use and more aggressive treatment of lipids, blood pressure, and glucose control; however, there was no significant reduction in cardiovascular events [73]. Further longer-term follow-up studies in this area are warranted.

Several issues need to be addressed before coronary CTA is used for personalized medicine. First, prospective randomized trials are necessary to evaluate appropriate statin dosing for plaque regression as well as hard cardiovascular outcomes. Second, qualitative and quantitative assessment must be further improved. Fully automated analysis software is not in widespread use. Third, coronary CTA provides detailed information regarding coronary plaques but not the functional significance of CAD. Fractional flow reserve derived from CT (FFR-CT) was recently introduced in the clinical setting [74, 75]. FFR-CT is derived from routinely obtained anatomic images (acquired at rest only) and subsequent mathematically simulated hyperemia without the need for vasodilator administration. No data regarding the impact of lipid-lowering therapy on FFR-CT are available.

Conclusions

Large numbers of clinical trials have demonstrated the great benefit of lipid-lowering therapy on primary and secondary prevention of cardiovascular diseases. However, despite guideline-directed medical therapy, adverse events still occur in a substantial number of patients receiving statins. No biomarkers with which to identify these patients are yet available. The noncalcified plaque burden as measured by IVUS is independently associated with cardiac outcomes, making the change in the plaque burden a potentially applicable biomarker for personalized risk assessment. Recent advances in coronary CTA technology can allow for the measurement of changes in the noncalcified coronary plaque burden and high-risk plaque features. The clinical relevance of quantitative changes in coronary plaques has not been established, and the lack of optimal methods with which to reduce the plaque burden is a problem that remains to be solved. Further research in this field could help physicians to incorporate personalized medicine into clinical treatment.

Compliance with Ethical Standards

Conflict of Interest Toru Miyoshi, Kazuhiro Osawa, Keishi Ichikawa, Kazuki Suruga, Takashi Miki, Masashi Yoshida, Koji Nakagawa, Hironobu Toda, Kazufumi Nakamura, Hiroshi Morita, and Hiroshi Ito declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Collaborators GBDD. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2019;393:1958–72. https://doi.org/10.1016/S0140-6736(19)30041-8.
2. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383–9.
3. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301–7. https://doi.org/10.1056/NEJM199511163332001.
4. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713–22. https://doi.org/10.1056/NEJMoa1615664.
5. Writing Group M, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Executive summary: heart disease and stroke statistics–2016 update: a report from the American Heart Association. Circulation. 2016;133(4):447–54. https://doi.org/10.1161/CIR.0000000000000366.
6. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med. 2011;365(22):2078–87. https://doi.org/10.1056/NEJMoa1110874.
7. Stegman B, Shao M, Nicholls SJ, Elshazly M, Cho L, King P, et al. Coronary atheroma progression rates in men and women following high-intensity statin therapy: a pooled analysis of reversal, asteroid and saturn. Atherosclerosis. 2016;254:78–84. https://doi.org/10.1016/j.atherosclerosis.2016.09.059.
8. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med. 2008;359(22):2324–36. https://doi.org/10.1056/NEJMoa0806576.
9. Doh JH, Koo BK, Nam CW, Kim JH, Min JK, Nakazato R, et al. Diagnostic value of coronary CT angiography in comparison with invasive coronary angiography and intravascular ultrasound in patients with intermediate coronary artery stenosis: results from the prospective multicentre FIGURE-OUT (Functional Imaging criteria for GUiding REview of invasive coronary angiOgraphy, intravascular Ultrasound, and coronary computed Tomographic angiography) study. Eur Heart J Cardiovasc Imaging. 2014;15(8):870–7. https://doi.org/10.1093/ehjci/jeu009.
10. Xie JX, Cury RC, Leipsic J, Crim MT, Berman DS, Gransar H, et al. The coronary artery disease-reporting and data system (CAD-RADS): prognostic and clinical implications associated with standardized coronary computed tomography angiography reporting. JACC Cardiovasc Imaging. 2018;11(1):78–89. https://doi.org/10.1016/j.jcmg.2017.08.026.
11. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364(3):226–35. https://doi.org/10.1056/NEJMoa1002358.
12. Stone PH, Saito S, Takahashi S, Makita Y, Nakamura S, Kawasaki T, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION study. Circulation. 2012;126(2):172–81. https://doi.org/10.1161/CIRCULATIONAHA.112.096438.
13. Cheng JM, Garcia-Garcia HM, de Boer SP, Kardys I, Heo JH, Akkerhuis KM, et al. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the ATHEROREMO-IVUS study. Eur Heart J. 2014;35(10):639–47. https://doi.org/10.1093/eurheartj/eht484.
14. Rodriguez-Granillo GA, Carrascosa P, Bruining N, Waksman R, Garcia-Garcia HM. Defining the non-vulnerable and vulnerable patients with computed tomography coronary angiography: evaluation of atherosclerotic plaque burden and composition. Eur Heart J Cardiovasc Imaging. 2016;17(5):481–91. https://doi.org/10.1093/ehjci/jew012.
15. Choi BJ, Kang DK, Tahk SJ, Choi SY, Yoon MH, Lim HS, et al. Comparison of 64-slice multidetector computed tomography with spectral analysis of intravascular ultrasound backscatter signals for characterizations of noncalcified coronary arterial plaques. Am J Cardiol. 2008;102(8):988–93. https://doi.org/10.1016/j.amjcard.2008.05.060.
16. Fischer C, Hulten E, Belur P, Smith R, Voros S, Villines TC. Coronary CT angiography versus intravascular ultrasound for estimation of coronary stenosis and atherosclerotic plaque burden: a meta-analysis. J Cardiovasc Comput Tomogr. 2013;7(4):256–66. https://doi.org/10.1016/j.jcct.2013.08.006.
17. Park HB, Lee BK, Shin S, Heo R, Arsanjani R, Kitslaar PH, et al. Clinical feasibility of 3D automated coronary atherosclerotic plaque quantification algorithm on coronary computed tomography angiography: comparison with intravascular ultrasound. Eur Radiol. 2015;25(10):3073–83. https://doi.org/10.1007/s00330-015-3698-z.
18. Kashiwagi M, Tanaka A, Kitabata H, Tsujioka H, Kataiwa H, Komukai K, et al. Feasibility of noninvasive assessment of thin-cap fibroatheroma by multidetector computed tomography. JACC Cardiovasc Imaging. 2009;2(12):1412–9. https://doi.org/10.1016/j.jcmg.2009.09.012.
19. Thomsen C, Abdulla J. Characteristics of high-risk coronary plaques identified by computed tomographic angiography and associated prognosis: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging. 2016;17(2):120–9. https://doi.org/10.1093/ehjci/jev325.
20. Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ, et al. CAD-RADS(TM) Coronary Artery Disease - Reporting and Data System. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the north American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology. J Cardiovasc Comput Tomogr. 2016;10(4):269–81. https://doi.org/10.1016/j.jcct.2016.04.005.
21. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol. 2009;54(1):49–57. https://doi.org/10.1016/j.jacc.2009.02.068.
22. Otsuka K, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshikawa J, et al. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. JACC Cardiovasc Imaging. 2013;6(4):448–57. https://doi.org/10.1016/j.jcmg.2012.09.016.
23. Halon DA, Lavi I, Barnett-Griness O, Rubinshtein R, Zafrir B, Azencot M, et al. Plaque morphology as predictor of late plaque events in patients with asymptomatic type 2 diabetes: a long-term observational study. JACC Cardiovasc Imaging. 2018. https://doi.org/10.1016/j.jcmg.2018.02.025.
24. Conte E, Annoni A, Pontone G, Mushtaq S, Guglielmo M, Baggiano A, et al. Evaluation of coronary plaque characteristics with coronary computed tomography angiography in patients with

non-obstructive coronary artery disease: a long-term follow-up study. Eur Heart J Cardiovasc Imaging. 2017;18(10):1170–8. https://doi.org/10.1093/ehjci/jew200.

25. Jensen LO, Thayssen P, Pedersen KE, Stender S, Haghfelt T. Low variation and high reproducibility in plaque volume with intravascular ultrasound. Int J Cardiol. 2004;97(3):463–9. https://doi.org/10.1016/j.ijcard.2003.10.036.
26. Symons R, Morris JZ, Wu CO, Pourmorteza A, Ahlman MA, Lima JA, et al. Coronary CT angiography: variability of CT scanners and readers in measurement of plaque volume. Radiology. 2016;281(3):737–48. https://doi.org/10.1148/radiol.2016161670.
27. Hagenaars T, Gussenhoven EJ, van Essen JA, Seelen J, Honkoop J, van der Lugt A. Reproducibility of volumetric quantification in intravascular ultrasound images. Ultrasound Med Biol. 2000;26(3):367–74.
28. Takayama T, Hiro T, Ueda Y, Saito S, Kodama K, Komatsu S, et al. Remodeling pattern is related to the degree of coronary plaque regression induced by pitavastatin: a sub-analysis of the TOGETHAR trial with intravascular ultrasound and coronary angioscopy. Heart Vessel. 2015;30(2):169–76. https://doi.org/10.1007/s00380-014-0468-9.
29. Egede R, Jensen LO, Hansen HS, Hansen KN, Junker A, Thayssen P. Influence of high-dose lipid lowering treatment compared to low-dose lipid lowering treatment on plaque composition assessed by intravascular ultrasound virtual histology in patients with ST-segment elevation acute myocardial infarction: the VIRHISTAMI trial. EuroIntervention. 2013;8(10):1182–9. https://doi.org/10.4244/EIJV8I10A182.
30. Puri R, Libby P, Nissen SE, Wolski K, Ballantyne CM, Barter PJ, et al. Long-term effects of maximally intensive statin therapy on changes in coronary atheroma composition: insights from SATURN. Eur Heart J Cardiovasc Imaging. 2014;15(4):380–8. https://doi.org/10.1093/ehjci/jet251.
31. Raber L, Taniwaki M, Zaugg S, Kelbaek H, Roffi M, Holmvang L, et al. Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study. Eur Heart J. 2015;36(8):490–500. https://doi.org/10.1093/eurheartj/ehu373.
32. Nozue T, Yamamoto S, Tohyama S, Fukui K, Umezawa S, Onishi Y, et al. Comparison of change in coronary atherosclerosis in patients with stable versus unstable angina pectoris receiving statin therapy (from the treatment with statin on atheroma regression evaluated by Intravascular Ultrasound With Virtual Histology [TRUTH] study). Am J Cardiol. 2013;111(7):923–9. https://doi.org/10.1016/j.amjcard.2012.12.008.
33. Kini AS, Baber U, Kovacic JC, Limaye A, Ali ZA, Sweeny J, et al. Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). J Am Coll Cardiol. 2013;62(1):21–9. https://doi.org/10.1016/j.jacc.2013.03.058.
34. Inoue K, Motoyama S, Sarai M, Sato T, Harigaya H, Hara T, et al. Serial coronary CT angiography-verified changes in plaque characteristics as an end point: evaluation of effect of statin intervention. JACC Cardiovasc Imaging. 2010;3(7):691–8. https://doi.org/10.1016/j.jcmg.2010.04.011.
35. Lo J, Lu MT, Ihenachor EJ, Wei J, Looby SE, Fitch KV, 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(2):e52–63. https://doi.org/10.1016/S2352-3018(14)00032-0.
36. van der Giessen AG, Toepker MH, Donelly PM, Bamberg F, Schlett CL, Raffle C, et al. Reproducibility, accuracy, and predictors of accuracy for the detection of coronary atherosclerotic plaque composition by computed tomography: an ex vivo comparison to intravascular ultrasound. Investig Radiol. 2010;45(11):693–701. https://doi.org/10.1097/RLI.0b013e3181e0a541.
37. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol. 2010;55(21):2399–407. https://doi.org/10.1016/j.jacc.2010.02.026.
38. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364(3):226–35. https://doi.org/10.1056/NEJMoa1002358.
39. Ridker PM, Mora S, Rose L. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. Eur Heart J. 2016;37(17):1373–9. https://doi.org/10.1093/eurheartj/ehw046.
40. Kristensen TS, Kofoed KF, Kuhl JT, Nielsen WB, Nielsen MB, Kelbaek H. Prognostic implications of nonobstructive coronary plaques in patients with non-ST-segment elevation myocardial infarction: a multidetector computed tomography study. J Am Coll Cardiol. 2011;58(5):502–9. https://doi.org/10.1016/j.jacc.2011.01.058.
41.• Hell MM, Motwani M, Otaki Y, Cadet S, Gransar H, Miranda-Peats R, et al. Quantitative global plaque characteristics from coronary computed tomography angiography for the prediction of future cardiac mortality during long-term follow-up. Eur Heart J Cardiovasc Imaging. 2017;18(12):1331–9. https://doi.org/10.1093/ehjci/jex183 This study was the largest cohort that ingestigated the impact of quantitaitve plaque characteristics on cardiac mortality.
42. Sheahan M, Ma X, Paik D, Obuchowski NA, St Pierre S, Newman WP 3rd, et al. Atherosclerotic plaque tissue: noninvasive quantitative assessment of characteristics with software-aided measurements from conventional CT angiography. Radiology. 2018;286(2):622–31. https://doi.org/10.1148/radiol.2017170127.
43. Burgstahler C, Reimann A, Beck T, Kuettner A, Baumann D, Heuschmid M, et al. Influence of a lipid-lowering therapy on calcified and noncalcified coronary plaques monitored by multislice detector computed tomography: results of the New Age II Pilot Study. Investig Radiol. 2007;42(3):189–95. https://doi.org/10.1097/01.rli.0000254408.96355.85.
44. Schmid M, Achenbach S, Ropers D, Komatsu S, Ropers U, Daniel WG, et al. Assessment of changes in non-calcified atherosclerotic plaque volume in the left main and left anterior descending coronary arteries over time by 64-slice computed tomography. Am J Cardiol. 2008;101(5):579–84. https://doi.org/10.1016/j.amjcard.2007.10.016.
45. Lehman SJ, Schlett CL, Bamberg F, Lee H, Donnelly P, Shturman L, et al. Assessment of coronary plaque progression in coronary computed tomography angiography using a semiquantitative score. J Am Coll Cardiol Img. 2009;2(11):1262–70. https://doi.org/10.1016/j.jcmg.2009.07.007.
46. Tardif JC, L'Allier PL, Ibrahim R, Gregoire JC, Nozza A, Cossette M, et al. Treatment with 5-lipoxygenase inhibitor VIA-2291 (Atreleuton) in patients with recent acute coronary syndrome. Circ Cardiovasc Imaging. 2010;3(3):298–307. https://doi.org/10.1161/CIRCIMAGING.110.937169.
47. Hoffmann H, Frieler K, Schlattmann P, Hamm B, Dewey M. Influence of statin treatment on coronary atherosclerosis visualised using multidetector computed tomography. Eur Radiol. 2010;20(12):2824–33. https://doi.org/10.1007/s00330-010-1880-x.
48. Papadopoulou SL, Neefjes LA, Garcia-Garcia HM, Flu WJ, Rossi A, Dharampal AS, et al. Natural history of coronary atherosclerosis by multislice computed tomography. JACC Cardiovasc Imaging. 2012;5(3 Suppl):S28–37. https://doi.org/10.1016/j.jcmg.2012.01.009.
49. Zeb I, Li D, Nasir K, Malpeso J, Batool A, Flores F, et al. Effect of statin treatment on coronary plaque progression - a serial coronary CT angiography study. Atherosclerosis. 2013;231(2):198–204. https://doi.org/10.1016/j.atherosclerosis.2013.08.019.

50. Li Z, Hou Z, Yin W, Liu K, Gao Y, Xu H, et al. Effects of statin therapy on progression of mild noncalcified coronary plaque assessed by serial coronary computed tomography angiography: a multicenter prospective study. Am Heart J. 2016;180:29–38. https://doi.org/10.1016/j.ahj.2016.06.023.
51. Shin S, Park HB, Chang HJ, Arsanjani R, Min JK, Kim YJ, et al. Impact of intensive LDL cholesterol lowering on coronary artery atherosclerosis progression: a serial CT angiography study. JACC Cardiovasc Imaging. 2017;10(4):437–46. https://doi.org/10.1016/j.jcmg.2016.04.013.
52. Nakanishi R, Ceponiene I, Osawa K, Luo Y, Kanisawa M, Megowan N, et al. Plaque progression assessed by a novel semi-automated quantitative plaque software on coronary computed tomography angiography between diabetes and non-diabetes patients: a propensity-score matching study. Atherosclerosis. 2016;255:73–9. https://doi.org/10.1016/j.atherosclerosis.2016.11.004.
53. Tamarappoo B, Otaki Y, Doris M, Arnson Y, Gransar H, Hayes S, et al. Improvement in LDL is associated with decrease in non-calcified plaque volume on coronary CTA as measured by automated quantitative software. J Cardiovasc Comput Tomogr. 2018;12(5):385–90. https://doi.org/10.1016/j.jcct.2018.05.004.
54. Auscher S, Heinsen L, Nieman K, Vinther KH, Logstrup B, Moller JE, et al. Effects of intensive lipid-lowering therapy on coronary plaques composition in patients with acute myocardial infarction: assessment with serial coronary CT angiography. Atherosclerosis. 2015;241(2):579–87. https://doi.org/10.1016/j.atherosclerosis.2015.06.007.
55. Lee SE, Chang HJ, Sung JM, Park HB, Heo R, Rizvi A, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. J Am Coll Cardiol Img. 2018;11(10):1475–84. https://doi.org/10.1016/j.jcmg.2018.04.015.
56.• Andelius L, Mortensen MB, Norgaard BL, Abdulla J. Impact of statin therapy on coronary plaque burden and composition assessed by coronary computed tomographic angiography: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging. 2018;19(8):850–8. https://doi.org/10.1093/ehjci/jey012 This study was a meta-analysis showing the effect of statin therapy on plaque volume and compostion.
57. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, 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 Cardiovasc Comput Tomogr. 2010;4(6):407.e1–33. https://doi.org/10.1016/j.jcct.2010.11.001.
58. Stocker TJ, Deseive S, Leipsic J, Hadamitzky M, Chen MY, Rubinshtein R, et al. Reduction in radiation exposure in cardiovascular computed tomography imaging: results from the PROspective multicenter registry on radiaTion dose estimates of cardiac CT angIOgraphy iN daily practice in 2017 (PROTECTION VI). Eur Heart J. 2018;39(41):3715–23. https://doi.org/10.1093/eurheartj/ehy546.
59.• McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, 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(15):1643–53. https://doi.org/10.1016/j.jacc.2015.08.035 This study demonstrated the posible role of coronary atery calcification in optimizing patients to whom statins would benefit the most.
60. Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the multi-ethnic study of atherosclerosis (MESA). Circulation. 2016;133(9):849–58. https://doi.org/10.1161/CIRCULATIONAHA.115.018524.
61. Mortensen MB, Falk E, Li D, Nasir K, Blaha MJ, Sandfort V, et al. Statin trials, cardiovascular events, and coronary artery calcification: implications for a trial-based approach to statin therapy in MESA. JACC Cardiovasc Imaging. 2018;11(2 Pt 1):221–30. https://doi.org/10.1016/j.jcmg.2017.01.029.
62. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol. 2018. https://doi.org/10.1016/j.jacc.2018.11.003.
63. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary. Circulation. 2018. https://doi.org/10.1161/CIR.0000000000000624.
64. Budoff MJ, Tayek J. Coronary artery calcium progression: increasing CAC is associated with increased events. JACC Cardiovasc Imaging. 2018;11(3):517–8. https://doi.org/10.1016/j.jcmg.2018.01.014.
65. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (multi-ethnic study of atherosclerosis). J Am Coll Cardiol. 2013;61(12):1231–9. https://doi.org/10.1016/j.jacc.2012.12.035.
66. Budoff MJ, Hokanson JE, Nasir K, Shaw LJ, Kinney GL, Chow D, et al. Progression of coronary artery calcium predicts all-cause mortality. JACC Cardiovasc Imaging. 2010;3(12):1229–36. https://doi.org/10.1016/j.jcmg.2010.08.018.
67. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA. 2014;311(3):271–8. https://doi.org/10.1001/jama.2013.282535.
68. Ferencik M, Chatzizisis YS. Statins and the coronary plaque calcium "paradox": insights from non-invasive and invasive imaging. Atherosclerosis. 2015;241(2):783–5. https://doi.org/10.1016/j.atherosclerosis.2015.05.021.
69. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014;63(4):380–406. https://doi.org/10.1016/j.jacc.2013.11.009.
70. Kang SH, Park GM, Lee SW, Yun SC, Kim YH, Cho YR, et al. Long-term prognostic value of coronary CT angiography in asymptomatic type 2 diabetes mellitus. JACC Cardiovasc Imaging. 2016;9(11):1292–300. https://doi.org/10.1016/j.jcmg.2016.01.040.
71. Min JK, Labounty TM, Gomez MJ, Achenbach S, Al-Mallah M, Budoff MJ, et al. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. Atherosclerosis. 2014;232(2):298–304. https://doi.org/10.1016/j.atherosclerosis.2013.09.025.

72. Kim JJ, Hwang BH, Choi IJ, Choo EH, Lim S, Kim JK, et al. Impact of diabetes duration on the extent and severity of coronary atheroma burden and long-term clinical outcome in asymptomatic type 2 diabetic patients: evaluation by coronary CT angiography. Eur Heart J Cardiovasc Imaging. 2015;16(10):1065–73. https://doi.org/10.1093/ehjci/jev106.
73. Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, Knight S, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. JAMA. 2014;312(21):2234–43. https://doi.org/10.1001/jama.2014.15825.
74. Miyoshi T, Osawa K, Ito H, Kanazawa S, Kimura T, Shiomi H, et al. Non-invasive computed fractional flow reserve from computed tomography (CT) for diagnosing coronary artery disease - Japanese results from NXT trial (analysis of coronary blood flow using CT angiography: next steps). Circ J. 2015;79(2):406–12. https://doi.org/10.1253/circj.CJ-14-1051.
75. Nakanishi R, Budoff MJ. Noninvasive FFR derived from coronary CT angiography in the management of coronary artery disease: technology and clinical update. Vasc Health Risk Manag. 2016;12:269–78. https://doi.org/10.2147/VHRM.S79632.