J Cardiovasc Imaging. 2021 Oct;29(4):301-315
https://doi.org/10.4250/jcvi.2021.0016
pISSN 2586-7210·eISSN 2586-7296

Journal of Cardiovascular Imaging JCVI

Review Article

Check for updates

Current Progress of Studies of Coronary CT for Risk Prediction of Major Adverse Cardiovascular Event (MACE)

Jianan Zheng, MD, and Bin Lu, MD

Department of Radiology, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

OPEN ACCESS

Received: Jan 24, 2021
Revised: May 16, 2021
Accepted: May 31, 2021

Address for Correspondence:
Bin Lu, MD
Department of Radiology, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No.167 North Lishi Road, Xicheng District, Beijing 100037, China.
E-mail: blu@vip.sina.com

ORCID iDs
Jianan Zheng
https://orcid.org/0000-0002-7518-9675
Bin Lu
https://orcid.org/0000-0002-1744-7584

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Writing - original draft: Zheng J; Writing - review & editing: Lu B.

ABSTRACT

Cardiovascular disease is a serious threat to human health, and early risk prediction of major adverse cardiovascular event in people suspected of coronary heart disease can help guide prevention and clinical decisions. Coronary computed tomography (CT) is a useful imaging tool for evaluation of coronary heart disease, and its ability to reflect coronary atherosclerosis shows potential value for risk prediction. In recent years, various new techniques and studies of coronary CT have emerged for risk prediction of major adverse cardiovascular event in people suspected of coronary heart disease. We will review the background and current study advances of using coronary artery calcium score, coronary CT angiography, and artificial intelligence in this field.

Keywords: Coronary artery disease; Computed tomography angiography; Prognosis

INTRODUCTION

Cardiovascular disease, which mainly includes coronary heart disease (CHD) and stroke, is the leading cause of death worldwide.[1] Several clinical guidelines and expert consensus recommend risk assessment of major adverse cardiovascular event (MACE) in people suspected of CHD to guide primary prevention and clinical decisions through risk stratification. Coronary computed tomography (CT) is a widely used noninvasive imaging tool for evaluation and management of CHD in clinical practice, serving as a "gatekeeper" before invasive coronary angiography (ICA). In recent years, in addition to traditional risk factors, advances in the studies of coronary artery calcification score (CACS) and the anatomical and functional parameters of coronary CT angiography (CCTA) have provided new potential value for risk prediction of MACE. We will review the research background and current advances of CACS and CCTA anatomical and functional studies, as well as the application of artificial intelligence (AI) in this field (**Table 1**).

Journal of Cardiovascular Imaging JCVI

Table 1. Individual study breakdown of MACE prediction

Study type	Author	Year	Follow-up time (median, yrs)	Population	No. of participants	MACE						
						Total (%)	Cardiovascular death	Non-fatal MI	Stroke	Unstable angina	Hospitalization for heart failure	Revascularization (> 90 days)
CAC	Budoff et al.[2]	2018	11.1	Free of clinical cardiovascular disease	6,814	500 (7.3)	95	217	188	NR	NR	NR
	Kavousi et al.[7]*	2016	7.0–11.6	Women with 10-year ASCVD risk lower than 7.5%	6,739	165 (2.4)	29	64	72	NR	NR	NR
Stenosis	Bittner et al.[23]	2019	2.1	Stable outpatients with chest pain	3,840	91 (2.4)	29	16	NR	46	NR	NR
Plaque	Yoon et al.[27]	2020	4.0	Stroke patients without previous cardiac disease or chest pain	1,418	108 (7.6)	34	17	NR	12	11	34
	Feuchtner et al.[29]	2017	7.8	Unknown CAD and low-to-intermediate PTP	1,469	41 (2.8)	7	32	NR	2	NR	NR
	Nadjiri et al.[30]	2016	5.7	Suspected CAD	1,168	46 (3.9)†	6	9	NR	3	NR	36
	Ferencik et al.[31]	2018	2.1	Stable symptomatic outpatients without known CAD	4,415	102 (2.3)	31	24	NR	47	NR	NR
	Senoner et al.[32]	2020	10.6	Unknown CAD and low-to-intermediate ASCVD risk	1,430	57 (3.9)	25	32	NR	NR	NR	NR
CT-score	Suh et al.[42]	2015	3.8	Suspected CAD	339	30 (8.8)†	9	1	NR	6	NR	19
CTP	Nakamura et al.[49]	2018	2.5	Suspected CAD	332	19 (5.7)	2	3	NR	7	7	NR
CT-FFR	Ihdayhid et al.[51]	2019	4.7	Suspected CAD	206	20 (9.7)†	NR	3	NR	NR	NR	19‡

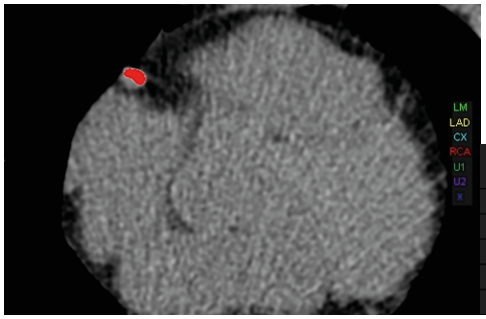
ASCVD: atherosclerotic cardiovascular disease, CAC: coronary artery calcium, CAD: coronary artery disease, CT: computed tomography, CT-FFR: computed tomography-derived fractional flow reserve, CTP: computed tomography perfusion, MACE: major adverse cardiovascular event, MI: myocardial infarction, NR: not reported, PTP: pre-test probability.
*Represents a meta-analysis study; †Some patients had both late revascularization and another endpoint; ‡The definition of unplanned revascularization in this study is any subsequent revascularization occurring at a minimum of 6 weeks after index invasive coronary angiography.

CACS

CACS is a widely used and studied imaging marker that correlates with overall coronary atherosclerosis burden and is an independent predictor of risk of MACE.[2] The CT quantification methods of coronary artery calcification are the Agatston score, volume score, and mass score. The most commonly used method is the Agatston score, which calculates the overall score of all calcified lesions on the coronary arteries. The Agatston score is derived by multiplying the calcified area by an assigned value based on the density of the calcified lesion (> 130 hounsfield unit [HU]), which is obtained commonly from CT plain scan images (**Figure 1**).

CACS has been validated to have predictive value for MACE. In the Multi-Ethnic Study of Atherosclerosis, Budoff et al.[2] found that CACS had a strong gradient association with 10-year risk of incident atherosclerotic cardiovascular disease (ASCVD) events independent of standard risk factors. Furthermore, the rates of events were less than 5% in those with CACS = 0, over 7.5% in those with CACS ≥ 100, and increased with CACS category regardless of age, gender, and ethnicity. The investigators also estimated a 14% relative increase in risk of events for each doubling of CACS. A meta-analysis[3] including 34,041 patients from 19 observational studies demonstrated that increased levels of CACS were significantly and independently associated with increased risk of MACE among stable and symptomatic patients suspected of CHD. In addition to the traditional risk factors, adding CACS to the risk prediction model can improve the predictive power and optimize risk stratification of the target population.[4][5] In particular,

https://doi.org/10.4250/jcvi.2021.0016



	Lesion	Volume/ mm³	Mass/ mg	Agatston score
LM	0	0.0	0.00	0.0
LAD	0	0.0	0.00	0.0
CX	0	0.0	0.00	0.0
RCA	2	272.4	81.31	342.1
Total	2	272.4	81.31	342.1

Figure 1. CACS calculation. The patient had 2 calcified lesions in the RCA, and the Agatston score was 342.1. Also visible are the results of volume score and mass score.
CACS: coronary artery calcification score, CX: circumflex, LAD: left anterior descending; LM: left main, RCA: right coronary artery.

CACS = 0 had a strong negative predictive value and significantly downward-shifted the risk stratification of cardiovascular disease events.[6] A meta-analysis[7] showed that CACS = 0 was associated with a decreased risk of incident ASCVD among women at low ASCVD risk and modestly improved prognostic accuracy compared with traditional risk factors. In the Heinz Nixdorf Recall study, Lehmann et al.[8] demonstrated that progression of CACS was associated with coronary and cardiovascular events. In the study, after re-scanning for CACS at an average of 5.1 years after baseline scan, participants with double-zero CACS had a lower risk of events compared with those with incident coronary artery calcification. When CACS progressed from 1–399 to ≥ 400, risk of coronary and total cardiovascular events was nearly two-fold higher compared with those whose CACS values remained < 400. Based on extensive studies on the prediction value of CACS for MACE, 2019 American College of Cardiology/American Heart Association Guidelines on the Primary Prevention of Cardiovascular Disease referred to CACS as a Class IIa recommendation in adults at intermediate risk (≥ 7.5% to < 20% 10-year ASCVD risk) or select adults at borderline risk (5% to < 7.5% 10-year ASCVD risk) to guide the clinician-patient risk discussion.[9]

In addition, as a proven independent predictor of MACE, CACS can guide primary prevention. A systematic review and meta-analysis by Gupta et al.[10] showed that initiation or continuation of pharmacological and lifestyle therapies was higher in individuals with nonzero CACS than in those with CACS = 0 for prevention of cardiovascular disease. Also, some studies demonstrated that CACS had value for allocation of aspirin and guidance of therapeutic decisions of antihypertension treatment in certain populations.[11][12] It is beneficial to develop tools including CACS and clinical risk factors to guide primary prevention for reducing CHD and MACE.

Approximately 30 years have passed since Agatston first proposed the concept of CACS. Although CACS, mainly represented by the Agatston score, has been validated widely and used in practice, the discussion of CACS continues. Increase of coronary artery calcification density is considered the manifestation of the late stage of coronary artery atherosclerotic plaque development toward stabilization, which is reflected in the increased value on coronary CT. However, the Agatston score increases with increase in calcification density, which seems inconsistent with the pathophysiological progression of coronary artery atherosclerosis plaques from an unstable stage to a stable stage. It has been shown that coronary artery calcification density was associated negatively with risk of MACE at all levels of coronary artery calcification volume.[13] In particular, the 1K plaque (CT attenuation > 1,000

https://doi.org/10.4250/jcvi.2021.0016

Journal of Cardiovascular Imaging JCVI

HU) was associated with lower risk of future acute coronary syndrome,[14] which suggests that the effect of density in evaluating coronary artery calcification should be considered. In addition, the regional distribution of coronary artery calcification, such as being "diffuse" and located in the left main coronary artery, was associated with risk of MACE.[15][16] Therefore, the Agatston score can be used to construct a new CACS system integrated with calcification density, volume, distribution, and vulnerable plaque characteristics to better reflect the overall coronary artery plaque burden and to further improve the predictive ability.

CCTA ANATOMICAL ANALYSIS

Luminal stenosis

Coronary artery luminal stenosis is a strong predictor of risk of MACE, and it is the primary basis for defining obstructive CHD on CCTA and for clinical decisions on primary prevention and further treatment strategies. The evaluation of coronary artery luminal stenosis includes severity, extent, and location of stenosis. Early studies showed that number of vessels with ≥ 50% and ≥ 70% stenosis as well as left main and proximal left anterior descending artery stenosis were predictors of all-cause mortality in patients with chest pain (all $p < 0.0001$).[17] However, risk stratification of the target population based simply on location or severity of a single stenosis cannot satisfy subsequent clinical needs, so many researchers have proposed more refined categories considering the severity and distribution of coronary artery luminal stenosis.

In the Prospective Multicenter Imaging Study for Evaluation of Chest Pain, Hoffmann et al.[18] categorized patients with stable chest pain according to CCTA as severely abnormal (≥ 70% stenosis in 2 major vessels or ≥ 50% left main stenosis or ≥ 70% proximal left anterior descending stenosis), moderately abnormal (≥ 70% stenosis in 1 major vessel), mildly abnormal (1%–69% stenosis in any major vessel or < 50% left main stenosis), or normal (absence of coronary atherosclerosis). The MACE rates (including cardiovascular death, myocardial infarction, and unstable angina) for severely abnormal, moderately abnormal, mildly abnormal, and normal were 9.77%, 6.72%, 2.32%, and 0.53%, respectively, and the respective hazard ratios (HRs) were 17.26, 12.03, and 4.08. Notably, about 52% of the patients in the study who suffered a MACE were mildly abnormal on baseline CCTA. One of the advantages of CCTA over functional tests is early detection of coronary artery atherosclerotic lesions in the nonobstructive CHD stage, providing the possibility of early risk stratification for the target population by CCTA. In addition, segment involvement score (SIS) and segment stenosis score (SSS), which are based on the severity and distribution of coronary artery luminal stenosis, can reflect the overall burden of coronary artery plaque burden on individuals and provide predictive value for all-cause mortality or MACE in people suspected of CHD.[17][19-21] SIS is the number of segments with plaque (0–16 points). SSS is based on the severity of stenosis in each of the 16 coronary artery segments, with normal, mild, moderate, and severe stenosis assigned a score of 0–3, and the scores across the 16 segments being summed (0–48 points).[17] To facilitate and standardize reporting of CHD on CCTA, the Society of Cardiovascular Computed Tomography, the American College of Radiology, and the North American Society for Cardiovascular Imaging established the Coronary Artery Disease Reporting and Data System (CAD-RADS) in 2016[22] (**Figure 2**). CAD-RADS provided higher discrimination than traditional stenosis-based assessments and added incremental prognostic value beyond ASCVD risk score and CACS.[23] In addition to prediction of MACE by CCTA baseline scan, dynamic observation of progression of coronary artery luminal stenosis by repeat CCTA also provided prognostic value. A retrospective study by Gu et al.[24] showed

https://doi.org/10.4250/jcvi.2021.0016

Journal of Cardiovascular Imaging JCVI

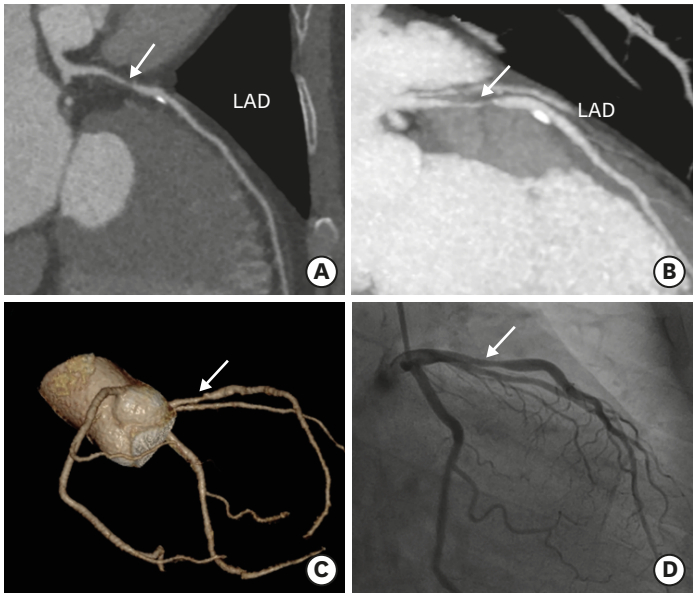


Figure 2. CAD-RADS 4A. The patient was a 38-year-old male with precordial distress for 2 weeks. CCTA showed a focal non-calcified plaque in the proximal LAD (arrow) with 70%–99% diameter stenosis; (A) Curved planar reformation, (B) maximum intensity projection, (C) volume rendering. The left main, LCX, and RCA were unremarkable. Invasive coronary angiography confirmed 70%–99% stenosis in the proximal LAD (arrow) (D). CAD-RADS: Coronary Artery Disease Reporting and Data System, CCTA: coronary computed tomography angiography, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery.

that patients with progressive coronary artery stenosis had a significantly higher incidence of MACE than those without (all $p < 0.05$), and coronary artery luminal stenosis was an independent predictor of MACE (HR, 4.327; $p < 0.001$).

Whether coronary artery luminal stenosis is an independent predictor of MACE was investigated by Mortensen et al.[25] in Denmark. Analyzing the results after a median of 4.3 years of follow-up for 23,759 symptomatic patients, they found that the events rate positively correlated with CACS and number of vessels with obstructive disease. However, when they further stratified CACS into 5 groups, patients with obstructive CHD did not show a higher risk of events compared to those with nonobstructive CHD in most subgroups. The results of this study suggested that coronary artery plaque burden, as represented by CACS in this study, is a better predictor of adverse events than is luminal stenosis; in other words, nonobstructive CHD patients with comparable plaque burden have a similar risk of adverse events to those with obstructive CHD. Thus, the mechanisms behind coronary artery luminal stenosis and its predictive value for risk of MACE deserve further research, and the existing paradigm of CHD risk might be challenged. Furthermore, additional sub-population studies are needed.

Plaque characteristics

With the development of CT software and hardware technology, the imaging quality of CCTA has improved, and CCTA can now not only assess coronary artery luminal stenosis, but also observe and quantitatively analyze characteristics of coronary artery atherosclerotic plaque (**Figure 3**). Tesche et al.[26] retrospectively evaluated some quantitative markers derived from CCTA and found that MACE-related lesions had higher median total plaque volume, non-calcified plaque volume, and plaque burden; greater lesion length; and a higher prevalence of napkin-ring sign (all $p < 0.05$). In addition, plaque burden (plaque burden = [plaque area/vessel area] × 100%) had predictive value for MACE both on a per-patient level ($p = 0.0002$)

https://doi.org/10.4250/jcvi.2021.0016

Journal of Cardiovascular Imaging JCVI

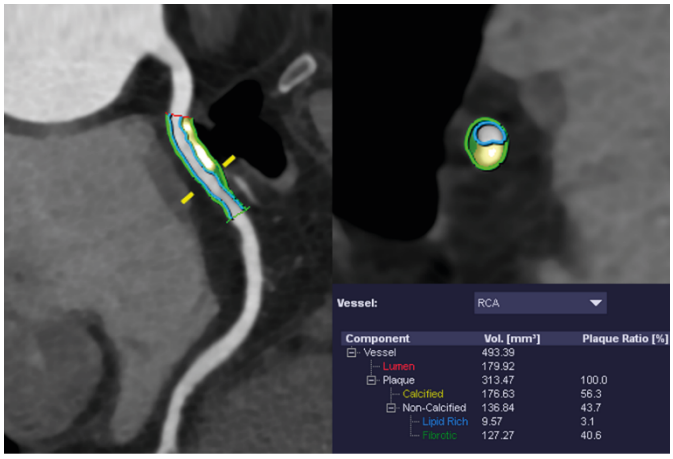


Figure 3. Plaque composition analysis. Yellow represents the calcified component of the plaque. Green represents the fibrotic component of the plaque. Blue represents the lipid-rich component of the plaque (not shown).

and on a per-lesion level (p = 0.018). Yoon et al.[27] further demonstrated that combining plaque type (high-risk, non-calcified, mixed, or calcified plaques) with the existing prediction model significantly improved reclassification and discrimination of the model.

At the same time, the concept of "vulnerable plaque" or "high-risk plaque" has come to the forefront with advances in CHD pathology and medical imaging (especially intracoronary imaging). Vulnerable plaques are prone to rupture or erosion leading to vascular thrombosis and can trigger acute coronary artery events, which are pathologically characterized by a large necrotic or lipid core, thin fibrous cap, macrophage infiltration, etc. On CCTA, vulnerable plaque characteristics include low-attenuation plaque, positive remodeling, napkin-ring sign, and spotty calcium pattern of calcification (**Figure 4**). Previous studies respectively showed that low-attenuation plaque, napkin-ring sign, and positive remodeling were predictors of MACE[28-32] and can have potential value for further risk stratification in people with nonobstructive CHD.[31][33] However, attempts to predict MACE by identifying a single vulnerable plaque through intracoronary imaging have been controversial.[34][35] In addition to

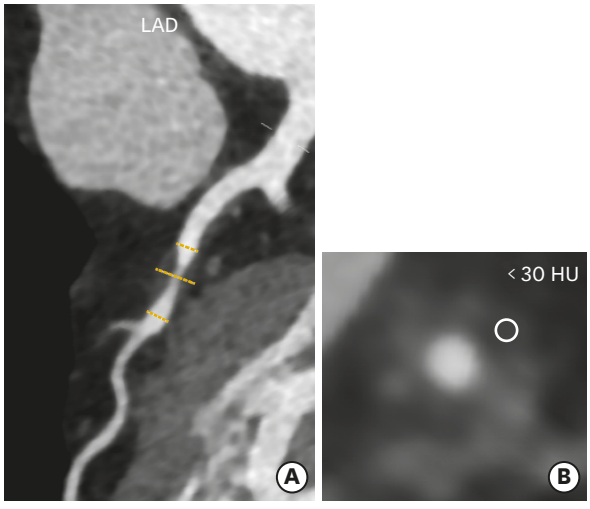


Figure 4. Vulnerable plaque. The patient was a 55-year-old female with chest distress and dyspnea for one month. CCTA showed a vulnerable plaque in the proximal LAD with positive remodeling (A) and low-attenuation plaque (B). CCTA: coronary computed tomography angiography, LAD: left anterior descending artery.

https://doi.org/10.4250/jcvi.2021.0016

Journal of Cardiovascular Imaging JCVI

plaque rupture and erosion, the occurrence of acute coronary artery events is accompanied by a series of complex processes such as thrombosis and activation of the fibrinolytic system, plaque healing, etc. The rupture or erosion of a single vulnerable plaque does not necessarily lead to an acute coronary artery event, and plaque rupture and healing were common in the coronary arteries of both patients with stable angina and patients with acute coronary syndrome.[36] A study by Motoyama et al.[37] showed that, although CCTA-verified high-risk plaque (positive remodeling with remodeling index ≥ 1.1), low-attenuation plaque (≤ 30 HU), and plaque progression were predictors of acute coronary syndrome, the cumulative number of patients who developed acute coronary syndromes among those with high-risk plaques was similar to that of those without high-risk plaques. In this study, the transformation between high-risk plaque and non-high-risk plaque was detected by short-interval serial CCTA. Therefore, one of the advantages of CCTA over intracoronary imaging techniques such as optical coherence tomography and intravascular ultrasound is the ability to evaluate atherosclerosis of the coronary artery tree on an overall level, and CCTA also provides semi-quantitative or quantitative measures of plaque characteristics and overall plaque burden, allowing for systematic evaluation of obstructive or nonobstructive CHD to predict the risk of MACE. For example, a study from the multicenter Scottish Computed Tomography of the HEART trial[38] showed that low-attenuation plaque burden detected by CCTA was the strongest predictor of fatal or nonfatal myocardial infarction, independent of clinical cardiovascular risk score, CACS, and coronary artery area stenosis. In addition, patients with low-attenuation plaque burden > 4% were nearly 5 times more likely to have myocardial infarction (HR, 4.65; 95% confidence interval [CI], 2.06–10.5; $p < 0.001$). It further demonstrated the predictive value of CCTA for combined evaluation of plaque characteristics and plaque burden.

Comprehensive score of coronary CT parameters

According to the large number of studies on the predictive value of coronary CT in evaluating luminal stenosis and plaque for risk prediction of MACE, various scoring systems combining coronary CT parameters have emerged. For example, the computed tomography-adapted Leaman score (CT_LeSc) is a CT scoring system that integrates the location and severity of coronary artery luminal stenosis with plaque composition to better reflect individual atherosclerotic plaque burden, which was shown to be a long-term independent predictor of hard cardiac events (cardiac death and nonfatal myocardial infarction). Event-free survival in nonobstructive CHD patients with high CT_LeSc (78.6%) was similar to that in obstructive CHD patients with high CT_LeSc (76.5%).[39] In addition, the COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter (CONFIRM) study combined the existing clinical cardiovascular risk National Cholesterol Education Program Adult Treatment Panel III score with coronary CT parameters (number of proximal segments containing calcified or mixed plaques and number of proximal segments containing a stenosis with > 50% luminal obstruction) to establish the CONFIRM score. When validated in the cohort with a 5-year follow-up, the CONFIRM score significantly improved the long-term prediction of all-cause mortality over clinical risk scores.[40] The Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score was originally an angiographic score to quantify the complexity of CHD; it has value in predicting MACE in patients with varying extents of CHD[41] and can be estimated by CCTA. Suh et al.[42] demonstrated that the CT-based SYNTAX score had no significant difference in integrated area under the curve compared with the ICA-based SYNTAX score and can be a useful method for predicting MACE, especially in patients with complex CHD. With further study on coronary CT parameters, selection and integration of coronary CT-related predictors including CACS, luminal stenosis, and plaque characteristics might better reflect coronary artery atherosclerotic plaque burden.

https://doi.org/10.4250/jcvi.2021.0016

Journal of Cardiovascular Imaging JCVI

Furthermore, establishment and optimization of the scoring system by integrating clinical risk factors could yield a greater value of coronary CT for risk prediction of MACE.

Other anatomical indicators

In addition to evaluation of coronary artery luminal stenosis and atherosclerotic plaque, several other anatomical indicators on coronary CT have been found to provide value in risk prediction of MACE. In a study published in the Lancet in 2018, Oikonomou's team proposed a new imaging marker, the fat attenuation index (FAI).[43] It was developed based on the change of perivascular fat attenuation on CCTA due to coronary inflammation, which is closely related to progression of coronary artery atherosclerosis. Therefore, FAI is an imaging marker reflecting vascular inflammation during progression of coronary artery atherosclerosis. The study also demonstrated that perivascular FAI improved cardiac risk prediction and re-stratification over the current state-of-the-art assessment on CCTA, and the high perivascular FAI value (cutoff ≥ –70.1HU) was an indicator of increased cardiac mortality and could guide primary and secondary prevention in the target population. Also, several studies reported that other anatomical indicators on coronary CT, such as left ventricular mass, left ventricular index, epicardial adipose tissue volume, and thoracic aortic calcification, could provide value in risk prediction of MACE.[44][45]

CCTA FUNCTIONAL IMAGING

In addition to the advances in CCTA anatomical evaluation of the coronary artery, CCTA has been developing for functional evaluation of CHD and mainly includes myocardial CT perfusion (CTP) imaging and CT-derived fractional flow reserve (CT-FFR). These two techniques, combined with coronary CT anatomical evaluation, are expected to provide a one-stop comprehensive evaluation of patients for both cardiac anatomy and function, motivating a new era of coronary CT based on anatomical plus functional diagnosis and management.

CTP

CTP is a technique used to evaluate myocardial perfusion to obtain functional information of the myocardium to determine the presence of myocardial ischemia or myocardial infarction (**Figure 5**). The techniques of CTP include static CTP and dynamic CTP. Static CTP is mainly used for qualitative or semi-quantitative diagnosis, which is simpler technically and has a lower radiation dose. The CORE320 multicenter study evaluating stress static CTP showed that combined CCTA and CTP predicted 2-year MACE, late MACE, and event-free survival similarly to ICA and single-photon emission CT.[46] Dynamic CTP involves several scans under contrast flow from the coronary artery into the myocardium, so it obtains multiple data sets to create time attenuation curves and quantitative parameters, such as myocardial blood flow, to evaluate myocardial perfusion. Several studies showed that myocardial blood flow or related quantitative parameters obtained by stress dynamic CTP provided incremental prognostic value beyond that of anatomical stenosis on coronary CT and clinical risk factors.[47][48] Abnormal perfusion demonstrated by dynamic CTP was significantly associated with hazards for MACE (HR, 5.7; 95% CI, 1.9–16.9; p = 0.002) in obstructive CHD patients, and the addition of stress dynamic CTP to CCTA optimized risk stratification in people with suspected CHD and improved the risk prediction of MACE.[47] In addition, stress dynamic CTP combined with CT delayed enhancement could better identify myocardial scarring and

https://doi.org/10.4250/jcvi.2021.0016

Journal of Cardiovascular Imaging JCVI

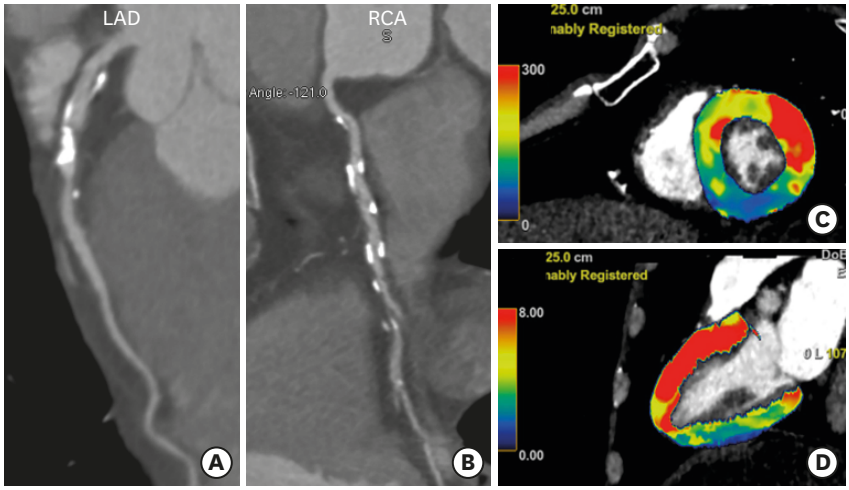


Figure 5. CTP. The patient was a 58-year-old male with chest pain for 2 months and syncope twice. CCTA showed mixed plaques with predominant calcification in the proximal LAD (A) and multiple calcified plaques (B) in the RCA. The evaluation of luminal stenosis was limited for LAD and RCA. The short-axis view (C) and two-chamber view (D) of CTP showed lower MBF value in the inferior wall of the left ventricle, confirming the presence of hemodynamically significant stenosis in the RCA but not in the LAD.
CTP: computed tomography perfusion, CCTA: coronary computed tomography angiography, LAD: left anterior descending artery, RCA: right coronary artery, MBF: myocardial blood flow.

provide prognostic value over CCTA in people with suspected CHD or known CHD and was useful prognostically in subgroups of patients with stent, heavy calcification, or obstructive CHD, compensating for the anatomical evaluation deficiency of CCTA for these patients.[49] Compared with magnetic resonance myocardial perfusion imaging and radionuclide myocardial perfusion imaging, CCTA-based CTP can take into account both anatomical and functional cardiac evaluation, while being faster and less expensive. In the future, after further improving the control of radiation dose and standardization, clinical application of the technique of CTP will expand.

CT-FFR

Anatomical stenosis identified by ICA is the gold standard of diagnosis for CHD at present, but anatomical stenosis alone cannot fully reflect the hemodynamic significance of lesions. FFR is an indicator to evaluate the hemodynamic significance of a coronary stenotic lesion and assesses the ratio of flow across the stenotic lesion to putative flow in the absence of the stenosis. Traditionally, CT-FFR is based on the CCTA computational fluid dynamics model to noninvasively obtain the FFR value of a stenotic lesion (**Figure 6**). A prospective multicenter trial lead by Nørgaard et al.[50] showed that CT-FFR provided high diagnostic accuracy and discrimination for hemodynamically significant CHD, with invasive FFR as the reference standard, and the per-patient sensitivity and specificity to identify myocardial ischemia were 86% (95% CI, 77–92) and 79% (95% CI, 72–84), respectively, for CT-FFR. As for the prognostic value of CT-FFR, a prospective study by Ihdayhid et al.[51] showed that the incidence of the primary end point (death, myocardial infarction, any revascularization) was higher in participants with positive CT-FFR (≤ 0.8) than in participants with significant stenosis (≥ 50%) on CCTA (73.4% [80 of 109] vs. 48.7% [91 of 187], respectively; $p < 0.001$), and corresponding HRs were 9.2 (95% CI, 5.1–17; $p < 0.001$) for CT-FFR and 5.9 (95% CI, 1.5–24; $p = 0.01$) for CCTA. The researchers in the study concluded that CT-FFR ≤ 0.8 was a predictor of long-term

https://doi.org/10.4250/jcvi.2021.0016

Journal of Cardiovascular Imaging JCVI

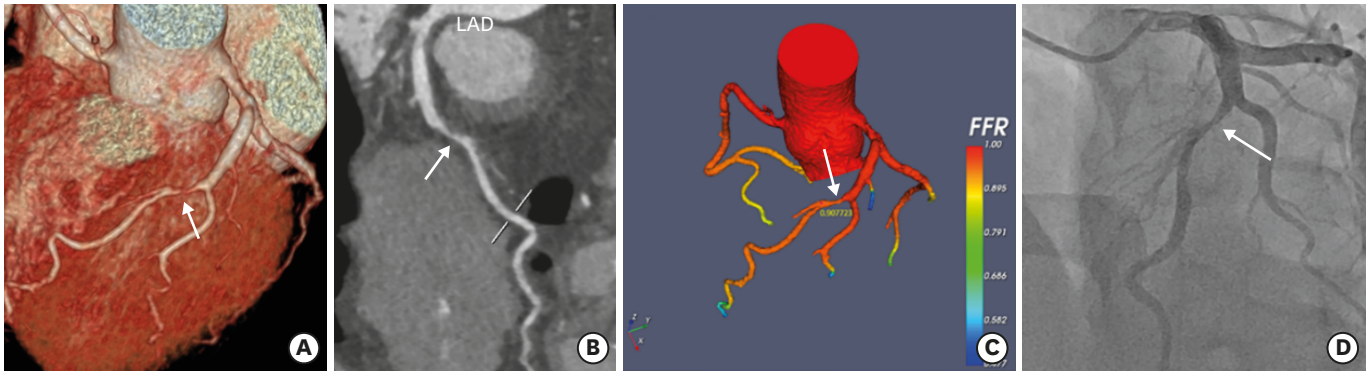


Figure 6. CT-FFR. The patient was a 41-year-old male with chest distress for 6 months. CCTA showed a non-calcified plaque in the mid-LAD (arrow) with 50%–70% diameter stenosis (A, volume rendering; B, multi-planar reformation). The CT-FFR value of the lesion was 0.91 (C), demonstrating no hemodynamically significant stenosis, and the invasive FFR value was 0.88 on invasive coronary angiography (D), confirming the validity of CT-FFR.
CT-FFR: computed tomography-derived fractional flow reserve, CCTA: coronary computed tomography angiography, LAD: left anterior descending artery, FFR: fractional flow reserve.

outcomes superior to that of clinically significant stenosis on CCTA, and the numeric value of CT-FFR was an independent predictor of outcome. A real-world study further demonstrated that treatment recommendations modified by CT-FFR in two-thirds of the participants were associated with less negative ICA, predicted revascularization compared with CCTA alone, and had a lower risk of adverse events through 90 days.[52] CT-FFR can provide hemodynamically significant assessment results based on CCTA without adding additional scans, improving the risk predictive value of MACE based on anatomical evaluation of CCTA, helping to guide clinical decisions to achieve optimal treatment benefits for patients. The diagnostic performance of CT-FFR was proven to be good at different extents of coronary calcification severity compared with CCTA interpretation alone.[53] However, in practice, lesions with large or diffuse calcification affect extraction of the coronary tree and the resultant calculation of CT-FFR. The diagnostic accuracy of CT-FFR can be affected by image quality and a "grey zone." A systematic review by Cook et al.[54] showed that the diagnostic accuracy was only 46.1% for CT-FFR values between 0.70 and 0.80, which was determined as a grey zone of CT-FFR and invasive FFR. A poor diagnostic accuracy of CT-FFR in this spectrum of disease affects MACE prediction using CT-FFR. Therefore, for this group of patients, it is necessary to combine clinical and other imaging risk predictors to assess the risk of MACE and guide clinical decisions, rather than relying solely on a single parameter.

AI

In recent years, application of AI in the medical field, especially in medical imaging, has received much attention and has been explored by a large number of studies. Among the algorithms of AI, machine learning (ML) provides the ability to identify patterns and learn rules from large data sets and then process a multitude of complex variables and finally output results. It was shown that ML-based CT-FFR performed equally but faster in detecting lesion-specific ischemia compared with the conventional computational fluid dynamics-based CT-FFR, and both methods outperformed the accuracy of CCTA and quantitative coronary angiography in detecting flow-limiting stenosis.[55] The incorporation of CT parameters into datasets for analysis and learning also provides value for AI in risk prediction of MACE. Eslami et al.[56] defined a radiomic-based score by extracting radiomic features from coronary artery calcium on coronary CT images and using ML techniques to select and

https://doi.org/10.4250/jcvi.2021.0016

Journal of Cardiovascular Imaging JCVI

classify radiomic features predicting events. The radiomic-based score was proven to improve the ability to identify individuals at highest risk of MACE and increase the discriminatory capacity of the Agatston score. Ambale-Venkatesh et al.[57] tested the ability of random survival forests, an ML technique, to predict 6 cardiovascular outcomes compared with standard cardiovascular risk scores. The results showed that imaging, electrocardiography, and serum biomarkers featured heavily in the prediction of cardiovascular outcomes. Among these, CACS was the most important predictor of CHD and all ASCVD-combined outcomes; meanwhile, left ventricular structure and function were the important predictors for incident heart failure. ML in conjunction with imaging, electrocardiography, serology, and clinical risk factors improved the risk prediction accuracy of cardiovascular events in an initially asymptomatic population. In addition, an ML model built by Motwani et al.[58] based on 25 clinical and 44 CCTA parameters improved the prediction of 5-year all-cause mortality in people suspected of CHD, significantly outperforming existing clinical or CCTA parameters alone. After the perivascular FAI identified by CCTA was found to be associated with MACE by Oikonomou's team, they developed a new AI-powered imaging biomarker, the fat radiomic profile, which was derived by ML-powered radiomic analysis of perivascular adipose tissue remodeling. This expanded the imaging characterization of perivascular fibrosis and vascularity remodeling beyond that of inflammation and significantly improved cardiac risk prediction over that of the current gold standard.[59] In practice, since AI is based on large datasets for learning and training to build prediction models, the quality and standardization of data determine the practicality and generalizability of the final models. Whether AI-based predictive models can be legally and socially accepted for clinical applications to guide prevention or treatment strategies is yet to be determined.

CONCLUSION

From CACS to CCTA anatomical and functional parameters and to coronary CT imaging combined with AI, coronary CT has provided substantial value for risk prediction of MACE and is being studied and developed. From the early nonobstructive CHD stage to the later obstructive CHD stage, one of the major advantages of coronary CT is its ability to provide a full-stage and overall evaluation of a patient's coronary atherosclerotic lesions from both anatomical and functional perspectives. This provides a multi-parametric risk prediction of MACE for risk stratification, which enables early preventive intervention or treatment to improve prognosis for the target population. With development and application of AI in the medical imaging field, comprehensive predictive models that integrate imaging parameters, serum biomarkers, clinical risk factors, and even relevant genes are expected to be further developed and optimized, and the potential predictive value of the risk of MACE in the large amounts of medical data available should yield good potential upon further exploration.

REFERENCES

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1736-88.
PUBMED | CROSSREF
2. Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). *Eur Heart J* 2018;39:2401-8.
PUBMED | CROSSREF

https://doi.org/10.4250/jcvi.2021.0016

3. Lo-Kioeng-Shioe MS, Rijlaarsdam-Hermsen D, van Domburg RT, et al. Prognostic value of coronary artery calcium score in symptomatic individuals: a meta-analysis of 34,000 subjects. *Int J Cardiol* 2020;299:56-62.
PUBMED | CROSSREF
4. Khera A, Budoff MJ, O'Donnell CJ, et al. Astronaut cardiovascular health and risk modification (Astro-CHARM) coronary calcium atherosclerotic cardiovascular disease risk calculator. *Circulation* 2018;138:1819-27.
PUBMED | CROSSREF
5. Mahabadi AA, Möhlenkamp S, Lehmann N, et al. CAC score improves coronary and CV risk assessment above statin indication by ESC and AHA/ACC primary prevention guidelines. *JACC Cardiovasc Imaging* 2017;10:143-53.
PUBMED | CROSSREF
6. Blaha MJ, Cainzos-Achirica M, Greenland P, 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;133:849-58.
PUBMED | CROSSREF
7. Kavousi M, Desai CS, Ayers C, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: a meta-analysis. *JAMA* 2016;316:2126-34.
PUBMED | CROSSREF
8. Lehmann N, Erbel R, Mahabadi AA, et al. 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;137:665-79.
PUBMED | CROSSREF
9. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019;140:e596-646.
PUBMED | CROSSREF
10. Gupta A, Lau E, Varshney R, et al. The identification of calcified coronary plaque is associated with initiation and continuation of pharmacological and lifestyle preventive therapies: a systematic review and meta-analysis. *JACC Cardiovasc Imaging* 2017;10:833-42.
PUBMED | CROSSREF
11. Cainzos-Achirica M, Miedema MD, McEvoy JW, et al. Coronary artery calcium for personalized allocation of aspirin in primary prevention of cardiovascular disease in 2019: the MESA study (Multi-Ethnic Study of Atherosclerosis). *Circulation* 2020;141:1541-53.
PUBMED | CROSSREF
12. McEvoy JW, Martin SS, Dardari ZA, et al. Coronary artery calcium to guide a personalized risk-based approach to initiation and intensification of antihypertensive therapy. *Circulation* 2017;135:153-65.
PUBMED | CROSSREF
13. Criqui MH, Knox JB, Denenberg JO, et al. Coronary artery calcium volume and density: potential interactions and overall predictive value: the multi-ethnic study of atherosclerosis. *JACC Cardiovasc Imaging* 2017;10:845-54.
PUBMED | CROSSREF
14. van Rosendael AR, Narula J, Lin FY, et al. Association of high-density calcified 1k plaque with risk of acute coronary syndrome. *JAMA Cardiol* 2020;5:282-90.
PUBMED | CROSSREF
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;9:1407-16.
PUBMED | CROSSREF
16. Tota-Maharaj R, Joshi PH, Budoff MJ, et al. Usefulness of regional distribution of coronary artery calcium to improve the prediction of all-cause mortality. *Am J Cardiol* 2015;115:1229-34.
PUBMED | CROSSREF
17. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol* 2007;50:1161-70.
PUBMED | CROSSREF
18. Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation* 2017;135:2320-32.
PUBMED | CROSSREF

19. Al-Mallah MH, Qureshi W, Lin FY, et al. Does coronary CT angiography improve risk stratification over coronary calcium scoring in symptomatic patients with suspected coronary artery disease? Results from the prospective multicenter international CONFIRM registry. *Eur Heart J Cardiovasc Imaging* 2014;15:267-74.
PUBMED | CROSSREF

20. van Rosendael AR, Bax AM, Smit JM, et al. Clinical risk factors and atherosclerotic plaque extent to define risk for major events in patients without obstructive coronary artery disease: the long-term coronary computed tomography angiography CONFIRM registry. *Eur Heart J Cardiovasc Imaging* 2020;21:479-88.
PUBMED | CROSSREF

21. Ayoub C, Erthal F, Abdelsalam MA, et al. Prognostic value of segment involvement score compared to other measures of coronary atherosclerosis by computed tomography: a systematic review and meta-analysis. *J Cardiovasc Comput Tomogr* 2017;11:258-67.
PUBMED | CROSSREF

22. Cury RC, Abbara S, Achenbach S, 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;10:269-81.
PUBMED | CROSSREF

23. Bittner DO, Mayrhofer T, Budoff M, et al. Prognostic value of coronary CTA in stable chest pain: CAD-RADS, CAC, and cardiovascular events in PROMISE. *JACC Cardiovasc Imaging* 2020;13:1534-45.
PUBMED | CROSSREF

24. Gu H, Gao Y, Hou Z, et al. Prognostic value of coronary atherosclerosis progression evaluated by coronary CT angiography in patients with stable angina. *Eur Radiol* 2018;28:1066-76.
PUBMED | CROSSREF

25. Mortensen MB, Dzaye O, Steffensen FH, et al. Impact of plaque burden versus stenosis on ischemic events in patients with coronary atherosclerosis. *J Am Coll Cardiol* 2020;76:2803-13.
PUBMED | CROSSREF

26. Tesche C, Plank F, De Cecco CN, et al. Prognostic implications of coronary CT angiography-derived quantitative markers for the prediction of major adverse cardiac events. *J Cardiovasc Comput Tomogr* 2016;10:458-65.
PUBMED | CROSSREF

27. Yoon SH, Kim E, Jeon Y, et al. Prognostic value of coronary CT angiography for predicting poor cardiac outcome in stroke patients without known cardiac disease or chest pain: the assessment of coronary artery disease in stroke patients study. *Korean J Radiol* 2020;21:1055-64.
PUBMED | CROSSREF

28. 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.
PUBMED | CROSSREF

29. 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;18:772-9.
PUBMED | CROSSREF

30. Nadjiri J, Hausleiter J, Jähnichen C, et al. Incremental prognostic value of quantitative plaque assessment in coronary CT angiography during 5 years of follow up. *J Cardiovasc Comput Tomogr* 2016;10:97-104.
PUBMED | CROSSREF

31. 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;3:144-52.
PUBMED | CROSSREF

32. Senoner T, Plank F, Barbieri F, et al. Added value of high-risk plaque criteria by coronary CTA for prediction of long-term outcomes. *Atherosclerosis* 2020;300:26-33.
PUBMED | CROSSREF

33. Conte E, Annoni A, Pontone G, 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;18:1170-8.
PUBMED | CROSSREF

34. Arbab-Zadeh A, Fuster V. From detecting the vulnerable plaque to managing the vulnerable patient: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;74:1582-93.
PUBMED | CROSSREF

35. Nissen SE. Vulnerable plaque and Einstein's definition of insanity. *J Am Coll Cardiol* 2020;75:1383-5.
PUBMED | CROSSREF

36. Wang C, Hu S, Wu J, et al. Characteristics and significance of healed plaques in patients with acute coronary syndrome and stable angina: an in vivo OCT and IVUS study. *EuroIntervention* 2019;15:e771-8.
PUBMED | CROSSREF

37. 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;66:337-46.
PUBMED | CROSSREF

38. Williams MC, Kwiecinski J, Doris M, et al. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: results from the multicenter SCOT-HEART trial (Scottish Computed Tomography of the HEART). *Circulation* 2020;141:1452-62.
PUBMED | CROSSREF

39. Mushtaq S, De Araujo Gonçalves P, Garcia-Garcia HM, et al. Long-term prognostic effect of coronary atherosclerotic burden: validation of the computed tomography-Leaman score. *Circ Cardiovasc Imaging* 2015;8:e002332.
PUBMED | CROSSREF

40. Deseive S, Shaw LJ, Min JK, et al. Improved 5-year prediction of all-cause mortality by coronary CT angiography applying the CONFIRM score. *Eur Heart J Cardiovasc Imaging* 2017;18:286-93.
PUBMED | CROSSREF

41. Sinning C, Lillpopp L, Appelbaum S, et al. Angiographic score assessment improves cardiovascular risk prediction: the clinical value of SYNTAX and Gensini application. *Clin Res Cardiol* 2013;102:495-503.
PUBMED | CROSSREF

42. Suh YJ, Hong YJ, Lee HJ, et al. Prognostic value of SYNTAX score based on coronary computed tomography angiography. *Int J Cardiol* 2015;199:460-6.
PUBMED | CROSSREF

43. Oikonomou EK, Marwan M, Desai MY, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. *Lancet* 2018;392:929-39.
PUBMED | CROSSREF

44. Klein R, Ametepe ES, Yam Y, Dwivedi G, Chow BJ. Cardiac CT assessment of left ventricular mass in mid-diastasis and its prognostic value. *Eur Heart J Cardiovasc Imaging* 2017;18:95-102.
PUBMED | CROSSREF

45. Mahabadi AA, Lehmann N, Möhlenkamp S, et al. Noncoronary measures enhance the predictive value of cardiac CT above traditional risk factors and CAC score in the general population. *JACC Cardiovasc Imaging* 2016;9:1177-85.
PUBMED | CROSSREF

46. Chen MY, Rochitte CE, Arbab-Zadeh A, et al. Prognostic value of combined CT angiography and myocardial perfusion imaging versus invasive coronary angiography and nuclear stress perfusion imaging in the prediction of major adverse cardiovascular events: the CORE320 multicenter study. *Radiology* 2017;284:55-65.
PUBMED | CROSSREF

47. Nakamura S, Kitagawa K, Goto Y, et al. Incremental prognostic value of myocardial blood flow quantified with stress dynamic computed tomography perfusion imaging. *JACC Cardiovasc Imaging* 2019;12:1379-87.
PUBMED | CROSSREF

48. van Assen M, De Cecco CN, Eid M, et al. Prognostic value of CT myocardial perfusion imaging and CT-derived fractional flow reserve for major adverse cardiac events in patients with coronary artery disease. *J Cardiovasc Comput Tomogr* 2019;13:26-33.
PUBMED | CROSSREF

49. Nakamura S, Kitagawa K, Goto Y, et al. Prognostic value of stress dynamic computed tomography perfusion with computed tomography delayed enhancement. *JACC Cardiovasc Imaging* 2020;13:1721-34.
PUBMED | CROSSREF

50. Nørgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol* 2014;63:1145-55.
PUBMED | CROSSREF

51. Ihdayhid AR, Norgaard BL, Gaur S, et al. Prognostic value and risk continuum of noninvasive fractional flow reserve derived from coronary CT angiography. *Radiology* 2019;292:343-51.
PUBMED | CROSSREF

52. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE registry. *Eur Heart J* 2018;39:3701-11.
PUBMED | CROSSREF

53. Nørgaard BL, Gaur S, Leipsic J, et al. Influence of coronary calcification on the diagnostic performance of CT angiography derived FFR in coronary artery disease: a substudy of the NXT trial. *JACC Cardiovasc Imaging* 2015;8:1045-55.
PUBMED | CROSSREF

54. Cook CM, Petraco R, Shun-Shin MJ, et al. Diagnostic accuracy of computed tomography-derived fractional flow reserve: a systematic review. *JAMA Cardiol* 2017;2:803-10.
PUBMED | CROSSREF

55. Tesche C, De Cecco CN, Baumann S, et al. Coronary CT angiography-derived fractional flow reserve: machine learning algorithm versus computational fluid dynamics modeling. *Radiology* 2018;288:64-72.
PUBMED | CROSSREF

56. Eslami P, Parmar C, Foldyna B, et al. Radiomics of coronary artery calcium in the Framingham heart study. *Radiol Cardiothorac Imaging* 2020;2:e190119.
PUBMED | CROSSREF

57. Ambale-Venkatesh B, Yang X, Wu CO, et al. Cardiovascular event prediction by machine learning: the multi-ethnic study of atherosclerosis. *Circ Res* 2017;121:1092-101.
PUBMED | CROSSREF

58. Motwani M, Dey D, Berman DS, et al. Machine learning for prediction of all-cause mortality in patients with suspected coronary artery disease: a 5-year multicentre prospective registry analysis. *Eur Heart J* 2017;38:500-7.
PUBMED

59. Oikonomou EK, Williams MC, Kotanidis CP, et al. A novel machine learning-derived radiotranscriptomic signature of perivascular fat improves cardiac risk prediction using coronary CT angiography. *Eur Heart J* 2019;40:3529-43.
PUBMED | CROSSREF