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In search of new gatekeepers: coronary CT (Computed Tomography) in acute coronary syndrome

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Coronary computed tomography (CCT) is a non-invasive imaging method that allows visualization of the epicardial coronary arteries. The diagnostic and prognostic role of CCT has been demonstrated by various randomized trials to such an extent that it has been included as a Class I, level of evidence B recommendation in the latest European Society of Cardiology (ESC) guidelines for the diagnosis of chronic coronary syndrome in patients at intermediate-low cardiovascular risk. In addition to the anatomical evaluation, the CCT allows to evaluate the presence of high-risk characteristics of the atherosclerotic plaque (napkin-ring sign, positive remodelling, spotty calcification, and low-attenuation plaque), thus discriminating the stability of the atheromatous pathology. Furthermore, among the potential of cardiac CT in the emergency department, the possibility of making a triple rule-out must be underlined, excluding three potential big killers as the cause of acute chest pain: acute coronary syndrome, pulmonary embolism, and aortic dissection. Various randomized clinical studies have demonstrated that the prognosis of the patient with chronic coronary artery disease (CAD) improves only if a haemodynamically significant stenosis is treated, generally investigated with invasive fractional flow reserve (FFR); CCT technological advances have made it possible to create an algorithm for calculating the FFR-CT, an index of haemodynamic significance of coronary stenosis, whose correlation with the invasive FFR data and, consequently, with the prognosis has been demonstrated of patients with CAD.

Coronary computed tomography (CCT) is a non-invasive imaging method that allows you to visualize the coronary arteries by investigating their anatomy, origin, course, and relationships with other cardiac structures. Its characteristic of being born as a three-dimensional examination allows to study the calibre of the vessels, verifying the presence of atherosclerotic disease and the degree of stenosis, up to being able to estimate the composition of the atheromatous plaque and the nature of the perivascular tissues that surround it. The technological advances in favour of this method and the amount of scientific evidence in its favour are so impressive that they have allowed this test to obtain, in a few years, a role of primary importance in the study of chronic ischaemic heart disease: in the most recent guidelines ESC in fact the execution of this examination in the suspicion of chronic coronary syndrome is in Class I, level of evidence B.[1]

The advantages of this method also extend to the acute coronary syndrome (ACS). Since the first years of the new millennium, important scientific works have followed that have allowed us to demonstrate the usefulness of CCT in the emergency setting, summarized in *Table 1*.

The first important work on the subject is the Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT) trial published in 2009 on *Journal American College of Cardiology* (*JACC*). This study demonstrated on a cohort of patients with chest pain, non-ischaemic electrocardiogram (ECG), and unchanged troponins that CCT very effectively highlights the presence of obstructive coronary atheromasia with 100% sensitivity and with a negative predictive value of 100% in

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Table 1 Trials investigating feasibility and accuracy of Computed Tomography in Emergency Department settings

Authors/year	Objective	Design	CT method	Study population	*N* patients	Country	Primary endpoint and other clinically relevant endpoints	Results
Goldstein et al.,[3]	Utility of CTA in ACS	CTA vs. standard of care	CTA by 64-detector row scanner	Suspected ACS at low risk	197 (99 vs. 98)	United States	Test complications time from randomization until completion of testing interpretation	0.0% vs. 0.0%; P = NA 3.4 h vs. 15.0 h; $P < 0.001$
Chang *et al.*, 2008	Utility of CTA in ACS	CTA vs. standard of care	CTA by 64-detector row scanner	Low-to-high risk for ACS	266 (133 vs. 133)	Korea	Admission death, MI, or target vessel revascularization at 1 month	41% vs. 50%; $P = 0.14$ 0.0% vs. 0.8%; P = NA
Miller *et al.*, 2011	Utility of CTA in ACS	CTA vs. standard of care	CTA by 64-detector row scanner	Suspected ACS without cardiac enzyme elevation	60 (30 vs. 30)	United States	Total cost at 90 days	$10,134 vs. $16 579; $P = 0.144$
C T-STAT, 2011	Utility of CTA in ACS	CTA vs. myocardial perfusion SPECT	CTA by 64- or 320-detector row scanner	Suspected ACS at low-to-intermediate risk	699 (361 vs. 338)	United States	Time from randomization to when test results were called to emergency department physicians	2.9 h vs. 6.3 h; $P < 0.001$
ROMICAT-II, 2012	Utility of CTA in ACS	CTA vs. standard of care	CTA by ≥64-detector row scanner	Suspected ACS	1000 (501 vs. 499)	United States	Length of stay in the hospital	23.2 h vs. 30.8 h; $P < 0.001$
ACRIN PA 4005, 2012	Utility of CTA in ACS	CTA vs. standard of care	CTA by ≥64-detector row scanner	Suspected ACS at low-to-intermediate risk	1370 (908 vs. 462)	United States	Cardiac death or MI within 30 days in patients with a negative CTA examination Death or MI at 30 days	0.0% (0/640) 1.10% vs. 1.08%; difference 0.02% (5.6% to 5.7%)
CATCH, 2013	Utility of CTA in ACS	CTA vs. standard of care	CTA by 320-detector row scanner	Suspected ACS	600 (299 vs. 301)	Denmark	Cardiac death, MI, hospitalization for unstable angina, late symptom-driven revascularization, or readmission for chest pain	11% vs. 16% (a median follow-up of 18.7 months); $P = 0.04$
CT-COMPARE, 2014	Utility of CTA in ACS	CTA vs. exercise stress ECG	CTA by 64- or 128-detector row scanner	Low-to-intermediate risk for ACS	562 (322 vs. 240)	Australia	Diagnostic performance for ACS Hospital cost at 30 days	AUC 0.97 vs. 0.87; $P = 0.22$ A$2193 vs. A $2704; $P < 0.001$
Levsky *et al.*, 2015	Utility of CTA in ACS	CTA vs. myocardial perfusion SPECT	CTA by 64-detector row scanner	Suspected ACS	400 (200 vs. 200)	United States	ICA not leading to revascularization within 1 y	7.5% vs. 10%; $P = 0.44$
BEACON, 2016	Utility of CTA in ACS	CTA vs. standard of care	CTA by ≥64-detector row scanner	Suspected ACS	500 (250 vs. 250)	The Netherlands	The number of patients requiring revascularization within 30 days	9% vs. 7%; P = 0.40
Levsky *et al.*, 2018	Utility of CTA in ACS	CTA vs. stress echocardiography	CTA by 64-detector row scanner	Low-to-intermediate risk for ACS	400 (201 vs. 199)	United States	Hospitalization rate Median emergency department length of stay for discharged patients Median hospital length of stay	19% vs. 11%; P ¼ 0.026 5.4 h vs. 4.7 h; $P <$ 0.001 58 h vs. 34 h; $P = 0.002$

Continued

Table 1 Continued

Authors/year	Objective	Design	CT method	Study population	*N* patients	Country	Primary endpoint and other clinically relevant endpoints	Results
CARMENTA, 2019	Utility of CTA in NSTEMI	Routine clinical care vs. CMR first vs. CTA first	CTA first CTA by second-generation dual-source scanner	Suspected NSTEMI	207 (69 vs. 68 vs. 70)	The Netherlands	Proportion of patients referred to ICA during initial hospitalization	100% vs. 66% ($P = 0.001$ vs. routine care) vs. 87% ($P < 0.001$ vs. routine care
Chinnaiyan *et al.*,[10]	Feasibility, safety, clinical outcomes, and costs associated with FFR-CT in acute chest pain	CTA vs. CTA and FFR-CT	CTA by dual-source CT scanner	Acute chest pain in ED	555 (258 vs. 297)	United States	MACE at 90 days Diagnostic failure Cost difference	4.3% vs. 2.7%; $P = 0.310$); 1.9% vs. 1.68%; $P =$ NS; $8582 vs. $8048; $P = 0.550$
Fischer *et al.*,[13]	Assess outcomes in FFR-CT negative patients admitted in emergency department for acute chest pain	CTA and subsequent FFR-CT	2nd- or 3rd-generation dual-source CT systems FFR-CT by HeartFlow	Acute chest pain in ED	59 (32 FFR > 0.8)	United States	MACE at 30 days, repeat presentation/admission for chest pain, revascularization, and additional testing	100% of negative FFR-CT had no MACE at follow-up
Meier *et al.*,[14]	determine the role of CTA and FFR-CT in high-risk NSTE-ACS	CTA and FFR-CT and subsequent ICA (± FFR)	256-slice multi-detector CT FFR-CT by HeartFlow	High-risk NSTE-ACS	250	United States	Non-invasive identification of patient with high-risk NSTE-ACS who could avoid ICA would reduce related risk and costs.	–

Adapted from Serruys *et al.*, *Coronary Computed Tomographic Angiography for Complete Assessment of Coronary Artery Disease: JACC State-of-the-Art Review, Journal of the American College of Cardiology*, 2021.

patients with ACS.[2] A 2-year follow-up of these patients also allowed us to demonstrate a substantial difference in the incidence of major adverse cardiac events (MACE) in patients who did not demonstrate obstructive coronary atheroma compared to patients who had significant coronary artery disease (CAD) at the first evaluation.

A better ability to discriminate patients with a high probability of ACS in the emergency department (ED) also leads to advantages in terms of time and costs: The Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT STAT) trial is a randomized controlled trial (RCT) in which it was shown that the use of CCTA allowed a reduction of 54% of time to diagnosis compared to other provocative imaging methods (median 2.9 h vs. 6.3 h $P < 0.0001$). Costs were 38% lower than the standard (median \$2.137 vs. \$3.458, $P < 0.0001$). The choice of diagnostic method did not lead to a difference in MACE (0.8% in the CCT arm vs. 0.4% in the other arm, $P = 0.29$).[3]

In 2012, a couple of trials were published in the *New England Journal of Medicine* that definitively confirmed CCT's role in acute patients: ROMICAT is an RCT that evaluated 1000 with symptoms suggestive of ACS in the absence of ECG or troponin alterations at the first evaluation dividing them 1:1 in arm with early CCT vs. arm of standard of care. The average length of stay in the emergency room was reduced by 7.6 h ($P < 0.001$), with an increase in direct discharge from the ED (47% vs. 12%, $P < 0.001$), in the absence of undiagnosed ACS and no increase in MACE at one month. In this work, an increase in downstream diagnostic tests was reported in the CCT arm, at the same cost of \$4289 vs. \$4060 ($P = 0.65$).[4]

The Better Evaluation of Acute Chest Pain with Computed Tomography Angiography (BEACON) trial is an RCT that evaluated 1370 patients with intermediate-low probability of ACS randomized 2:1 in CCT vs. standard of care. Among patients with negative CCTs, none reported myocardial infarction or death at 30 days. In the CCT arm, the ED discharge rate proved to be higher (49.6% vs. 22.7%), the stay in the hospital was reduced (18.0 h vs. 24.8 h; $P < 0.001$), and the CAD diagnosis rate was higher (9.0% vs. 3.5%), in the absence of differences on significant adverse events.[5]

Furthermore, the additional assessment of atheromatous plaque composition for the identification of high-risk plaques is a known benefit of CCT. A sub-analysis of ROMICAT II evaluated in the CCT arm the presence of non-obstructive CAD (1–49% stenosis), significant CAD (≥50% or ≥70%), and the presence of at least one high-risk plaque feature [remodelling positive, low attenuation plaque <30 Hounsfield unit (HU), napkin-ring sign, and spotty calcification].[6]

With the implementation of high-sensitivity troponin assays, a more accurate and rapid diagnosis of myocardial infarction has been achieved. A prospective, multi-centre, randomized trial of standard treatment and CCT vs. standard treatment, conducted in Europe on 500 patients, confirmed the added value of using CCT in the ED: the percentage of patients discharged from the ED was not different in two arms (65% vs. 59%, $P = 0.16$), as well as the length of stay (6.3 h in both groups; $P = 0.80$). However, a reduction in treatment costs was highlighted in the CCT arm (€337 vs. €511, $P < 0.01$) and a reduction in post-discharge investigations. Furthermore, a difference in undiagnosed ACS was not recorded.[7]

Subsequent work by Liu Ting's group in China evaluated patients with acute chest pain by categorizing risk profiles (low–medium–high) based on high-sensitivity troponin. Coronary computed tomography made it possible to qualitatively evaluate the presence of significant CAD (≥50% stenosis), characterizing the plaque composition and vulnerable plaque features (positive remodelling, low attenuation plaque <30 HU, napkin-ring sign, and spotty calcifications). The mean age of the population was 50.3 ± 8.2 (43% women). The diagnosis of ACS was made in 16.3% of patients. Across the high-sensitivity troponin I (hsTnI)-based risk categories, there was an increase in the prevalence of obstructive atheromasia (≥50% stenosis) in 0%, 11.5%, and 61.9% of patients, respectively ($P < 0.001$), and high-risk plaques, respectively 0%, 36.0%, and 85.7% of patients ($P < 0.001$). None of the low-risk patients developed ACS, while 10.1% and 52.3% of intermediate-risk and high-risk patients developed ACS, respectively. It was also shown that the prevalence of high-risk plaques and the severity of stenosis correlated with elevated hsTnI levels.[8]

In the clinical context of acute chest pain in the ED, in addition to assessing the presence of obstructive coronary stenosis, among the potential of CCT, we should consider the ability to perform the so-called triple rule-out; with a single non-invasive, rapid, and widely available diagnostic exam, with the appropriate technical precautions during the acquisition phase, it is possible to reliably exclude the presence of three 'big killer' pathological conditions with a single exam session: significant CAD, pulmonary embolism, and acute aortic dissection.[9]

Cardiac CT therefore allows the anatomical evaluation, with evidence of the presence or absence of obstructive CAD and the determination of the extent of the stenosis, and the qualitative evaluation of the characteristics of the atherosclerotic plaque with particular reference to those phenotypes associated with the so-called unstable plaque (e.g. positive remodelling, low-attenuation plaque, napkin-ring sign, and spotty calcification).

However, some multi-centre trials have shown that the prognosis of patients with ischaemic heart disease improves only when a coronary stenosis is treated, which is also functionally significant, i.e. capable of causing myocardial ischaemia.

The reference technique for defining the haemodynamic relevance of a coronary stenosis is the fractional flow reserve (FFR), an invasive hyperaemic technique, measured during maximal coronary flow, which is based on the ratio between the pressure present downstream of a coronary stenosis and a reference pressure, usually measured at the aortic level, for which a cut-off of 0.8 was established by the trials to define its significance.

Given the increasingly important role of cardiac CT in the suspicion of ischaemic heart disease, the idea arose of trying to obtain the same functional data obtainable from invasive FFR starting from the information acquired during the CCT at rest.

The FFR-CT technique allows to calculate, using computational fluid dynamics algorithms, in a non-invasive way, the FFR values on all the main epicardial coronary vessels, based on a purely anatomical data set of images of the coronary tree obtained with CCT without the need to administer a pharmacological stress. Essential criteria for the feasibility of FFR-CT analysis are the acquisition of images

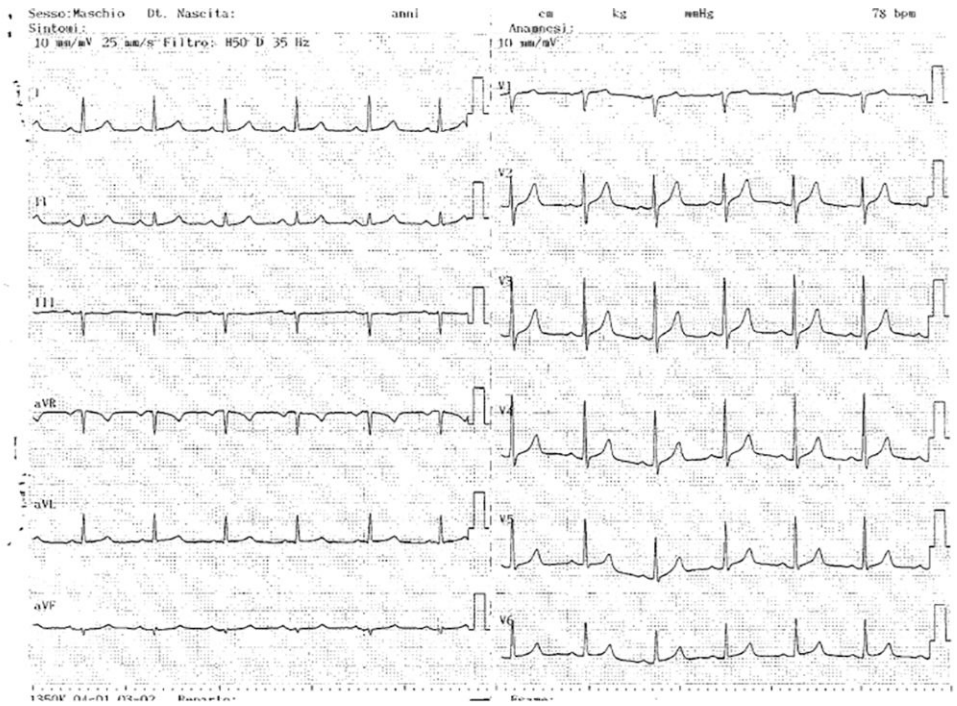

Figure 1 Electrocardiogram tracing of a 56-year-old hypertensive man who smoked. Access to emergency department for atypical angina, negative high-sensitivity troponin I in serial measurements.

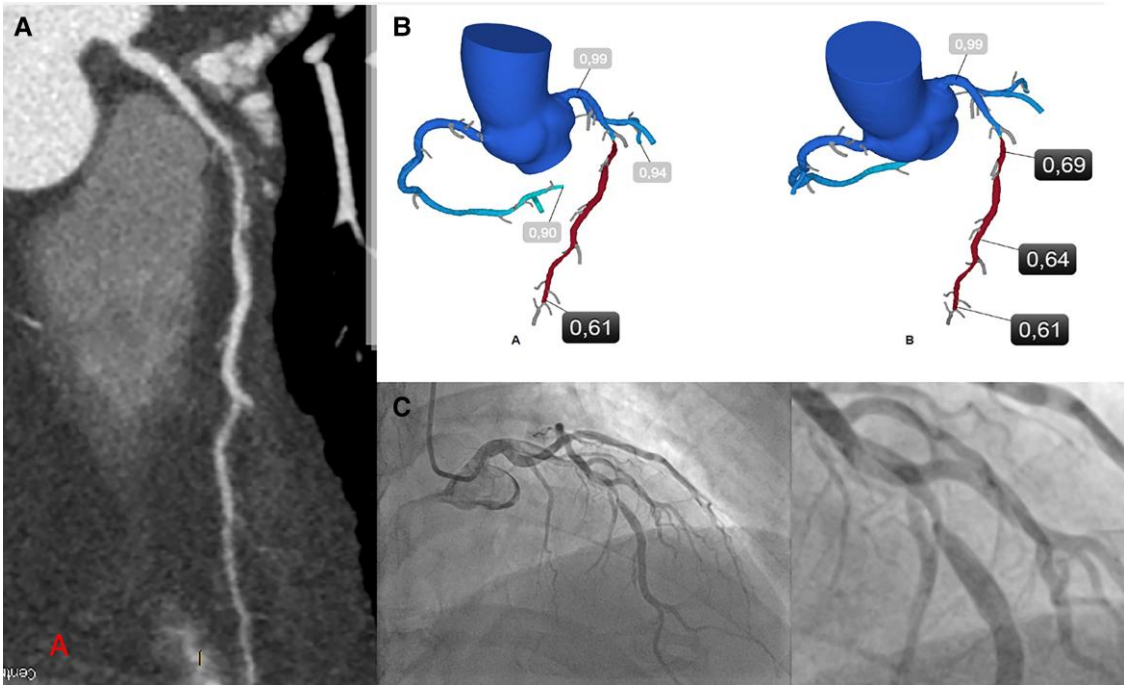

Figure 2 Coronary computed tomography showed high-risk fibrolipidic plaque at the proximal IVA causing severe stenosis (*A*). Fractional flow reserve-computed tomography analysis showed significant values downstream of the lesion (*B*). Coronary angiography confirmed the finding (*C*).

with a scanner of no less than 64 slices, the use of sublingual nitrates, and adequate image quality.

To solve the complex computational fluid dynamics algorithms at the basis of the FFR-CT, software has been developed capable of simulating the behaviour of the coronary microcirculation in conditions of maximum hyperaemia; currently, the only available commercial software approved by the Food and Drug Administration is owned by the US company HeartFlow (HeartFlow Inc., Redwood, CA, USA).

Multi-centre trials in the literature have demonstrated the reliability of the FFR-CT measured with HeartFlow software and its correlation with the invasive FFR data.

Until the introduction of the FFR-CT, there was no CT technique that in basal conditions and without the need for administration of pharmacological stimulus could evaluate the haemodynamic significance of a coronary stenosis in a non-invasive way.

In view of the demonstrated diagnostic and prognostic role of FFR-CT in stable ischaemic heart disease, in the last period, there has been growing interest in evaluating its applicability in the ED in the clinical setting of acute chest pain.

Chinnaiyan *et al.*,[10] in their study published in 2020 in JACC Cardiovascular imaging, demonstrated that in patients with acute chest pain, adding functional data with FFR-CT is feasible without resulting in a significant increase in MACE compared to CT anatomical coronary artery. Furthermore, they demonstrated that deferring revascularization is safe with a negative FFR-CT, a condition associated with a higher prevalence of non-obstructive disease on coronary angiography.

The feasibility was also confirmed by results from the work of Eberhard *et al.*,[11] where the authors emphasize that sufficient image quality is required for the applicability of the FFR-CT analysis.

Additionally, a sub-analysis of the ROMICAT II trial in patients with acute chest pain demonstrated the association of FFR-CT significance with degree of stenosis, high-risk characteristics of plaque, and relative risk of ACS and the need for coronary revascularization.[12]

Finally, also in patients with acute chest pain, the value of FFR-CT plays a prognostic role, as evidenced by Fischer *et al.*,[13] which demonstrated that its negativity (FFR-CT > 0.8) is associated with the absence of MACE 30 days after discharge from the ED.

A study is also underway to evaluate the applicability of FFR-CT in patients hospitalized with low-risk non-ST-elevation ACS (NSTE-ACS) to evaluate the possible possibility of avoiding the use of coronary angiography and consequently the reduction of related costs, in that part of patients with negative FFR-CT; from the results of this work, it will be possible to understand the possible applicability of this technique also in a subgroup of patients with ACS, further expanding the contexts in which CCT would play a first-line test role.[14]

In support of this discussion, we bring a practical example of how the use of CCT can prove decisive in the diagnostic work-up of chest pain: *Figure 1* shows the ECG tracing of a 56-year-old man, hypertensive and smoker, with no previous cardiological history. The patient presented to the ED for atypical angina. Physical examination and serial measurement of hsTnI were negative.

Figure 2 shows images of the CCT that identified a high-risk fibrolipidic plaque on proximal left anterior descending (LAD) artery, resulting in severe stenosis (*A*). The FFR-CT analysis showed significant values downstream of the lesion (*B*). Invasive coronary angiography confirmed the finding (*C*). The patient was then treated with percutaneous coronary intervention (PCI) with an excellent final result.

From the data presented, therefore, emerges an increasing role of CCT in patients with acute chest pain, able in the first place to exclude potentially fatal conditions if not promptly diagnosed such as aortic dissection and pulmonary embolism, but above all for the ability to highlight the presence or absence of obstructive CAD with, in cases that require it, the possibility of also adding a functional evaluation, obtaining the haemodynamic significance data in a single exam.

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Data availability

No new data were generated or analysed in support of this research.

References

1. Knuuti J, Wijns W, Saraste A *et al.* 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. The task force for the diagnosis and management of chronic coronary syndromes of the ESC. *Eur Heart J* 2020;**41**:407–477.
2. Hoffmann U, Bamberg F, Chae CU *et al.* Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. *J Am Coll Cardiol* 2009;**53**:1642–1650.
3. Goldstein JA, Chinnaiyan KM, Abidov A *et al.* The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol* 2011;**58**:1414–1422.
4. Hoffmann U, Truong QA, Schoenfeld DA *et al.* Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med* 2012;**367**:299–308.
5. Litt HI, Gatsonis C, Snyder B *et al.* CT Angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med* 2012;**366**:1393–1403.
6. Puchner SB, Liu T, Mayrhofer T *et al.* High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol* 2014;**64**:684–692.
7. Dedic A, Lubbers MM, Schaap J *et al.* Coronary CT angiography for suspected ACS in the era of high-sensitivity troponins: randomized multicenter study. *J Am Coll Cardiol* 2016;**67**:16–26.
8. Liu T, Wang G, Li P *et al.* Risk classification of highly sensitive troponin I predict presence of vulnerable plaque assessed by dual source coronary computed tomography angiography. *Int J Cardiovasc Imaging* 2017;**33**:1831–1839.
9. Rogers IS, Banerji D, Siegel EL *et al.* Usefulness of comprehensive cardiothoracic computed tomography in the evaluation of acute undifferentiated chest discomfort in the emergency department (CAPTURE). *Am J Cardiol* 2011;**107**:643–650.
10. Chinnaiyan KM, Safian RD, Gallagher ML *et al.* Clinical use of CT-derived fractional flow reserve in the emergency department. *JACC Cardiovasc Imaging* 2020;**13**:452–461.
11. Eberhard M, Nadarevic T, Cousin A *et al.* Machine learning-based CT fractional flow reserve assessment in acute chest pain: first experience. *Cardiovasc Diagn Ther* 2020;**10**:820–830.
12. Ferencik M, Lu MT, Mayrhofer T *et al.* Non-invasive fractional flow reserve derived from coronary computed tomography angiography in patients with acute chest pain: subgroup analysis of the ROMICAT II trial. *J Cardiovasc Comput Tomogr* 2019;**13**:196–202.
13. Fischer AM, van Assen M, Schoepf UJ *et al.* Non-invasive fractional flow reserve (FFRCT) in the evaluation of acute chest pain. Concepts and first experiences. *Eur J Radiol* 2021;**138**:109633.
14. Meier D, Skalidis I, De Bruyne B *et al.* Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTE-ACS admitted in the emergency department with chest pain, study design and rationale. *Int J Cardiol Heart Vasc* 2020; **27**:100496.