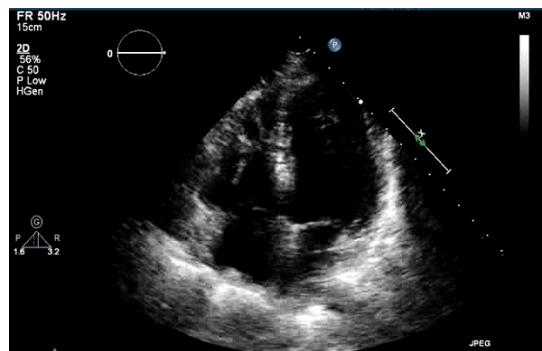




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07 | COVID-19 pandemic and cardiac imaging: EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel



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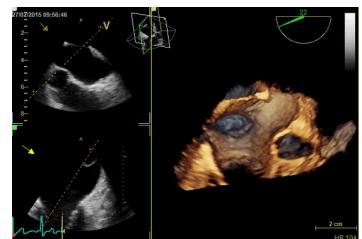
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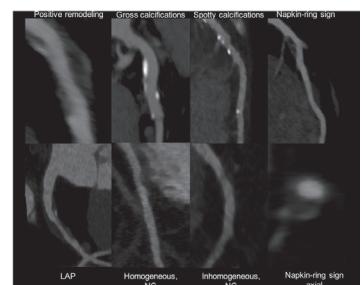
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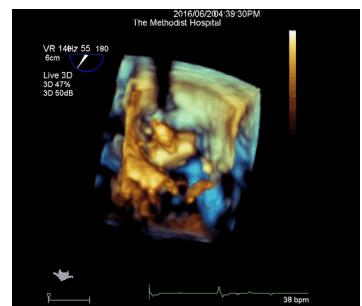


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COVID-19 pandemic and cardiac imaging: EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has created new and unpredictable challenges for modern medicine and healthcare systems. Preliminary reports have demonstrated that older age, previous cardiovascular disease, diabetes, and hypertension are risk factors for increased mortality.¹ Data on the cardiac affinity of the virus and its potential to harm the cardiovascular system and the mechanisms by which this occurs are sparse.^{2,3} A systemic infection generally increases demand on the heart, and can exacerbate underlying cardiac conditions. When the lungs are heavily involved, as seen in COVID-19 patients, this may have a major impact on cardiac function, particularly that of the right ventricle. Finally, COVID-19 may have direct effects on the heart, as may some drugs being used in its treatment.

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for COVID-19 and is transmitted by droplets from person to person.⁴ Echocardiographers in particular, and cardiac imagers more generally, are in close contact with patients and therefore likely to have a high risk of being infected. To decrease the risk of patient to patient, patient to imager, and imager to patient contamination, the indication for any cardiac imaging test should be carefully considered, and only those tests considered essential to patient care performed.

Cardiologists and cardiology departments are heavily affected by this rapidly changing situation.⁵ The COVID-19 pandemic also increases the burden on cardiac imaging services generally. However, given its wide availability and key role as a bedside test, echocardiography is the most affected cardiac imaging modality. Common challenges faced by all cardiac imaging modalities during the pandemic

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include limited expert staff availability [sickness or redeployment in prioritized areas, such as intensive care units (ICUs)] and the risk of peri-procedural transmission of SARS-CoV-2 between patients and staff. The scope of these EACVI recommendations is to summarize how these challenges may be addressed during the pandemic. In particular, we focus upon bold prioritization and provide specific indications and recommendations on how to perform an echocardiogram during the pandemic whilst safeguarding both patient and staff.

Some of our recommendations relating to the appropriate use of imaging modalities in the COVID-19 pandemic must be considered only as expert advice due to the lack of evidence-based scientific data and the rapidly changing global situation.

General considerations

For all modalities, the main question is: ‘Will undertaking this study substantially change patient management or be lifesaving?’ If the answer is yes, use the imaging modality with the best capability to meet the request, but also consider the safety of medical staff regarding exposure. It is very important that every cardiac imaging study is performed appropriately to minimize the risk of further dissemination of the disease ([Key point 1](#) and [Figure 1](#)).

Key point 1

Important considerations in patients with suspected or confirmed COVID-19

- Cardiac imaging should be performed if appropriate and only if it is likely to substantially change patient management or be lifesaving
- Use the imaging modality with the best capability to meet the request, but consider also the safety of medical staff regarding exposure
- Elective non-urgent and routine follow-up exams may be postponed or even cancelled

This question needs to be considered in detail for each echocardiogram requested given the risk of cross-infection and the consumption of personal protective equipment. However, computed tomography (CT) and cardiac magnetic resonance (CMR) may also have a significant potential for contamination of personnel and patients, especially linked to transportation, but also via direct contamination during the scan. In parallel with echocardiography and other imaging modalities, CMR and CT should only be performed if the expected information is critical for clinical management and can be justified in the face of the following considerations: (i) risk of transportation of critically ill or high-risk patients; (ii) time duration of CMR; (iii) possible/significant risk of infection for professionals (technicians, physicians, nurses, and other personnel); (iv) possible/significant risk of contamination

of equipment and facilities, leading to the need for full disinfection; and (v) whether the test is necessary to confirm the diagnosis, or whether this can be achieved based simply upon the clinical probability. In many countries, imaging exams for elective non-urgent patients have been cancelled or postponed. However, cardiac imaging is still being widely requested for inpatients or those presenting to the Emergency Department ([Key point 2](#)).

Key point 2

Risks of contamination in patients with suspected or confirmed COVID-19 include

- Possible/significant risk of infection for professionals (technicians, physicians, nurses, other personnel)
- Possible/significant risk of contamination of equipment and facilities
- Risk of widespread contamination due to transportation of critically ill or high-risk patients—the echo machine should be brought to the patient
- Prolonged duration of a cardiac imaging study will increase the likelihood of contamination

Indications

Patients with suspected or confirmed COVID-19 and no previous history of cardiac disease

The chest radiograph is the most commonly used imaging test in COVID-19 patients, but CT is frequently used to confirm COVID-19 pneumonia. Whilst this might conceivably provide some possible synergies and opportunities to gain information about the cardiovascular system, this requires bespoke protocols that are not widely employed. Dedicated coronary CT angiography is therefore usually required. One emerging clinical issue is that numerous patients with pneumonia caused by COVID-19 experience elevated troponins with and without signs of obstructive coronary artery disease. In this situation, coronary CT angiography can be of great help in excluding or confirming an acute coronary syndrome if the clinical picture is uncertain, substituting for an invasive coronary angiogram and the associated exposure of all the members of the cardiac catheterization laboratory team.⁶ Coronary CT angiography is also increasingly used to assess patients with chronic coronary syndromes, and can be considered in the COVID-19 pandemic in patients with severe symptoms. Another important and emerging role for CT in the pandemic is as a replacement for transoesophageal echocardiography (TOE) to rule out the presence of thrombus in the left atrial appendage before direct current (DC) cardioversion, thereby limiting operator exposure ([Key point 3](#)).

Key point 3

Advice for cardiac imaging

- Echocardiography should not routinely be performed in patients with COVID-19 disease
- A range of different cardiovascular manifestations can be found in COVID-19 which may require cardiac imaging, including a bedside echocardiographic study
- A focused cardiac ultrasound study (FoCUS) is recommended to reduce the duration of exposure
- The risk of contamination of equipment and personnel is very high during TOE—consider repeat TTE, CT scan, or CMR as alternatives
- Chest CT is frequently used to confirm COVID-19 pneumonia and might provide possible synergies and opportunities of cardiac imaging
- Coronary CT angiography can exclude or confirm an acute coronary syndrome in COVID-19 pneumonia where elevated troponins are common
- LV function can be assessed by LV angiogram in patients with acute coronary syndromes during the invasive revascularization procedure
- Positive troponins and myocardial dysfunction or severe arrhythmia suggestive of Tako-tsubo or myocarditis may be an indication for acute CMR if of vital importance for treatment, and patient can be safely transferred for imaging
- Indications for foetal echocardiography remain the same as outside the COVID-19 pandemic

Echocardiography should not routinely be performed in patients with typical signs of COVID-19 disease. Indeed, it should be restricted to those patients in whom it is likely to result in a change in management. Nevertheless, many COVID-19 patients will develop a range of different cardiovascular manifestations which will require a bedside echocardiographic study.⁷ Moreover, there are reasons to believe that the need for echocardiography might expand further as we understand more about COVID-19, with early reports indicating that patients with established cardiovascular disease and cardiovascular risk factors have worse prognosis than others, and are more likely to be admitted to hospital and need respiratory support.¹

Dyspnoea is a typical finding in patients with cardiac disease, and echocardiography may be indicated in the diagnostic work-up, particularly in patients with subacute onset of dyspnoea, oedema, or cardiac murmurs and elevated cardiac biomarkers. Conversely, a normal pro-BNP test can frequently be used to exclude the need for an echocardiogram in patients with dyspnoea or oedema.

In the ICU, echocardiography has sometimes been used to routinely monitor the progress of certain patients.⁷ This should not be routinely performed in the COVID-19 pandemic. Instead, echocardiography should be restricted to patients with cardiovascular instability or signs of right ventricular dysfunction or pulmonary hypertension. Lung ultrasound to detect COVID-19 pneumonia is also useful.⁸ Thickening of the pleurae, the appearance of B-lines, and lung consolidation indicate pneumonia, with pleural effusions rarely reported. Due to its bedside availability, scanning of the lungs by ultrasound can be performed as a quick diagnostic tool.

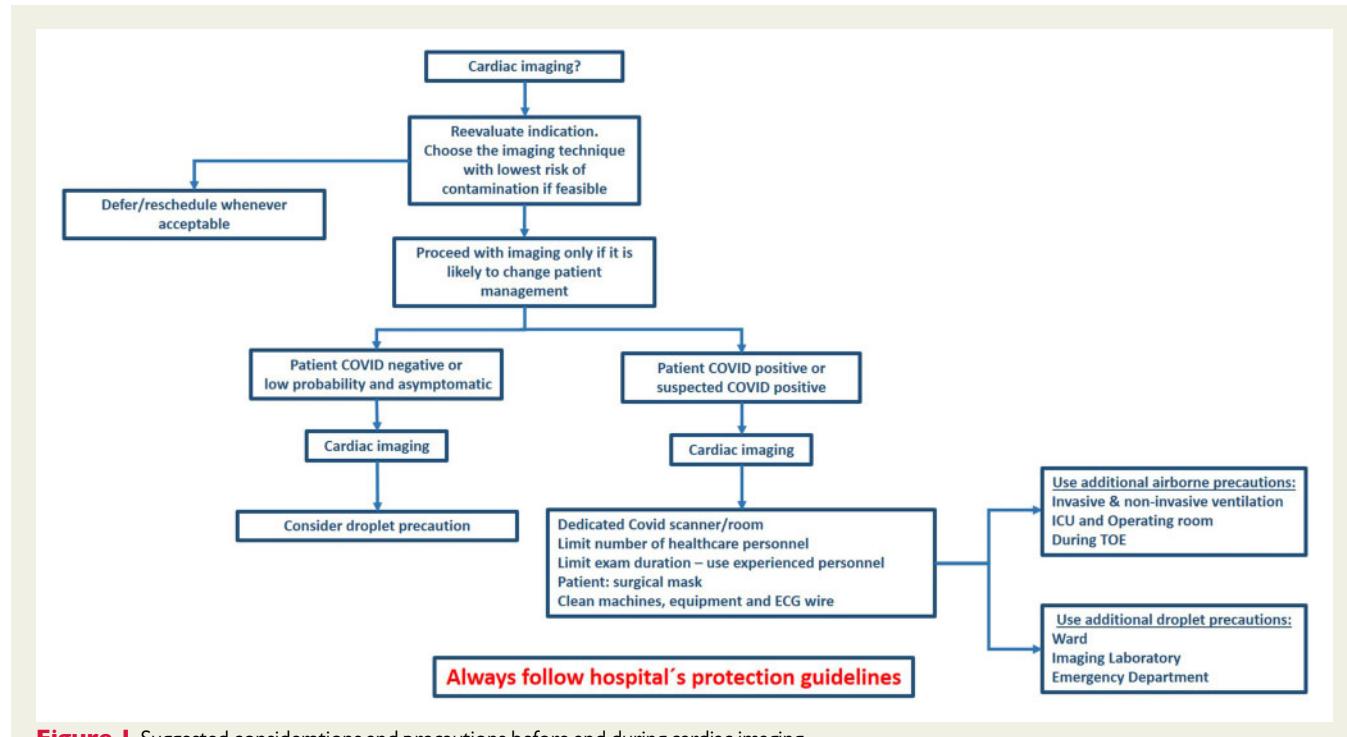


Figure 1 Suggested considerations and precautions before and during cardiac imaging.

Transthoracic echocardiography protocol

If transthoracic echocardiography (TTE) is required to change patient management, we recommend a focused cardiac ultrasound study (FoCUS) as described below. The aim is to reduce the time of exposure with the patient and to decrease the risk of contamination.⁹ Hand-held or smaller lap-top-based scanners may have an advantage as they are easier to cover, clean, and disinfect than larger machines with higher capability.¹⁰ At a minimum, such a focused echocardiographic study in patients with verified or suspected COVID-19 should include the following.

Left ventricle: systolic global function (ejection fraction), signs of regional dysfunction, end-diastolic cavity dimension.

Right ventricle: global function [right ventricular fractional area change (RVFAC) or tricuspid annular plane systolic excursion (TAPSE)], end-diastolic cavity dimension, tricuspid regurgitation pressure gradient (TRP) (if possible).

Valves: gross signs of valvar disease, but only in cases of critical clinical importance should an in-depth evaluation be considered.

Pericardium: thickening or effusion.

ECG monitoring during imaging can be omitted and measurements should be performed offline to reduce exposure and contamination. If a curtailed echocardiogram is performed because of the COVID-19 situation, this should be stated in the report.

Patients with confirmed COVID-19 and known or acute cardiac disease

Due to increased metabolic and haemodynamic demands, infection and concomitant fever act as a cardiac stress test potentially aggravating the effects of pre-existing valve disease, heart muscle disease, coronary artery disease, and congenital heart disease. Similar and additional effects can be caused by reduced oxygenation of the blood due to respiratory failure. This may help explain why co-existing cardiovascular disease is a negative predictor in COVID-19 patients.¹ Clinical decision-making may be complicated in these critically ill patients, and cardiac imaging may be decisive. However, unnecessary examinations should be avoided to reduce risk of contamination of personnel and misuse of resources. Indeed, careful consideration should be given to whether echocardiography and cardiac imaging will change management, including whether patients would be candidates for more advanced treatment strategies on the basis of the results of an echocardiogram. If not, the scan may be futile.

Patients without symptoms or signs of COVID-19 but with known or acute cardiac disease

Clinical priorities and procedures will change during this pandemic. Echocardiography should therefore generally be reserved for patients with symptomatic heart disease (NYHA III–IV) in this phase. Routine follow-up echocardiographic studies of patients with non-severe symptoms or those not eligible for invasive or surgical treatment should be postponed or cancelled. This includes patients with stable congenital heart disease. Patients with acute heart failure and patients with valvular heart disease with severe symptoms such as chest pain, syncope, and dyspnoea during daily activity should be prioritized and receive adequate treatment. Their prognosis without treatment is probably worse than that of most COVID-19 patients.

Acute endocarditis, with no relationship to COVID-19, will also continue to appear, and the number of patients may even increase as visits to the dentist are cancelled. Endocarditis has a high mortality, and these patients should continue to have a high priority for echocardiography and treatment according to state of the art recommendations.¹¹ If the patient has concomitant COVID-19, an individualized approach is necessary.

In ST-segment elevation myocardial infarction (STEMI) we recommend an LV angiogram for LV function in patients having an invasive revascularization procedure. Echocardiography can then be avoided in these patients, with the exception of those that become haemodynamically unstable or develop potential post-STEMI complications. In unstable non-STEMI patients with positive troponins and clinical signs of heart failure, echocardiography may be of importance to justify a faster invasive revascularization procedure. Patients with murmurs should undergo echocardiography to rule out valve disease as the cause of their presentation with chest pain.

Transoesophageal echocardiography

TOE might be stressful to our patients and should be avoided in most patients with ongoing COVID-19. The risk of contamination of equipment and personnel is also very high during the procedure due to droplets and aerosols containing virus. The incremental role of TOE over TTE should be carefully considered. This procedure should therefore be reserved for patients where the suspected findings are of crucial importance to confirm or exclude a diagnosis or to guide treatment.

Indication for other echocardiographic methods

Indications for stress echocardiography, as well as for other stress imaging techniques, seem very limited in the COVID-19 pandemic, and should be avoided in patients with acute infection. Coronary CT angiography should be the preferred method if patients are being investigated for chronic coronary syndromes.⁶ Ultrasonic contrast agent may be useful in some patients, but should not be used in circulatory unstable or critically ill patients.¹²

Foetal echocardiography

It is currently unclear whether maternal infection affects the foetus, by causing either structural heart disease or foetal myocarditis, and therefore routine foetal echocardiography in infected mothers is not recommended for the indication of COVID-19 infection alone. However, the indications for foetal echocardiography remain the same during the pandemic, in that pregnancies judged to be at high risk for foetal cardiac disease need to continue to be referred according to local guidelines, and assessed within the appropriate time frame.¹³ Counselling may be undertaken using video conferencing or other technology in order to reduce time in physical proximity to the

patient, and the minimum number of healthcare professionals should attend scanning and counselling.

Indication for other imaging methods

Given the acute nature of the disease, and restrictions of hospital facilities for chronic patients, there are probably few defined indications for coronary CT angiography, CMR, or nuclear cardiology in patients with COVID-19 infection during the acute phase.

Similar to the situation for echocardiography, patients scheduled for CMR, CT, and nuclear cardiology, with non-severe symptoms or not eligible for invasive or surgical treatment, should be postponed. Routine follow-up scans should be re-scheduled. A possible indication for CMR is the suspicion of COVID-19 myocarditis, but the clinical implication of detecting myocarditis in these patients is not determined. We suggest that positive troponins and myocardial dysfunction or severe arrhythmia not explained by other methods may be an indication for acute CMR if of crucial importance for the treatment and the patient is stable enough to be scanned.

Cleaning, disinfection, and protection in patients with suspected or confirmed COVID-19

Equipment

All equipment used in close contact with patients has the potential to carry droplets containing the virus. This includes ECG leads which should therefore be avoided when performing echocardiographic studies in COVID-19 patients.

Moderately warm water and a mild detergent constitute the basis of equipment cleaning in all cardiac imaging machines, including the echocardiographic probe. An ordinary water-soluble disinfectant should also be added, but not on the membrane. A non-alcoholic

disinfectant should be used on the echocardiographic probe (please confirm with recommendations for each vendor). Dedicated wipes may also be used in this process.

Protecting the echocardiographic machines with custom-made covers may be possible if available, but, if not, other protective equipment can be fashioned using local entrepreneurs and ingenuity. It is, however, important not to cover the screen in a way that reduces the view for the echocardiographer. This may reduce the quality of the study and increase scan duration. Similarly, the keyboard should be fully operative during the investigation. To facilitate the cleaning of the scanner, all additional 3-D and single-Doppler probes should be removed before the scanning starts, if they are not needed for proper diagnosis. ECG leads should also be removed, although this may make the recordings of loops more difficult and potentially more time consuming. In high-volume centres, one can consider dedicating separate scanners to be used exclusively for COVID-19-positive patients, that remain within designated COVID-19 areas. No additional disinfection procedure is necessary for a TOE probe as every location should have proper routines for cleaning and disinfection of these probes. A protective coat on the TOE probe might also be considered.

The positioning of the patient vs. the echocardiographer and the scanner may be of importance. Patients placed in the left lateral position with the scanner positioned on the right side of the bench will result in the longest possible distance between the faces of the patient and the echocardiographer. The contamination of the scanner by airborne droplets from the patient will also probably be minimized. However, the preferred patient position is different among echocardiographers, and these recommendations should not be a hindrance to performing high-quality fast echocardiograms. A surgical mask on the patient will also reduce contamination by air droplets.

Facilities

The echocardiographic study will usually be performed in the ICU or in emergency rooms in critically ill patients. Less critical patients are usually examined in their ward rooms. Dedicated room(s) may be prepared in the echocardiographic lab, where unnecessary equipment can be removed to make the cleaning of the room as easy as possible. However, there is less risk of virus spread if the

Table I Recommendations during TTE and foetal echo

Risk of contamination	Handwashing	Surgical mask and gloves	Protective clothing, eye protection	Head cap	Study completeness	Equipment protection
Lower risk	Obligatory	Preferable	Probably not	No	Full	None
Moderate risk	Obligatory	Obligatory	Preferable	No	Preferably full/depending on severity of the cardiac pathology	Intermediate/protection of probe, leads, and other parts near the patient
Severe risk/ confirmed COVID-19	Obligatory	Advanced mask: FFP2/FFP3/N95/N99	Obligatory	Obligatory	Problem focused, adjusted for clinical importance of the cardiac pathology	Full cover/dedicated scanners

Lower risk, patients with no symptoms, no increased risk behaviour, a recent negative virus test, or in areas with low risk of COVID-19. Moderate risk, patients with non-specific/unclear symptoms or patients without symptoms in an area with moderate or high risk of COVID-19. Severe risk, patients with typical symptoms or confirmed COVID-19. FFP2, Filtering Facepiece Particulate class 2 (FFP2 corresponds to US N95, FFP3 corresponds to US N99).

echocardiographer brings the echocardiographic machine to the patient, and the patient can remain in their isolation. Local factors must be considered with dedicated COVID-19 areas respected, ensuring COVID-19 'clean' and 'dirty' areas are not mixed.

Reading and conference rooms where echocardiograms are presented on small PC screens may prevent the recommended 2 m distance between the experts. Thus, larger rooms, with projectors that can present the images on large screens are recommended. Virtual communication technology that allows several colleagues to simultaneously visualise images on geographically remote screens is the preferred solution for multidisciplinary team meetings.

Healthcare personnel

All advice regarding personal protective equipment (PPE) should follow the internal rules in each institution. This will vary according to the local nature of the pandemic and the availability of PPE. We here offer some general advice. Repeated and thorough handwashing is the basis of virus protection for everyone, including patients and health professionals. In addition to handwashing after every examination, disinfecting agents should be used on the hands.

When examining a patient with confirmed or suspected COVID-19, protective clothing, gloves, headcovers, specific face-masks, and eye shields must be used (*Table 1*). Patients should wear a surgical mask during imaging (*Table 2*). During TOE, medical protective masks must be used due to risk of aerosols and airborne spread (*Table 3*). How to adequately dress and undress is

described in several publications and is not further described here.

When performing an echocardiogram in patients without confirmed COVID-19, surgical facemasks should be used in regions where the risk of virus spread is high or uncertain. Non-sterile gloves should also be used and renewed between every patient since the persistence of the virus on plastic is long. If the patient has low risk of infection due to low risk in the respective regions or has no symptoms, this may be omitted, especially if there is shortage of face masks or gloves in the hospital.

Precautions in other imaging modalities

Precautions for all the other imaging modalities are similar. Imagers and technologists should wear protective clothing, gloves, and face-masks while undergoing scanning, and patients should wear a surgical mask during imaging. The scanner, coils, and ECG cables are mandatory for cardiac CMR and CT scans but need to be thoroughly disinfected after imaging (*Table 1*). Cleaning of the scanners after imaging patients with COVID-19 infection is also obligatory (see above). An important strategy to reduce contamination is to reserve one scanner for known infected patients and another for low-risk and non-infected patients.

Conclusion

The COVID-19 pandemic has forced us to reconsider how best to perform cardiac imaging in the right patients at the right time and how to minimize the risk of cross-infection for imagers and patients alike. These recommendations are suggested as tools to guide good clinical practice during what is a turbulent period in our practice, and one that is rapidly changing both the premises and demands for cardiac imaging. We expect our understanding of how best to image patients during the COVID-19 pandemic to change rapidly and will adapt our guidance accordingly.

Conflict of interest: none declared.

Table 2 Recommendations for patients during all imaging modalities

Risk of infection	Surgical mask
Lower risk	Preferable
Moderate risk	Obligatory
Severe risk/confirmed COVID-19	Obligatory

Table 3 Recommendations during TOE

Risk of contamination	Handwashing	Surgical mask and gloves	Protective clothing, eye protection, head cap	Study completeness	Equipment protection
Lower risk	Obligatory	Obligatory	Optional/Preferable	Full	None/protection of parts near the patient
Moderate risk	Obligatory	Obligatory	Obligatory	Preferably full/depending on severity of the cardiac pathology	Intermediate/protection of leads and other parts near the patient
Severe risk/confirmed COVID-19	Obligatory	Obligatory (double gloves, protective masks FFP2/FFP3/N95/N99)	Obligatory 'advanced kit'	Problem focused adjusted for clinical importance of the cardiac pathology	Full cover/dedicated scanners

For definition of risks of contamination, see *Table 1*. Washing and disinfection of the TOE probe and its leads are not further described as standard procedures should include sufficient virus protection.

References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;doi:10.1001/jama.2020.2648.
2. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020;doi:10.1038/s41569-020-0360-5.
3. Xiong T-Y, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. *Eur Heart J* 2020;doi:10.1093/eurheartj/ehaa231.
4. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, Xing F, Liu J, Yip CC-Y, Poon RW-S, Tsui H-W, Lo SK-F, Chan K-H, Poon VK-M, Chan W-M, Ip JD, Cai J-P, Cheng VC-C, Chen H, Hui CK-M, Yuen K-Y. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020;**395**:514–523.
5. Elkind MS, Harrington RA, Benjamin IJ. Role of the American Heart Association in the global COVID-19 pandemic. *Circulation* 2020;doi:10.1161/CIRCULATIONAHA.120.046749.
6. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.
7. Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, Flachskampf FA, Hassager C, Pasquet A, Gargani L, Galderisi M, Cardim N, Haugaa KH, Ancion A, Zamorano JL, Donal E, Bueno H, Habib G. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. *Eur Heart J Cardiovasc Imaging* 2015;**16**:119–146.
8. Peng Q-Y, Wang X-T, Zhang L-N, Chinese Critical Care Ultrasound Study Group (CCUSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019–2020 epidemic. *Intensive Care Med* 2020;doi: 10.1007/s00134-020-05996-6
9. Neskovic AN, Skinner H, Price S, Via G, De Hert S, Stankovic I, Galderisi M, Donal E, Muraru D, Sloth E, Gargani L, Cardim N, Stefanidis A, Cameli M, Habib G, Cosyns B, Lancellotti P, Edvardsen T, Popescu BA. Reviewers: This document was reviewed by members of the 2016–2018 EACVI Scientific Documents Committee. Focus cardiac ultrasound core curriculum and core syllabus of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2018;**19**:475–481.
10. Cardim N, Dalem H, Voigt J-U, Ionescu A, Price S, Neskovic AN, Edvardsen T, Galderisi M, Sicari R, Donal E, Stefanidis A, Delgado V, Zamorano J, Popescu BA. The use of handheld ultrasound devices: a position statement of the European Association of Cardiovascular Imaging (2018 update). *Eur Heart J Cardiovasc Imaging* 2019;**20**:245–252.
11. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL, ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;**36**:3075–3128.
12. Neglia D, Liga R, Caselli C, Carpegiani C, Lorenzoni V, Sicari R, Lombardi M, Gaemperli O, Kaufmann PA, Scholte AJHA, Underwood SR, Knuuti J, EVINCI Study Investigators. Anatomical and functional coronary imaging to predict long-term outcome in patients with suspected coronary artery disease: the EVINCI-outcome study. *Eur Heart J Cardiovasc Imaging* 2019;doi:10.1093/eihci/jez248
13. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, Cuneo BF, Huhta JC, Jonas RA, Krishnan A, Lacey S, Lee W, Michelfelder EC, Rempel GR, Silverman NH, Spray TL, Strasburger JF, Tworetzky W, Rychik J. American Heart Association Adults With Congenital Heart Disease Joint Committee of the Council on Cardiovascular Disease in the Young and Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Council on Cardiovascular and Stroke Nursing. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation* 2014;**129**:2183–2242.

IMAGE FOCUS

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Video-assisted transmitral resection of primary cardiac lipoma originated from the left ventricular apex

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A 77-year-old woman who suffered from weight loss was referred to our hospital. She lost 8 kg of weight a year, and whole-body computed tomography (CT) scan was performed for the evaluation of malignancies. Contrast enhanced CT demonstrated a low-intensity (-100 to -120 Hounsfield) mass without contrast opacification (Panel A). Echocardiography revealed a high echogenic and well-demarcated movable mass (25 × 28 mm) located in the left ventricular apex (Panel B, arrow; see Supplementary data online, [Video S1](#)). T2 and fat suppression T2 magnetic resonance imaging suggested that the tumour was a lipoma (Panels C and D, arrow). Transmitral endoscopy via the left atrium demonstrated the yellowish and well-demarcated mass originating from the left ventricular wall (Panel E, arrow; see Supplementary data online, [Video S2](#)). Intraoperative consultation revealed that the tumour was a lipoma without malignancy (Panel F), which was completely resected by transmitral approach without ventriculotomy. The patient was event free with no relapse for at least a year.

Cardiac lipomas are rare and often asymptomatic. Benign lipomas are sometimes difficult to diagnose; therefore, surgical resection of the tumour may be warranted for the precise diagnosis. Recently, video-assisted removal of cardiac tumours, which can avoid a left ventriculotomy, has been reported to be a useful method of resecting cardiac tumours. In this case, transmitral endoscopy via the left atrium clearly showed the appearance of the tumour and the intra-cardiac anatomy, which enabled us to avoid an unnecessary ventriculotomy.

Conflict of interest: None declared.

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IMAGE FOCUS

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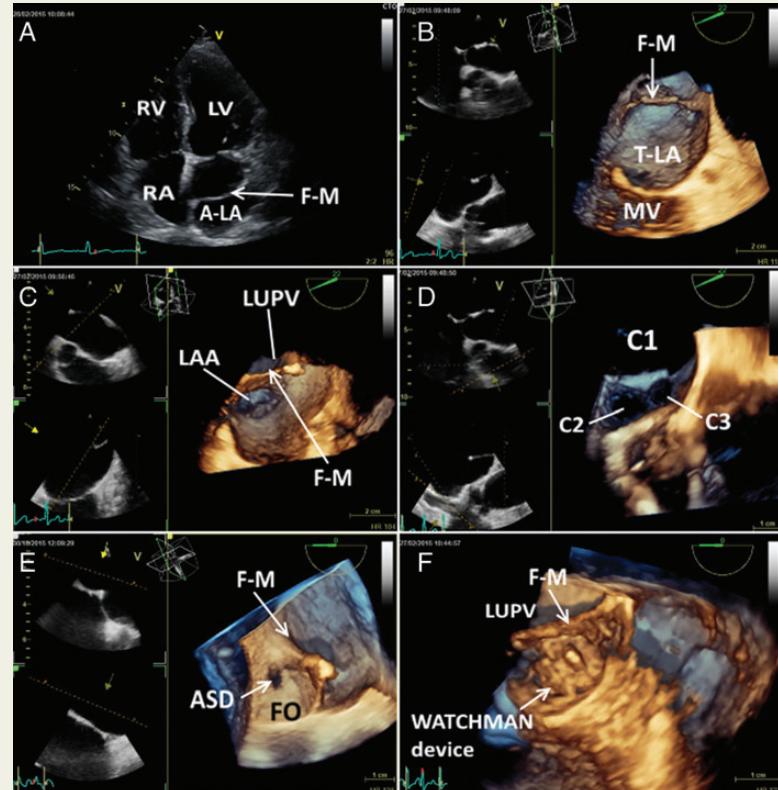
Left atrial appendage closure in a patient with cor triatriatum and ASD: the added value of 3D echocardiography

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A 47-year-old woman with cor triatriatum (Panel A, see Supplementary data online, [Video S1](#) and [S2](#)) and small ostium secundum atrial septal defect (ASD) was evaluated for percutaneous closure of left atrial appendage (LAA) due to permanent AF and Cooley's disease (CHA2-DS2-VASC:2;HAS-BLED:4). 3D transoesophageal echocardiography shows the fibromuscular membrane (F-M) dividing the left atrium into two chambers: the accessory left atrium (A-LA) receives venous blood, whereas the true left atrium (T-LA) is in contact with mitral valve (MV), fossa ovalis (FO), and LAA (Panels B and C, see Supplementary data online, [Video S3](#) and [S4](#)). There is one large unrestrictive communication between the two chambers (C1) with mean gradient of 2 mmHg at Doppler interrogation and two smaller communications in the membrane itself (C2–C3) corresponding to Loeffler's classification type 3 (Panel D, see Supplementary online data, [Video S5](#)). A small ASD just below the membrane is also associated (Panel E, see Supplementary data online, [Video S6](#)). During the procedure, after exclusion of clots and definition of LAA anatomy, a transseptal puncture was performed to cross the interatrial septum not through the ASD but in a more postero-inferior position below the membrane to reach easily the LAA (see Supplementary data online, [Video S7](#)). A Watchman device n.21 was implanted. The final result shows the device inside the LAA, with no interference with the membrane originating from the infold separating the LAA and left upper pulmonary vein (Panel F, see Supplementary data online, [Video S8](#)). 3D transoesophageal reconstruction is a useful tool to understand the anatomy of this rare case of congenital heart disease in detail, even more when interventional procedures are needed.



Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

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IMAGE FOCUS

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Tricuspid regurgitation repair with a MitraClip device: the pivotal role of 3D transoesophageal echocardiography

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A 77-year-old male presented with congestive heart failure (NYHA class IV) despite maximal medical therapy. Right sided features were predominant; transoesophageal echocardiography (TEE) revealed severe tricuspid regurgitation (TR) (Panel A: 1: 3D TEE; 2. 2D TEE, 3. Colour Doppler; see Supplementary data online, [Video 1](#)) without leaflet coaptation (white asterisk). Due to prohibitive surgical risk, a catheter based intervention with a MitraClip (Abbott, USA) device was considered.

Under general anaesthesia and with 3DTEE guidance (Panel B), a MitraClip was delivered through the right femoral vein to the mid right atrium (RA, B1), advanced to approximately 1 cm above the tricuspid plane, oriented (B2, B3), and advanced into the right ventricle (RV). The septal (S) and anterior leaflet (A) were initially targeted for device placement; however the coaptation gap was too wide (B4). MitraClip deployment from the posterior (P) to septal leaflet was then targeted (B5, B6). After several attempts, the leaflets were captured (see Supplementary data online, [Video 2](#)) and closure of the MitraClip produced an immediate reduction in TR severity (Panel C, see Supplementary data online, [Video 3](#)). Although TR remained at least moderate, the patient was discharged home 3 days later and experienced a dramatic diuresis (> 30 lbs) over the following two weeks. Three month after the procedure, he continues to report improved functional status (NYHA class II).

3D TEE guidance of these procedures was critical as it provided clear definition of the valve leaflet anatomy, as well as real-time evaluation of the MitraClip placement and function. As tricuspid valve interventions continue to be developed these early procedural experiences will become increasing important.

Supplementary video are available at *European Heart Journal—Cardiovascular Imaging* online.

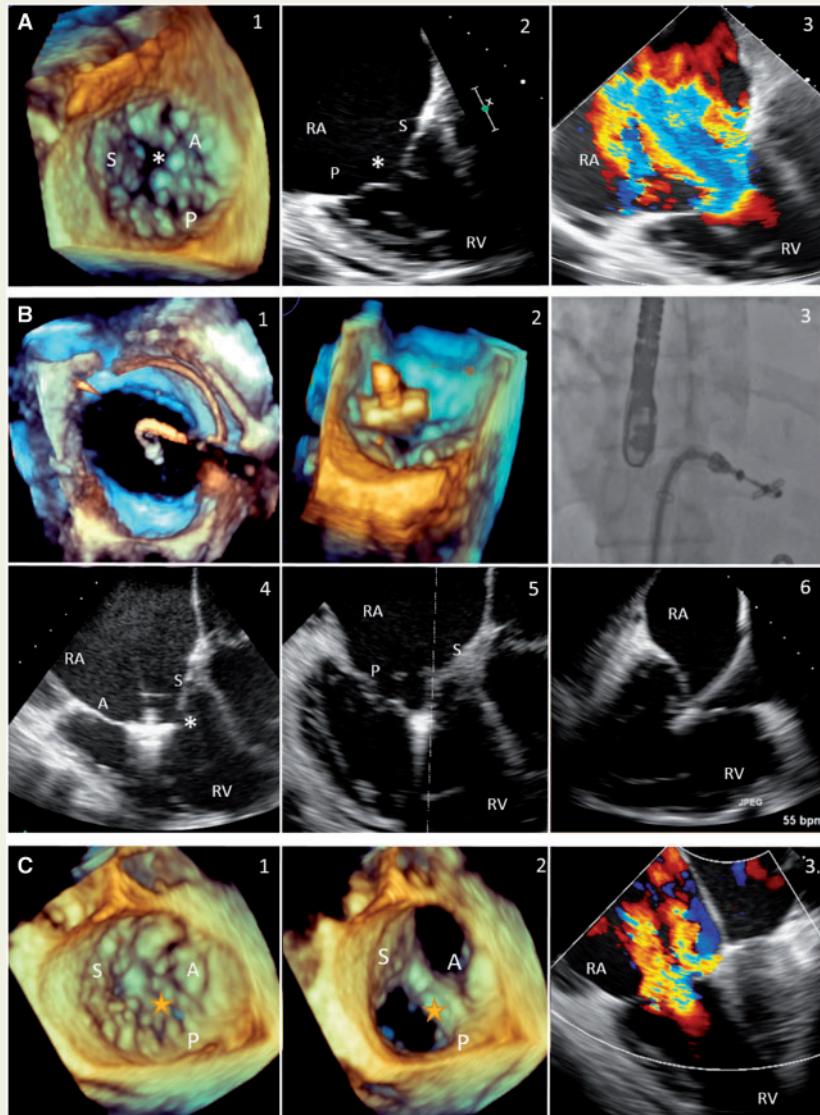


IMAGE FOCUS

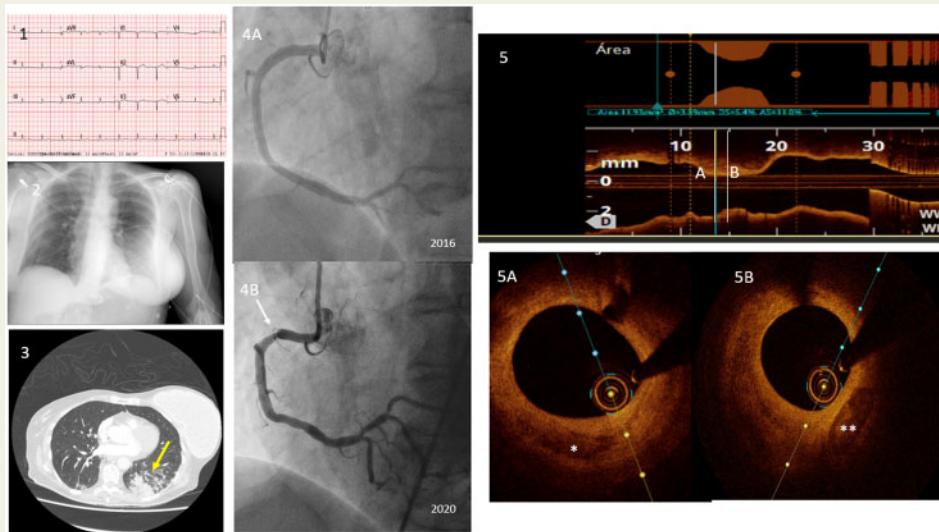
doi:10.1093/ehjci/jeaa147

Unusual presentation of acute coronary syndrome in a patient with SARS-CoV-2 infection**Luisa Salido-Tahoces*, Angel Sánchez-Recalde, Ana Pardo-Sanz, and José Luis Zamorano Gómez**

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A 62-year-old woman with hypertension and chronic ischaemic heart disease was referred to the hospital for asthenia and self-limiting episodes of chest pain. ECG showed no evidence of acute ischaemia (Figure 1). High sensitivity troponin T and C-reactive protein were elevated. Chest X-ray showed a subtle consolidation on the left lung base (Figure 2). Baseline chest scan confirmed an opacity on the left lung (yellow arrow) and ruled out pulmonary embolism (Figure 3). Nasopharyngeal swab was positive for SARS-CoV-2.

Due to the persistence of chest pain, coronary angiography was requested. Coronary angiography showed a focal and moderate stenosis (white arrow) in the proximal right coronary artery (Figure 4B; [Supplementary material, Video 1](#)), that was not present in the previous coronary angiography 2 years previously (Figure 4A; [Supplementary material, Video 2](#)). Optical coherence tomography showed a plaque with a crescent-shaped low-signal region (*) with heterogeneous content adjacent to the calcification (**) that suggested intraplaque haemorrhage (Figure 5A and B; [Supplementary material, Video 3](#)). There was no disruption of the intima or thrombus. Intraplaque haemorrhage is described as an unstable plaque mechanism, so it was decided to implant a drug-eluting stent. The patient evolved well without new episodes of chest pain and a benign course of COVID-19 disease. The systemic inflammatory response of SARS-CoV-2 infection could trigger a focal inflammatory response in the coronary wall and be responsible for the instability of an atherosclerotic plaque. We showed the first direct evidence of complicated atherosclerotic plaque in a COVID-19 patient, undergoing optical coherence tomography characterization.

**Supplementary material**

[Supplementary material](#) is available online at *European Heart Journal – Cardiovascular Imaging*.

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Long-term prognostic value of morphological plaque features on coronary computed tomography angiography

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Aims

To investigate the incremental prognostic value of morphological plaque features beyond clinical risk and coronary stenosis levels. Although associated with the degree of coronary stenosis, most cardiac events occur on the basis of ruptured non-obstructive plaques and consecutive vessel thrombosis. As such, identification of vulnerable plaques is paramount for cardiovascular risk prediction and treatment decisions.

Methods and results

A total of 1615 patients with suspected but not previously diagnosed coronary artery disease (CAD) were examined by coronary computed tomography angiography and morphological plaque features were assessed. Mean follow-up was 10.5 (interquartile range 9.2–11.4) years. Cox proportional hazards analysis was used for the composite endpoint of cardiac death and non-fatal myocardial infarction. The study endpoint was reached in 51 patients (36 cardiac deaths, 15 non-fatal myocardial infarctions). In addition to quantitative parameters (presence of any calcified/non-calcified plaque or elevated plaque load), morphologic plaque features such as a spotty or gross calcification pattern and napkin-ring sign (NRS) were predictive for events. However, only spotty calcified plaques and NRS could confer additive prognostic value beyond clinical risk and coronary stenosis level. In a stepwise approach, endpoint prediction beyond clinical risk (Morise score) could be improved by inclusion of CAD severity (χ^2 of 27.5, $P < 0.001$) and further discrimination for spotty calcified plaques (χ^2 of 3.89, $P = 0.049$).

Conclusion

Improved cardiovascular risk prediction beyond clinical risk and coronary stenosis levels can be made by discriminating for the presence of spotty calcified plaques. Thus, an intensified prophylactic anti-atherosclerotic treatment appears to be warranted in patients with coronary plaques that show spotty calcifications.

Keywords

coronary computed tomography angiography • coronary artery disease • prognosis • high-risk plaque features • vulnerable plaque

Introduction

Through numerous studies, coronary computed tomography angiography (CCTA) has evolved to become a reliable non-invasive tool to assess coronary luminal stenosis and diagnose coronary artery disease (CAD).¹ However, most acute coronary syndromes (ACSs) occur after rupture of non-obstructive plaques and subsequent coronary thrombosis.^{2,3} The Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT)-I trial has shown, that

the sole presence of stenosis >50% has only limited diagnostic power to predict future ACSs or perfusion defects on Single-photon emission computed tomography (SPECT).⁴ On the other hand, many patients exhibit non-stenotic plaques but only a fraction of those plaques are prone to ruptures and consecutive development of an ACS. In an effort to decipher why some plaques are more keen to rupturing than others, the concept of plaque vulnerability was introduced. Invasive studies have determined that thin-capped fibroatheromas (TCFAs) are a frequent precursor lesion to plaque rupture and

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account for most coronary thrombi.^{5,6} Morphologically, TCFAs are atherosclerotic plaques containing a large necrotic core speckled with inflammatory cells and covered by a thin overlying fibrous cap. The hope is that prospective recognition of such plaques might identify future culprit lesions before they result in ACSs. With that in mind, CCTA-based therapeutic decision-making using intraluminal stenosis alone is sub-optimal. In fact, one strength of CCTA lies in its ability to not only assess luminal stenosis but also the surrounding vessel wall and plaque composition.

Therefore, extending coronary vessel evaluation beyond the degree of stenosis and attempting to identify vulnerable plaques with CCTA has become an area of considerable research interest. Recent studies have led to the proposal to consider positive remodelling, low attenuating plaques, napkin-ring sign (NRS), and spotty calcifications as high-risk plaque features (HRPF). Imaging counterparts to plaque instability have before been proposed for intravascular ultrasound and optical coherence tomography studies.⁷⁻⁹ HRPF as an independent predictor for adverse cardiac events have been established in large population studies, yet its incremental value to the degree of coronary obstruction on a long-term basis remains uncertain.¹⁰⁻¹² We, therefore, extended our follow-up of previous studies and adjudicated outcomes out to 10 years to answer the question how plaque morphology can contribute to the long-term prediction of adverse cardiac events, especially in addition to established CCTA parameters.¹³

Methods

Study population

Eligible for analysis were all consecutive patients undergoing CCTA at our institution from 01 October 2004 to 31 September 2007 with suspected but not previously diagnosed CAD. Clinical suspicion of CAD was raised by the referring cardiologist on the basis of a heightened cardiovascular risk profile, thoracic pain, or abnormalities on stress electrocardiogram. Written informed consent was obtained before the investigation. Exclusion criteria were patients in an acute life-threatening situation, patients who presented with ACSs or who had no stable sinus rhythm during the exam. A structured interview was held before the investigation and information about age, weight, and height of the patient, symptoms, cardiac history, and current medication was collected. The following cardiac risk factors were recorded: (i) presence and degree of hypertension (for binary analysis hypertension was defined as a systolic blood pressure of >140 mmHg or administration of antihypertensive therapy), (ii) diabetes mellitus (defined as fasting blood glucose level >7 mmol/L, use of oral anti-diabetic therapy, or subcutaneous insulin), (iii) smoking (defined as current smoker or previous smoker within the last year), and (iv) positive family history (defined as presence of CAD in first-degree relatives younger than 55 years in males or 65 years in females). In addition, laboratory results for total cholesterol, LDL- and HDL-fraction, and triglycerides were collected. From these data, the Morise-score was calculated, stratification for low- (0–8 points), intermediate- (9–15 points), and high- (>15 points) risk was done as proposed.¹⁴ This score evaluates both, cardiovascular risk factors as well as clinical symptoms and was best suited to evaluate cardiac risk in our study population. The study design was approved by the local ethics committee.

Computed tomography procedure

The detailed scan protocol has been described elsewhere.¹⁵ Different CT hardware has been used during the study period. A 64-slice single-source computed tomography (CT) scanner was used from October 2004 to September 2006 and a 64-slice dual-source CT scanner from October 2006 to September 2007 (both Siemens Healthineers, Erlangen, Germany).

Coronary artery segmentation was done according to the simplified American Heart Association classification, using the first 15 of the original 18 segments. Vessel segments >1.5 mm in diameter were evaluated by one of two physicians with an experience of having read more than 400 cardiac CTs at the time the scan was performed. Disagreements were settled by consensus.

Each stenosis was rated visually according to CAD severity as proposed by Ostrom et al.¹⁶ with the categories 'normal' for 0% stenosis, 'non-obstructive' for 1–50% stenosis, and 'obstructive' for >50% stenosis (which was itself divided into 'one-vessel obstructive', 'two-vessel obstructive', and 'three-vessel obstructive'). Segments with artefacts were assigned to the most appropriate group.

Stratification according to the Coronary Artery Disease-Reporting and Data System

(CADRADS), as proposed by Cury et al.¹⁷ was further performed for primary analysis. In an effort to grasp the generalized extent of CAD, the segment involvement score (SIS) (number of segments with any stenosis ≥25% or any calcified, partially calcified, or non-calcified plaque irrespective of the degree of stenosis) was calculated. Addition of affected segments results in a SIS ranging from 0 to 15.¹⁸

All plaques were re-evaluated using an advanced imaging workstation (Syngo via, Siemens Healthineers, Erlangen, Germany) and the following morphological plaque features were assessed.

- Positive vessel remodelling was reported for >10% (remodelling 110%) or >30% (remodelling 130%) greater vessel diameter at plaque site in comparison to the diameter of a normal appearing proximal segment.
- Local plaque load (LPL) as given by the ratio of plaque volume to vessel volume at plaque site.
- Calcified plaques were defined as having a signal intensity above the contrasted vessel volume and further discriminated for gross calcifications (calcifications ≥3 mm in any direction) or spotty calcifications (calcifications <3 mm in any direction).
- Non-calcified plaques were defined as any non-calcified stenosis ≥25% with a signal intensity between the surrounding fatty tissue and contrasted vessel lumen. The appearance of non-calcified plaques was further visually specified as homogeneous, inhomogeneous, or consistent with NRS (low-attenuating central portion with ring-like higher attenuation).
- Low-attenuation plaques (LAPs) were defined as having a core intensity <30 HU.
- Plaques presenting both, calcified and non-calcified portions but no other defined plaque feature were defined as partially calcified plaques.

Representative pictures of the investigated plaque features are given in Figure 1.

Follow-up

Follow-up information was obtained by clinical visits if available, by detailed questionnaires sent by mail or, if the questionnaires were not returned, by phone contact. All reported events were verified by hospital records or phone contact with the attending physician if possible, and adjudicated by two physicians in consensus. The primary endpoint of this study was a composite of cardiac death or non-fatal myocardial infarction.

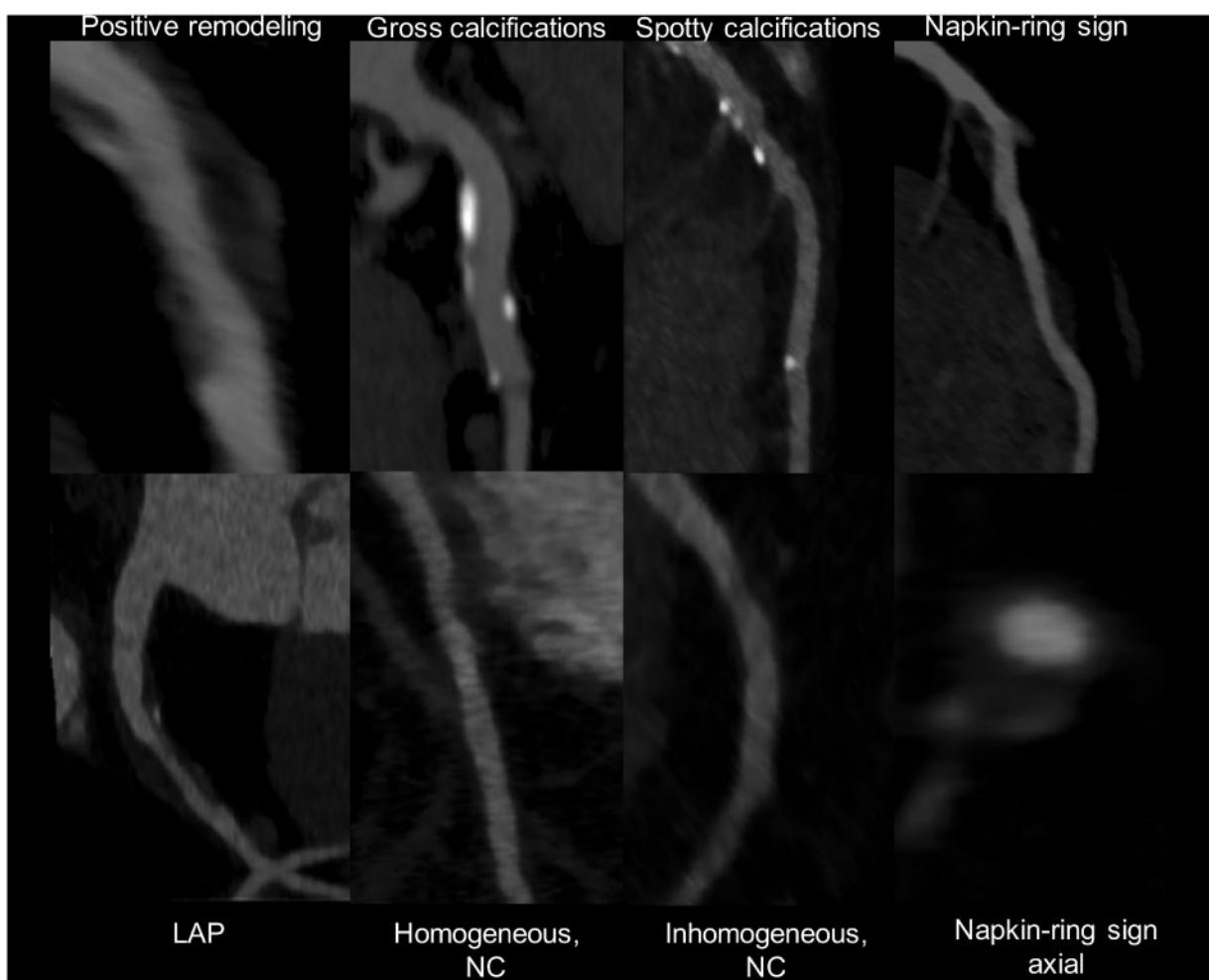


Figure 1 Examples of the investigated plaque features on curved planar reformation images. LAP, low-attenuation plaque; NC, non-calcified plaque.

Information on early (≤ 90 days after index CCTA) and late (> 90 days after index CCTA) revascularizations during follow-up was noted and a composite of cardiac death, non-fatal myocardial infarction, and late revascularization was defined as secondary endpoint.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, continuous variables are described as means \pm standard deviation or as median (interquartile range, IQR) for time intervals. All statistical evaluations are based on the event-free survival for the study endpoint using the Kaplan–Meier method. Multivariable analyses were performed using the Cox proportional hazards method. Concordance c-indices were evaluated from time-to-event data as proposed by Harrell et al. C-indices were calculated for Morise and selected CCTA parameters. The Morise score was chosen as clinical risk parameter as thoracic pain was the most frequent indication for CCTA in our study cohort and this score has been validated in symptomatic patients. A three-step, multivariate model composed of Morise, the degree of coronary vessel obstruction and morphological plaque features was calculated to identify the plaque features most predictive for the composite endpoint. All statistical tests were performed two-sided and significance level of 5% was used. The statistical

package R version 2.10.1 including the package rms was used for statistical analysis.^{19,20}

Results

Study population and patient characteristics

During the study period, 1744 patients with suspected but not previously diagnosed CAD underwent CCTA. In total, 71 patients were excluded; 5 patients with acute aortic dissection undergoing CCTA as a pre-operative assessment, 1 patient with an ACS, and 65 patients who did not have a stable sinus rhythm during the scan. Out of the remaining 1673 patients, 1615 patients could be contacted for follow-up at a median of 10.5 years (IQR 9.2–11.4 years) and were included into the study. This translates to a follow-up rate of 97%.

Mean patient age was 59 ± 11 years, 1076 patients (67%) were male. The pre-test risk assessed by Morise risk score was low in 319 patients (20%), moderate in 1199 patients (74%), and high in 97

Table 1 Patient baseline characteristics

Patient characteristics	Study population, n = 1615 (%)	Patients lost on follow-up, n = 58 (%)	P-value
Age	60.3 ± 11.1	53.9 ± 9.2	0.013
Male gender	1076 (66.6)	43 (74.1)	0.26
Body mass index (kg/m ²)	26.2 ± 3.9	25.6 ± 4.2	0.0014
Arterial hypertension	957 (59.3)	29 (50.0)	0.18
Smoking	548 (33.9)	23 (39.7)	0.4
Diabetes	120 (7.4)	8 (13.8)	0.079
Hypercholesterolaemia	861 (53.3)	29 (50.0)	0.69
Family history of CAD	511 (31.6)	18 (31.6)	1
Angina			
No	936 (58.0)	34 (58.6)	0.99
Atypical	592 (36.7)	20 (34.5)	0.94
Typical	87 (5.4)	4 (6.9)	0.88
Dyspnoea (NYHA >2)	68 (4.2)	2 (3.5)	1
Positive test for ischaemia	138 (8.5)	5 (8.6)	1
Total cholesterol (mg/dL)	215 ± 43.1	211 ± 32.2	0.72
LDL (mg/dL)	129 ± 36.7	129 ± 35.9	0.61
HDL (mg/dL)	57.0 ± 19.5	56.3 ± 20.3	0.99
Triglycerides (mg/dL)	123 ± 98.9	116 ± 80.1	0.44
Morise risk score			
Low	319 (19.8)	16 (27.6)	0.34
Intermediate	1199 (74.2)	37 (63.8)	0.21
High	97 (6.0)	5 (8.6)	0.72
Indication for CCTA			
CAD risk assessment	471 (29.2)	21 (36.2)	0.51
Dyspnoea	93 (5.8)	5 (8.6)	0.66
Ischaemia	116 (7.2)	2 (3.5)	0.55
Arrhythmia	315 (19.5)	5 (8.6)	0.12
Thoracic pain	568 (35.2)	19 (32.8)	0.93
Other	52 (3.2)	6 (10.3)	0.014

Data are given as means ± standard deviation or absolute numbers (percentages). Only the leading symptom is counted for each patient.

patients (6%). Detailed patient baseline characteristics are provided in Table 1.

Endpoints and clinical correlation

With a total of 36 deaths for cardiac cause and 15 non-fatal myocardial infarctions, the study endpoint occurred in a total of 51 patients (3% of study population). Forty-four patients died from non-cardiac causes, resulting in a total of 95 deaths (6% of study population, annual all-cause mortality rate of 0.6%). Morise score had a decent discriminatory ability for composite endpoint with a χ^2 of 11.9 and c-index of 0.622 ($P < 0.001$). A total of 157 early (<90 days after index CCTA) and 67 late (≥ 90 days after index CCTA) revascularizations were performed during follow-up.

Computed tomography results

Analysis for CAD severity showed that 479 patients had no evidence of CAD, 691 patients had non-obstructive coronary stenosis, and 445 patients had obstructive CAD. Of the patients with obstructive CAD, 213 had one-vessel obstructive CAD, 146 patients had two-

vessel obstructive CAD, and 86 patients had three-vessel obstructive CAD.

Advanced image analysis for plaque morphology showed that 939 (58%) patients had spotty calcified plaques, 61 (4%) patients had LAPs, and 98 (6%) patients had plaques consistent with NRS. Vessel remodelling of 110% and 130% was present in 449 (28%) and 274 (17%) patients, respectively. Grossly calcified plaques were present in 330 (20%) patients; non-calcified plaques were homogeneous in 99 (6%) patients and inhomogeneous in 366 (23%) patients. Detailed information of plaque characteristics in patients who did and did not reach the endpoint is shown in Table 2.

Discriminatory ability of established CCTA parameters

Analysis for composite endpoint revealed that for quantitative CCTA parameters CAD severity correlated best with outcome with a univariate χ^2 of 39.2 ($P > 0.001$) and multivariate χ^2 of 27.5 ($P < 0.001$) after adjustment to clinical risk. Survival analysis for quantitative CCTA parameters is shown in Table 3. Annual event rates for the

Table 2 Univariate prognostic value of morphological plaque features

	No events (n = 1564)	Events (n = 51)	Hazard ratio	χ^2	P-value
Calcified plaques	1.53 ± 2.21	3.35 ± 3.13	1.54 (1.31–1.82)	27.4	<0.001
Non-calcified plaques	0.83 ± 1.37	1.47 ± 1.91	1.47 (1.36–1.58)	6.95	0.008
Mixed plaques	0.61 ± 1.23	0.88 ± 1.26	1.16 (0.97–1.39)	2.64	0.1
Homogeneous plaques	96 (6.1%)	3 (5.9%)	1.49 (0.45–4.96)	0.44	0.5
Inhomogeneous plaques	352 (22.5%)	14 (27.5%)	1.82 (0.95–3.51)	3.21	0.07
Local plaque load	36.0 ± 23.3	45.8 ± 26.9	1.94 (1.28–2.92)	9.9	0.002
Gross calcifications	309 (19.8%)	21 (41.2%)	2.80 (1.60–4.90)	13.1	<0.001
Spotty calcifications	894 (57.2%)	45 (88.2%)	5.47 (2.33–12.8)	15.3	<0.001
Napkin-ring sign	89 (5.7%)	9 (17.6%)	3.26 (1.59–6.70)	10.4	0.001
Low-attenuation plaques	58 (3.7%)	3 (5.9%)	1.86 (0.58–5.97)	1.08	0.3
Remodelling 110%	430 (28.5%)	19 (37.3%)	1.68 (0.95–2.96)	3.17	0.08
Remodelling 130%	264 (16.9%)	10 (19.6%)	1.25 (0.63–2.51)	0.42	0.52

Table 3 Univariate prognostic value and improved prediction beyond Morise for established CCTA parameters

	Univariate model			Multivariate model, corrected for Morise			c-index after addition of CCTA
	Hazard ratio	χ^2	P-value	Hazard ratio	χ^2	P-value	
Morise	1.98 (1.34–2.92)	11.9	<0.001	Reference			0.622
CAD severity	3.65 (2.43–5.57)	39.2	<0.001	3.24 (2.11–4.99)	27.5	<0.001	0.622 → 0.728
CADRADS	5.15 (2.73–9.66)	25.8	<0.001	4.16 (2.13–8.16)	18.0	<0.001	0.622 → 0.710
SIS	2.76 (1.94–3.93)	32.1	<0.001	2.45 (1.67–3.60)	20.2	<0.001	0.622 → 0.718

Table 4 Multivariate prognostic value of morphological plaque features beyond Morise and stenosis level as given by CAD severity

	Multivariate model, corrected for Morise + CAD severity			c-index after addition of PF
	Hazard ratio	χ^2	P-value	
Morise + CAD severity	Reference			0.728
Calcified plaques	1.14 (0.92–1.41)	1.45	0.23	0.728 → 0.732
Non-calcified plaques	1.03 (0.88–1.20)	0.12	0.73	0.728 → 0.727
Mixed plaques	0.87 (0.71–1.07)	1.86	0.17	0.728 → 0.723
Homogeneous plaques	1.42 (0.43–4.73)	0.33	0.56	0.728 → 0.728
Inhomogeneous plaques	0.87 (0.44–1.74)	0.14	0.71	0.728 → 0.728
Local plaque load	1.09 (0.71–1.68)	0.16	0.69	0.728 → 0.733
Gross calcifications	0.97 (0.50–1.88)	0.001	0.93	0.728 → 0.728
Spotty calcifications	2.35 (0.94–5.90)	3.89	0.049	0.728 → 0.743
Napkin-ring sign	2.25 (1.09–4.65)	4.04	0.044	0.728 → 0.742
Low-attenuation plaques	1.29 (0.40–4.15)	0.17	0.68	0.728 → 0.728
Remodelling 110%	0.91 (0.51–1.64)	0.1	0.76	0.728 → 0.723
Remodelling 130%	0.62 (0.30–1.26)	1.92	0.17	0.728 → 0.734

CAD, coronary artery disease; PF, plaque features.

Table 5 Multivariate prognostic value (for the combined endpoint of cardiac death, myocardial infarction, and late revascularization) of morphological plaque features beyond Morise and stenosis level as given by CAD severity

	Multivariate model, corrected for Morise + CAD severity			
	Hazard ratio	χ^2	P-value	c-index after addition of PF
Morise + CAD severity	Reference			0.760
Calcified plaques	1.17 (1.00–1.36)	3.68	0.06	0.760 → 0.759
Non-calcified plaques	0.94 (0.82–1.07)	1.03	0.31	0.760 → 0.761
Mixed plaques	1.05 (0.92–1.21)	0.53	0.47	0.760 → 0.764
Local plaque load	1.20 (0.88–1.64)	1.36	0.24	0.760 → 0.766
Gross calcifications	1.29 (0.81–2.05)	1.13	0.29	0.760 → 0.761
Spotty calcifications	1.81 (1.04–3.13)	4.95	0.026	0.760 → 0.767
Napkin-ring sign	2.36 (1.32–4.22)	6.73	0.01	0.760 → 0.767
Low-attenuation plaques	1.38 (0.56–3.40)	0.45	0.50	0.760 → 0.758
Remodelling 110%	1.22 (0.81–1.84)	0.93	0.34	0.760 → 0.765
Remodelling 130%	1.31 (0.83–2.08)	1.26	0.26	0.760 → 0.760

CAD, coronary artery disease; PF, plaque features.

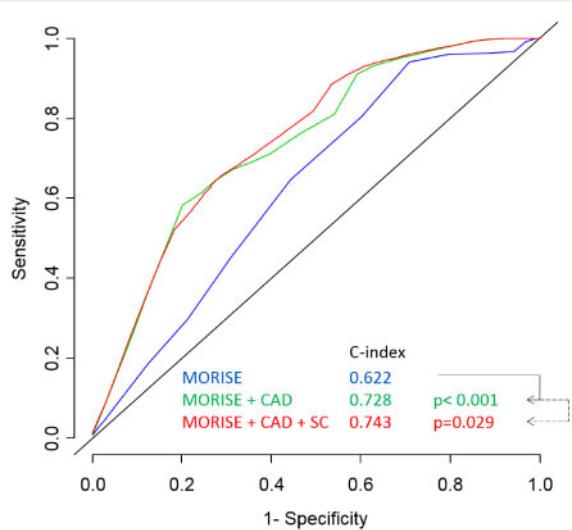


Figure 2 Receiver operator curves for the clinical risk assessed by Morise score and the stepwise incremental predictive value of CAD-severity as well as a composite of CAD-severity and spotty calcifications. CAD, CAD-severity; SC, spotty calcifications.

primary endpoint ranged from 0.04% [confidence interval (CI) 0.01–0.18%] for patients with normal coronary arteries to 1.17% (0.61–2.25%) for patients with three-vessel obstructive CAD.

Predictive power of plaque features

Presence of spotty calcifications, gross calcifications, or napkin ring-sign translated to significantly elevated hazard ratios (HRs) of 5.47 (95% CI 2.33–12.8; $P < 0.001$), 2.80 (95% CI 1.60–4.90; $P < 0.001$), and 3.26 (95% CI 1.59–6.70; $P = 0.001$), respectively. Further, elevated LPL (HR 1.94, 95% CI 1.28–2.92; $P = 0.02$) as well as the presence of any calcified (HR 1.54, 95% CI 1.31–1.82; $P < 0.001$) or non-

calcified (HR 1.47, 95% CI 1.36–1.58; $P = 0.008$) plaque correlated with outcome. Neither the proposed HRPF of low attenuating plaques (HR 1.86, 95% CI 0.58–5.97; $P = 0.3$) and positive remodelling at 110% (HR 1.68, 95% CI 0.95–2.96; $P = 0.08$) or 130% (HR 1.25, 95% CI 0.63–2.51; $P = 0.52$) nor differentiation between homogeneous (HR 1.07, 95% CI 0.34–3.43; $P = 0.50$) and inhomogeneous (HR 1.39, 95% CI 0.77–2.54; $P = 0.07$) non-calcified plaques or partially calcified plaques (HR 1.16, 95% CI 0.07–1.39; $P = 0.10$) were able to predict the primary endpoint.

After adjustment to Morise and CAD severity, spotty calcifications and NRS remained predictive with HRs of 2.35 (95% CI 0.94–5.90; $P = 0.049$) and 2.25 (95% CI 1.09–4.65; $P = 0.044$). On the other hand, grossly calcified plaques (HR 0.97, 95% CI 0.50–1.88; $P = 0.93$), elevated LPL (HR 1.09, 95% CI 0.71–1.68; $P = 0.69$), as well as the presence of any calcified (HR 1.14, 95% CI 0.92–1.41; $P = 0.23$) and non-calcified (HR 1.03, 95% CI 0.88–1.20; $P = 0.73$) plaque could not maintain their predictive power on multivariate analysis (Table 4). Similar to univariate analysis, low-attenuating plaques, remodelled plaques, as well as homogeneous and inhomogeneous non-calcified plaques or partially calcified plaques were not predictive on multivariate analysis. Exploratory analysis revealed that a model containing Morise, CAD severity, and both, spotty calcifications and NRS was not incremental to a three-step model with Morise, CAD-severity and spotty calcifications alone (χ^2 of 2.88, $P = 0.09$).

In analogy to above-described findings, spotty calcified plaques and NRS were the sole investigated plaque features to remain predictive for the secondary endpoint (also containing late revascularizations) after multivariate adjustment for clinical risk and CAD severity with respective HRs of 1.81 (95% CI 1.04–3.13; $P = 0.026$) and 2.36 (95% CI 1.32–4.22; $P = 0.01$). Multivariate analysis of CCTA features for the secondary endpoint is given in Table 5. An additional analysis was performed excluding the 157 patients with early revascularization to exclude a possible confounding effect of sealing the high-risk plaque during intervention. For spotty calcification and NRS, this analysis yielded similar results with respective HRs of 2.20 (95% CI 0.87–5.57;

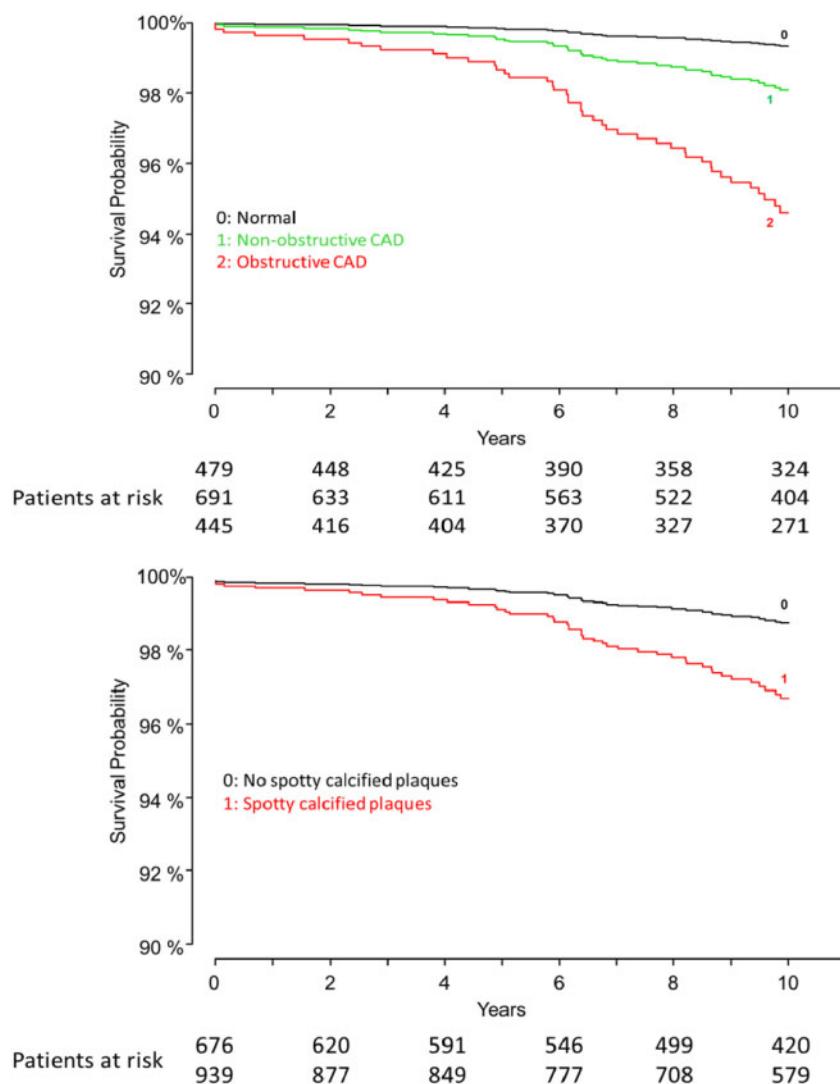


Figure 3 Kaplan–Meier curves for event-free survival (primary endpoint) stratified according to stenosis level and lack/presence of spotty calcified plaques. CAD, coronary artery disease.

$P=0.075$) and 2.71 (95% CI 1.14–6.46; $P=0.045$) (as given in the [Supplementary data](#)).

Receiver operator curves for clinical risk, CAD severity and the composite of CAD severity and spotty calcifications are given in [Figure 2](#). In a three-step model, the reference area under the receiver operator curve for clinical risk is 0.622, rising to 0.728 ($P<0.001$) after adding CAD severity to the model and further rising to 0.743 when considering the presence or absence of spotty calcified plaques ($P=0.029$), respectively rising to 0.742 when discerning for NRS ($P=0.016$).

Kaplan–Meier curves for patients with normal, non-obstructive and obstructive CAD, as well as the lack or presence of spotty calcified plaques are given in [Figure 3](#) for the primary endpoint and in [Figure 4](#) for the secondary endpoint. Survival analysis for patients with plaques showing either spotty calcifications or NRSs is given in [Figure 5](#). Kaplan–Meier endpoint analysis for a composite of stenosis

level and lack or presence of spotty calcifications and NRS is given in [Figure 6](#) (primary endpoint) and [Figure 7](#) (secondary endpoint), respectively.

Discussion

The main findings of this study are (i) in a patient population with suspected but not previously diagnosed CAD, the presence of any calcified/non-calcified plaque but also specific plaque features (spotty or gross calcifications, NRS, elevated local plaque load) was associated with long-term cardiac death or non-fatal myocardial infarction; (ii) the presence of spotty calcified plaques or NRS provides incremental prognostic value to a composite of clinical risk and stenosis level; thereby allowing for improved cardiovascular risk stratification.

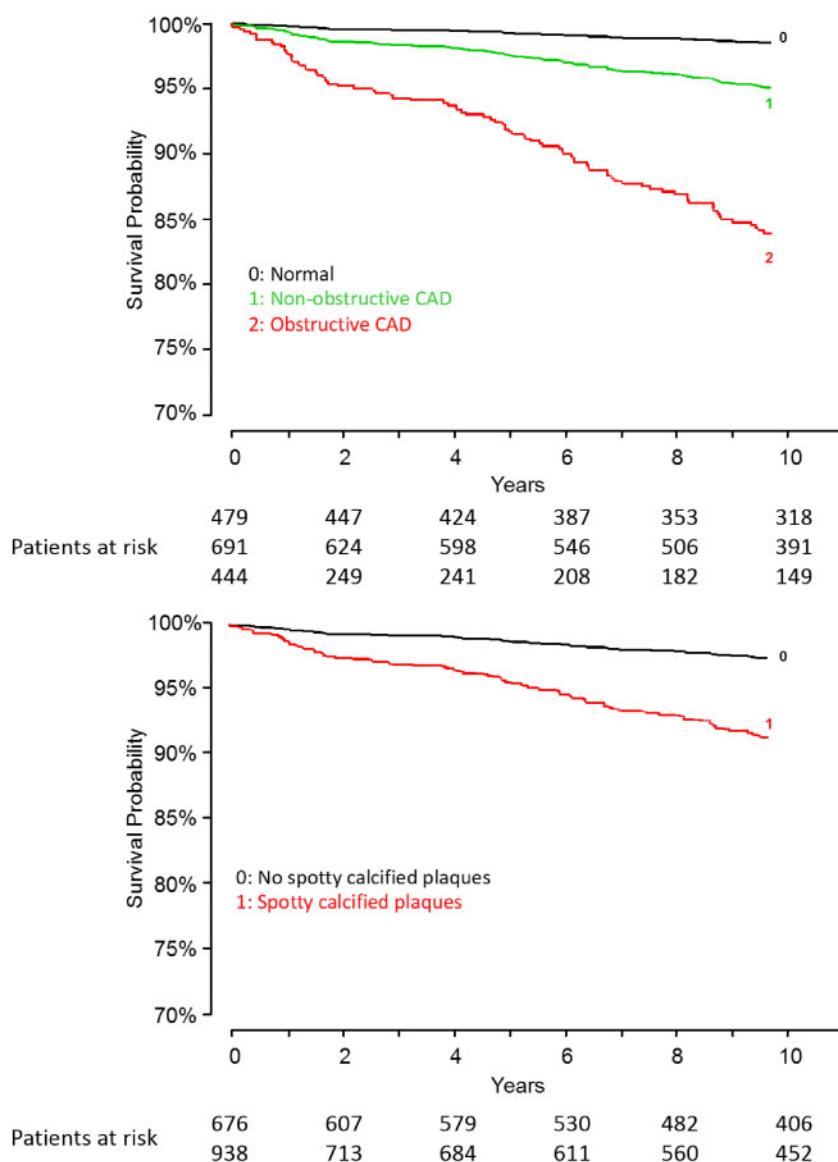


Figure 4 Kaplan–Meier curves for event-free survival (secondary endpoint) stratified according to stenosis level and lack/presence of spotty calcified plaques. CAD, coronary artery disease.

The aim of this study was to identify how plaque characteristics such as recently proposed HRPF might be associated with cardiac death or myocardial infarction on long-term follow-up and can provide additive prognostic power beyond clinical risk and coronary stenosis level. Correlation of HRPF with adverse cardiac events has been described in symptomatic and asymptomatic patients on shorter follow-up periods and for softer endpoints.^{11–13,21,22}

The present study identifies calcified/non-calcified plaques, elevated LPL, plaques with a spotty or gross calcification pattern as well as the presence of the NRS to be predictive for hard cardiac events over the long-term, while spotty calcifications and NRS are incrementally predictive to a composite of clinical risk and coronary stenosis level.

Corrected for clinical risk and coronary stenosis level, patients with spotty calcified plaques or NRS had more than twice the risk for

cardiac death or myocardial infarction. This result underlines the findings from Motoyama *et al.*,¹⁰ who were among the first to link HRPF to fatal and non-fatal ACS on follow-up of nearly 4 years and interestingly found that patients who developed HRPF on serial CCTA had the highest likelihood for future adverse cardiac events.

Further comparison of our results to published data reveals that a correlation of NRS and positive remodelling with ACSs has been reported on follow-up of 2 years.¹¹ Analysis of symptomatic patients from the ROMICAT-trial linked the presence of HRPF to myocardial infarction or unstable angina during index hospitalization after adjustment to vessel stenosis and clinical risk.¹² Previous results from our working group confirmed the predictive power of NRS, LAP and positive remodelling for softer endpoints (all-cause death, myocardial infarction, and coronary revascularization later than 90 days after

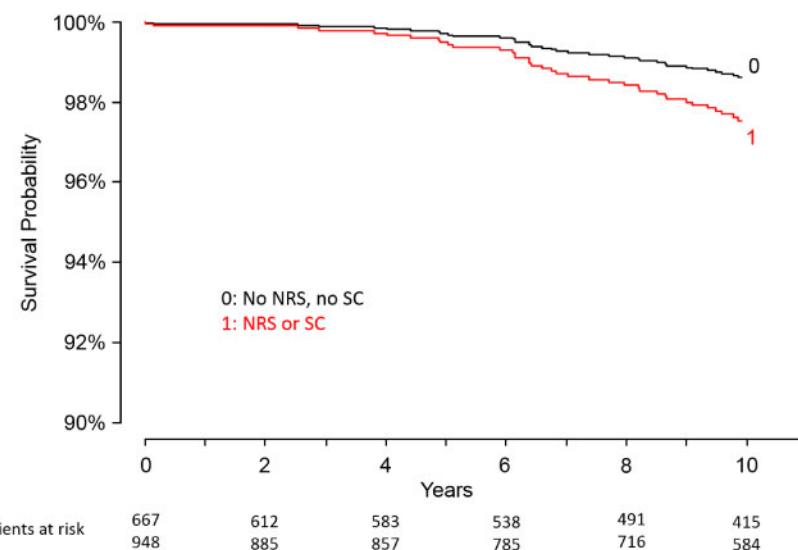


Figure 5 Kaplan–Meier curves for event-free survival (primary endpoint) stratified according to the lack/presence of either spotty calcified plaques or napkin-ring sign. CAD, coronary artery disease.

CCTA) on follow-up of 5 years and could confine additional prognostic value to LAP beyond clinical risk and generalized plaque burden.¹³ Partially in contrast to these reports, LAP and positively remodelled plaques were noted less often and non-predictive for endpoint in the underlying study, possibly due to a much harder endpoint in the present study as well as a more elaborate plaque analysis (axial reconstructions with semi-automated plaque analysis) in the previous work.^{12,13}

Our results further confirm the specificity of spotty calcifications as vulnerable plaque feature given that gross calcifications beyond a size of 3 mm lost their predictive value on multivariate analysis. Their fading prognostic utility after adjustment to mainly age-driven clinical risk opens the door for the assumption that gross calcifications caused by healed plaques are accumulable, comparable to calcium-score levels, while spotty calcifications are the hallmark of active inflammation.^{23,24} Today, it is widely accepted that atherosclerosis is a chronic inflammatory state that finally results in the calcification of lipid-loaded plaques. Although eventually believed to be stable, plaque calcification is a stepwise process that includes initial phases of stability-reducing microcalcifications before evolving into a highly calcified, stable lesion.²⁵ Early research focused on the stress distribution within coronary plaques indicated that fissuring tends to appear at the interfaces of different tissue compositions, i.e. the borderzone between small calcifications that are embedded into an elastic soft plaque.²⁶ On histology, speckled calcifications have been linked to vulnerable plaque features on numerous occasions.^{27–29} Data from serial CCTA have further shown that spotty calcifications are associated with accelerated plaque progression.³⁰ Thus, vast evidence has recently accumulated to highlight the role of spotty calcifications in plaque instability.

Correlation of spotty calcified plaques with cardiac events on short- and intermediate-term follow-up has before been reported for intravascular ultrasound and optical coherence tomography.^{31–33}

The multimodality of such findings strengthens our observation that irrespective of the degree of stenosis, the presence or lack of spotty calcifications or NRS allows for risk-stratification of patient subgroups.

Interestingly, this opposes recent findings from Conte et al.³⁴ who could not link spotty calcified plaques to adverse cardiac events on follow-up of roughly 8 years, a discrepancy possibly explained by the choice of softer endpoints (in particular the inclusion of non-cardiac death and revascularization). Above-mentioned study did identify NRS to be highly predictive for adverse cardiac events beyond clinical risk, in agreement to the supposition that NRS can reliably identify thin-capped fibroatheroma, known to be associated with ACS.^{35,36} Our results are consistent with this report and should encourage future research on the usefulness of above-mentioned plaque features in a higher risk collective (i.e. as in stable angina).

To conclude one has to note that the before-mentioned pathogenesis of coronary plaques underlines the dynamic nature of atherosclerosis and allows for the assumption that HRPF might also be variable in time, possibly progressing to calcified lesions (similar to calcium score levels) on the long-term. Hence, these features might only be an ephemeral, macroscopic tip-of-the-iceberg, reflecting the impaired metabolic processes that underlie in patients with heightened cardiovascular risk.

Limitations

The underlying study is not without limitations. First of all, baseline CT-scans of this long-term follow-up study have been generated on older generation scanners. While these have been state-of-the art at the time, the resulting imaging quality is certainly inferior to newest generation multidetector scanners and has most likely resulted in a false-low number of detected plaque features, especially true for

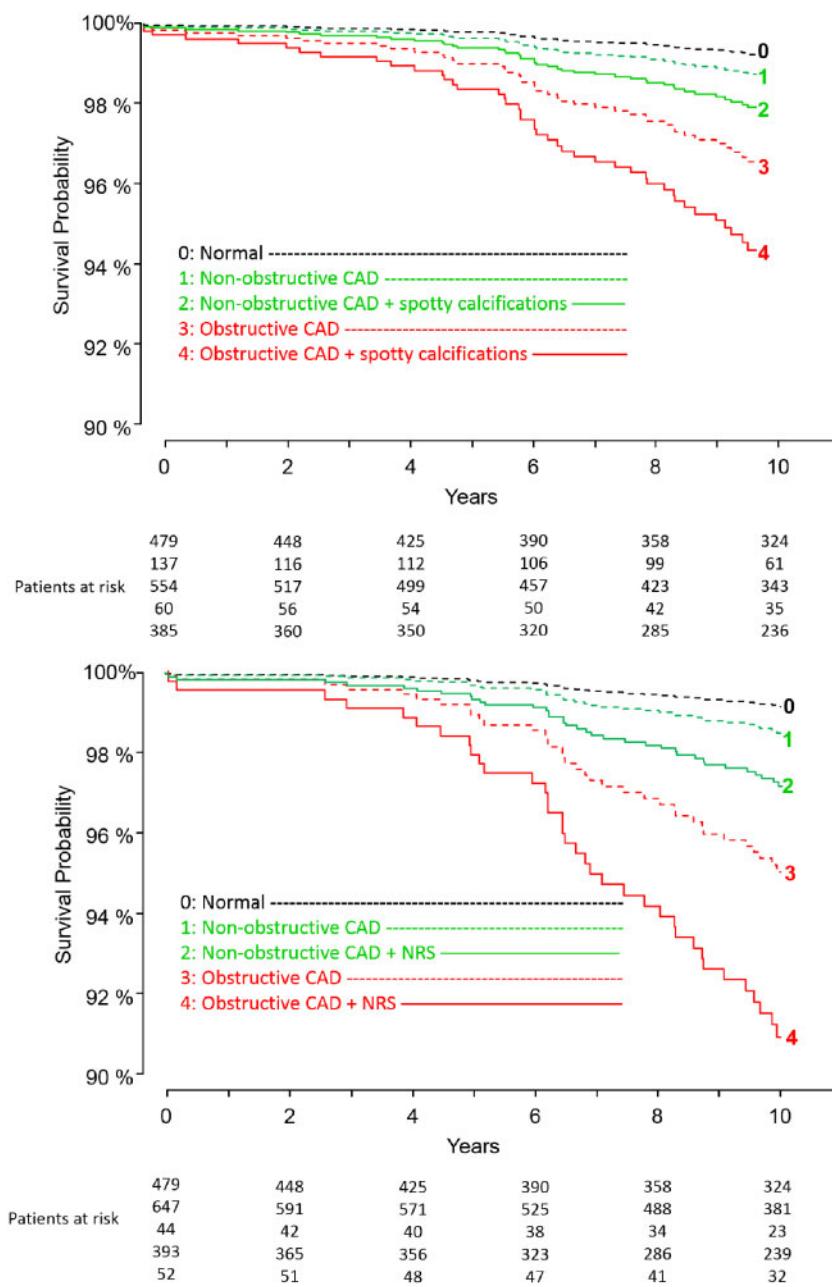


Figure 6 Kaplan–Meier curves for event-free survival (primary endpoint) stratified for a composite of stenosis level and lack/presence of spotty calcified plaques, respectively NRS. NRS, napkin-ring sign.

low-attenuating and positively remodelled plaques. A second important consideration is the low-to intermediate pre-test risk in our patients mostly referred for CAD-screening, possibly further contributing to the lower reported frequencies of plaque features compared to other studies. Results from index CCTA have doubtlessly guided referring physicians to cardioprotective treatment, supposedly leading to a higher percentage of patients on primary preventive treatment in our cohort than in the general population. Treatment decisions during follow-up were taken by the referring physician, no data in this regard was available for analysis. This is a significant

limitation but as this was a single-centre study with cardiology referers only, medical therapy is likely to have been optimal and relatively uniform. Further, the revascularization of patients within the first three months after index CCTA could have lead to a confounding effect as high-risk plaques might have been sealed. However, an analysis after exclusion of these patients revealed that NRS nonetheless remained predictive for the primary endpoint.

Finally, the relatively low number of events ($n=51$) might soften the statistical power of our analysis. We are however convinced that restrictive cardiovascular endpoint analysis best

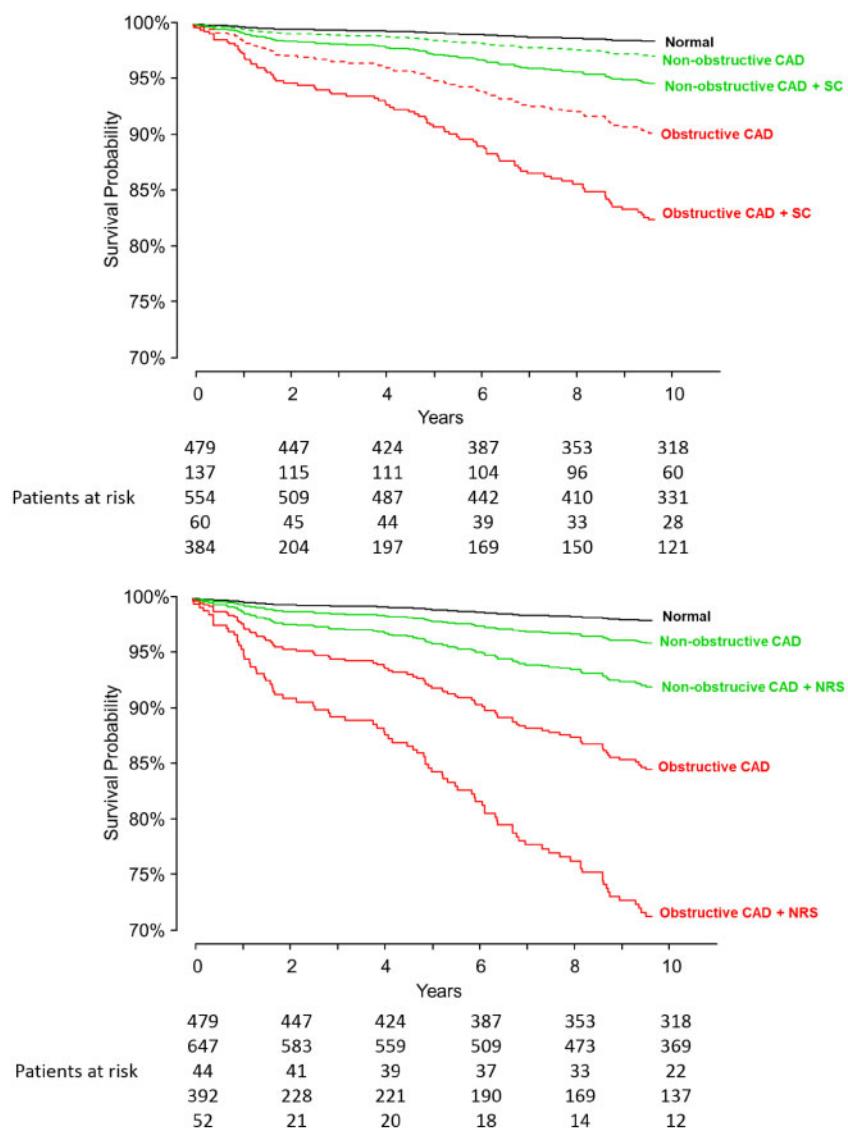


Figure 7 Kaplan–Meier curves for event-free survival (secondary endpoint) stratified for a composite of stenosis level and lack/presence of spotty calcified plaques, respectively NRS. NRS, napkin-ring sign.

reflects the utility of plaque features in cardiovascular risk prediction. While a lesion-specific endpoint analysis might certainly have added value to the underlying study, acquisition of such data would have been incompatible with national data protection law. Differences to reported event rates (Morise) can at least be partially explained by the more cardiac-specific endpoint in the underlying study.

Conclusion

Taken together the findings of this study help illuminate the prognostic usefulness of morphological plaque features. While a clear risk stratification based on calcified or non-calcified plaques alone is not feasible, a spotty pattern in calcified plaques and the presence of NRS

in non-calcified plaques are both incrementally predictive vulnerable plaque features beyond clinical risk and stenosis level. While the detection of some plaque features (low-attenuating plaques, positively remodelled plaques) might necessitate sophisticated evaluation tools, reporting of NRS and spotty calcifications as a modifier variable in CCTA reports, consistent with the initial proposition by CADRADS could prove valuable in risk-stratifying patients.³⁷

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

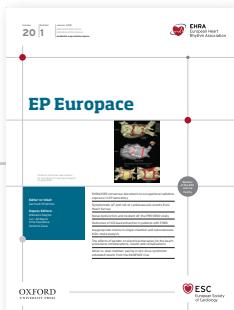
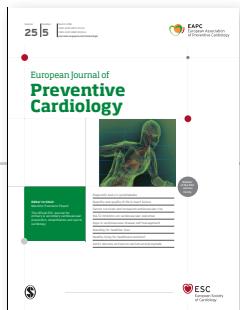
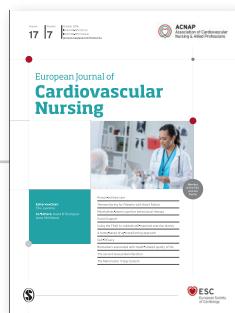
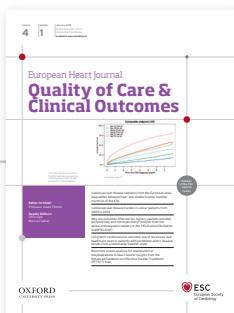
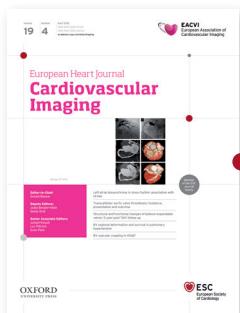
Conflict of interest: J.H. received speaker honoraria and research support from Abbott Vascular and Edwards Lifesciences.

References

1. Mowatt G, Cook JA, Hillis GS, Walker S, Fraser C, Jia X et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. *Heart* 2008;**94**:1386–93.
2. Arbustini E, Dal Bello B, Morbini P, Burke AP, Bocciarelli M, Specchia G et al. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. *Heart* 1999;**82**:269–72.
3. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 1988;**12**:56–62.
4. Ahmed W, Schlett CL, Uthamalingam S, Truong QA, Koenig W, Rogers IS et al. Single resting hsTnT level predicts abnormal myocardial stress test in acute chest pain patients with normal initial standard troponin. *JACC Cardiovasc Imaging* 2013; **6**:72–82.
5. Virmani R, Burke AP, Kolodgie FD, Farb A. Vulnerable plaque: the pathology of unstable coronary lesions. *J Interv Cardiol* 2002; **15**:439–46.
6. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol* 2006; **47**:C13–18.
7. Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. *Circulation* 2002; **105**:939–43.
8. 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**:639–47.
9. Toutouzas K, Karanassos A, Tousoulis D. Optical coherence tomography for the detection of the vulnerable plaque. *Eur Cardiol* 2016; **11**:90–5.
10. 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**:49–57.
11. Otsuka K, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshiyama M et al. Prognosis of vulnerable plaque on computed tomographic coronary angiography with normal myocardial perfusion image. *Eur Heart J Cardiovasc Imaging* 2014; **15**:332–40.
12. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL 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**:684–92.
13. Nadjiri J, Hausleiter J, Jahnichen C, Will A, Hendrich E, Martinoff S 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.
14. Morise AP, Haddad WJ, Beckner D. Development and validation of a clinical score to estimate the probability of coronary artery disease in men and women presenting with suspected coronary disease. *Am J Med* 1997; **102**:350–6.
15. Hadamitzky M, Taubert S, Deseive S, Byrne RA, Martinoff S, Schomig A et al. Prognostic value of coronary computed tomography angiography during 5 years of follow-up in patients with suspected coronary artery disease. *Eur Heart J* 2013; **34**:3277–85.
16. Ostrom MP, Gopal A, Ahmadi N, Nasir K, Yang E, Kakadiaris I et al. Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography. *J Am Coll Cardiol* 2008; **52**:1335–43.
17. Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ et al. CAD-RADS™ 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.
18. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol* 2007; **50**:1161–70.
19. Team RDC. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. <http://www.r-project.org> (15 April 2018, date Last accessed).
20. Harrell FE Jr. rms: Regression Modeling Strategies. Chapter 4, 2017, pp. 63–102.
21. Ferencik M, Mayrhofer T, Bittner DO, Emami H, Puchner SB, Lu MT 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.
22. Yamamoto H, Kitagawa T, Ohashi N, Utsunomiya H, Kunita E, Oka T et al. Noncalcified atherosclerotic lesions with vulnerable characteristics detected by coronary CT angiography and future coronary events. *J Cardiovasc Comput Tomogr* 2013; **7**:192–9.
23. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2006; **113**:30–7.
24. New SE, Goetttsch C, Aikawa M, Marchini JF, Shibasaki M, Yabasaki K et al. Macrophage-derived matrix vesicles: an alternative novel mechanism for microcalcification in atherosclerotic plaques. *Circ Res* 2013; **113**:72–7.
25. Collin J, Gossel M, Matsuo Y, Cilluffo RR, Flammer AJ, Loeffler D et al. Osteogenic monocytes within the coronary circulation and their association with plaque vulnerability in patients with early atherosclerosis. *Int J Cardiol* 2015; **181**:57–64.
26. Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. *Lancet* 1989; **2**:941–4.
27. Abedin M, Tintut Y, Demer LL. Vascular calcification: mechanisms and clinical ramifications. *Arterioscler Thromb Vasc Biol* 2004; **24**:1161–70.
28. Burke AP, Weber DK, Kolodgie FD, Farb A, Taylor AJ, Virmani R. Pathophysiology of calcium deposition in coronary arteries. *Herz* 2001; **26**:239–44.
29. Kolodgie FD, Burke AP, Farb A, Gold HK, Yuan J, Narula J et al. The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. *Curr Opin Cardiol* 2001; **16**:285–92.
30. Kataoka Y, Wolski K, Uno K, Puri R, Tuzcu EM, Nissen SE et al. Spotty calcification as a marker of accelerated progression of coronary atherosclerosis: insights from serial intravascular ultrasound. *J Am Coll Cardiol* 2012; **59**:1592–7.
31. Mizukoshi M, Kubo T, Takarada S, Kitabata H, Ino Y, Tanimoto T et al. Coronary superficial and spotty calcium deposits in culprit coronary lesions of acute coronary syndrome as determined by optical coherence tomography. *Am J Cardiol* 2013; **112**:34–40.
32. Fujii K, Carlier SG, Mintz GS, Takebayashi H, Yasuda T, Costa RA et al. Intravascular ultrasound study of patterns of calcium in ruptured coronary plaques. *Am J Cardiol* 2005; **96**:352–7.
33. Ehara S, Kobayashi Y, Yoshiyama M, Shimada K, Shimada Y, Fukuda D et al. Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. *Circulation* 2004; **110**:3424–9.
34. 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**:1170–8.
35. Maurovich-Horvat P, Schlett CL, Alkadhri H, Nakano M, Otsuka F, Stolzmann P et al. The napkin-ring sign indicates advanced atherosclerotic lesions in coronary CT angiography. *JACC Cardiovasc Imaging* 2012; **5**:1243–52.
36. 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**:226–35.
37. Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ et al. Coronary Artery Disease-Reporting and Data System (CAD-RADS): an expert consensus document of SCCT, ACR and NASCI: endorsed by the ACC. *JACC Cardiovasc Imaging* 2016; **9**:1099–113.

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