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Questions and answers on workup diagnosis and risk stratification: a companion document of the 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

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Biomarkers and differential diagnosis

Q1. You are on rounds in the emergency department and your intern asks you: what is the main difference between non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina?

NSTEMI is characterized by ischaemic symptoms associated with acute cardiomyocyte injury (=rise and/or fall in cardiac troponin T/I), while ischaemic symptoms at rest (or minimal effort) in the absence of acute cardiomyocyte injury define unstable angina. This translates into an increased risk of death in NSTEMI patients, while unstable angina patients are at relatively low short-term risk of death (sections 3.3.1 and 3.3.2, Figure 1).

Q2. A 72-year-old patient with hypertension and hypercholesterolaemia as cardiovascular risk factors (CVRF) presents to the emergency department with typical chest pain of 3 h duration, palpitations, atrial fibrillation with a ventricular rate of about 120 beats per minute, ST depression on electrocardiogram (ECG), and a mild elevation in cardiac troponin (cTn) (twice the upper limit of normal [ULN]). Is it correct to state that the underlying process is a rupture, ulceration, fissuring, or erosion of a coronary atherosclerotic plaque?

No. According to the universal definition of myocardial infarction (MI), two main subtypes of NSTEMI have to be differentiated: type 1 MI, characterized by any of the processes just previously described, and type 2 MI, in which an extra-coronary condition is the main cause of imbalance between myocardial oxygen supply and demand (e.g. tachycardia, anaemia, hypertension, or hypotension). The patient described may have had both (sections 3.3.1 and 3.3.2, Figure 1).

Q3. Which are the three mandatory diagnostic cornerstones of the early diagnosis of non-ST-elevation acute coronary syndrome (NSTEMI) among the following: past clinical history including a detailed description of the chest pain characteristics, 12-lead ECG, chest X-ray, elevated and dynamic rise in cTn, treadmill test, computed tomography (CT) angiography, and myocardial perfusion scan?

Early diagnosis of NSTEMI relies on clinical assessment (i.e. past clinical history including a detailed description of the chest pain characteristics), 12-lead ECG, and cTn (sections 3.3 and 3.3.2, Figure 1).

Q4. You are challenged by a new cardiology fellow regarding the cTn assay used in your institution. She states that current ESC guidelines recommend using a high-sensitivity cTn (hs-cTn) assay and that your current assay is not high-sensitivity. What are the advantages of hs-cTn?

Hs-cTn measurements are recommended over less sensitive ones, as they provide higher diagnostic accuracy at identical low cost. The higher diagnostic accuracy mainly translates into the possibility for earlier and safer rule-out of MI, and therefore shorter length of stay in the emergency department and lower treatment cost (which are mainly determined by the time in the emergency department) (section 3.3.2, Figure 2).

Q5. You plan to introduce the measurement of hs-cTn in your hospital. A fellow asks: what will the impact be on the diagnosis of NSTEMI and unstable angina in patients presenting to the emergency department with acute chest pain?

With the introduction of hs-cTn there will be some increase in the prevalence of NSTEMI and a reciprocal decrease in the incidence of unstable angina. The percentage of reclassified patients depends on the difference in sensitivity between the current and the new assay. If the current assay has low sensitivity and is a 'conventional' cTn assay, an increase in NSTEMI diagnoses is to be expected by approximately 4% absolute and 20% relative, with a corresponding decrease in unstable angina. If the current assay is already a sensitive cTn assay, then the percentage of reclassified patients will be smaller (e.g. 1–2% absolute, 5–10% relative) (section 3.3.2, Figure 2).

Q6. You are called by a fellow from the emergency department regarding an 85-year-old patient presenting with a hip fracture following a fall. For unknown reasons, cTn has been measured and the concentration is twice the upper limit of normal. The 12-lead ECG is normal. He said that the elevated cTn allows him to diagnose NSTEMI and asks for the need for early invasive coronary angiography.

It is very unlikely that NSTEMI is the correct diagnosis in this patient. Accordingly, there is no need for early invasive coronary angiography. A mild and probable constant and chronic cTn elevation is common in the elderly patient and a reflection of the pre-existing cardiac disease (known or unknown to the patient), resulting in chronic cardiomyocyte injury (section 3.3.2, Figure 2).

Q7. A 50-year-old patient with no relevant past medical history presents with persistent severe retrosternal chest pain radiating to both shoulders and arms which started 4 h earlier. Haemodynamic status is stable and the initial physical examination is unremarkable. The 12-lead ECG is normal. The initial hs-cTn T concentration is 300 ng/L (ULN < 14 ng/L). Is it possible to make a clear working diagnosis or do you need a second hs-cTn measurement?

There is no need for a second troponin assessment. The diagnosis of NSTEMI is made and appropriate treatment should be initiated. The positive predictive value for NSTEMI in patients with typical symptoms and a substantial (> 20 times the 99th percentile) elevation in cTn is > 90% (section 3.3.3). If the institution uses the ESC hs-cTn T 0h/1 h-algorithm, an initial hs-cTn T concentration above 52 ng/L allows triage of patients towards rule-in (section 3.3.3, Figure 3, Table 5).

The next four scenarii highlight how to use the available different types of hs-cTn.

Q8. A 60-year-old patient without prior history of coronary artery disease (CAD) presents to the emergency department with recurrent right-sided thoracic chest pain. The last chest pain episode started 5 h prior to hospital admission and is still ongoing. He is haemodynamically stable and the physical examination is normal. The 12-lead ECG is also normal. The initial hs-cTn T level is normal at 4 ng/L (ULN < 14 ng/L). The intern in the emergency department asks you as a cardiology consultant if this single very low hs-cTn T concentration allows the rule-out of NSTEMI.

Yes. As the patient presented more than 3 h after chest pain onset, the single measurement rule-out pathway of the ESC hs-cTn T 0h/1 h-algorithm can be applied, which allows the rapid and safe triage towards rule-out of NSTEMI if the hs-cTn T concentration is < 5 ng/L. The negative predictive value for the rapid rule-out of NSTEMI in this setting is > 99.5%. Most of these patients are also excellent candidates for rapid discharge and outpatient management, possibly including non-invasive stress testing (preferably with imaging) (section 3.3.3, Figure 3, Table 5).

Q9. A 60-year-old patient without prior history of CAD presents to the emergency department with recurrent right-sided thoracic chest pain. The last chest pain episode started 5 h prior to hospital admission and is still ongoing. He is haemodynamically stable and the physical examination is normal. The 12-lead ECG is also normal. The initial hs-cTn I (Architect) level is normal at 2 ng/L (ULN < 26 ng/L). The intern in the emergency department asks you as a cardiology consultant if this single very low hs-cTn I Architect concentration allows the rule-out of NSTEMI.

Yes. As the patient presented more than 3 h after chest pain onset, the single measurement rule-out pathway of the ESC hs-cTn I Architect 0 h/1 h-algorithm can be applied, which allows the rapid and safe triage towards rule-out of NSTEMI if the hs-cTn I concentration is < 4 ng/L. The negative predictive value for the rapid rule-out of NSTEMI in this setting is > 99.5%. Most of these patients are also excellent candidates for rapid discharge and outpatient management, possibly including non-invasive stress testing (preferably with imaging) (section 3.3.3, Figure 3, Table 5).

Q10. A 60-year-old patient without prior history of CAD presents to the emergency department with recurrent right-sided thoracic chest pain. The last chest pain episode started 5 h prior to hospital admission and is still ongoing. He is haemodynamically stable and the physical examination is normal. The 12-lead ECG is also normal. The initial hs-cTn I Centaur level is normal at 2 ng/L (ULN < 47 ng/L). The intern in the emergency department asks you as a cardiology consultant if this single very low hs-cTn I Centaur concentration allows the rule-out of NSTEMI.

Yes. As the patient presented more than 3 h after chest pain onset, the single measurement rule-out pathway of the ESC hs-cTn I Centaur 0 h/1 h-algorithm can be applied, which allows the rapid and safe triage towards rule-out of NSTEMI if the hs-cTn I Centaur concentration is < 3 ng/L. The negative predictive value for the rapid rule-out of NSTEMI in this setting is > 99.5%. Most of these patients are also excellent candidates for rapid discharge and outpatient management, possibly including non-invasive stress testing (preferably with imaging) (section 3.3.3, Figure 3, Table 5).

Q11. A 60-year-old patient without prior history of CAD presents to the emergency department with recurrent right-sided thoracic chest pain. The last chest pain episode started 5 h prior to hospital admission and is still ongoing. He is haemodynamically stable and the physical examination is normal. The 12-lead ECG is also normal. The initial hs-cTn I Access level is normal at 3 ng/L (ULN < 18 ng/L). The intern in the emergency department asks you as a cardiology consultant if this single very low hs-cTn I Access concentration allows the rule-out of NSTEMI.

Yes. As the patient presented more than 3 h after chest pain onset, the single measurement rule-out pathway of the ESC hs-cTn I Access 0 h/1 h-algorithm can be applied, which allows the rapid and safe triage towards rule-out of NSTEMI if the hs-cTn I Access concentration is < 4 ng/L. The negative predictive value for the rapid rule-out of NSTEMI in this setting is > 99.5%. Most of these patients are also excellent candidates for rapid discharge and outpatient management, possibly including non-invasive stress testing (preferably with imaging) (section 3.3.3, Figures 3 and 4, Table 5).

Q12. A 60-year-old patient without prior history of CAD presents to the emergency department with recurrent right-sided thoracic chest pain. The last chest pain episode started 5 h prior to hospital admission and is still ongoing. He is haemodynamically stable and the physical examination is normal. The 12-lead ECG is also normal. The initial hs-cTn I Vitros level is normal at 0.7 ng/L (ULN < 11 ng/L). The intern in the emergency department asks you as a cardiology consultant if this single very low hs-cTn I Vitros concentration allows the rule-out of NSTEMI.

Yes. As the patient presented more than 3 h after chest pain onset, the single measurement rule-out pathway of the ESC hs-cTn I Vitros 0 h/1 h-algorithm can be applied, which allows the rapid and safe triage towards rule-out of NSTEMI if the hs-cTn I Vitros concentration is < 1 ng/L. The negative predictive value for the rapid rule-out of NSTEMI in this setting is > 99.5%. Most of these patients are also excellent candidates for rapid discharge and outpatient management, possibly including non-invasive stress testing (preferably with imaging) (section 3.3.3, Figure 3, Table 5).

Q13. A 60-year-old patient without prior history of CAD presents to the emergency department with intermittent recurrent moderate right-sided thoracic chest pain without radiation over the last 2 days. The last chest pain episode started 2 h prior to hospital admission and lasted for 30 min. He is haemodynamically stable and the physical examination is normal. The 12-lead ECG is also normal. The initial hs-cTn T level is normal at 4 ng/L (ULN <14 ng/L). The intern in the emergency department asks you as a cardiology consultant if the patient can be discharged.

No. As the patient presented very early after chest pain onset, the intern needs to wait for the second cTn measurement at 1 h if using the ESC hs-cTn T 0 h/1 h-algorithm or at 2 h if using the ESC hs-cTn T 0 h/2 h-algorithm. If the second measurement is also within normal limits and there is NO relevant change to the measurement at presentation, NSTEMI can be reliably ruled-out and the patient is to be considered at low risk of cardiac events. From a cardiology perspective, he may then be discharged home. If no clear alternative explanation such as, for example, musculoskeletal chest pain or bronchitis is found to explain the patient's symptoms, he may undergo non-invasive stress testing (preferably with imaging) on an outpatient basis (section 3.3.3, Table 5, Figure 3).

Q14. A 60-year-old patient with a history of CAD presents to the emergency department with chest pain and cough lasting for 2 days. The right-sided thoracic chest pain is persistent, moderate in intensity, non-radiating, and increases in intensity during inspiration. The last episode of chest pain started 8 h prior to admission and the patient is still mildly symptomatic in the emergency department. He is haemodynamically stable and the physical examination is unremarkable. The 12-lead ECG shows T-wave inversion in lead I and aVL, which were already noted in the ECG performed last year. The initial hs-cTn I Architect concentration is very low/undetectable at 2 ng/L (ULN < 26 ng/L). The emergency department intern, a bright young physician who wants to become a cardiologist, challenges you by saying that 'it is obvious that the chest pain does not represent acute MI and no additional investigations or blood tests in this respect are needed'. Is she right?

Yes. NSTEMI, based on the delay between symptom onset and blood test, can be reliably ruled-out with a single very low level of hs-cTn T/I. In addition, unstable angina is extremely unlikely since prolonged ischaemia is expected to lead to some degree of cTn elevation. An alternative diagnosis such as pneumonia/bronchitis should be considered (section 3.3.3, Tables 4 and 5, Figure 3).

Q15. You are supervising the emergency department/chest pain unit (CPU) and see an 80-year-old patient with a history of CAD, prior MI, and hypertensive heart disease presenting with persistent moderate right-sided thoracic chest pain ongoing for 7 h that increases in intensity during exercise and inspiration. In addition, he has mild fever and an increasing productive cough over the last 3 days. He is haemodynamically stable and the initial physical examination reveals rales over the base of the right lung. ECG shows T-wave inversion in V3–V6, which were already noted on the ECG performed 3 years ago. A chest X-ray shows an infiltrate in the right lung suggestive of pneumonia. Your intern is about to order blood cultures (plus legionella and pneumococcus antigen in the urine) and prescribe antibiotics when the hs-cTn T level is reported from the laboratory as elevated. Your intern now asks you if the patient needs treatment for pneumonia, NSTEMI, or both.

This patient has a high likelihood for pneumonia and a low likelihood for NSTEMI. To answer the question whether he has concomitant NSTEMI, you need to know the exact value of hs-cTn at presentation as well as the dynamics after 1 h or 2 h. If the hs-cTn levels are only mildly elevated (e.g. according to the assay 18 ng/L if ULN is 14 ng/L), then the mild elevation in hs-cTn in this specific patient can be attributed to cardiac causes other than NSTEMI (e.g. pre-existing CAD/MI or hypertensive heart disease plus some degree of cardiomyocyte injury related to sepsis/pneumonia) and no specific treatment is needed. A rise or fall in hs-cTn is required for the diagnosis of NSTEMI, and most NSTEMIs have higher concentrations 7 h after the onset of acute chest pain (section 3.3.3, Figures 3 and 4, Tables 4 and 5).

Q16. You are the cardiology consultant responsible for the training of residents starting their rotation in the emergency department. When discussing patient pathways, a resident asks you whether the majority of patients presenting with acute chest pain to the emergency department ultimately require hospitalization to reliably rule-out or rule-in acute MI (AMI).

No. Using either a hs-cTn T/I 0 h / 1 h-algorithm or a hs-cTn T/I 0h/2 h-algorithm, the majority of patients (75%) can be reliably ruled-out or ruled-in within the first hours in the emergency department (sections 3.3.2 and 3.3.3). Ultimately, the majority of patients (> 60%) can be discharged after rapid rule-out of AMI and managed as outpatients using these algorithms (section 3.3.3, Figure 3, Table 5).

Q17. You are supervising the emergency department/CPU. A resident questions you regarding the further management of a 60-year-old woman with a history of CAD presenting with ongoing moderate left-sided thoracic chest pain without radiation that started 2 h prior to admission and resolved spontaneously in the emergency department. She is haemodynamically stable and the physical examination and 12-lead ECG are unremarkable. Levels of hs-cTn T assessed at presentation and 1 h were normal and identical at 7 ng/L (ULN < 14 ng/L). Can NSTEMI be ruled-out?

Yes, the negative predictive value for MI in patients classified as 'rule-out' by the hs-cTn T 0 h/1 h-algorithm is 99–100%. Used in conjunction with clinical assessment and the 12-lead ECG as mandatory additional sources of information, the 0 h/1 h-algorithm allows the early rule-out of MI and early detection of patients that are candidates for outpatient management (i.e. no further investigation or non-invasive imaging). It is important to highlight that prior to discharge, other life-threatening causes of acute chest pain, such as aortic dissection, pulmonary embolism, and tension pneumothorax, need to be considered (section 3.3.3, Figures 3 and 4, Tables 4 and 5).

Q18. You are supervising the emergency department/CPU. A resident asks you about the further management of a 64-year-old woman without CVRFs and without known CAD

presenting with moderate retrosternal chest pain without radiation that started 3 h prior to admission and lasted for 1 h. She is haemodynamically stable, pain free, and the physical examination as well as the 12-lead ECG are normal. Levels of hs-cTn I Architect at presentation are 100 ng/L (ULN < 26 ng/L). Your intern is using the assay-specific ESC 0 h/1 h-algorithm you just introduced in the hospital and he tells you that according to the algorithm the patient can be 'ruled-in'. Now the intern wants to know what it means: does the patient have NSTEMI?

The positive predictive value for MI in patients classified as 'rule-in' by the hs-cTn T 0 h/1 h-algorithm is 70–80%. Used in conjunction with clinical assessment and the 12-lead ECG — mandatory additional sources of information — the 0 h/1 h-algorithm allows the early detection of patients who are candidates for early invasive coronary angiography, particularly as most of the rule-in patients with a diagnosis other than acute MI will have conditions that also usually require inpatient coronary angiography for accurate diagnosis, including Takotsubo syndrome, myocarditis, and unstable angina. This patient should undergo early invasive coronary angiography (section 3.3.3, Figure 3, Table 4).

Q19. The measurement of hs-cTn T/I is mandatory in all patients presenting with suspected NSTE-ACS. Is it necessary to routinely measure other cardiovascular biomarkers in addition to hs-cTn T/I? If yes, which ones?

It is NOT necessary to routinely measure other cardiovascular biomarkers in addition to hs-cTn T/I (section 3.3.2).

Q20. Your colleague from the emergency room asks you if adding copeptin to the blood sample of a patient arriving with acute chest pain might help for the early rule-out of MI.

The added value of copeptin depends on the sensitivity of the cTn assay used. If using a cTn assay with poor sensitivity, copeptin does provide incremental diagnostic value and is advised as an aid for the rapid rule-out of MI within a dual marker strategy. However, if using, as recommended in the ESC Guidelines, a hs-cTn T/I assay within a hs-cTn T/I 0 h/1 h-algorithm or hs-cTn T/I 0 h/2 h-algorithm, copeptin does not have added value and should not be used (section 3.3.2.2).

Q21. Your fellow asks you if B-type natriuretic peptide (BNP) may help in the diagnosis of patients with suspected MI.

No, BNP does not help in the diagnosis. However, it provides important prognostic information for death and/or the development of heart failure, particularly in patients with established NSTE-ACS (section 3.3.2.2).

Q22. A point-of-care test (POCT) has been set up in the emergency department. Your colleague asks you if he can use one of the ESC hs-cTn T/I 0 h/1 h-algorithms for rule-in/rule-out of NSTEMI in patients presenting with acute chest pain.

Most likely, this is not possible. The new ESC hs-cTn T/I 0 h/1 h-algorithms for rule-in/rule-out of NSTEMI in patients presenting with acute chest pain can only be used with hs-cTn T/I assays. Unfortunately, the vast majority of current POCTs do have poor sensitivity and cannot be used for rapid rule-out/rule-in protocols. However, there is one exception and others are in development (section 3.3.2.1).

Q23. A 69-year-old woman with a past medical history of thoracic radiotherapy for breast cancer and diabetes mellitus on glucagon-like peptide 1 (GLP1) agonist therapy is admitted to the emergency department for acute retrosternal chest pain with radiation to the left arm. She remains in pain despite sublingual nitrates. The physical examination is normal. The 12-lead ECG shows 3 mm ST-segment depression in leads V2–V6, I, and aVL. The emergency department physician asks you whether the patient should undergo coronary angiography right now or whether she has to wait for the results of the first cTn measurement, which are expected to come back from the lab in about 45 minutes.

Given the very high likelihood of ongoing myocardial ischaemia, and the large myocardial territory at risk, the patient should undergo immediate invasive coronary angiography (section 3.3.1, Figure 9).

Risk assessment

Q24. You are working in the emergency department on Friday at 9 pm. A new patient (male, 77 years) arrives with de-novo angina at minimal exertion, which started 3 days ago. The ECG on admission excludes a STEMI and shows no other ST-segment alterations. The laboratory studies reveal normal levels for hs-cTn at presentation and 1 h thereafter as well as a serum creatinine level of 102 μmol/L. The patient is haemodynamically stable (systolic blood pressure 115 mmHg, heart rate 82 beats per min [bpm]) but has rales in the basal portion of both lungs (i.e. Killip class II). Life-threatening arrhythmias are not documented. Your colleague states that you can transfer the patient to the ward and sign him on invasive coronary angiography for Monday. Is he right?

No. You should calculate the GRACE [Global Registry of Acute Coronary Events] risk score because subgroup analyses of two major trials indicated that patients with a high risk for in-hospital death, according to the original GRACE risk score published by Granger et al (i.e. > 140 points) (https://www.outcomes-umassmed.org/risk_models_grace_orig.aspx for the GRACE risk score 1.0 and https://www.outcomes-umassmed.org/grace/acs_risk2/index.html for the GRACE risk score 2.0), may do better with an early invasive strategy as compared to a delayed invasive strategy. The GRACE risk score is 154 points for this patient. Therefore, according to guidelines an invasive coronary angiography within 24 h should be performed and you should schedule the patient for Saturday (< 24 h from now) (section 4.3, Figure 9).

Q25. Two hours later, another patient (female, 75 years) enters the emergency department because she experienced chest pain at rest for around 35 minutes earlier in the day. The patient is haemodynamically stable, has no life-threatening arrhythmias, and no ST-segment elevation

is documented. The hs-cTn level is 52 and 68 ng/L (ULN 14 ng/L) at presentation and 1 h later (ESC 0 h/1 h-algorithm rule-in path). Your colleague gets enthusiastic about the GRACE risk score that is 129 based on the following criteria: Killip class I, systolic blood pressure 145 mmHg, heart rate 72 bpm, serum creatinine level 79 μmol/L, no ST-segment alterations, no cardiac arrest before admission. Your colleague states that the workload for the interventional cardiologist on duty can be limited because the patient can wait until Monday morning (GRACE risk score not above 140 points). Is he correct this time?

No. The patient's hs-cTn T level is elevated with a rise compatible with MI. This is a high-risk criterion irrespective of the GRACE risk score; therefore, the patient should also undergo invasive coronary angiography within 24 h (i.e. Saturday and not Monday). However, risk prediction is recommended irrespective of the timing decision. Short- and long-term ischaemic risk can be accurately and conveniently assessed using the GRACE 2.0 web calculator. Objective risk assessment by means of the GRACE risk score has proven superior over subjective assessment done by the physician (section 4.3, Figure 9).

Q26. Following your expertise on ischaemic risk prediction, your colleague then asks you whether similar scores have been developed regarding the risk for major bleeding.

Yes, there are also bleeding risk scores. However, their clinical utility is challenged by the overlap between bleeding and ischaemic risk factors and the overall modest accuracy of the bleeding risk scores. However, these risk scores (e.g. CRUSADE) may still be useful to inform clinicians and patients (section 4.3).

Non-invasive imaging

Q27. A 48-year-old man with a history of dyslipidaemia is referred to the emergency department because of acute chest pain with radiation to his shoulders and arms. This was accompanied by heavy sweating and nausea which lasted for 30 minutes, starting after his lunch, now 4 h ago. At first medical contact, the patient was pain free and the physical examination was unremarkable. The 12-lead ECG indicates no ST and/or T wave abnormalities. The initial as well as the 1 h follow-up level of hs-cTn is below the ULN without a significant dynamic change. The GRACE risk score is 59. The emergency department physician asks the cardiology fellow on call whether an invasive or non-invasive coronary assessment should follow.

Further investigations depend on patient and test characteristics, as well as local setting and expertise. The patient belongs to the low-risk group with a GRACE risk score of 59, indicative of < 3% risk of death up to 6 months following the index event. Therefore, a non-invasive assessment is recommended, e.g. functional testing by stress echocardiography or cardiac magnetic resonance (CMR) imaging or anatomic imaging by coronary CT angiography (CCTA) (sections 3.3.3 and 3.3.5, Figures 3 and 4, Table 6).

Q28. The emergency department physician decided to perform CCTA to exclude obstructive CAD. Your fellow would like to know whether this strategy is in accord with current guidelines.

Correct. Non-invasive anatomical imaging with CCTA is one of the recommended options in this case. CCTA should be considered to exclude obstructive CAD in haemodynamically stable patients with acute chest pain suggestive of NSTE-ACS, but with initial negative hs-cTn, without ischaemic ECG changes and low GRACE score (section 3.3). This approach avoids 30% of invasive coronary angiography procedures.

Q29. A 55-year-old woman presents with shortness of breath, a tight feeling on the chest, and palpitations for 3 h. In addition, she mentions a few episodes of intermittent chest discomfort over the last 6 months, lasting minutes but sometimes hours, occurring both at rest and during exercise. She has a positive family history for CAD. The initial ECG demonstrated atrial fibrillation with a heart rate of 130 bpm and then 96 bpm with no ischaemic changes after 30 minutes of a resting period. Initial and 1 h hs-cTn measures were 30 ng/L and 36 ng/L (ULN 14 ng/L), respectively. A resident asks you, as supervisor of the emergency department/CPU, whether CCTA should be performed now to rule-out obstructive coronary artery disease.

CCTA has a high diagnostic accuracy for ruling out occlusive CAD. However, image quality and interpretability may be hampered when irregular heart rhythm is present. Although elevated levels of hs-cTn may be attributable to myocardial injury due to rapid ventricular rate response, a CCTA is recommended because of the chest discomfort during the last 6 months and the positive family history for CAD (section 3.3.5, Figures 3 and 4).

Q30. A just-appointed radiologist challenges the work-up of patients with acute chest pain by stating the following: 'Why bother with clinical evaluation, repeated cTn testing, and ECG assessments in patients with suspected NSTE-ACS? In the end, all need CCTA'. Is this statement correct?

Not at all. Broad adoption of non-invasive anatomic testing, in terms of CCTA, among inadequately risk stratified patients, has been shown to increase downstream testing and costs without clinical benefit for the patient. In addition, despite the reduction in radiation doses achieved in recent years, acquisition of high-quality images with low radiation exposure, as well as appropriate interpretation of CT images, is not usually available on a 24/7 basis at every institution (section 3.3 and Figures 3 and 4).

Q31. You are on call as a resident in the emergency department and you evaluate a 50-year-old woman with new acute left-sided chest pain without radiation, lasting for 3 h. She is known for cigarette smoking, hypertension, and hypercholesterolaemia. The 12-lead ECG and serial measurements of hs-cTn (ESC 0 h/1 h algorithm) are below the ULN (14 ng/L). The senior cardiologist states that this patient very likely has unstable angina and she should therefore undergo early invasive coronary angiography. Is he right?

No. There is no evidence of severe ischaemia or myocardial necrosis. Therefore, early invasive coronary angiography is not required. This patient may have unstable angina, but also non-cardiac causes of

acute chest pain. CCTA is useful to assess whether this patient has obstructive CAD (*sections 3.3 and 4.3, Figure 3, Figure 4*).

Myocardial infarction with non-obstructed coronary arteries (MINOCA)

Q32. A 62-year-old woman, former smoker, with no prior relevant medical history, is admitted to the emergency department because of a prolonged typical chest pain lasting > 6 h. Vital signs are normal except for body temperature that is 37.6°C. The ECG shows 0.5 mm horizontal ST depression in the anterior and inferior leads. Transthoracic echocardiography shows borderline left ventricular function. The first hs-cTn I is 270 ng/L (ULN <14 ng/L). She immediately receives aspirin and unfractionated heparin and, a few hours later, undergoes invasive coronary angiography which shows no significant stenosis. Your colleague argues that the problem is microvascular spasm/obstruction and suggests treating the patient with standard NSTE-ACS drug therapy. Is he right?

No. MINOCA is a working diagnosis until further assessment excludes other possible causes for cTn elevation. Intracoronary functional tests (acetylcholine/ergonovine) may be performed when coronary or microvascular spasm is suspected and, in this specific case, CMR should be performed to exclude myocarditis or specify other causes for the cTn elevation. Standard NSTE-ACS therapy may not be the correct choice since pharmacological therapy will vary according to the final diagnosis (*section 7, Figure 12, Table 14*).

Q33. A 70-year-old man, with hypertension and dyslipidaemia, presents to the emergency department because of recurrent episodes of chest pain, not associated with exercise, lasting for a few minutes. At admission, physical examination is unremarkable. First and second hs-cTn I levels are both within normal range and the first ECG is normal. Two hours later, the patient has a recurrence of chest pain with transient ST-segment elevation of 0.5 mm in leads II, III, and aVF. Immediate invasive coronary angiography is performed and a mild focal disease on the right coronary artery and left circumflex artery is found. The fellow tells you that there is an available slot for CMR in 30 minutes. Would you do additional invasive tests while waiting for the CMR?

Clinical history and symptoms suggest that coronary spasms may be the cause. Therefore, while waiting for CMR to be done, intracoronary functional tests (acetylcholine/ergonovine) may be performed. Intracoronary imaging with intravascular ultrasound or optical coherence tomography (OCT) may also be helpful for the detection of unrecognized plaque ruptures, erosions, or spontaneous coronary artery dissection (SCAD) (section 7, Figure 12, Table 14).

Q34. Your fellow is writing the discharge summary of a 70-year-old woman admitted for recurrent chest pain, positive hs-cTn I (peak value of 550 ng/L), and normal echocardiography. Coronary angiography did not show any significant lesion. Invasive imaging (OCT) showed some stable plaques and CMR did not show late gadolinium enhancement. She is not willing to prescribe any drug after discharge. Do you agree?

No. Patients with a final diagnosis of MINOCA of unknown cause may be treated according to secondary prevention guidelines for atherosclerotic disease. Pharmacological therapy with aspirin and statins is recommended and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blockers, and calcium channel blockers (in case vasospasm is suspected) may be considered (section 7, Figure 12, Table 14).

Q35. A 45-year-old man comes to your outpatient clinic for a follow-up visit two weeks after a short hospitalization for recurrent atypical chest pain with significantly elevated cTn. Echocardiography shows mild hypokinesia of the mid and apical segments but invasive coronary angiography is normal. He is discharged with the recommendation of 12-months dual antiplatelet therapy (DAPT), statins, and beta-blockers. CMR is scheduled for 2 months later. What is your strategy?

This patient was discharged without a complete diagnostic work-up assuming NSTEMI to be the most probable cause of MINOCA. CMR was correctly indicated to exclude/confirm possible myocarditis and Takotsubo syndrome but should have been performed earlier to identify the correct diagnosis. It would be useful, therefore, to perform CMR as soon as possible (section 7, Figure 12, Table 14).

Q36. A 75-year-old diabetic woman is referred to the emergency department for chest pain associated with intense and prolonged palpitations a few hours earlier. The ECG shows sinus rhythm, supraventricular extrasystoles, and no significant ST-segment changes. The hs-cTn is 180 ng/L (ULN 14 ng/L) and echocardiography shows a normal left ventricular ejection fraction and a dilated left atrium. Invasive coronary angiography performed the following day is normal. Recurrence of chest pain with concomitant 15 min episodes of high penetrance atrial fibrillation occurs. Your colleague thinks this MINOCA case should be treated as an NSTEMI but you disagree.

It is highly probable that symptoms and myocardial injury are related to the episodes of tachyarrhythmia. It is recommended to manage patients with an initial diagnosis of MINOCA and a final established underlying cause according to the disease-specific guidelines. This patient should be treated according to the atrial fibrillation ESC Guidelines with oral anticoagulation based on stroke risk assessment and preventive treatments of atrial fibrillation episodes (section 7, Figure 12, Table 14).

Q37. How would you diagnose and treat a MINOCA patient suspected for myocarditis that lives in an area where CMR is not available?

CMR is one of the key diagnostic tools in the MINOCA diagnostic algorithm for either differential diagnosis of Takotsubo syndrome, myocarditis, or also true MI. In case intracoronary imaging and the provocative test are negative

and CMR is not available, patients should undergo echocardiography to identify left ventricular wall abnormalities, e.g. regional wall motion evaluation, speckle tracking, strain imaging/mapping, real-time myocardial contrast, which may help to identify the underlying cause. If myocarditis is still considered the most probable cause, the patient should be treated according to the specific guidelines. If the final diagnosis is MI of unknown/unclear causes, the pharmacological treatment should follow the secondary prevention guidelines for atherosclerotic disease (section 7, Figure 12, Table 14).

Q38. A 39-year-old woman, of athletic constitution with no prior relevant medical history, arrives at the emergency department after experiencing prolonged chest pain while running. She still has some chest discomfort during the physical examination, the ECG shows a 1 mm ST depression in the lateral leads (I-aVL, V5–V6), and there is mild hypokinesia of the lateral wall at echocardiography. Baseline and 2 h hs-cTn I samples are 450 ng/L and 820 ng/L (ULN 14 ng/L), respectively. She receives aspirin and unfractionated heparin and is sent to the catheterization lab. Invasive coronary angiography shows some contrast dye staining with a multiple radiolucent lumen of the obtuse marginal branch with preserved coronary flow. Your colleague suggests treating this patient with coronary stenting and 12-month DAPT. Is he right?

According to the available data, apart from very high-risk profile patients, a conservative approach should be the preferred strategy in type I SCAD with no coronary obstructions and preserved coronary flow. Optimal medical treatment is still undetermined but because hypertension is an independent predictor of recurrent SCAD, hypertensive therapy should be considered and beta-blockers should be the first choice in this subset of patients. The benefit of antithrombotic therapy among these patients is still controversial. In selected patients, invasive coronary angiography or CCTA may be considered as follow-up in addition to clinical visits (section 6.1.5, Figure 11).