The management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: key points from the ESC 2020 Clinical Practice Guidelines for the general and emergency physician

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There have been significant advances in the diagnosis and management of non-ST-segment elevation myocardial infarction over recent years, which has been reflected in an international decline in mortality rates. This article provides an overview of the 2020 European Society of Cardiology Clinical Practice Guidelines for the topic, concentrating on areas relevant to the general or emergency physician. The recommendations and underlying evidence basis are analysed in three key areas: diagnosis (the recommendation to use high sensitivity troponin and how to apply it), pathways (the recommendation to facilitate early invasive coronary angiography to improve outcomes and shorten hospital stays) and treatment (a paradigm shift in the use of early intensive platelet inhibition). Gaps in the evidence base are highlighted, including the optimal management strategy for older people and the antiplatelet regime to consider when angiography may be delayed.

KEYWORDS: acute coronary syndrome, NSTEMI, myocardial infarction, ESC clinical practice guideline, coronary angiography

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Introduction

Non-ST-segment elevation myocardial infarction (NSTEMI) is the most prevalent acute coronary syndrome (ACS) presentation in the UK. Data from the UK Myocardial Infarction National Audit Project (MINAP) found that between April 2017 and March 2018 there were 56,493 admissions nationally for NSTEMI, an increase of 5% from the previous year. Over recent years, however, there have been substantial therapeutic advances in how we care for people with NSTEMI, and this has been reflected in an international decline in mortality rates. In September 2020, the European Society of Cardiology (ESC) published updated Clinical Practice Guidelines for the management of ACS in patients presenting without persistent ST-segment elevation, 5 years after the last iteration.

The guidelines stipulate a number of updated recommendations (supplementary material S1). The strength of a recommendation and level of evidence used to justify it are weighted and graded according to predefined scales (Table 1). This focused review provides learning points derived from the guidelines in areas relevant to general and emergency physicians, including diagnosis (recommendation to use high sensitivity troponin), pathways (recommendation to proceed to invasive coronary angiography [ICA] within 24 hours if invasive strategy is deemed suitable), and treatment (review of the merits of early prescription of P2Y12 receptor inhibitors). In line with the guidelines, acute myocardial infarction (AMI) is defined according to the 4th universal definition of myocardial infarction (Table 2).

Diagnosis

Background

Cardiac troponins are the most sensitive and specific markers of cardiomyocyte injury, superseding older biomarkers such as creatine kinase (CK), its myocardial band isoenzyme (CK-MB) and myoglobin. They rise quickly (within 1 hour of symptom onset) and stay elevated for several days. Refinement to produce high sensitivity troponin (hs-cTn) assays has led to an increased detection of previously undetectable cardiomyocyte injury and thus increased diagnostic accuracy at identical low cost to less sensitive versions.

Recommendation

It is recommended to use hs-cTn assay as part of a ‘0 hour/1 hour’ or ‘0 hour/2 hour’ rule-in and rule-out algorithm (class of recommendation I, level of evidence B).

Rationale

Due to the higher sensitivity of hs-cTn, the interval between the first and second troponin measurement may be shortened.
Table 1. Definitions of class of recommendation and supporting level of evidence used in European Society of Cardiology (ESC) guidelines

| Recommendations | Definition | Wording used |
|-----------------|-----------|--------------|
| Class I         | Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective | It is recommended or indicated |
| Class II        | Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure | |
| Class IIa       | Weight of evidence/opinion is in favour of usefulness/efficacy | Should be considered |
| Class IIb       | Usefulness/efficacy is less well established by evidence/opinion | May be considered |
| Class III       | Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful | It is not recommended |

Levels of evidence

| Levels | Definition |
|--------|------------|
| A      | Data derived from multiple randomised clinical trials or meta-analyses |
| B      | Data derived from a single randomised clinical trial or large non-randomised studies |
| C      | Consensus of opinion of the experts and/or small studies, retrospective studies, registries |

Optimal thresholds for each available assay have been defined for ‘very low’, ‘low’, ‘high’ and ‘delta change’ to allow a negative predictive value (NPV) of 99% and minimal positive predictive value (PPV) of 70%. The current recommendation is to use these assays in the emergency department as part of a rapid rule-in/rule-out algorithm – either ‘0 hour/1 hour’ (blood drawn for hs-cTn at 0 hours and 1 hour of attendance) or ‘0 hour/2 hours’ (blood drawn for hs-cTn at 0 hours and 2 hours of attendance) depending on the specific hs-cTn assay available at a centre (Fig 1).

In the recent multi-centre RAPID-TnT randomised controlled trial (RCT), the 0 hour/1 hour protocol was shown to be non-inferior to the standard repeat troponin assessment at 3 hours with a significantly higher rate of discharge, shorter stay in the emergency department, lower referral for further functional cardiac testing and an NPV for 30-day death or myocardial infarction of 99.6%. With ever-increasing demand on acute care, this may facilitate faster decision-making and appropriate discharge, especially as contemporary data suggest that 65% of chest pain presentations to the emergency department are not ACS. In order to facilitate this process, the emergency department team should obtain blood samples for hs-cTn at the respective timepoints regardless of clinical details, even though this may introduce a proportion of unnecessary troponin measurements.

Fig 1. A rapid rule-in/rule-out algorithm for chest pain using the hs-cTn assay in the emergency department, based on the European Society of Cardiology 2020 guidelines

Table 2. Definition of acute myocardial infarction as per the fourth universal definition of myocardial infarction (European Society of Cardiology, 2018)

Acute myocardial infarction:
Detection of an increase and/or decrease of a cardiac biomarker with at least one value above the 99th percentile of the upper reference limit and at least one of:
> symptoms of myocardial ischaemia
> new ischaemic ECG changes or development of pathological Q waves
> imaging evidence of a loss of viable myocardium or new regional wall motion abnormality in pattern consistent with ischaemic aetiology
> intracoronary thrombus detected on angiography or autopsy.

Non-ST-segment elevation myocardial infarction:
The criteria for AMI met without persistent ST-segment elevation (>20 minutes) or new left bundle branch block
have shown a reduction in risk of death or myocardial infarction from an invasive strategy in NSTEMI, especially for patients of high ischaemic risk. Thus, the guidelines recommend pursuing an invasive coronary strategy within specific time bands based on baseline patient risk.

Recommendation

Very high risk – immediate invasive strategy (<2 hours) [akin to primary PCI (PPCI)] if at least one of the following present: (class of recommendation I, level of evidence C)

- haemodynamic instability
- life-threatening arrhythmias
- mechanical complication eg severe mitral regurgitation
- acute heart failure
- cardiogenic shock
- recurrent or refractory chest pain
- ST-segment depression >1 mm in 6 leads plus ST-segment elevation in AVR and/or V1.

High risk – early invasive strategy (<24 hours) if at least one of the following present: (class of recommendation I, level of evidence A)

- dynamic rise or fall in troponin with at least 1 value above the 99th percentile of the upper reference limit (NSTEMI)
- GRACE risk score >140
- dynamic new or presumably new contiguous ST/T-segment changes
- transient ST-segment elevation
- resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock.

Rationale

The recommendation for invasive coronary angiography within 24 hours for any patient with a diagnosis of NSTEMI is more aggressive than the recent National Institute for Health and Care Excellence (NICE) quality statement, which recommends invasive coronary angiography within 72 hours of admission.

The two largest studies assessing the benefit of invasive coronary angiography within 24 hours (‘early’), TIMACS (Timing of Intervention in Patients with Acute Coronary Syndromes) and VERDICT (Very Early vs Deferred Invasive evaluation using Computerised Tomography), showed a benefit with the ‘early’ invasive strategy for composite ischaemic endpoints among those with a GRACE risk score >140 (the preferred risk scoring system for mortality following ACS). Furthermore, a meta-analysis found lower mortality rates in the ‘early’ intervention group when patients had at least one of the following: elevated cardiac biomarkers at baseline (diagnosis of NSTEMI), diabetes mellitus, a GRACE risk score >140, age >75 years. From a health economics standpoint, another meta-analysis has shown that ‘early’ invasive coronary angiography leads to shorter in-hospital stays and a UK analysis showed that such a strategy is cost-effective in high-risk patients.

Gaps in the evidence

The recommendation for immediate invasive coronary angiography in patients with a ‘very high’ risk characteristic is based on the adverse short- and long-term prognosis of this cohort if left untreated. It must be remembered, however, that such patients are usually excluded from RCTs, and so the low...
level of evidence attributed to this recommendation reflects a
 gap in robust data, which is being addressed by the British Heart
 Foundation funded RapidNSTEMI (Very Early Versus Delayed
 Angiography +/- Intervention on Outcomes in Patients with
 NSTEMI) trial.14
 Moreover, under-representation of older patients in landmark RCTs
 of PCI has led to uncertainty as to whether an invasive coronary
 strategy confers benefit in this group. Recently, a small open-label
 RCT suggested a reduction in major adverse cardiovascular events
 (mainly driven by the prevention of further myocardial infarction
 or urgent revascularisation), without an increase in bleeding
 complications, from an early invasive coronary strategy in patients
 >80 years of age.13 Thus, the updated recommendation is to employ
 the same interventional strategies in older patients as younger
 patients. Separately, frail patients with NSTEMI have longer hospital
 stays, higher risk of death and major bleeding.12 The lack of robust
 evidence in this group means clinicians may have to make case-
 by-case decisions on whether to proceed with an invasive coronary
 strategy by assessing the risks of future cardiovascular events versus
 peri-procedural complications, but also life expectancy, comorbidities,
 quality of life and patient preferences. The ongoing British Heart
 Foundation funded SENIOR-RITA (older patients with non-ST
 SEgment elevation myocardial infarction Randomised Interventional
 Treatment) trial comparing invasive versus conservative strategies for
 patients >75 years of age will also address frailty status, and should
 help provide a stronger evidence basis.19

 **Treatment**

 **Background**

 The previous recommended treatment for NSTEMI comprised
 routine use of dual antiplatelet treatment (DAPT) and anticoagulant
 (usually fondaparinux at 2.5 mg subcutaneous/day) from the time
 of diagnosis. The favoured antiplatelet regime was the combination
 of aspirin (300 mg loading dose then 75 mg/day) alongside
 ticagrelor (180 mg loading dose then 90 mg twice daily).20
 Aspirin irreversibly inactivates cyclooxygenase activity and
 suppresses thromboxane A2 production throughout the platelet
 lifespan. Meta-analysis of data from the pre-PCI era has shown a
 46% reduction for major vascular events with aspirin treatment
 for ACS.21 The addition of a P2Y12 receptor inhibitor at diagnosis
to inhibit adenosine diphosphate (ADP)-induced platelet
 aggregation was initially shown to reduce ischaemic events in ACS
 in patients presenting without persistent ST-segment elevation
 with clopidogrel in the CURE trial (Clopidogrel in Unstable Angina
 to Prevent Recurrent Events).22 This was superseded by ticagrelor
 after the PLATO (PLATElet inhibition and patient Outcomes) trial
 found its greater potency led to a further reduction in ischaemic
 events without an increase in fatal or life-threatening bleeds,
 irrespective of receipt of PCI.23 Prasugrel (another potent P2Y12
 receptor inhibitor) also led to a reduction in ischaemic events
 when compared with clopidogrel, but with more frequent severe
 bleeding complications.24

 **Recommendation**

 > Prasugrel should be considered in preference to ticagrelor for
 patients who proceed to PCI (class of recommendation IIa, level
 of evidence B).
 > If an early invasive management strategy is planned it is not
 recommended to routinely administer pre-treatment with a
 P2Y12 receptor inhibitor (class of recommendation III, level of
 evidence A).
 > If an early invasive management strategy is not planned then
 administration of pre-treatment with a P2Y12 receptor inhibitor
 may be considered in the absence of high bleeding risk (class of
 recommendation IIb, level of evidence C).

 **Rationale**

 Contemporary data challenge the concept of early intense platelet
 inhibition with P2Y12 receptor inhibitors for patients who are planned
 for an invasive strategy (‘pre-treatment’). Observational data from
 a large Swedish dataset showed that pre-treatment was associated
 with a significantly increased risk of bleeding events without an
 improvement in ischaemic outcomes.25 Of course, pre-treatment may
 be associated with patient harm should the diagnosis not be AMI
 but, for example, aortic dissection or subarachnoid haemorrhage.
 The more rapid onset of action after loading doses of prasugrel and
 ticagrelor (30 minutes) also makes it viable to only administer them
during invasive coronary angiography once the coronary anatomy
has been delineated and it is decided to proceed to PCI.

 The ISAR-REACT (Intracoronary stenting and antithrombotic
 regimen: Rapid Early Action for Coronary Treatment) 5 trial
 compared the strategy of pre-treatment with ticagrelor to
defered loading with prasugrel (60 mg then 10 mg/day) at
 invasive coronary angiography once the decision was made for
 PCI. In a trial with a high proportion of patients treated with PCI
 (84%), the prasugrel arm showed a significantly lower composite
 endpoint of all-cause death, myocardial infarction and stroke
 at 1 year (primarily driven by a reduced incidence of myocardial
 infarction) without an increased incidence in major bleeding
 events.26 The 2020 ESC guidelines therefore no longer recommend
 pre-treatment with a P2Y12 receptor inhibitor if an ‘early’ invasive
 management strategy is planned, and recommend prasugrel
 loading when PCI has been decided upon.
 For patients who will receive ‘delayed’ invasive coronary angiography,
 the prescription of P2Y12 receptor inhibitors should no longer be routine,
 but carefully considered after factoring in the patient’s bleeding risk.
 The bleeding risk may be estimated from scoring systems such as
 CRUSADE (Can Rapid Risk stratification of Unstable angina patients
 Suppress Adverse outcomes with Early Implementation of the ACC/ AHA guidelines) or by identifying major and minor criteria according
to ARC-HBR (Academic Research Consortium for High Bleeding Risk).22,26 Among patients for whom conservative management is
planned, DAPT (preferably with ticagrelor) is still recommended at the
time of diagnosis and fondaparinux is still recommended for both a
conservative strategy and when invasive coronary angiography is not
possible within 24 hours.4
 The long-term combination and duration of antiplatelet/s following
NSTEMI is at the discretion of the treating interventionalist and
is dependent on ischaemic risk, bleeding risk and whether there
is a co-existent indication for oral anticoagulation. The other
components of the long-term management of NSTEMI have seen
updates from the most recent guidelines on hypertension, diabetes
mellitus and hypercholesterolaemia (supplementary material S2).

 **Gaps in the evidence**

 The most recent evaluation of UK clinical practice found 19.1% of
patients with NSTEMI received invasive coronary angiography
within 24 hours.1 As such, most patients will require careful
consideration of their bleeding risk before the prescription of
a P2Y<sub>12</sub> receptor inhibitor. Data have shown thatprasugrel’s predominant benefit is when PCI will definitely occur, whereas early prescription is associated with bleeding complications. Therefore RCTs which compare pre-treatment with ticagrelor versus placebo against loading at the time of invasive coronary angiography, within a timeframe of 72 hours of presentation, could help clarify the optimal antiplatelet regimen when ‘early’ invasive coronary angiography is not possible.

**Conclusion**

Over the last 25 years, there has been substantial progress in the management of ACS in patients presenting without persistent ST-segment elevation, driven by major advances in invasive coronary techniques, new pharmacotherapies and biochemical assays. The 2020 ESC guidelines emphasise the importance of a personalised approach to care which involves the use of these innovations. This includes more sensitive detection of NSTEMI, a more precise approach to antiplatelet therapy to reduce bleeding complications, and the potential benefit from an expedient invasive coronary strategy for higher-risk patients. Even so, there are important gaps in the knowledge base, which may be clarified by robust evidence from RCTs, such as the optimal treatment strategy for older people and the safest antiplatelet regimen when ‘early’ invasive coronary angiography is not possible.

**Supplementary material**

Additional supplementary material may be found in the online version of this article at www.rcpjournals.org/clinmedicine:

S1 – Key recommendations from the 2020 ESC guidelines for the management of non-ST-segment elevation myocardial infarction

S2 – Long-term management of non-ST-segment elevation myocardial infarction

**References**

1. National Institute for Cardiovascular Outcomes Research. Myocardial Ischaemia National Audit Project: 2019 summary report (2017/18 data). NICE, 2019. Available from www.hqip.org.uk/resource/myocardial-ischaemia-national-audit-project-minap-2019-summary-report/.
2. Hall M, Dondo TB, Yan AT et al. Association of clinical factors and therapeutic strategies with improvements in survival following non-ST-elevation myocardial infarction, 2003–2013. JAMA 2016;316:1073–82.
3. Simonsson M, Wallentin L, Alfredsson J et al. Temporal trends in bleeding events in acute myocardial infarction: insights from the SWEDHEART registry. Eur Heart J 2020;41:833–43.
4. Collet JP, Thiele H, Barbato E et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020, in press (DOI: 10.1093/eurheartj/ehaa575).
5. Thygesen K, Alpert JS, Jaffe AS et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237–69.
6. Shah AS V, Anand A, Strachan FE et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. Lancet 2018;392:919–28.
7. Chew DP, Lambrakis K, Blyth A et al. A randomized trial of a 1-hour troponin T protocol in suspected acute coronary syndromes: the rapid assessment of possible acute coronary syndrome in the emergency department with high-sensitivity troponin T Study (RAPID-TnT). Circulation 2019;140:1543–56.
8. Miller-Hodges E, Anand A, Shah AS et al. High-sensitivity cardiac troponin and the risk stratification of patients with renal impairment presenting with suspected acute coronary syndrome. Circulation 2018;137:425–35.
9. Fox KAA, Clayton TC, Dammann P et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome: a meta-analysis of individual patient data. J Am Coll Cardiol 2010;55:2435–45.
10. National Institute of Health and Care Excellence. Quality statement 3: Coronary angiography and PCI within 72 hours for NSTEMI or unstable angina. In Acute coronary syndromes in adults. Quality standard [Q568]. NICE, 2014. www.nice.org.uk/guidance/qs568/chapter/Quality-statement-3-Coronary-angiography-and-PCI-within-72-hours-for-NSTEMI-or-unstable-angina.
11. Mehta SR, Granger CB, Boden WE et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165–75.
12. Kofoed KF, Kelbaek H, Hansen PR et al. Early versus standard care invasive examination and treatment of patients with non-st-segment elevation acute coronary syndrome. Circulation 2018;138:2741–50.
13. Jobs A, Mehta SR, Montalescot G et al. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. Lancet 2017;390:737–46.
14. Bonello L, Laine M, Puymirat E et al. Timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes and clinical outcomes: an updated meta-analysis. JACC Cardiovasc Interv 2016;9:2267–76.
15. Henriksson M, Epstein DM, Palmer S et al. The cost-effectiveness of an early interventional strategy in non-ST-elevation acute coronary syndrome based on the RITA 3 trial. Heart 2008;94:717–23.
16. Kite TA, Gersh BJ, Gershlick AH. Spotlight on N-STEMI ACS: getting the right patients the right treatment, and at the right time. EuroIntervention 2019;15:e1041–5.
17. Tegn N, Abdelnoor M, Aaberge L et al. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet 2016;387:1057–65.
18. Ekerstad N, Swahn E, Janzon M et al. Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction. Circulation 2011;124:2397–404.
19. Chan D, Lawson L, Kunadian V. Management of older patients presenting with non-ST-elevation acute coronary syndrome. EuroIntervention 2018;14:e258–60.
20. Roffi M, Patrono C, Collet JP et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2016;37:267–315.
21. Antithrombotic Trialsists’ Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.
22. Mehta SR, Bassand JP, Chrolavicius S et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:699–702.
23. Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.
24. Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
25. Dworeck C, Redfors B, Angerus O et al. Association of pretreatment with P2Y<sub>12</sub> antagonists preceding percutaneous coronary intervention in non-ST-segment elevation acute coronary syndromes with outcomes. JAMA Netw Open 2020;3:e2018735.
26 Schüpke S, Neumann F-J, Menichelli M et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med* 2019;381:1524–34.

27 Subherwal S, Bach RG, Chen AY et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation* 2009;119:1873–82.

28 Urban P, Mehran R, Colleran R et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J* 2019;40:2632–53.

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