

# 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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## ABSTRACT

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.<sup>1</sup> 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

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international decline in mortality rates.<sup>2,3</sup> 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,<sup>4</sup> 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 P2Y<sub>12</sub> receptor inhibitors). In line with the guidelines, acute myocardial infarction (AMI) is defined according to the 4th universal definition of myocardial infarction (Table 2).<sup>5</sup>

## Diagnosis

### Background

Cardiac troponins are the most sensitive and specific markers of cardiomyocyte injury, superseding older biomarkers such as creatinine 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.<sup>6</sup>

### 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

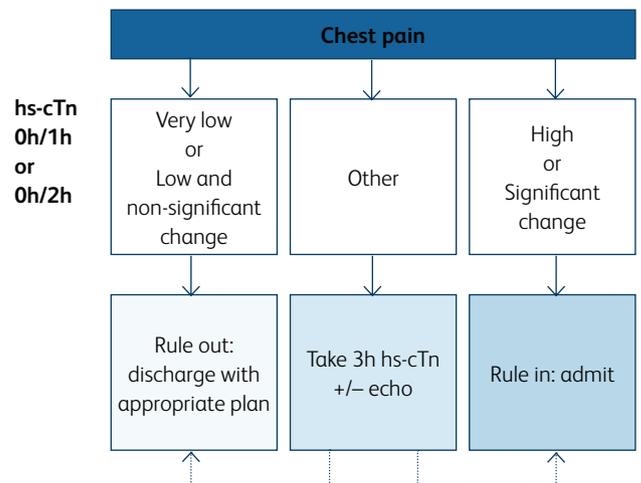
Due to the higher sensitivity of hs-cTn, the interval between the first and second troponin measurement may be shortened.

**Table 1. Definitions of class of recommendation and supporting level of evidence used in European Society of Cardiology (ESC) guidelines<sup>4</sup>**

Recommendations		
Class of Recommendation	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%.<sup>4</sup> 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%.<sup>7</sup> With ever-increasing demand on acute



**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<sup>4</sup>**

**Table 2. Definition of acute myocardial infarction as per the fourth universal definition of myocardial infarction (European Society of Cardiology, 2018)<sup>5</sup>****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

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.<sup>4</sup> 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.

Notably, the interpretation of high hs-cTn values always requires due clinical diligence. The assay is a continuous variable and the probability of AMI increases with greater values. Elevations beyond five times the upper limit of normal have a greater than 90% PPV for AMI, but elevations up to three times the upper limit of normal have a PPV of only 50–60%.<sup>4</sup> There are a range of conditions other than AMI that may lead to cardiomyocyte injury and thus hs-cTn elevation

### Box 1. Common conditions other than acute myocardial infarction associated with cardiomyocyte injury and cardiac troponin elevation

#### Cardiovascular conditions

Tachyarrhythmias  
Heart failure  
Hypertensive crisis  
Valvular heart disease  
Myocarditis  
Takotsubo syndrome

#### Non-cardiovascular conditions

Sepsis  
Aortic dissection  
Pulmonary embolism  
Stroke or subarachnoid haemorrhage  
Renal dysfunction with associated cardiac disease  
Extreme endurance efforts  
Burns

(Box 1), and outcomes for some of these will be adversely affected by the prescription of antiplatelet agents. In addition, age (comparing very old with very young), chronic kidney disease (comparing very high with very low estimated glomerular filtration rate [eGFR]), and time from chest pain onset may cause up to a 300% difference in troponin values, while sex can cause up to a 40% difference.<sup>8</sup>

#### Gaps in the evidence

Currently, a uniform cut-off hs-cTn level is used for the early diagnosis of AMI despite the aforementioned variables that may affect its concentration. The development of an information technology tool that can incorporate all four variables to arbitrate appropriate cut-offs for individual patients for the diagnosis of AMI may be of help in routine clinical practice. In addition, for the cohort of patients whose two hs-cTn concentrations are in an intermediate range between rule-in and rule-out, the optimum diagnostic strategy is uncertain, with options including the use of additional biomarkers or non-invasive imaging. Studies that randomise patients to diagnostic pathways with or without the such tests in addition to usual care could help clarify the most efficient and cost-effective diagnostic strategy.

#### Pathways

##### Background

Invasive coronary angiography helps clarify whether chest pain may be due to myocardial ischaemia secondary to a culprit lesion in the epicardial coronary arteries. Obstructive coronary lesions can then be treated by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery depending on their morphology and the patient's clinical characteristics. Although all invasive procedures have inherent risk, these have been somewhat mitigated by advances including radial access and modern drug-eluting stents. Many RCTs have compared a routine invasive strategy with a selective invasive strategy (where invasive coronary angiography would only be performed in the context of recurrent symptoms or evidence of obstructive coronary artery disease from non-invasive tests). Meta-analyses of data from these RCTs

have shown a reduction in risk of death or myocardial infarction from an invasive strategy in NSTEMI, especially for patients of high ischaemic risk.<sup>9</sup> 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.<sup>10</sup> 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).<sup>11,12</sup> 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.<sup>13</sup> 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.<sup>14,15</sup>

#### 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.<sup>16</sup>

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.<sup>17</sup> 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.<sup>18</sup> 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.<sup>19</sup>

## 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).<sup>20</sup>

Aspirin irreversibly inactivates cyclooxygenase activity and suppresses thromboxane A<sub>2</sub> 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.<sup>21</sup> The addition of a P2Y<sub>12</sub> 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).<sup>22</sup> 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.<sup>23</sup> Prasugrel (another potent P2Y<sub>12</sub> receptor inhibitor) also led to a reduction in ischaemic events when compared with clopidogrel, but with more frequent severe bleeding complications.<sup>24</sup>

### 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

P2Y<sub>12</sub> 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 P2Y<sub>12</sub> 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 P2Y<sub>12</sub> 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.<sup>25</sup> 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 deferred 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.<sup>26</sup> The 2020 ESC guidelines therefore no longer recommend pre-treatment with a P2Y<sub>12</sub> 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 P2Y<sub>12</sub> 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).<sup>27,28</sup> 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.<sup>4</sup>

The long-term combination and duration of antiplatelets 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.<sup>1</sup> 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 that prasugrel'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 regime 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](http://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

- National Institute for Cardiovascular Outcomes Research. *Myocardial Ischaemia National Audit Project: 2019 summary report (2017/18 data)*. NICOR, 2019. Available from [www.hqip.org.uk/resource/myocardial-ischemia-national-audit-project-minap-2019-summary-report/](http://www.hqip.org.uk/resource/myocardial-ischemia-national-audit-project-minap-2019-summary-report/).
- 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.
- 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.
- Collet J-P, 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).
- Thygesen K, Alpert JS, Jaffe AS *et al*. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237–69.
- 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.
- 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.
- 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.
- Fox KAA, Clayton TC, Damman 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.
- 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 [QS68]*. NICE, 2014. [www.nice.org.uk/guidance/qs68/chapter/Quality-statement-3-Coronary-angiography-and-PCI-within-72-hours-for-NSTEMI-or-unstable-angina](http://www.nice.org.uk/guidance/qs68/chapter/Quality-statement-3-Coronary-angiography-and-PCI-within-72-hours-for-NSTEMI-or-unstable-angina).
- 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.
- Kofoed KF, Kelbæk 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.
- 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.
- 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.
- Henriksson M, Epstein DM, Palmer SJ *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.
- 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.
- 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.
- 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.
- Chan D, Lawson L, Kunadian V. Management of older patients presenting with non-ST-elevation acute coronary syndrome. *EuroIntervention* 2018;14:e258–60.
- Roffi M, Patrono C, Collet J-P *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.
- Antithrombotic Trialists' 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.
- 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;345:494–502.
- 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.
- 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.
- Dworeck C, Redfors B, Angeras 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, Collieran 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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