From prolonged time to diagnosis

Faster, evidence-based algorithms for treatment decisions based on the 2020 NSTE-ACS Guidelines from the European Society of Cardiology

WHERE CARE LEADS

References

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Biomarkers for the diagnosis of ACS

Key update from the 2020 NSTE-ACS Guidelines from the ESC

1. Measurement of a biomarker of cardiomyocyte injury, preferably hs-cTn, is mandatory in all patients with suspected NSTE-ACS.

2. If the clinical presentation is compatible with myocardial ischaemia, then a dynamic elevation of cTn >99th percentile of healthy individuals indicates Myocardial Infarction (MI).

3. The ESC 0/1-h algorithm is now recommended as the first-choice diagnostic algorithm (Class I B).

4. As an alternative to the ESC 0/-1h algorithm, it is recommended to use the ESC 0/2-h algorithm, if an hs-cTn test with a validated 0/2-h algorithm is available (Class I B).

5. The 0/3-h algorithm recommendation was downgraded to a Class IIa B recommendation.

6. While cTnT-hs and hs-cTnI have comparable diagnostic accuracy, cTnT-hs has greater prognostic accuracy.

7. Biomarkers should always be used in combination with clinical assessment and 12-lead ECG in the diagnosis, risk stratification, and treatment of patients with suspected NSTE-ACS.

ACS, acute coronary syndrome; ECG, electrocardiogram; ESC, European Society of Cardiology; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome.
The ESC 0/1-h algorithm to accelerate the time to diagnosis and to drive immediate therapeutic consequences for the diagnosis of ACS

The first algorithm to rule-in or rule-out AMI within 0 to 1 h using cTnT-hs is confirmed by the 2020 ESC Guidelines

Risk of MI at index visit was <0.3% for the rule-out group, ~10% for the observe group, and >65% for the rule-in group; Risk of 30-day MACE was <0.5% for the rule-out group, 15–20% for the observe group, and >70% for the rule-in group.

* If chest pain onset was >3 h
AMI, acute myocardial infarction; ECG, electrocardiogram; ESC, European Society of Cardiology; MACE, major adverse cardiac event; MI, myocardial infarction; NSTE-ACS, non ST-elevation acute coronary syndrome

0/1-h algorithm benefits

Reduce length of observation time
Reduced overall length of ED stay
Lower hospital & overall AMI diagnostic cost

The ESC 0/1-h algorithm complemented with cut-offs specific for cTnT-hs

cTnT-hs values in patients presenting to the emergency department with chest pain

Rule-out

0 h < 5 ng/L
Rule-in

0 h ≥ 52 ng/L OR Δ 1 h ≥ 5 ng/L

Observational zone (additional cTnT-hs testing after 3 h is recommended)

New in the guidelines: The ESC 0/2-h algorithm

Indicated as an alternative to the ESC 0/1-h algorithm

The ESC 0/2-h algorithm complemented with cut-offs specific for cTnT-hs

cTnT-hs values in patients presenting to the emergency department with chest pain

Rule-out

0 h < 5 ng/L
Rule-in

0 h ≥ 52 ng/L OR Δ 1 h ≥ 5 ng/L

Observational zone (additional cTnT-hs testing after 3 h is recommended)
Caveats to consider with rapid algorithms

Algorithms should always be interpreted in conjunction with clinical and ECG findings.

Troponin release is time-dependent. An additional cTn measurement at 3 h should be considered in patients presenting <1 h after chest pain onset and triaged towards rule-out.

Late increases in cTn concentrations have been described. Serial cTn testing should be carried out if clinical suspicion remains high or in patients with recurrent chest pain.

Assessing the rise and/or fall of cTn levels can help differentiate AMI from other conditions associated with cardiomyocyte injury.

Collect blood samples for hs-cTn measurements at admission (0 h) and 1 h later. The team should not wait for other clinical details or pending results.

The exact time of 0 h blood draw should be recorded to accurately estimate the time window (±10 min) of the 1 h blood draw. In case the 1 h (±10 min) collection is not possible, blood should be collected at 2 h and the 0/2-h algorithm should be used.

Take note: Early measurements may seem unnecessary in some patients. However, evaluating troponin dynamics early accelerates the process of ruling in and ruling out MI.

Timing of the blood draws and time of clinical decision differ.

An important point to consider when using the 0/1-h algorithm.

The ESC 2020 NSTE-ACS Guidelines recommend the measurement of cardiac troponins with high-sensitivity assays immediately after admission. The results should be available within 60 minutes of blood sampling (Class I, Level B). The ESC 0/1-h algorithm is used irrespective of the local turnaround time. In the 0/1-h algorithm, 0 h and 1 h refer to the timepoint at which blood is taken. To calculate the earliest timepoint for clinical decision, the local TAT should be added to the time of blood collection.

Compared to other algorithms, the 0/1-h algorithm possesses clinical and economic benefits, independent of the local TAT.

Quicker diagnosis + shorter hospital stay = reduced resource utilisation. Fewer blood draws, ECGs and imaging studies are required.

*Those with very low 0 h concentrations/cheast pain onset >3 h
ESC, European Society of Cardiology; MI, myocardial infarction
The performance and safety of rapid rule-out using the ESC 0/1-h algorithm with cTnT-hs is confirmed by multiple studies.\(^5-11\)

### Publications and trials using cTnT-hs values for patient assignment to the rule-out zone

<table>
<thead>
<tr>
<th>Study</th>
<th>NPV (95% CI)</th>
<th>All-cause mortality or MACE in the rule-out zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 h &lt; 12 ng/L and Δ 1 h &lt; 3 ng/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACE(^5)</td>
<td>100%</td>
<td>30 days all-case mortality: 0.2% 2 years all-cause mortality: 1.9%</td>
</tr>
<tr>
<td>APACE(^6)</td>
<td>99.9% (99.3–100%)</td>
<td>30 days all-case mortality: 0% 2 years all-cause mortality: 1.1%</td>
</tr>
<tr>
<td>TRAPID-AMI(^7)</td>
<td>99.1% (98.2–99.7%)</td>
<td>30 days all-case mortality: 0.1% 2 years all-cause mortality: 0.7%</td>
</tr>
<tr>
<td>Mokhtari et al.(^8)</td>
<td>NPV* for 30 days MACE: 99.5% (98.6–99.9%)*</td>
<td>30 days MACE*: 0.5% and 0% without UA</td>
</tr>
<tr>
<td>0 h &lt; 5 ng/L or 0 h &lt; 12 ng/L and Δ 1 h &lt; 3 ng/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACE(^5)</td>
<td>100%</td>
<td>30 days and 1-year all-case mortality: 0.2%</td>
</tr>
<tr>
<td>RAPID-TnT(^9)</td>
<td>99.6% (99.0–99.9%) for 30 days death or MI</td>
<td>30 days all-case mortality and MI: 0.4%</td>
</tr>
<tr>
<td>Shiozaki et al.(^1)</td>
<td>100% (96.8–100%)</td>
<td>30 days all-case mortality: 0%</td>
</tr>
</tbody>
</table>

The high NPV (99.1–100%) of the 0/1-h algorithm and the low 30-day mortality (0–0.4%) in the rule-out zone confirms the safety of this approach for early discharge.

In three prospective studies and more than 8000 patients interventional studies confirm the excellent performance of the 0/1-h algorithm using cTnT-hs.\(^9,10,12\)

### The ESC 0/1-h cTnT-hs algorithm

- **Rule-out**
  - 0 h <5 ng/L OR 0 h <12 ng/L and Δ1 h <3 ng/L
  - 61.8% of patients triaged within 1 h
- **Observe**
  - 0 h ≥52 ng/L OR Δ1 h ≥5 ng/L
  - 12.8% of patients triaged
- **Rule-in**
  - 0 h ≥52 ng/L OR Δ1 h ≥5 ng/L
  - 75% triaged

The ESC 0/1-h cTnT-hs algorithm triages over three-quarters of ED chest pain patients: 75–84% of patients triaged within 1 hour (plus lab time).

### The safety of the ESC 0/1-h algorithm using cTnT-hs is confirmed by the low incidence of 30-day MACE or mortality in rule-out patients*

- **Twerebold R et al.\(^9\)**
  - 30-day MACE rate: 0.3%
  - 0.2% in the rule-out group
- **Chew DP et al.\(^10\)**
  - 30-day all-cause death or MI rate: 0.5%
  - 0.1% among patients triaged to outpatient care†
- **Stoyanov KM et al.\(^12\)**
  - 30-day mortality rate: 0.4%
  - 0.08% among patients triaged to outpatient care†

The low 30-day MACE rate (0.1–0.3%) among patients discharged directly from the ED confirms the safety of this approach for early discharge.

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* When using the extended algorithm adding ECG and patient history as recommended by the ESC guidelines. ACS, acute coronary syndrome; CI, confidence interval; ECG, electrocardiogram; NPV, negative predictive value; MACE, major adverse cardiac event; MI, myocardial infarction; UA, unstable angina

† Rule-out group indicates patients recommended to be ruled-out for MI by the algorithm. † Outpatient care indicates patients in which the final management decision made was direct discharge from the ED CI, confidence interval; ED, emergency department; ESC, European Society of Cardiology; MACE, major adverse cardiac events; MI, myocardial infarction
The ESC 0/1-h algorithm using cTnT-hs is robust in important patient subgroups (e.g. early presenters, sex, age)\(^9\)

Forest plots illustrating efficacy and safety of the ESC 0/1-h cTnT-hs algorithm in pre-defined subgroups\(^9\)

<table>
<thead>
<tr>
<th>CPO</th>
<th>Proportion rule-out/in</th>
<th>Proportion outpatients</th>
<th>In rule-out group</th>
<th>In outpatients</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3 hours</td>
<td>81% p&lt;0.001</td>
<td>69% p&lt;0.001</td>
<td>0.9% p=0.3</td>
<td>0.9% p=0.4</td>
</tr>
<tr>
<td>&gt;3 hours</td>
<td>68% p=0.001</td>
<td>58% p=0.001</td>
<td>0.3% p=0.1</td>
<td>0.3% p=0.1</td>
</tr>
<tr>
<td>Sex</td>
<td>Females</td>
<td>83% p&lt;0.001</td>
<td>70% p&lt;0.001</td>
<td>0.2% p=0.1</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>69% p=0.001</td>
<td>59% p=0.001</td>
<td>0.2% p=0.1</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;65 years</td>
<td>97% p&lt;0.001</td>
<td>84% p&lt;0.001</td>
<td>0.1% p=0.1</td>
</tr>
<tr>
<td></td>
<td>&gt;75 years</td>
<td>93% p&lt;0.001</td>
<td>80% p&lt;0.001</td>
<td>0.1% p=0.1</td>
</tr>
<tr>
<td>All Patients</td>
<td>(n=2296)</td>
<td>75%</td>
<td>71%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

**30-day MACE rates were low in all subgroups**

For early presenters (CPO ≤3 h), the 0/1-h algorithm triaged 80% to rule-out or rule-in, with a 0% 30-day MACE rate in rule-out patients\(^9\)

The ESC 0/1-h algorithm using cTnT-hs reduces LoS in ED & acute care\(^9,10,12\)

**Median reduction of 1–2 hours of length of stay* compared with standard of care\(^9,10,12\)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twerenbold R et al.(^9)</td>
<td>2.25 h</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Stoyanov KM et al.(^12)</td>
<td>2.1 h</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Chew DP et al.(^10)</td>
<td>1 h</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Chew DP et al.(^10)</td>
<td>1.1 h</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

**Improves ED patient flow**

- Triage 75–84% of patients to rule-in or rule-out within 1 hour (plus lab time)\(^9,10,12\)
- Rule-out of AMI possible in 62–72%\(^9,10,12\) of patients with a NPV of 99.6%\(^9\)

**Shortens length of stay (compared to 0/3-h algorithm) without compromising safety**

- Significantly increases ED discharge rates compared with the standard of care\(^9,10,12\)
- Reduces ED LoS by 1.0 – 2.25 h\(^9,10,12\)
- Reduces acute care LoS by 1.1 h\(^12\)

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*Comparisons are with pre-implementation / standard algorithm; AMI, acute myocardial infarction; ED, emergency department; ESC, European Society of Cardiology; LoS, length of stay; NPV, negative predictive value.
Conclusions from the three studies\textsuperscript{9,10,12}  

The implementation of the ESC 0/1-h algorithm using cTnT-hs\textsuperscript{13}

**cTnT-hs is safe**

- Low 30-day event rate 0.2 - 0.5\% (MACE, all cause mortality and MI, or mortality)\textsuperscript{9,10,12}  
- 0.08\% 30-day mortality in patients triaged to out-patient care\textsuperscript{12}

**cTnT-hs is feasible**

- 94\% algorithm adherence\textsuperscript{9}  
- 45 minute median reduction in the time between initial and second cTnT-hs sample\textsuperscript{12}

**cTnT-hs does not increase the use of diagnostic resources\textsuperscript{9,10,12}**

- Significant reduction in functional cardiac testing\textsuperscript{10}  
- No increase in coronary angiography\textsuperscript{10,12}

**Biomarkers as tools for prognostication and risk assessment**

Beyond its diagnostic role, it is recommended to measure hs-cTn serially for the estimation of prognosis (Class I B)\textsuperscript{1}

- cTnT-hs and hs-cTnI possess comparable diagnostic accuracy, however, cTnT-hs has greater prognostic accuracy\textsuperscript{1}

- hs-cTn adds prognostic information with regards to short- and long-term mortality to clinical and ECG variables\textsuperscript{1}

- The higher the hs-cTn levels, the greater the risk of death. Serial measurements can be used to detect peak levels of cardiac troponin and risk stratify patients with established MI\textsuperscript{1}

- BNP/NT-proBNP, serum creatinine and eGFR also affect prognosis and should be measured concomitantly\textsuperscript{1}

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ECG, electrocardiogram; cGFR, estimated glomerular filtration rate; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide (BNP)
Conclusions

Elecsys® Troponin T hs intended use\textsuperscript{14}

**Supported by numerous (> 1300) publications and has multiple intended uses**

1. **Aid in diagnosis**
   - Aid in the differential diagnosis of acute coronary syndrome to identify necrosis, e.g. acute myocardial infarction\textsuperscript{14}

2. **Rapid rule-out**
   - Aid for early discharge and out-patient management for patients suspected of acute coronary syndrome (ACS)\textsuperscript{14}

3. **Risk stratification - ACS**
   - Risk stratification of patients presenting with acute coronary syndrome\textsuperscript{14}

4. **Risk stratification – chronic renal failure**
   - Cardiac risk stratification in patients with chronic renal failure\textsuperscript{14}

5. **Selection of therapy and intervention**
   - The test may also be useful for the selection of more intensive therapy and intervention in patients with elevated levels of cardiac troponin T\textsuperscript{11}

6. **Perioperative use**
   - To predict the perioperative risk of major adverse cardiac events and for the aid in diagnosis of (MINS) and PMI in non-cardiac surgeries\textsuperscript{14}

7. **General population**
   - To aid in stratifying the long-term risk of cardiovascular death, myocardial infarction, coronary revascularization, heart failure, or ischemic stroke and all-cause mortality in asymptomatic individuals\textsuperscript{13}

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**NEW**

ACS, acute coronary syndrome; AMI, acute myocardial infarction; MI, myocardial infarction; MINS, myocardial injury after non-cardiac surgery; PMI, perioperative myocardial infarction

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**The 0/1-h algorithm (best option, blood draw at 0h and 1h) and the 0/2-h algorithm (second best option, blood draw at 0h and 2h) are the preferred rapid algorithms and are recommended with a Class IB recommendation\textsuperscript{1}**

Both algorithms have **data driven assay-specific cut-offs**, derived and validated to achieve predefined performance characteristics, for both rule-out and rule-in of AMI, justifying immediate therapeutic consequences\textsuperscript{1}

Multiple hs-cTn assays can be used with both algorithms and are supported by real life studies documenting safe and efficient implementation\textsuperscript{1}

The 0/1-h algorithm using cTnT-hs is **validated in numerous prospective trials\textsuperscript{9,10,12}**

Roche cTnT-hs is the first hs-cTn assay to introduce a **rapid rule-out claim for early discharge** and out-patient management for patients suspected of ACS\textsuperscript{14}