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What Is New in the 2023 European Society of Cardiology Guidelines for the Management of Acute Coronary Syndromes

Marco Roffi*

Abstract

For the first time, European Society of Cardiology (ESC) guidelines have aggregated in 1 single document recommendations for the management of patients with non-ST-segment elevation acute coronary syndromes (NSTEMI) and ST-elevation myocardial infarction (STEMI). From a clinical perspective, this is coherent, as the spectrum of clinical presentations in acute coronary syndromes (ACS) may range from new onset or progressive troponin-negative angina to STEMI, cardiogenic shock, or cardiac arrest. In addition, the management pathways of NSTEMI and STEMI patients are widely similar. Compared with previous editions of the guidelines, the extensive document is improved also from a graphic perspective, containing several appealing and easy-to-understand figures. New or modified recommendations include, among others, the topics of diagnostic work-up, timing of invasive strategy, revascularization in multi-vessel disease, intravascular imaging, cardiac arrest, cardiogenic shock, and antithrombotic treatment. For the first time in the field of ACS, ESC guidelines have incorporated a section on patient perspectives with dedicated recommendations. Some of the most relevant changes in recommendations impacting clinical practice are discussed in this article.

Keywords: Acute coronary syndromes; Guidelines; European Society of Cardiology

1. Introduction

The 2023 European Society of Cardiology (ESC) guidelines for the management of acute coronary syndromes (ACS) have been presented at the ESC meeting in Amsterdam, the Netherlands, on August 25, 2023, and published simultaneously in the *European Heart Journal*.^[1] The dedicated task force has been led by the chairpersons Robert Byrne from Ireland and Borja Ibanez from Spain. A total of 26 opinion leaders in the field, mainly from Europe, have contributed over a time span of 2 years to produce this extensive document, consisting of a main paper of 107 pages and 936 references and a supplementary data set of 52 pages and 449 references. A total of 193 recommendations are included, 55% of them being Class I, 25% Class IIa, 9% Class IIb, and 11% Class III [Table 1]. As a proof of the continuous output of high-quality studies in the field of ACS, 29% of the recommendation have a level of evidence (LoE) A (ie, derived from multiple randomized clinical trials (RCTs) or meta-analyses), whereas the corresponding figures for the 2020 ESC non-ST-segment elevation ACS (NSTEMI) and the 2017 ESC ST-elevation myocardial infarction (STEMI) guidelines were 24% and 23%, respectively. In parallel, the number of recommendations with a LoE C (ie, based on the consensus of opinion of experts or low-quality studies) has decreased from

49% in the 2017 STEMI guidelines, to 43% in the 2020 NSTEMI guidelines, to 38% in the current document. As a novelty in the field of ACS, ESC guidelines have incorporated a section on patient perspectives. Seven recommendations encompassing, among others, guidance on patient-centered care, inclusion of patients in decision-making, and assessment of patient well-being are included. The present report focuses solely on ESC guidelines and seeks to highlight the changes in recommendations from previous editions with the greatest impact on clinical practice.

For the first time, NSTEMI and STEMI recommendations have been aggregated in 1 single ESC document. From a clinical perspective, this is coherent, as the spectrum of ACS patients may range from individuals with new onset or progressive angina, which may be troponin negative and have no associated ischemic electrocardiography (ECG) changes, to patients with ECG changes and/or dynamic troponin elevation, to patients with ongoing ischemia, STEMI, or presenting with cardiogenic shock or cardiac arrest. In addition, with the exception of the timing of invasive strategy, the management pathways of NSTEMI and STEMI patients are similar in terms of diagnostic testing, antithrombotic treatment, revascularization, hospital care and long-term pharmacologic treatment, and lifestyle changes implementation.

Compared with previous editions, the document is also improved from a graphic perspective, containing many appealing and easy-to-understand figures as well as easy-to-catch messages. As an example, the authors propose the “A.C.S.” thought process for the initial patient triage and assessment, which consists of an ECG to check for Abnormalities or evidence of ischemia, a targeted clinical history to investigate the clinical Context of the presentation, and a targeted clinical examination to assess for clinical and hemodynamic Stability. At the official guideline presentation during the 2023 ESC meeting, the guideline leadership provided the audience with an animation summarizing in a very catchy way the management of ACS patients. Finally, the guideline task force included for the first time evidence tables in a 226-page appendix, with a detailed description

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Table 1
Classes of recommendation of the European Society of Cardiology guidelines.

| Class | Definition | Wording |
|-----------|---|---------------------------------|
| Class I | Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective | Is recommended/ is 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 favor 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 | Is not recommended |

of the most important trials discussed in the recommendation tables.

2. Diagnostic work-up

As in previous guidelines, the guidelines recommend (Class I) rapid “rule-in” and “rule-out” algorithms for myocardial infarction (MI) in all patients with suspected NSTEMI-ACS with measurements of high-sensitivity cardiac troponin levels on admission and at 1 h (0 h/1 h) or, if not available/feasible, on admission and at 2 h (0 h/2 h). Both algorithms have been derived and validated in large multicenter studies. Patients who do not meet the criteria for the “rule-out” or “rule-in” strategies are assigned to the “observe” pathway, with an additional troponin level measurement at 3 h, and if needed echocardiography, to guide further management.

As compared with previous guidelines, the role of coronary computed tomography angiography (CCTA) for suspected NSTEMI-ACS has been downgraded from a Class I indication in the 2020 NSTEMI-ACS guidelines to Class IIa in the current document. Accordingly, in the context of high-sensitivity cardiac troponins, the RCT Better Evaluation of Acute Chest Pain with Coronary Computed Tomography Angiography (RCT BEACON) showed no reduction of in-hospital stay or hospital admission associated with CCTA as compared with a standard management pathway.^[2] Similarly, in the Multicenter Study to Rule Out Myocardial Infarction by Cardiac Computed Tomography (ROMICAT II) trial, CCTA use was associated with an increase in downstream testing and no decrease in overall costs.^[3] And finally, in the Rapid Assessment of Potential Ischaemic Heart Disease with CTCA (RAPID-CTCA) trials enrolling 1,748 patients with suspected NSTEMI-ACS, a default approach using early non-invasive CCTA did not alter overall coronary therapeutic interventions or improve clinical outcomes at 1 year, whereas it was associated with a modest increase in the duration and cost of hospital stay.^[4]

3. Timing of invasive strategy

Regarding the STEMI pathway, there are no changes compared with the previous edition of the guidelines, with the goal of crossing the culprit lesion with a wire within 60 min if the patient is admitted to a percutaneous coronary intervention (PCI) center and in less than 90 min if the patient is transferred from a non-PCI center. If PCI is not possible within 120 min at the time of diagnosis, then a fibrinolytic strategy with immediate transfer to a PCI center after administration of a fibrinolytic agent is indicated.

Although the 2020 NSTEMI-ACS guidelines stratified the patients a “very high-risk” “high-risk” and “low-risk” the current document defines “non-high-risk” patients previously labeled as “low-risk” estimating that this denomination conveys better the true risk status of the patients. Although for the “very high-risk” and the “non-high-risk” categories, the management has not changed (ie, immediate angiography for the former and selective angiography/non-invasive testing for the latter), for the “high-risk” patient—ie, patients with established Non-STEMI (NSTEMI), with GRACE risk score >140, or with dynamic ECG changes—the recommendations regarding the delays to coronary angiography have been modified. Accordingly, although previous guidelines recommended (Class I) early (ie, within 24 h) invasive strategy for all high-risk patients, this edition of the guidelines gives a Class I for coronary angiography within the index hospital stay but a Class IIa for early angiography. The downgrading for early invasive strategy is based on a 2022 meta-analysis of early *vs.* delayed invasive strategy including 10,209 patients and 17 RCTs showing no benefit of an early invasive strategy in terms of mortality or MI but only a reduction in recurrent ischemia as well as a shorter hospital stay.^[5] The guideline task force recognizes that data interpretation is limited by the fact that time to angiography in the comparator group (ie, the delayed invasive strategy) was heterogeneous across the trials and that the diagnosis of NSTEMI was not based on high-sensitivity cardiac troponin algorithms.

4. Revascularization in patients with multi-vessel disease

In STEMI patients with multi-vessel coronary artery disease, the indication for complete revascularization, to be performed either during the index procedure or within 45 d, has been upgraded from Class IIa to Class I. The change is largely due to the publication in 2019 of the Complete *vs.* Culprit-Only Revascularization to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial, showing in 4,041 STEMI patients with multi-vessel disease the superiority of a complete *vs.* culprit-only revascularization in terms of cardiovascular death or MI at a median follow-up of 3 years.^[6] A subsequent meta-analysis including 7,030 patients showed a significant benefit in terms of cardiovascular mortality at 30 months for patients undergoing complete revascularization.^[7] Focusing on the diagnostic modality to identify which vessel should be revascularized in STEMI patients with multi-vessel disease, the preference is for angiography-guided revascularization (Class I), whereas a physiology-based strategy during index PCI has a Class III recommendation. Accordingly, in the Flow Evaluation to Guide Revascularization in Multivessel STEMI (FLOWER-MI) trial a fractional flow reserve (FFR)-guided PCI strategy was not superior to an angiography-based one for the revascularization of non-infarct-related arteries in 1,163 STEMI patients with multi-vessel disease.^[8] In addition, withholding revascularization of lesions judged relevant by visual estimation but not by FFR (ie, FFR > 0.80) was associated in the trial with higher rates of death, MI, or unplanned urgent revascularization.^[9]

In stable NSTEMI-ACS patients with multi-vessel disease, the evidence for complete revascularization has remained unchanged (Class IIa) with a low LoE (C). Accordingly, no RCT has compared culprit-only *vs.* complete revascularization in this setting, whereas a large-scale observational study suggested a mortality benefit associated with complete revascularization.^[10]

5. Intravascular imaging

The first new recommendation on intravascular imaging is that this diagnostic modality should be considered to guide PCI (Class IIa), based mainly on subgroup analyses of RCTs showing

similar positive effects on outcomes of intravascular imaging-guided as compared with angiography-guided PCI in ACS and non-ACS patients. A meta-analysis of RCTs including over 12,000 patients presented at the ESC 2023 meeting and comparing intravascular imaging-guided with angiography-guided PCI further supported this recommendation. Accordingly, it showed a significant benefit in favor of intravascular imaging-guided PCI in terms of ischemic endpoints, including cardiac and all-cause death.^[11] The second recommendation, of low level and based on a consensus of experts (Class IIb, LoE C), is that intravascular imaging (preferably with optical coherence tomography) may be considered in patients with ambiguous culprit lesions to help guide PCI. Finally, the guidelines underscore that in patients with a diagnosis of spontaneous coronary artery dissection on angiography and a plan for medical therapy, additional coronary instrumentation and intravascular imaging are not recommended on safety grounds.

6. Cardiac arrest and cardiogenic shock

Although in patients with STEMI and resuscitated cardiac arrest, the recommendation for immediate invasive strategy remains strong (Class I), for patients with resuscitated cardiac arrest but no ST-elevation on ECG or cardiogenic shock the recommendations have evolved over the years. Although the 2015 ESC NSTEMI-ACS guidelines^[12] gave a Class I indication for immediate angiography, based on a consensus of experts (LoE C), the 2020 NSTEMI-ACS labeled as Class IIa the recommendation for a delayed—as opposed to immediate—angiography in cardiac arrest survivors who did not have ST-elevation or shock. This recommendation was based on the results of the Coronary Angiography after Cardiac Arrest (COACT) study showing in 552 patients no mortality benefit of immediate angiography and, if appropriate, revascularization.^[13] The current guidelines have further downgraded immediate angiography in patients with resuscitated cardiac arrest but no ST-elevation on ECG or cardiogenic shock to a Class III, based on a meta-analysis of 6 RCTs and 1,529 patients showing no benefit of immediate invasive strategy *vs.* a delayed selective angiography in terms of mortality or good neurological outcome.^[14] While hypothermia had a Class I recommendation in patients with resuscitated cardiac arrest in the 2017 STEMI guidelines, temperature management in the current guidelines is limited to fever ($>37.7^{\circ}\text{C}$) avoidance (Class I), as the Targeted Hypothermia *vs.* Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial showed that in 1,850 comatose patients after out-of-hospital cardiac arrest, targeted hypothermia did not reduce mortality as compared with targeted normothermia.^[15]

As in the 2020 NSTEMI-ACS guidelines, in ACS patients with cardiogenic shock and multi-vessel disease, it is recommended to limit immediate PCI to the infarct-related artery (Class I), based on the results of the Culprit Lesion Only PCI *vs.* Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial.^[16] In the subset of patients with favorable outcomes post cardiogenic shock, a new Class IIa indication—albeit based on expert consensus (LoE C)—encourages staged complete revascularization based on symptoms, severity of ischemia, and comorbidities. The place for short-term mechanical support in ACS complicated by cardiogenic shock remains very limited and based on a consensus of experts, with a recommendation Class IIb LoE C, unchanged from the 2020 NSTEMI-ACS guidelines. The value of short-term mechanical circulatory support in ACS patients with shock was further questioned following the Extracorporeal Life Support in Cardiogenic Shock (ECLS-SHOCK) trial results, released at the same time as the guidelines at the 2023 ESC meeting, showing no mortality benefit at 30 d and more bleeding as well as vascular complications associated with of hemodynamic support by extracorporeal membrane oxygenation over standard of care in 420 patients.^[17] In addition, in the trial, no benefit was observed

in hemodynamic/organ dysfunction parameters such as arterial lactate, renal function, or SAPS-II score. As in previous documents, the routine use of intra-aortic balloon pumps in cardiogenic shock is not recommended (Class III).

7. Antithrombotic treatment

The role of bivalirudin as anticoagulant for primary PCI has been strengthened by the favorable results of the Bivalirudin With Prolonged Full-Dose Infusion During Primary PCI *vs.* Heparin Trial (BRIGHT)-4 study, showing superiority of bivalirudin bolus plus high-dose infusion over unfractionated heparin for the primary endpoint of all-cause death or Bleeding Academic Research Consortium 3 to 5 bleedings at 30 d as well as for stent thrombosis among 6,016 STEMI patients treated in Chinese hospitals.^[18] Nevertheless, the level of recommendation for the drug in the guidelines has not changed (Class IIa), possibly because a replication of the results in a non-Asian population is awaited.

Regarding P2Y₁₂ inhibitor pre-treatment in STEMI patients undergoing primary PCI, while the 2017 STEMI guidelines gave a Class I recommendation for the administration before (or at the latest at the time of) PCI, the current guidelines downgraded pre-treatment to a Class IIb. Accordingly, the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New STEMI to Open the Coronary Artery (ATLANTIC) study showed no benefit of P2Y₁₂ inhibitor pre-treatment on 70% or greater ST-segment elevation resolution before PCI, TIMI flow grade 3 in the infarct-related artery at initial angiography, or major adverse cardiovascular events at 30 d.^[19] In addition, an analysis of the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry including over 7,000 STEMI patients found no benefit of ticagrelor pre-treatment as compared with administration in the catheterization laboratory on all-cause mortality, MI or stent thrombosis or its individual components at 30 d.^[20] Finally, in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) including over 44,000 STEMI patients, no benefit of P2Y₁₂ inhibitor pre-treatment was detected.^[21]

Pre-treatment with P2Y₁₂ inhibitors in NSTEMI-ACS patients proceeding to coronary angiography has undergone multiple changes in recommendations over the years. While the 2015 NSTEMI-ACS guidelines gave no recommendation for clopidogrel or ticagrelor and a Class III recommendation for prasugrel pre-treatment based on A Comparison of Prasugrel at the Time of PCI or as Pretreatment at the Time of Diagnosis in Patients with NSTEMI (ACCOAST) trial,^[22] the 2017 ESC focused update on dual antiplatelet therapy (DAPT)^[23] gave a Class IIa recommendation, albeit with LoE C, for ticagrelor pre-treatment, or clopidogrel if ticagrelor was not an option. The rationale for it was that in the ticagrelor pivotal study of Platelet Inhibition and Patient Outcomes (PLATO),^[24] NSTEMI-ACS patients were all pre-treated. The results of the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial described below contributed to the downgrading to Class III for P2Y₁₂ pre-treatment in the 2020 NSTEMI-ACS guidelines.^[25] Accordingly, among the 2,365 NSTEMI-ACS patients enrolled in the ISAR-REACT 5 study, a strategy of prasugrel given at the time of angiography was superior to a strategy of ticagrelor given upstream with respect to all-cause death, MI, or stroke at 1 year.^[25] This recommendation is unchanged in the current guidelines, further supported by a meta-analysis of 7 RCTs enrolling 13,226 NSTEMI-ACS patients undergoing coronary angiography showing that P2Y₁₂ inhibitor pre-treatment was associated with an increased bleeding risk but no reduction of ischemic events at 30 d.^[26]

With respect to which potent P2Y₁₂ inhibitor (ie, prasugrel or ticagrelor) should be used in ACS patients proceeding to

PCI, current guidelines give the 2020 NSTEMI-ACS guidelines a Class IIa indication in favor of prasugrel, based on the results of ISAR-REACT 5 study showing among 4,018 ACS patients (both NSTEMI-ACS and STEMI) undergoing PCI a significant benefit in terms of death, MI or stroke at 1 year among patients allocated to prasugrel as compared with ticagrelor in the absence of a bleeding excess.^[25]

Regarding the duration of DAPT post-PCI, 12-month DAPT followed by aspirin alone remains the default strategy (Class I). However, the guideline task force recognizes alternative antiplatelet strategies to reduce bleeding risks such as abbreviated DAPT and DAPT de-escalation, that is, switching from a potent P2Y₁₂ inhibitor (ie, prasugrel or ticagrelor) to clopidogrel. Although the guidelines give a Class III recommendation for abbreviated DAPT lasting less than 1 month and for DAPT de-escalation in the first month, in high-bleeding risk (HBR) patients 1-month DAPT followed by a single antiplatelet agent has a Class IIb recommendation (unchanged) while reducing DAPT to 3 to 6 months has now a Class IIa recommendation in both HBR (unchanged) and non-HBR (new recommendation) patients. Accordingly, in patients who are event-free after 3 to 6 months of DAPT and who are not at high ischemic risk, single anti-platelet therapy (preferably with the P2Y₁₂ inhibitor) should be considered. In other words, regardless of bleeding risk, a single anti-platelet agent monotherapy is now a real option for patients not at high ischemic risk who are event-free at 3 to 6 months post PCI. De-escalation strategies after the first month carry a Class IIb (unchanged). The guideline task force underscores that any decision regarding DAPT abbreviation or P2Y₁₂ inhibitor de-escalation should not be made at the time of PCI, but instead, patients should be reassessed during the course of treatment. The somehow conservative approach with respect to DAPT duration is likely motivated by the observation that patients included in trials studying alternative regimens were at far lower risk (eg, less ACS as well as STEMI patients enrolled, far lower mortality observed) than those studies in the pivotal DAPT trials PLATO and Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in MI (TRITON-TIMI) 38.^[24,27]

Regarding antiplatelet treatment in ACS patients with an indication for oral anticoagulation, the recommendations remain unchanged compared with the 2020 NSTEMI-ACS guidelines. As a default strategy (Class I), it is recommended to administer triple antithrombotic therapy comprising a non-vitamin K oral anticoagulant (NOAC), clopidogrel, and aspirin for up to 1 week. This should be followed by NOAC and a single antiplatelet agent (Class I) for 11 months, after which NOAC alone can be continued. For patients at high ischemic risk, the Class IIa indication for triple therapy for up to 1 month remains unchanged.

8. Pharmacological long-term treatment

As in the 2020 NSTEMI-ACS guidelines, the default long-term (ie, beyond 12 months) antithrombotic treatment is aspirin monotherapy (Class I), while prolonged DAPT or the combination of aspirin and rivaroxaban 2.5 mg twice a day is given a Class IIa recommendation for patients at high ischemic risk but no HBR and a Class IIb for patients at moderate ischemic risk but no HBR. The current guidelines open the door for the first time to a P2Y₁₂ inhibitor long-term treatment (instead of aspirin) with a Class IIb recommendation, based on the results of a meta-analysis^[28] including 9 RCTs and more than 40,000 patients comparing the 2 regimens showing a borderline reduction in MI as well as on the results of the Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy (HOST-EXAM) trial^[29] showing in 5,530 South Korean patients the superiority of clopidogrel over aspirin, following 6- to 18-month DAPT post-PCI, both in terms of ischemic as well as bleeding events at 2 years. After the guidelines

were drafted, the extended follow-up of the HOST EXAM was published, showing that the benefit both in terms of ischemic as well as bleeding events associated with clopidogrel over aspirin persisted at a median of 5.8 years.^[30] The somehow restrictive recommendation for P2Y₁₂ inhibitor long-term treatment could mean that the guideline task force awaits these very provoking results to be replicated in other parts of the world.

With respect to low-density lipoprotein cholesterol lowering in patients presenting with ACS, the guidelines give a new Class I recommendation to intensify lipid-lowering therapy during the ACS hospitalization for patients who were on lipid-lowering therapy before admission, and also give a new Class IIb indication for the combination of statin plus ezetimibe during index hospitalization. Finally, the polypill enters ACS guidelines with a Class IIa recommendation to improve adherence and outcomes in the long-term treatment after ACS based on the Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE) study showing that in 2,499 post-MI patients, a polypill-based strategy consisting of aspirin, ramipril, and atorvastatin was superior to standard treatment in terms of cardiovascular death, MI, ischemic stroke, or urgent revascularization at 3 years.^[31]

9. Comorbid conditions

In elderly patients, the guidelines recommend to follow the same diagnostic patterns and therapeutic strategies as in younger patients. This strategy was further supported by the presentation at the 2023 ESC meeting of the FIRE trial showing that in 1,775 MI patients with multi-vessel disease older than 75 years of age complete revascularization was superior to culprit-only PCI for death, stroke, MI, or any revascularization as well as for death or MI at 1 year.^[32] For frail older patients with comorbidities, the guidelines give a Class I recommendation for the individualization of interventional and pharmacological treatments after careful evaluation of risks and benefits. In this perspective, the new recommendation Class IIb for clopidogrel has to be interpreted instead of the more potent prasugrel or ticagrelor as the P2Y₁₂ inhibitor component of DAPT in the elderly, especially if HBR. In cancer patients, while the guidelines give a new Class I recommendation for invasive strategy if life expectancy is estimated at more than 6 months, they also give a new Class IIa recommendation, albeit with LoE C, for a conservative treatment if the prognosis is poor (ie, life expectancy < 6 months) or if the patients are at very HBR.

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