

Antithrombotic therapy in patients with acute coronary syndrome: similarities and differences between a European expert consensus document and the 2023 European Society of Cardiology guidelines

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Antithrombotic therapy represents the cornerstone of the pharmacological treatment in patients with acute coronary syndrome (ACS). The optimal combination and duration of antithrombotic therapy is still matter of debate requiring a critical assessment of patient comorbidities, clinical presentation, revascularization modality, and/or optimization of medical treatment. The 2023 European Society of Cardiology (ESC) guidelines for the management of patients with ACS encompassing both patients with and without ST segment elevation ACS have been recently published. Shortly before, a European expert consensus task force produced guidance for clinicians on the management of antithrombotic therapy in patients with ACS as well as chronic coronary syndrome. The scope of this manuscript is to provide a critical appraisal of differences and similarities between the European consensus paper and the latest ESC recommendations on oral antithrombotic regimens in ACS patients.

Keywords Antithrombotic therapy • Acute coronary syndrome • Coronary artery disease • Antiplatelets

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Antithrombotic therapy represents the mainstay of the pharmacological treatment in patients with acute coronary syndrome (ACS).^{1,2} The optimal combination and duration of antithrombotic therapy (which agent, for whom, and for how long) is still a clinical conundrum that requires a critical assessment of clinical features including patient comorbidities, clinical presentation (acute or chronic coronary syndrome), and revascularization modality by percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or medical treatment alone.

Within this framework, a European expert task force produced a consensus on antithrombotic treatment strategies in patients with established coronary artery disease (CAD) including ACS as well as chronic coronary syndrome (CCS).³ Shortly afterwards, the 2023 European Society of Cardiology (ESC) guidelines for the management of patients with ACS encompassing patients with and without ST-segment elevation (NSTE)-ACS have been published.⁴

The scope of this manuscript is to provide a critical appraisal of differences and similarities between the European consensus paper and the latest ESC recommendations on oral antithrombotic regimens in ACS. This document does not address parenteral agents or antithrombotic therapy for ACS patients with clinical indication for oral anticoagulation (OAC), for which there have been limited updates in the field. When mentioning consensus statements and recommendations, this document refers to the 2022 clinical consensus document on antithrombotic treatment strategies in patients with established CAD³ and the latest 2023 ESC guidelines for ACS patients,⁴ respectively.

General concepts

Recommended tools for bleeding risk stratification

Different risk scores have been developed to predict the risk of bleeding at different time windows ranging from in-hospital to long-term events.⁵ The 2023 ESC guidelines recommend the use of the Academic Research Consortium—High Bleeding Risk (ARC-HBR) criteria⁶ for bleeding risk stratification in a footnote of the recommendation table 5.⁴ The PRECISE DAPT score is only referred to as an additional tool among ACS patients with clinical indication for OAC. It is important to note that the derivation and validation of the PRECISE DAPT score was performed in patients not taking OAC.⁷ The PRECISE DAPT score was derived from a pooled dataset of randomized controlled studies of patients undergoing PCI and integrates continuous covariates, such as age, creatinine clearance, white blood cell count, haemoglobin, together with prior bleeding.⁷ There is a solid rationale to propose both stratification systems (namely ARC-HBR and PRECISE DAPT score) for bleeding risk stratification purposes in ACS patients. The PRECISE DAPT score has been shown to be associated with consistent moderate bleeding risk discrimination in more than 20 external validation studies.⁸ However, it does not account for comorbidities, which have known implications for bleeding risk, such as those captured by the ARC-HBR criteria.⁶ The ARC initiative was groundbreaking in order to standardize bleeding risk assessment. While several studies suggested that the proposed ARC-HBR criteria (or some adaptations of the original proposal due to incomplete data availability) identify patients at higher bleeding risk compared with those with no ARC-defined HBR features, some suggested that additional HBR conditions or re-weighting the minor/major criteria may be associated with improved risk stratification.^{9,10} Pertinent to this discussion, a study showed that the ARC-HBR score discrimination was lower among ACS compared with CCS patients and that the inclusion of ACS as an additional minor risk criterion slightly improved the performance of the score in the overall study cohort.⁹ This suggests that, at least within this framework (where other markers of inflammation such as white blood cell count were not considered), the ARC-HBR definition

may consider including ACS as an additional minor risk criterion. Other data-driven observations suggest that minor criteria confer, in isolation, a bleeding risk which is similar to one attributed by consensus to the major criteria¹¹ and that the originally proposed ARC-HBR framework performs suboptimally among women,¹⁰ who are typically older than men when presenting with ACS.

Taking into account advantages and pitfalls of available bleeding risk tools, the consensus document endorses the use of both ARC-HBR and PRECISE DAPT score among ACS patients and assigns a generally higher weight to bleeding risk assessment and prevention.³

Dual antiplatelet therapy de-escalation

In the last decade, alternative strategies to standard 12-month dual antiplatelet therapy (DAPT) have been largely investigated, which may be summarized under the 'de-escalation' definition.¹² De-escalation is intended to decrease bleeding complications of antiplatelet therapy at a time when their risk is perceived to be greater than the risk of thrombotic complications.¹³ Reduced bleeding risk may be achieved by switching to a drug with less anticipated antiplatelet effect (de-escalation by switching), reducing the dose (de-escalation by dose reduction), or removing an antiplatelet agent (de-escalation by discontinuation).¹⁴ De-escalation by switching to clopidogrel can be either guided or unguided by genotype or platelet function test (PFT). The 2023 ESC guidelines do not list guided de-escalation as an alternative option to standard DAPT for ACS patients among recommendations.⁴ The lack of individual trial evidence of superiority of guided vs. unguided DAPT de-escalation and the increased complexity of the former over the latter treatment strategy may account for this omission from previous guidelines.¹⁵ Likewise, the consensus document does not support the routine use of PFT or genotyping to guide antiplatelet therapy.³

ACS managed by PCI

Non-high bleeding risk

For the first time, the 2023 ESC guidelines recommend considering some de-escalation strategies from 3 months of DAPT onwards in non-HBR patients, with a class of recommendation IIa.⁴ Despite mounting evidence from multiple randomized clinical trials (RCTs) and individual patient data (IPD) meta-analyses demonstrating a net benefit of abbreviated DAPT in patients with or without HBR, the 2023 ESC guidelines recommend DAPT for 12 months as the default strategy in all ACS patients unless there is HBR (class I, level of evidence A), in keeping with previous guidelines (Figure 1).¹⁶ These recommendations were generated leveraging on the following listed supportive studies: PCI-CURE,¹⁷ TRITON-TIMI 38,¹⁸ and PLATO.¹⁹ The CURE study was a landmark trial which, conducted more than 20 years ago, paved the way for DAPT in ACS patients by demonstrating that aspirin and clopidogrel combination was associated with a 20% relative risk reduction of the composite of cardiovascular death, myocardial infarction (MI), or stroke (relative risk 0.80; 95% confidence interval [CI]: 0.72–0.90) at the cost of increased bleeding compared with aspirin monotherapy.¹⁷ Findings from the same study suggesting a beneficial effect of clopidogrel pre-treatment were listed as supportive to routine 12-month DAPT but not for pre-treatment (class IIb, level of evidence C).²⁰ The TRITON-TIMI 38¹⁸ and PLATO¹⁹ studies demonstrated the superiority of prasugrel and ticagrelor for 12 months in combination with aspirin over clopidogrel-based DAPT for the primary composite endpoint of cardiovascular death, MI, or stroke with a comparable increase in major non-CABG-related bleeding. However, these pivotal studies compared ticagrelor and prasugrel with clopidogrel in aspirin-treated patients, including patients with and without HBR, who were treated with prior generation devices and techniques. In the largest head-to-head comparison of ticagrelor-based vs.

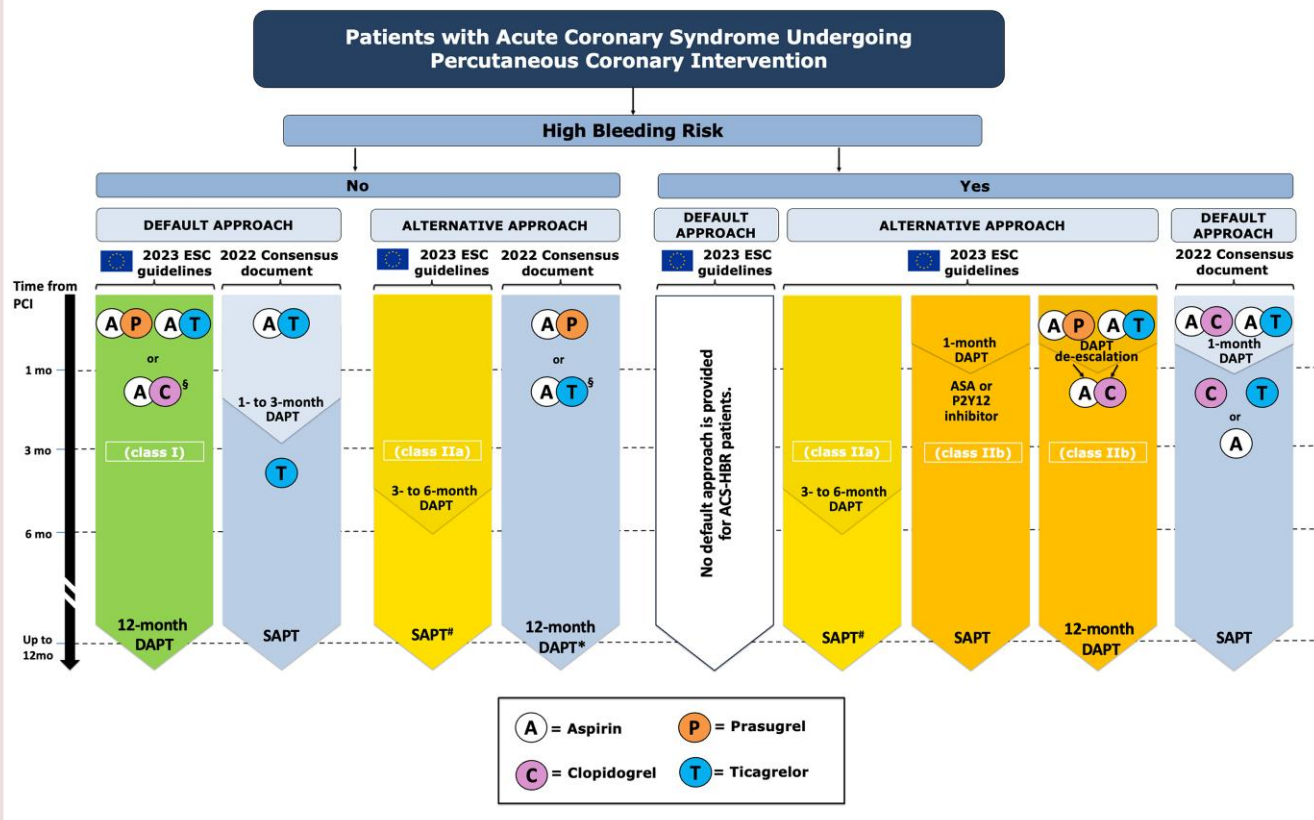


Figure 1 Summary of recommendations from the 2023 ESC guidelines and statements from the 2022 consensus document on antithrombotic treatment strategies in ACS patients undergoing PCI. Box colours of ESC guidelines reflect classes of recommendation. Treatment preferences within each box are presented from above to below, whereas treatments in the same line are reported in alphabetical order. [§]If patient is not eligible for above shown treatment options. *For patients at high ischemic risk and very low bleeding risk. #In patients not at high ischemic risk who are event-free after 3–6 months of DAPT. ACS, acute coronary syndrome; ASA, aspirin; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

prasugrel-based DAPT for 12 months (the ISAR REACT 5 trial), prasugrel was associated with a 26% relative reduction in the risk of cardiovascular death, MI, or stroke (hazard ratio [HR] 0.74; 95% CI: 0.59–0.92), mainly due to lower MI risk with prasugrel.²¹ Mortality and bleeding rates did not differ between the two groups.²¹ However, these findings should be interpreted in light of the open-label design, the low adherence to treatment assignment, and the major confounding element of having one drug tested in the pre-treatment phase and the other one only downstream (among NSTEMI-ACS patients).²²

Several trials investigated the treatment effects of shortening DAPT by discontinuing aspirin or P2Y₁₂ inhibitor at a point in time in ACS patients. In the SMART DATE trial,²³ 6-month DAPT followed by aspirin monotherapy was associated with bleeding benefit, but higher MI risk compared with standard DAPT in unselected ACS patients. Subgroup analyses of the one-month DAPT trial demonstrated a significant interaction for the net composite primary endpoint between the randomly allocated antiplatelet regimen and clinical presentation, suggesting a benefit of aspirin monotherapy in chronic coronary syndrome (CCS) but not ACS patients.²⁴ Therefore, aspirin monotherapy following abbreviated DAPT is not recommended after ACS within the first year in patients without HBR by both ESC guidelines⁴ and the consensus document.³ Several RCTs investigated the efficacy and safety of P2Y₁₂ inhibitor monotherapy after 1–3 months of DAPT. The inclusion of events in the initial DAPT phase (when experimental and control arms received

the same treatment regimen) was overcome by two IPD meta-analyses which censored events during the initial DAPT phase. The SIDNEY Collaboration,²⁵ including 14 628 patients from two trials (GLASSY²⁶ and TWILIGHT²⁷) demonstrated that ticagrelor monotherapy was associated with a 44% relative risk reduction in Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding (HR 0.56; 95% CI: 0.41–0.75) without increase in ischaemic events. The results remained consistent in ACS patients (*P* for interaction: 0.51). In the SIDNEY-2 Collaboration (24 096 patients from six trials), P2Y₁₂ inhibitor monotherapy was associated with lower risk of BARC 3 or 5 bleeding (HR 0.49, 95% CI: 0.39–0.63) compared with standard DAPT.²⁸ Additionally, P2Y₁₂ inhibitor monotherapy met non-inferiority for the primary composite endpoint of all-cause death, MI, and stroke (HR 0.93, 95% CI 0.79–1.09; *P* = 0.005 for non-inferiority) in the per-protocol population.²⁸ These findings remained consistent in ACS patients (*P* for interaction: 0.51). Pre-specified subgroup analyses demonstrated consistent treatment effects of P2Y₁₂ inhibitor monotherapy over standard DAPT also in patients undergoing complex PCI.²⁹ Despite these findings, the SIDNEY-2 Collaboration was listed by the 2023 ESC guidelines as supportive evidence to the use of P2Y₁₂ inhibitor monotherapy only in ACS patients not at high ischaemic risk who are event-free after 3–6 months of DAPT (class IIa, level of evidence A) (Figure 1).⁴ Thus, the conservative recommendation of 12-month DAPT as default approach and P2Y₁₂ inhibitor monotherapy after 3–6 months of DAPT as alternative

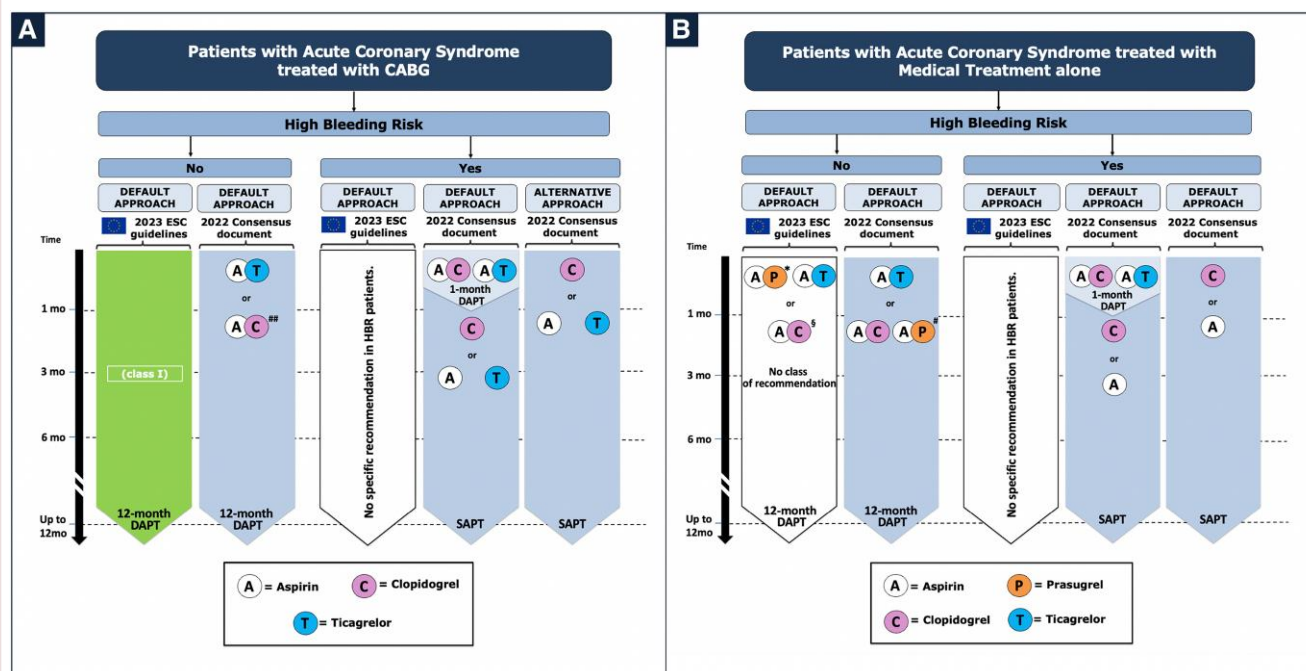


Figure 2 Summary of recommendations from the 2023 ESC guidelines and statements from the 2022 consensus document on antithrombotic treatment strategies in ACS patients treated with CABG (panel A) or medical treatment alone (panel B). Box colours of ESC guidelines reflect classes of recommendation. Treatment preferences within each box are presented from above to below, whereas treatments in the same line are reported in alphabetical order. *In patients with documented CAD at angiography. §Preferred treatment option in older ACS patients medically managed. #DAPT with aspirin and prasugrel is justifiable if clopidogrel and ticagrelor are contraindicated, such as in patients receiving strong CYP3A inhibitors if coronary artery disease is angiographically documented. ##If patient is not eligible for above shown treatment option. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; SAPT, single antiplatelet therapy.

approach does not appear supported by the consolidated evidence demonstrating a bleeding benefit without ischaemic harm of P2Y₁₂ inhibitor monotherapy in ACS and/or complex PCI patients. In addition, while the guidelines give a P2Y₁₂ inhibitor specific recommendation in favour of prasugrel in association with aspirin based on a single study,²¹ a general recommendation is provided for the monotherapy agent that needs to be continued after a short DAPT phase without specifying the strength of the evidence supporting each agent. In fact, trials and meta-analyses investigating P2Y₁₂ inhibitor monotherapy after abbreviated DAPT included mainly ticagrelor-treated patients, while only a small minority of subjects (~1%) were treated with prasugrel monotherapy. Clopidogrel monotherapy has been tested only in Asian patients. In the large STOP-DAPT 2 ACS trial,³⁰ which included 3008 Asian patients who were pooled with 1161 patients from the ACS cohort of the parent STOP-DAPT 2 trial,³¹ clopidogrel monotherapy after 1-month DAPT failed to show non-inferiority for the composite endpoint of cardiovascular death, MI, definite stent thrombosis and stroke compared with 12-month DAPT (HR 1.14, 95% CI: 0.80–1.62; *P* for non-inferiority = 0.06), mainly due to an excess of MI in the monotherapy arm (HR 1.91, 95% CI: 1.06–3.44). Clopidogrel monotherapy resulted in significantly lower rates of BARC type 3 or 5 bleeding compared with 12-month DAPT (HR 0.41, 95% CI: 0.20–0.83).

A network meta-analysis (NMA) including all available antithrombotic treatment options within 1 year after coronary revascularization and/or ACS (189 261 patients from 43 trials) demonstrated that ticagrelor monotherapy was the only regimen associated with significantly lower risks of cardiovascular mortality (HR 0.66; 95% CI: 0.49–0.88) without bleeding risk trade-off (HR 0.86, 95% CI: 0.64–1.16) compared with aspirin and clopidogrel combination.³² Compared with aspirin and

clopidogrel, aspirin and prasugrel combination was the only regimen associated with lower MI risk (HR 0.81, 95% CI: 0.70–0.94) with bleeding risk trade-off (HR 1.29, 95% CI: 1.05–1.58).³²

At variance with ESC guidelines and leveraging on available evidence,^{25,28,29,32} the consensus document suggests ticagrelor monotherapy after 1- to 3-month DAPT as default strategy for ACS non-HBR patients, while 12-month DAPT with prasugrel (first line) or ticagrelor (if subjects are not eligible for prasugrel) is proposed as an alternative approach for PCI-treated patients at high ischaemic and very low bleeding risk³ (Figure 1).

High bleeding risk

Patients at HBR represent a significant proportion of ACS patients (up to 40%) undergoing PCI.^{11,33} The optimal antithrombotic regimen for this subset of patients has been recently investigated in the MASTER DAPT trial, which randomized 4579 HBR patients who were free from adverse events after 1-month DAPT to single antiplatelet therapy (SAPT: clopidogrel in 54% of the patients, aspirin in 29%, ticagrelor in 13%, and prasugrel in 1%) or a more prolonged DAPT regimen of at least 3 months.^{34,35} Compared with standard antiplatelet regimen, 1-month DAPT followed by SAPT was non-inferior for net and major adverse clinical and cerebral events (HR 0.97, 95% CI: 0.78–1.20 and HR 1.02, 95% CI: 0.80–1.30, respectively) and was also associated with lower risks of major or clinically relevant non-major bleeding (HR 0.68, 95% CI: 0.55–0.84). The results remained consistent in patients with ACS who accounted for slightly less than one half of the study population.³⁶

According to the consensus document, the default approach for ACS-HBR patients should be 1-month DAPT followed by clopidogrel

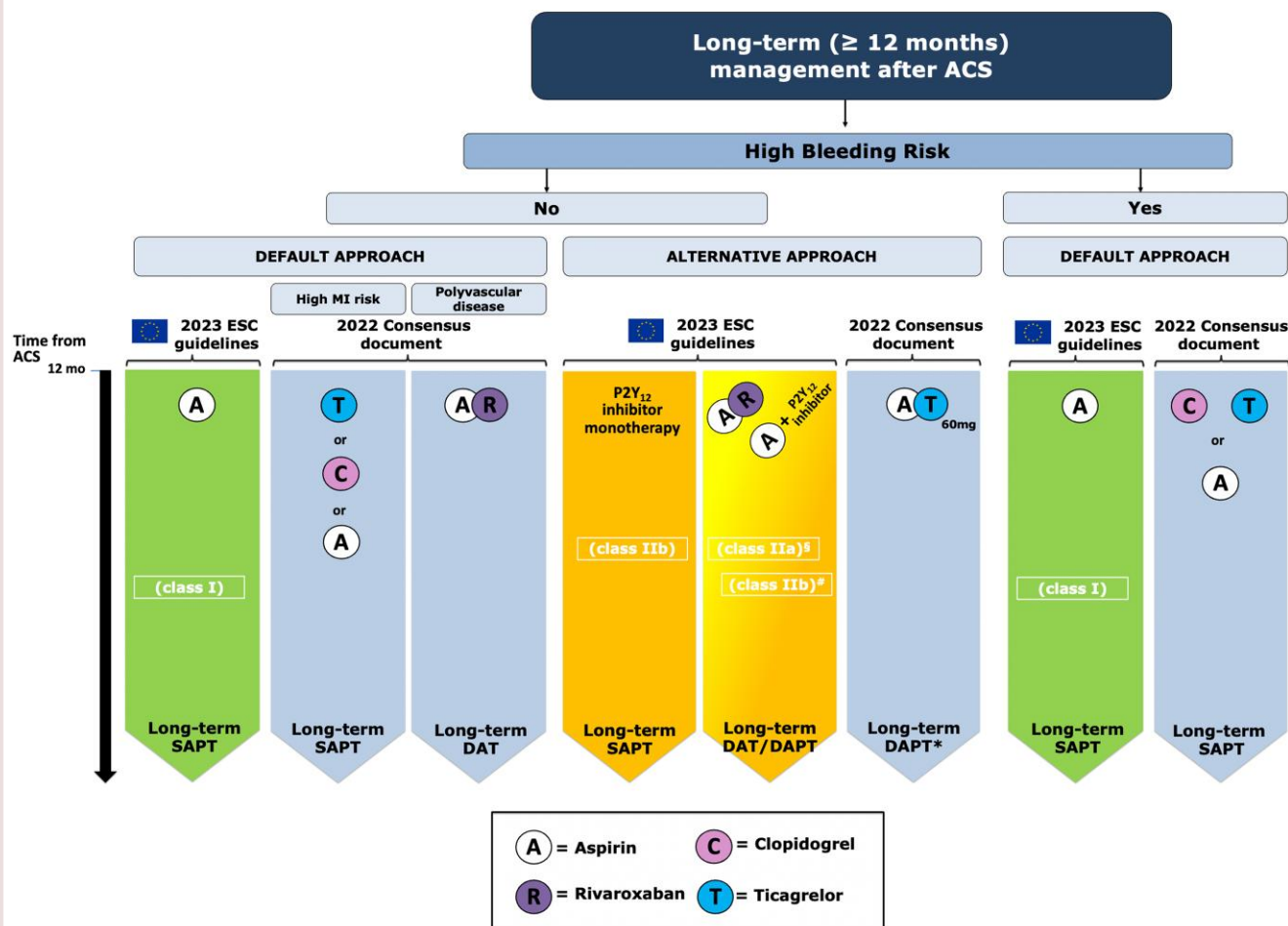


Figure 3 Summary of recommendations from the 2023 ESC guidelines and statements from the 2022 consensus document on long-term antithrombotic strategies after ACS (≥12 months). Box colours of ESC guidelines reflect classes of recommendation. Treatment preferences within each box are presented from above to below, whereas treatments in the same line are reported in alphabetical order. *For patients at high ischemic risk and very low bleeding risk. §For patients with high ischemic risk. #For patients with moderate ischemic risk. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; ESC, European Society of Cardiology; MI, myocardial infarction; SAPT, single antiplatelet therapy.

or ticagrelor monotherapy (first-line regimens) or aspirin monotherapy (second-line strategy) (Figure 1). While DAPT for 12 months remains the default strategy in 2023 ESC guidelines, irrespective of HBR status, an alternative approach consisting of aspirin or P2Y₁₂ inhibitor monotherapy after 1-month DAPT may be considered in ACS-HBR patients (class IIb, level of evidence B) (Figure 1). Consequently, the guidelines appear to give more weight to theoretical concerns of high ischaemic risk among HBR patients than the clear evidence of lower bleeding liability with an abbreviated compared with standard DAPT. Additional alternative approaches suggested by the ESC guidelines are shown in Figure 1.

ACS managed by CABG or medical treatment alone

Non-high bleeding risk

The antiplatelet therapy of ACS patients undergoing CABG is a clinical conundrum since these patients have higher risks of peri-operative

bleeding. A new recommendation from the guidelines suggests that ACS-CABG patients should resume DAPT after surgery for at least 12 months (class I, level of evidence C) (Figure 2, panel A).

Although the evidence of antiplatelet therapy for ACS-CABG patients comes from subgroup analyses of ACS trials, some aspects deserve further considerations. Subgroup analyses of the CURE trial demonstrated that DAPT with aspirin and clopidogrel was associated with lower risk of cardiovascular death, MI, or stroke in ACS patients (rate ratio 0.80, 95% CI: 0.72–0.90) irrespective of revascularization modality (*P* for interaction: 0.53).³⁷ In the PLATO trial, DAPT with ticagrelor resulted in lower all-cause (HR 0.49, 95% CI 0.32–0.77) and cardiovascular mortality (HR 0.52, 95% CI 0.32–0.85) compared with clopidogrel-based DAPT in ACS-CABG patients.³⁸ These findings supported the default approach endorsed by the consensus document consisting of 12-month DAPT with aspirin and ticagrelor over clopidogrel in ACS-CABG patients who are deemed not at HBR (Figure 2, panel A).

ESC guidelines recommend 12-month DAPT with potent P2Y₁₂ inhibitors as default strategy for medically managed ACS patients who are not at HBR (no class of recommendation is provided) (Figure 2, panel B). DAPT

with prasugrel is justified in preference to clopidogrel-based DAPT in case of angiography-confirmed CAD. However, the listed supportive evidence mainly comes from subgroup analyses of a trial with an overall neutral primary outcome measure.³⁹ Leveraging on PLATO subgroup analysis in medically-managed ACS patients, which showed a consistent treatment effect of DAPT with ticagrelor over clopidogrel on major adverse clinical events (HR 0.85, 95% CI: 0.73–1.00) without bleeding risk trade-off (HR 1.17, 95% CI: 0.98–1.39),⁴⁰ the consensus document supports 12-month ticagrelor-based DAPT as first-line option followed by clopidogrel or prasugrel (if ticagrelor or clopidogrel are contraindicated and CAD is angiographically confirmed) in combination with aspirin.

High bleeding risk

No specific recommendation on antiplatelet therapy for ACS-HBR treated with CABG or medical treatment alone is provided by the 2023 ESC guidelines (Figure 2). The consensus document supports 1-month DAPT followed by SAPT as the best balance to reduce bleeding risk while preserving efficacy in ACS-HBR patients treated with CABG or medical treatment alone. Alternative treatment options among ACS-CABG patients with very high bleeding risk are depicted in Figure 2 (panel A).

Long-term antithrombotic management after ACS (≥12 months)

Non-high bleeding risk

The 2023 ESC guidelines recommend aspirin as long-term (≥12 months) antithrombotic agent after ACS (class I, level of evidence A), while SAPT (preferably with a P2Y₁₂ inhibitor) should be considered after an uneventful 3- to 6-month course of DAPT in patients who are not deemed at high ischaemic risk (Class IIa, level of evidence A) (Figure 3). The recommendation for long-term aspirin stems from two collaborative meta-analyses of historical randomized trials conducted more than 20 years ago comparing aspirin vs. no-aspirin treatment.^{41,42}

In a recent patient-level data meta-analysis (PANTHER collaboration), including 24 325 patients from seven contemporary trials with established CAD,⁴³ P2Y₁₂ inhibitor monotherapy (62% clopidogrel, 28% ticagrelor) was associated with lower risks of the primary composite endpoint of cardiovascular death, MI, and stroke over 2 years (HR 0.88; 95% CI: 0.79–0.97) compared with aspirin monotherapy without bleeding risk trade-off. The observed difference in ischaemic outcomes was mainly due to significantly lower MI risk with ticagrelor than aspirin monotherapy (HR: 0.77; 95% CI: 0.66–0.90). The treatment effects remained consistent in ACS patients (*P* for interaction: 0.327), which represented slightly more than two thirds of the overall study population. Recently, the HOST EXAM trial randomized 5438 DAPT-treated patients who were free from adverse events 6–18 months after PCI to clopidogrel or aspirin monotherapy for 24 months.⁴⁴ More than two thirds of randomized patients had history of ACS and median time from PCI to randomization was nearly 1 year. Compared with aspirin, clopidogrel monotherapy was associated with a 27% relative reduction in the risk of net adverse clinical events (HR 0.73; 95% CI 0.59–0.90), mainly due to lower rates of readmission for ACS and major bleeding.

These findings are in line with a large-scale NMA investigating all antithrombotic treatment strategies 12 months after coronary revascularization and/or ACS, which demonstrated that, in comparison with aspirin, P2Y₁₂ inhibitor monotherapy (especially ticagrelor) was associated with a 24% relative risk reduction in MI without bleeding risk trade-off.³² Compared with aspirin monotherapy, aspirin and low-dose rivaroxaban combination resulted in a 42% relative risk reduction

in stroke, with an acceptable bleeding risk trade-off than other intensified antithrombotic strategies such as vitamin-K antagonists or DAPT with potent P2Y₁₂ inhibitors. This NMA informed the clinical consensus document,³ which supports P2Y₁₂ inhibitor monotherapy (particularly ticagrelor) as the default approach for ACS patients (≥12 months) at high MI risk (Figure 3). Among ACS patients at high risk of vascular events (e.g. cerebrovascular disease, peripheral artery disease), the combination of aspirin and low-dose rivaroxaban should be preferred over aspirin monotherapy (Figure 3). If this combination is not available or suited, SAPT with clopidogrel or ticagrelor should be preferred over aspirin in patients with concomitant peripheral artery disease, as the former was superior to aspirin in the CAPRIE trial⁴⁵ and the latter had non-inferior results over clopidogrel in the EUCLID trial.⁴⁶

High bleeding risk

The 2023 ESC guidelines recommend aspirin monotherapy for long-term (≥12 months) antithrombotic therapy after ACS (class I, level of evidence A) irrespective of HBR status (Figure 3). In a NMA including 139 086 patients from 19 trials investigating all antithrombotic treatment strategies beyond 12 months after ACS and/or PCI, P2Y₁₂ inhibitor monotherapy was associated with lower risk of MI (HR 0.76, 95% CI 0.61–0.95) without higher bleeding risk compared with aspirin monotherapy.³² When the type of P2Y₁₂ inhibitor was separately appraised, ticagrelor monotherapy was associated with a greater reduction of MI risk compared with aspirin.³² Therefore, the consensus document supports the use of clopidogrel or ticagrelor over aspirin monotherapy as default agents for long-term management of ACS-HBR patients after the DAPT phase.³

Conclusions

For the very first time, the 2023 ESC guidelines provide recommendations encompassing the entire spectrum of ACS patients. These guidelines summarized available evidence in order to guide clinicians in their decision-making process of which antithrombotic regimen(s) should be selected for each individual patient. However, the guidelines leave some uncertainties concerning the preferred management of patients with HBR and generally take a conservative approach to recommend de-escalation of antiplatelet therapy intensity prior to 12 months post-ACS. Despite some overlap between the ESC guidelines and the consensus document, the latter attaches more weight to available evidence for novel strategies, such as the emerging role of abbreviated DAPT followed by P2Y₁₂ inhibitor monotherapy, other DAPT de-escalation strategies and P2Y₁₂ inhibitors as agents of choice for secondary prevention of cardiovascular events.

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Data availability

No new data were generated or analysed in support of this research.

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