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 in Patients with Acute Coronary Syndrome: A Critical Appraisal of the 2023 European Society of Cardiology Guidelines

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Antithrombotic therapy represents the mainstay of the pharmacological treatment in patients with acute coronary syndrome (ACS) (1). The optimal combination and duration of antithrombotic therapy (which agent, for whom and for how long) is still a clinical conundrum which 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, the 2023 European Society of Cardiology (ESC) guidelines for the management of patients with ACS including both patients with and no-ST segment elevation (NSTE)-ACS have been recently published (2). Despite the limited time window from the previous guidelines on NSTE-ACS patients (3) which would hint at an extensive revision in clinical recommendations, the 2023 ESC guidelines appeared largely confirmatory and conservative, and not fully accounting for the most recent updates in the field of antithrombotic therapy in ACS patients.

The scope of this manuscript is to provide a critical appraisal of current ESC recommendations on oral antithrombotic regimens in ACS by systematic reviewing available evidence which was restrictively interpreted by the 2023 ESC guidelines. 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 recommendations and consensus statements, this document refers to the latest 2023 ESC guidelines for ACS patients (2) and the 2022 clinical consensus document in subjects with established coronary artery disease (CAD) (4).

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 endorse the use of the

Academic Research Consortium - High Bleeding Risk (ARC-HBR) criteria for bleeding risk stratification in a footnote of the recommendation table 5 (2), while the PRECISE DAPT score is only mentioned as additional tool among ACS patients with clinical indication for OAC. Notably, the derivation and validation of the PRECISE DAPT score was performed in patients not taking OAC (6). Although the ARC initiative was groundbreaking in order to standardize bleeding risk assessment, the ARC-HBR definition was purely based on expert consensus (7) and has shown lower discrimination in ACS patients (8). The inclusion of ACS at clinical presentation as covariate slightly improved the score performance suggesting that, at least in this framework (where other markers of inflammation such as white blood cell count were not considered), ARC-HBR definition should consider including ACS as an additional minor risk criterion (8). Other data-driven observations such as that minor criteria confer, in isolation, a bleeding risk which is similar to one attributed by consensus to the major criteria (9) and that the originally proposed ARC-HBR framework performs suboptimal among women (10) were not acknowledged or discussed.

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 with and without clinical indication for OAC (4).

DAPT de-escalation

In the last decade, alternative strategies to standard 12-month DAPT have been largely investigated which may be summarized under the "de-escalation" definition (11). DAPT de-escalation strategies include either shortening DAPT duration ("de-escalation in duration") by discontinuing aspirin or $P2Y_{12}$ inhibitor at a point in time or a reduction in $P2Y_{12}$ inhibitor dose or potency ("de-escalation in intensity"). De-escalation in intensity by switch to clopidogrel can be either guided or unguided by genotype or platelet function tests (PFT). The 2023 ESC guidelines do not list guided de-escalation as alternative option to standard DAPT for ACS patients among recommendations (2). The lack of

individual trial evidence of superiority of guided versus unguided DAPT de-escalation and the increased complexity of the latter over the former treatment strategy may account for this omission from previous guidelines (12). Likewise, the consensus document does not support the routine use of PFT or genotyping to guide antiplatelet therapy (4).

Acute coronary syndrome managed by PCI

Non-high bleeding risk

Despite mounting evidence from multiple randomized clinical trials (RCTs) and individual patient data (IPD) meta-analyses demonstrating a net benefit of abbreviated DAPT, the 2023 ESC guidelines recommend DAPT for 12 months for all ACS patients (class I, level of evidence A) in keeping with previous guidelines (**Figure 1**)(3), irrespective of the bleeding risk. These recommendations were generated leveraging on the following listed supportive studies: the PCI-CURE (13), the TRITON-TIMI 38 (14) and PLATO (15). The CURE is a landmark trial which, more than twenty years ago, paved the way forward to DAPT in ACS patients, 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 to 0.90) at the cost of increased bleeding compared with aspirin monotherapy (13). Findings from the same study suggesting a beneficial effect of clopidogrel pretreatment were listed as supportive to routine 12-month DAPT but not for pretreatment (class IIb, level of evidence C) (16). The TRITON-TIMI 38 (14) and PLATO (15) demonstrated the superiority of prasugrel and ticagrelor for 12 months in combination with aspirin over clopidogrel-based DAPT on 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, included patients with and without HBR, who were treated with prior generation devices and techniques. In the largest head-to-head comparison of ticagrelor- versus 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 to 0.92), mainly due to lower MI risk with prasugrel (17). Mortality and bleeding rates did not differ between the two groups (17). However, these findings should be interpreted in light of the low sample size, the open-label design and adherence to treatment assignment and the study design itself reflecting the drug labels and having one drug started in the pre-treatment phase and the other one administered once PCI was indicated (18).

Several trials investigated the treatment effects of shortening DAPT by discontinuing aspirin or $P2Y_{12}$ inhibitor at a point in time in ACS patients. In the SMART DATE trial (19), 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 (20). Therefore, aspirin monotherapy following abbreviated DAPT is not recommended after ACS within the first year in patients without HBR by both ESC guidelines (2) and the consensus document (4).

Several RCTs investigated the efficacy and safety of $P2Y_{12}$ inhibitor monotherapy after 1 to 3 months of DAPT. The inclusion of events in the initial DAPT phase (when experimental and control arm received the same treatment regimen) was overcame by two IPD meta-analyses which censored events during the initial DAPT phase. The SIDNEY Collaboration (21) including 14,628 patients from two trials (GLASSY (22) and TWILIGHT (23)) 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 to 0.75) without increase in ischemic events. The results remained consistent in ACS patients (P for interaction 0.51). In the SIDNEY-2 Collaboration (24,096 patients from six trials), $P2Y_{12}$ inhibitor monotherapy was associated with lower risk of BARC 3 or

5 bleeding (HR 0.49, 95% CI 0.39 to 0.63) compared with standard DAPT (24). Additionally, $P2Y_{12}$ inhibitor monotherapy met non-inferiority for the primary composite endpoint of all-cause death, MI, and stroke (HR 0.93, 95% CI 0.79 to 1.09; P=0.005 for non-inferiority) in the per-protocol population (24). These findings remained consistent in ACS patients (P for interaction 0.51). Prespecified subgroup analyses demonstrated consistent treatment effects of $P2Y_{12}$ inhibitor monotherapy over standard DAPT also in patients undergoing complex PCI (25). Despite these findings, the SIDNEY-2 Collaboration was listed by the 2023 ESC guidelines as supportive evidence to the use of $P2Y_{12}$ inhibitor monotherapy only in ACS patients not at high ischemic risk who are event-free after 3–6 months of DAPT (class IIa, level of evidence A) (**Figure 1**) (2). Thus, the conservative recommendation of 12-month DAPT as default approach and $P2Y_{12}$ inhibitor monotherapy after 3 to 6 months of DAPT as alternative approach does not appear supported by the newest evidence demonstrating a bleeding benefit without ischemic harm of $P2Y_{12}$ inhibitor monotherapy in ACS and/or complex PCI patients. In addition, it remains surprising that while a $P2Y_{12}$-inhibitor specific recommendation is given in favor of prasugrel with aspirin based on a single study (17), a generic $P2Y_{12}$ inhibitor recommendation is provided for the monotherapy type that needs to be continued after a short DAPT phase. In fact, trials and meta-analyses investigating $P2Y_{12}$ inhibitor monotherapy after abbreviated DAPT included mainly ticagrelor-treated patients, while only a small minority of subjects (~1%) were treated with prasugrel monotherapy, whereas clopidogrel monotherapy has been tested only in Asian patients and without fully supportive evidence. In the large STOP-DAPT 2 ACS trial (26) which included 3,008 Asian patients who were pooled with 1,161 patients from the ACS cohort of the parent STOP DAPT 2 trial (27), 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 to 1.62; P for non-inferiority = 0.06), mainly due to a MI excess in the monotherapy arm (HR 1.91, 95% CI 1.06 to 3.44). Clopidogrel monotherapy resulted in significantly lower rates of BARC 3 or 5 bleeding

compared with 12-month DAPT (HR 0.41, 95% CI 0.20 to 0.83). The generazibility of these findings to Western populations remains to be established.

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 to 0.88) without bleeding risk trade-off (HR 0.86, 95% CI: 0.64 to 1.16) compared with aspirin and clopidogrel combination (28). 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 to 0.94) with bleeding risk trade-off (HR 1.29, 95% CI: 1.05 to 1.58) (28).

At variance with ESC guidelines and leveraging on available evidence (21,24,25,28), 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 to prasugrel) as alternative approach for patients at high ischemic and very low bleeding risk (**Figure 1**).

Finally, the critical interpretation of the evidence for OAC patients with ACS in whom ESC guidelines recommend as default approach triple antithrombotic therapy for up to 1 week (which has shown to reduce bleeding with a significant increase in ischemic risk (29)) does not appear consistent with the interpretation of the evidence for non-OAC patients, in whom bleeding risk reduction does not seem to be valued even for treatment strategies with clear evidence for lower bleeding and no evidence for higher ischemic risks.

High bleeding risk

Patients at HBR represents a not negligible proportion of ACS patients (up to 40%) undergoing PCI (9,30). The optimal antithrombotic regimen for this subset of patients has been recently investigated

by the large Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated vs. Standard DAPT Regimen (MASTER DAPT) trial, which randomized 4,579 HBR patients who were free from adverse events after 1-month DAPT to single antiplatelet therapy (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 (31,32). 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 to 1.20 and HR 1.02; 95% CI: 0.80 to 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 to 0.84). The results remained consistent in patients with ACS who accounted for slightly less than one half of the study population (33).

According to the consensus document the default approach for ACS-HBR patients should be 1-month DAPT followed by clopidogrel or ticagrelor monotherapy (first-line regimens) or aspirin monotherapy (second-line strategy) (**Figure 1**). ESC guidelines recommend this approach as alternative stating that aspirin or $P2Y_{12}$ inhibitor monotherapy after 1-month DAPT may be considered in ACS-HBR patients (class IIb, level of evidence B) (**Figure 1**). Other alternative approaches suggested by the ESC guidelines are shown in **Figure 1**. Again, the theoretical concerns of high ischemic risk, which have not been actually observed among HBR patients are surprisingly valued more than the clear evidence of lower bleeding liability with an abbreviated compared with standard DAPT.

Acute coronary syndrome 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 statement from 2023 ESC guidelines recommends that ACS-CABG patients should resume DAPT after surgery for at least 12 months

(class I, level of evidence C) (**Figure 2, panel A**). However, little guidance is provided on the optimal timing and composition of DAPT.

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 to 0.90) irrespective of revascularization modality (P for interaction: 0.53) (34). In the PLATO trial, DAPT with ticagrelor resulted in lower all-cause (HR 0.49, 95% CI 0.32 to 0.77) and cardiovascular mortality (HR 0.52, 95% CI 0.32 to 0.85) compared with clopidogrel-based DAPT in ACS-CABG patients (35). 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 endorse 12-month DAPT with potent $P2Y_{12}$ inhibitors as default strategy for ACS patients medically managed 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 (36). 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 to 1.00) without bleeding risk trade-off (HR 1.17, 95% CI 0.98 to 1.39) (37), the consensus document endorses 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, panel A**). The consensus document recommends 1-month DAPT followed by SAPT as the best compromise 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 $P2Y_{12}$ inhibitor) should be considered after an uneventful 3- to 6-month course of DAPT in patients who are not deemed at high ischemic risk (Class IIa, level of evidence A) (**Figure 3**). This recommendation stems from two collaborative meta-analyses of historical randomized trials conducted more than 20 years ago comparing aspirin versus no-aspirin treatment (38,39).

In a recent patient-level data meta-analysis (PANTHER collaboration) including 24,325 patients from seven contemporary trials with established coronary artery disease (40), $P2Y_{12}$ 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 to 0.97) compared with aspirin monotherapy without bleeding risk trade-off. The observed difference in ischemic outcomes was mainly due to significantly lower MI risk with ticagrelor than aspirin monotherapy (HR: 0.77; 95% CI: 0.66 to 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 5,438 DAPT-treated patients who were free from adverse events 6 to 18 months after PCI to clopidogrel or aspirin monotherapy for 24 months (41). 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 to 0.90), mainly due to lower rates of readmission for ACS and major bleeding.

These findings are in line with a network meta-analysis investigating all antithrombotic treatment strategies 12 months after coronary revascularization and/or ACS, which demonstrated that $P2Y_{12}$ inhibitor monotherapy (especially ticagrelor) was associated with a 24% relative risk reduction in MI compared with aspirin without bleeding risk trade-off (28). Compared with aspirin monotherapy, aspirin and low-dose rivaroxaban resulted in a 42% relative risk reduction in stroke, with an acceptable bleeding risk trade-off than other intensified antithrombotic strategies as vitamin-K antagonists or DAPT with potent $P2Y_{12}$ inhibitors. This NMA informed the clinical consensus document (4) which endorses $P2Y_{12}$ 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 accidents, peripheral arterial disease), the combination of aspirin and low-dose rivaroxaban should be preferred over aspirin monotherapy (**Figure 3**).

These findings support $P2Y_{12}$ inhibitor monotherapy as the preferred long-term antithrombotic regimen after ACS given its superior efficacy and similar safety profile.

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, $P2Y_{12}$ inhibitor monotherapy was associated with lower risk of MI (HR 0.76, 95% CI 0.61 to 0.95) without higher bleeding risk compared with aspirin monotherapy (28). When the type of $P2Y_{12}$ inhibitor was separately appraised, ticagrelor

monotherapy was associated with a greater reduction of MI risk compared with aspirin (28). Therefore, the consensus document endorses the use of clopidogrel or ticagrelor over aspirin monotherapy as default agents for long-term management of ACS-HBR patients after the DAPT phase (4).

Conclusions

Providing for the first-time recommendations for the entire spectrum of ACS patients, the 2023 ESC guidelines attempted at summarizing available evidence in order to guide clinicians in their decision-making process of which antithrombotic regimen(s) should be selected for each individual patient. Uncertainties remain in light of questionable interpretation or sometimes disregard of available evidence, such as the emerging role of abbreviated DAPT followed by $P2Y_{12}$ inhibitor monotherapy, other DAPT de-escalation strategies and $P2Y_{12}$ inhibitors as agents of choice for secondary prevention of cardiovascular events.

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FIGURE LEGENDS

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 colors of ESC guidelines reflects 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. ^ Prasugrel should be considered in preference to ticagrelor for ACS patients undergoing PCI (class of recommendation IIa, level of evidence b); § 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. *Abbreviations: ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.*

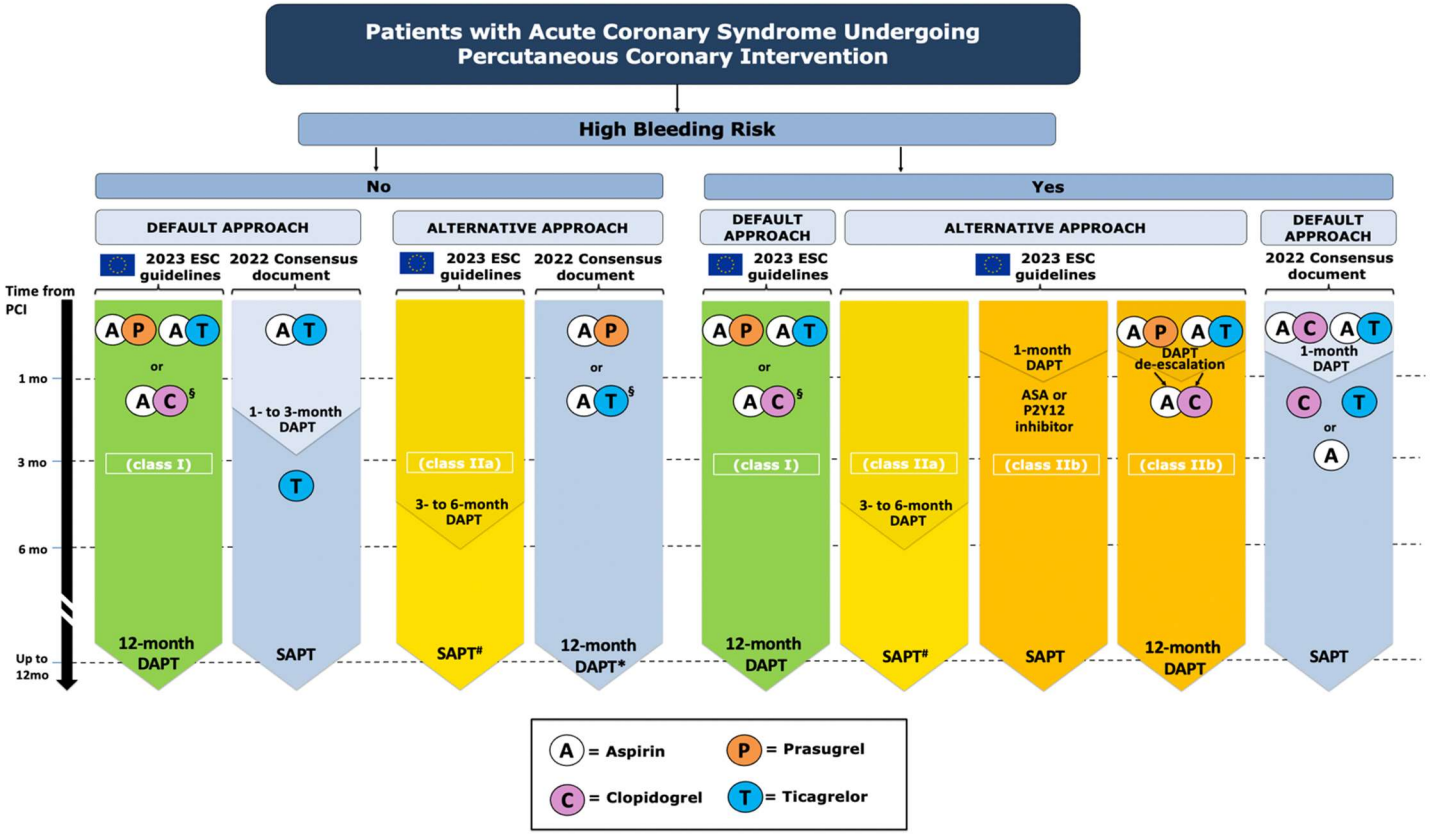

Figure 2. Summary of recommendations from the 2023 ESC Guidelines and statements from the 2022 consensus document on antithrombotic treatment strategies in ACS patients treated with CABG (panel A) or medical treatment alone (panel B). Box colors of ESC guidelines reflects classes of recommendation. Treatment 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. *Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; SAPT, single antiplatelet therapy.*

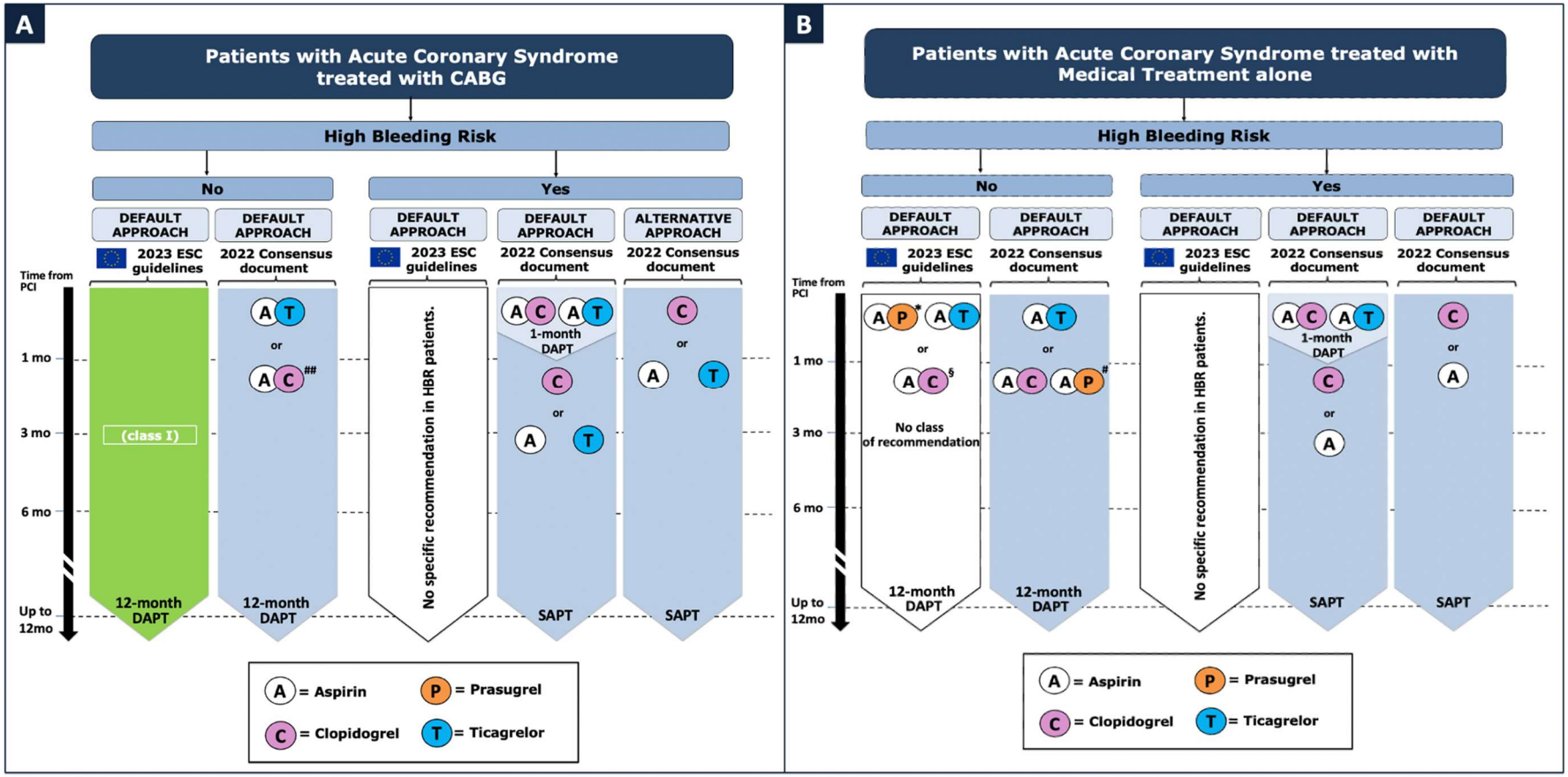

Figure 3. Summary of recommendations from the 2023 ESC Guidelines and statements from the 2022 consensus document on long-term antithrombotic strategies after ACS (≥12 months). Box colors of ESC guidelines reflects classes of recommendation. Treatment preferences within each box are presented from above 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. *Abbreviations: ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; ESC, European Society of Cardiology; MI, myocardial infarction; SAPT, single antiplatelet therapy.*