

Antithrombotic Therapy in Acute Coronary Syndromes: Current Evidence and Ongoing Issues Regarding Early and Late Management

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Abstract

A few decades ago, the understanding of the pathophysiological processes involved in the coronary artery thrombus formation has placed anticoagulant and antiplatelet agents at the core of the management of acute coronary syndrome (ACS). Increasingly potent antithrombotic agents have since been evaluated, in various association, timing, or dosage, in numerous randomized controlled trials to interrupt the initial thrombus formation, prevent ischemic complications, and ultimately improve survival. Primary percutaneous coronary intervention, initial parenteral anticoagulation, and dual antiplatelet therapy with potent P2Y₁₂ inhibitors have become the hallmark of ACS management revolutionizing its prognosis. Despite these many improvements, much more remains to be done to optimize the onset of action of the various antithrombotic therapies, for further treating and preventing thrombotic events without exposing the patients to an unbearable hemorrhagic risk. The availability of various potent P2Y₁₂ inhibitors has opened the door for individualized therapeutic strategies based on the clinical setting as well as the ischemic and bleeding risk of the patients, while the added value of aspirin has been recently challenged. The strategy of dual-pathway inhibition with P2Y₁₂ inhibitors and low-dose non-vitamin K antagonist oral anticoagulant has brought promising results for the early and late management of patients presenting with ACS with and without indication for oral anticoagulation. In this updated review, we aimed at describing the evidence supporting the current gold standard of antithrombotic management of ACS. More importantly, we provide an overview of some of the ongoing issues and promising therapeutic strategies of this ever-evolving topic.

Keywords

- ▶ antiplatelet agents
- ▶ acute myocardial infarction
- ▶ coronary syndrome

Introduction

Over the past 50 years, there has been considerable progress in the management of acute coronary syndrome (ACS), the most severe clinical presentation of coronary artery disease (CAD), leading to significant reduction of in-hospital mortality, from as high as 30% during the 1960s to approximately 3 to 8% nowadays.¹ This achievement was made possible by the

understanding of the pathophysiological process of intracoronary thrombus formation from atherosclerotic plaque erosion or rupture.^{2–4} Increasingly potent antithrombotic agents have been evaluated in the setting of ACS, in association with the development of urgent coronary reperfusion with primary percutaneous coronary intervention (PCI).² Despite these improvements, much more is needed, as CAD remains a leading cause of morbidity and mortality in our modern

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societies with over 9 million deaths every year.^{5,6} Consistently, the issue of the optimal antithrombotic therapy for the early and late management of ACS has remained an evolving debate, as pivotal randomized controlled trials (RCTs) have introduced or challenged therapeutic concepts.^{1,7,8} The purpose of this review is to provide a description of the current state of evidence in the field of antithrombotic therapy for ACS, and to describe novel axes of research for the near future.

Early Management of ACS: Reperfusing the Coronary Artery

The physiopathological hallmark of ACS is the formation of a completely or partially obstructive intracoronary blood clot, the composition which may vary over time.^{3,4} Initially, the erosion or rupture of the atherosclerotic plaque fibrous cap exposes the prothrombotic material contained in the necrotic core, such as collagen, von Willebrand factor, and tissue factor to the blood compartment.⁹ This leads to the activation of circulating platelets, triggering amplification loops of activation and aggregation, based in part, on thromboxane A₂, P2Y₁₂, or GPIIb/IIIa receptors, resulting in an early platelet-rich thrombus. In the meantime, the activation of the coagulation cascade results in the formation of thrombin by the activated factor X and ultimately the transformation of fibrinogen into fibrin, which stabilizes the thrombus.¹⁰⁻¹⁴ As such, primary PCI occurs in a highly prothrombotic state and requires both

antiplatelet and anticoagulant potent agents to prevent early stent thrombosis (► Fig. 1).

Current Evidence in Early Management of ACS

Antiplatelet Therapy

The beneficial impact of aspirin, the most ancient commercialized antiplatelet agent, in the setting of acute myocardial infarction (MI) was demonstrated by the Second International Study of Infarct Survival (ISIS-2) trial, more than 30 years ago.¹⁵ The superiority of a dual antiplatelet therapy (DAPT), the current gold standard for the early management of ACS, compared with single antiplatelet therapy was demonstrated by the pivotal Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) trial, published in 2001, where the association of aspirin and clopidogrel, a P2Y₁₂ inhibitor, was superior to that of aspirin and placebo.¹⁶ Clopidogrel is an inactive prodrug requiring hepatic conversion into its active metabolite using the cytochrome P450 enzymes, leading to a wide interindividual variability in terms of platelet inhibition according to drug–drug interaction, polymorphisms of CYP2C19 genetic variant, and other parameters such as older age, diabetes mellitus, chronic kidney disease, or active smoking.¹⁷⁻¹⁹ Such high on-treatment platelet reactivity has been associated with a significant increase of the risk of ischemic events.^{20,21} The more recent and potent P2Y₁₂ inhibitors prasugrel and ticagrelor both were proven superior to

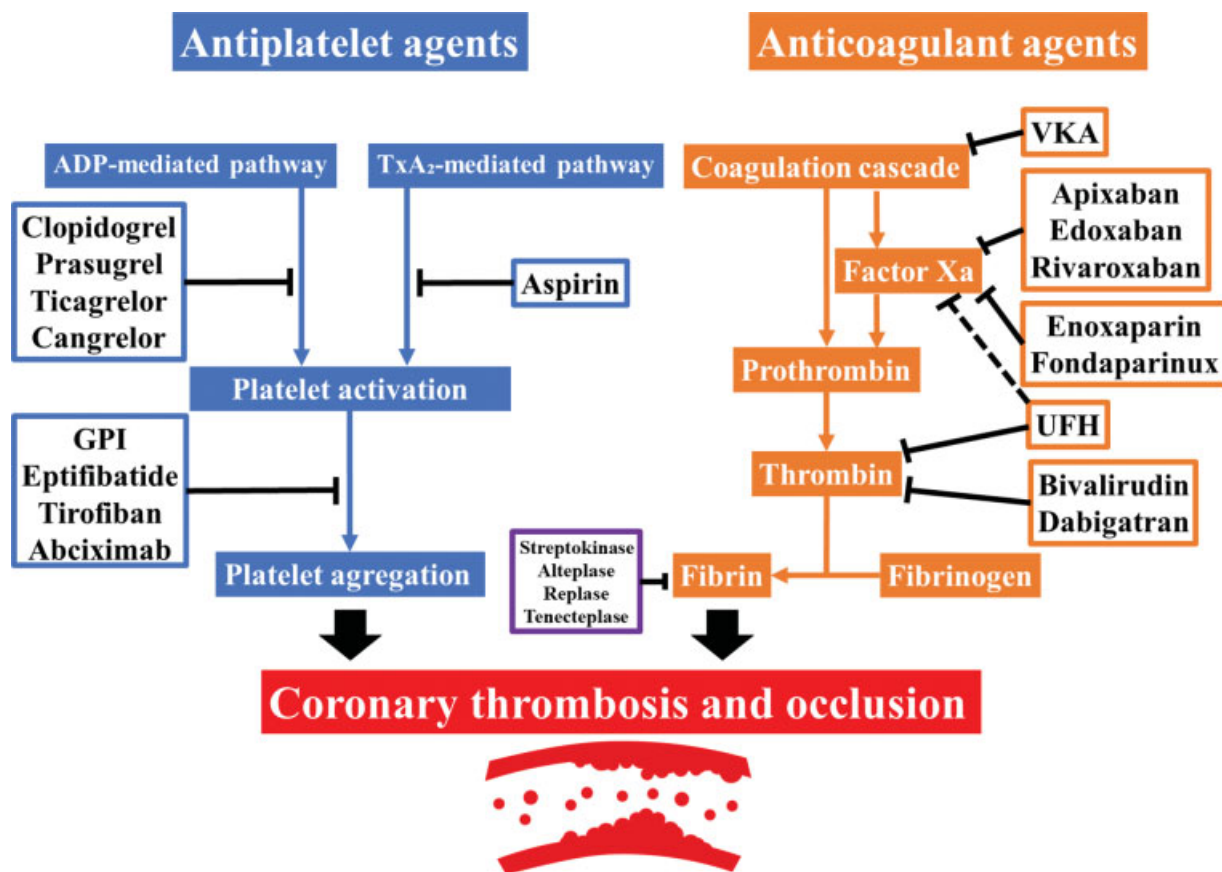


Fig. 1 Available antithrombotic agents for the management of acute coronary syndrome. GPI, glycoprotein IIb/IIIa inhibitor; UFH, unfractionated heparin; VKA, vitamin K antagonist.

clopidogrel for the treatment of patients with ACS in the landmark Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 and Platelet Inhibition and Patient Outcomes (PLATO) trials, respectively.^{22,23} Of note, these potent agents were even associated with a survival benefit compared with clopidogrel, albeit at the cost of increased risk of bleeding.^{23,24} Based on these trials, international societies have granted a class I recommendation with a strong level of evidence for the use of ticagrelor or prasugrel, in association with aspirin, in the setting of ACS, while clopidogrel should be limited to patients not able to receive the aforementioned agents, or requiring oral anticoagulation.^{25–27}

Cangrelor is a potent P2Y₁₂ inhibitor, administered intravenously, with a rapid onset and offset of action. This may be particularly of interest, considering that the biological impact of the other P2Y₁₂ inhibitors, with oral administration, may not be immediately maximal.²⁸ A pooled analysis of three RCTs comparing cangrelor to clopidogrel in 24,910 patients, a majority of whom presenting with ACS, reported the former to be associated with a significant 19% relative reduction in the risk of composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours, with a moderate, albeit significant, increase in the risk of GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) mild bleeding.²⁹ Cangrelor is a valuable option for ACS patients not pretreated with oral P2Y₁₂, unable to absorb oral treatment, or due to undergo urgent surgery, including coronary artery bypass grafting surgery.^{26,27,30}

The place of glycoprotein IIb/IIIa inhibitors (GPIs) for periprocedural anticoagulation of patients presenting with ACS has been extensively studied by large RCTs and meta-analyses. Some trials, performed prior to the era of systematic use of DAPT and potent P2Y₁₂ inhibitors, have reported a lower risk of ischemic events associated with GPI, as an adjunct therapy to unfractionated heparin (UFH) in the setting of ST-elevation MI (STEMI).³¹ Nonetheless, a systematic use of GPI has also been associated with a higher risk of major bleeding events, a complication strongly associated with an increased risk of subsequent mortality.^{32,33} Consequently, current guidelines limit the use of GPI in clinical practice to bail-out scenarios in the setting of thrombotic complications or no-reflow or in high-risk P2Y₁₂ inhibitor-naïve patients, while the use of GPI in patients in whom coronary artery is not known is not recommended.^{25–27,34}

Parenteral Anticoagulation Therapy

The three main anticoagulant agents available in contemporary practice are enoxaparin, UFH, and bivalirudin. Compared with UFH, enoxaparin presents with more reliable pharmacological properties resulting in a more predictable anticoagulant response.^{35–37} In the Acute STEMI Treated with primary PCI and intravenous enoxaparin Or UFH to Lower ischemic and bleeding events at short- and Long-term follow-up (ATOLL) trial, the use of enoxaparin, compared with UFH, did not result in a significant reduction of the primary composite endpoint of death, MI, procedural failure, or major bleeding at 30 days (17% relative risk reduction,

$p=0.063$); however, it did lead to a significant reduction of the main secondary composite endpoints of death, MI or ACS, or urgent revascularization (41% relative risk reduction, $p=0.015$). Moreover, in the per-protocol analysis, which included 87% of the overall population of the ATOLL trial, enoxaparin was associated with a significant reduction of the primary endpoint (24% relative risk reduction, $p=0.012$).³⁸ Consistently, a meta-analysis of 23 studies, comprising 30,966 patients, comparing enoxaparin to UFH during PCI, reported a survival benefit and a lower risk of major bleeding associated with the former.³⁹

Bivalirudin is an intravenous direct thrombin inhibitor, with intrinsic antiplatelet activity, that has been extensively compared with UFH in large RCTs in the last few decades. Initial RCTs reported a lower risk of net adverse clinical events with bivalirudin, including a lower risk of bleeding complications and even a survival benefit compared with UFH plus GPI, albeit an increased risk of early stent thrombosis was noted.^{40–42} However, more recent RCTs, reflecting contemporary practices with a larger use of radial artery access and a less liberal use of GPI, did not report any significant difference between the two agents in terms of mortality, as well as ischemic or bleeding complications.^{43,44} Of note, a large patient-level meta-analysis of eight RCTs comparing bivalirudin without systematic GPI to heparin (UFH or low-molecular-weight heparin) with or without systematic GPI and comprising 27,409 patients with STEMI or non-STEMI (NSTEMI) was recently presented.⁴⁵ This study found that in patients with STEMI undergoing PCI, use of bivalirudin was associated with a significant reduction of cardiac mortality (adjusted hazard ratio [aHR]: 0.72, 95% confidence interval [CI]: 0.57–0.91) and serious bleeding (aHR: 0.57, 95% CI: 0.47–0.68) at 30 days, albeit at the cost of increased risk of reinfarction (aHR: 1.29, 95% CI: 1.02–1.64) and stent thrombosis (aHR: 1.45, 95% CI: 1.05–1.91). In patients with NSTEMI undergoing PCI, use of bivalirudin was associated with a reduction of 30-day rate of serious bleeding (aHR: 0.63, 95% CI: 0.52–0.76), without significant impact on mortality or other ischemic complications.⁴⁶

Ongoing Issues and Future Development in the Early Management of ACS

Pretreatment of NSTEMI

Pretreatment refers to the initiation of a P2Y₁₂ inhibitor prior to the coronary angiogram. A posthoc analysis of the CURE trial, only including patients eventually undergoing PCI, reported “pretreatment” to be associated with a reduction of cardiovascular (CV) death, MI, or urgent revascularization.⁴⁷ However, only a minority of the overall population of the CURE trial was included in this subanalysis, with a mean duration prior to PCI of 10 days, which is not representative of current practice. The Clopidogrel for the Reduction of Events During Observation (CREDO) trial was the first large RCT to evaluate the impact of clopidogrel preloading in patients undergoing PCI, a majority of whom presenting with unstable angina. The study did not report a significant reduction of the composite endpoint of death, MI, or urgent target vessel revascularization (18.5% relative risk reduction,

$p = 0.23$). The largest study evaluating the issue of pretreatment in NSTEMI patients remains the ACCOAST (A Comparison of Prasugrel at the Time of PCI or as Pretreatment at the Time of Diagnosis in Patients with NSTEMI) trial, which compared prasugrel pretreatment with a 30-mg loading dose to placebo in patients with NSTEMI and positive troponin level.²⁸ The rate of the primary efficacy endpoint, a composite of CV death, MI, stroke, urgent revascularization, or GPI rescue therapy at 7 days did not differ between the two groups (HR: 1.02, 95% CI: 0.84–1.25, $p = 0.81$), while the risk of TIMI major bleeding was significantly increased in the case of pretreatment (HR: 1.90, 95% CI: 1.19–3.02, $p = 0.006$). Consistent results were reported by the ACCOAST-PCI sub-analysis, which only included patients undergoing PCI (68.7% of the ACCOAST population), and where prasugrel pretreatment was associated with a three- and sixfold increase of the risk of TIMI major and life-threatening bleeding, respectively, without significant impact on the primary efficacy endpoint.⁴⁸ A meta-analysis of seven trials comprising 32,383 patients presenting with NSTEMI reported P2Y₁₂ pretreatment to be associated with a significant increase in the risk of major bleeding (odds ratio [OR]: 1.27, 95% CI: 1.10–1.47 and OR: 1.23, 95% CI: 1.00–1.50, in the overall population and in patients undergoing PCI, respectively), without any significant differences in the risk of all-cause death (OR: 0.90, 95% CI: 0.75–1.07) in the overall population or the risk of major adverse CV events in patients undergoing PCI (OR: 0.83, 95% CI: 0.69–1.01).⁴⁹ These data have been further confirmed by large real-world registries where P2Y₁₂ pretreatment, mostly with clopidogrel, was beneficial in patients presenting with STEMI but not with NSTEMI, where it was associated with a significant increase of the bleeding risk.^{50,51} Conversely, pretreatment with ticagrelor was associated with improved outcomes in a subanalysis of the PLATO trial, although pretreatment was not randomized.⁵² However, these data have been recently challenged by the Downstream versus Upstream administration of P2Y₁₂ receptor Blockers In non-ST elevated acute coronary Syndromes with initial invasive indication (DUBIUS) trial, which included an open-label randomized comparison of pretreatment versus no pretreatment with ticagrelor of NSTEMI patients with planned invasive management. Although the trial was prematurely interrupted for futility after the randomization of 1,449 of the 2,560 patients initially planned, it did not show any hint in favor of a “downstream” strategy of pretreatment with respect to the primary endpoint of death due to CV causes, MI, stroke, or Bleeding Academic Research Consortium (BARC) type 3, 4, or 5 bleeding, compared with the “upstream” strategy (2.9 vs. 3.3%, respectively, absolute risk reduction: –0.46%, 95% CI: –2.87 to –1.89).⁵³ Consequently to the accumulating data emphasizing the increased risk of bleeding, without clear evidence of any potential ischemic complication preventions, the recent European Society of Cardiology (ESC) guidelines finally granted a level III class recommendation for routine pretreatment administration with a P2Y₁₂ inhibitor in patients with whom coronary anatomy is not known and early invasive management is planned.^{27,54} In the specific setting of patients who are not

planned to undergo an early invasive strategy and do not have a high risk of bleeding, a pretreatment with a P2Y₁₂ inhibitor may be considered (class IIB recommendations).²⁷ With respect to STEMI, there are only limited available data regarding pretreatment. The Administration of Ticagrelor in the Cath Laboratory or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial remains the sole RCT to date to evaluate the safety and efficacy of different timing of P2Y₁₂ inhibitors in patients presenting with STEMI.^{55,56} In this trial, 1,862 patients with ongoing STEMI of less than 6 hours' duration were randomized to receive ticagrelor in the cath laboratory or prior to hospital arrival. With only limited delay from randomization to angiography between the two strategies, the study did not find prehospital administration of ticagrelor to lead to a significant $\geq 70\%$ reduction of ST-segment elevation or improve TIMI flow in the culprit artery at initial angiography. However, the rate of definite stent thrombosis at 30 days was lower among pretreated patients (0.2 vs. 1.2%; OR: 0.19, 95% CI: 0.04–0.86), without significant difference in terms of bleeding event.

Which P2Y₁₂ Inhibitors in the Acute Setting?

The issue of the optimal antiplatelet agent in ACS patients has remained, until recently, an open debate, as head-to-head comparison of ticagrelor and prasugrel were lacking or inconclusive.⁵⁷ Nonetheless, the place of ticagrelor, as the P2Y₁₂ inhibitor of choice for ACS, progressively grew in clinical practice, based on the survival benefit observed in the PLATO trial, and the lack of significant increase of major bleeding compared with clopidogrel, conversely to prasugrel in the TRITON–TIMI 38 trial.^{58,59} This dynamics has been recently altered with the result of the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 open-labeled trial, where ticagrelor was associated with a significant increase of the risk of death, MI, or stroke (HR: 1.36 95% CI: 1.09–1.70, $p = 0.006$), without significant difference with respect to major bleeding (HR: 1.12, 95% CI: 0.83–1.51, $p = 0.46$) compared with prasugrel, in patients presenting with an ACS for which a invasive evaluation was planned.⁶⁰ It is however imperative to understand that the ISAR-REACT 5 trial did not just compare two different antiplatelet agents but rather two therapeutic strategies, with an individualized strategy based on the use of prasugrel compared with a one-size-fits-all strategy with ticagrelor. Indeed, ticagrelor was administered as soon as possible after randomization, while prasugrel was administered only after delineation of the coronary anatomy in the case of NSTEMI, and at reduced maintenance dosage of 5 mg among patients aged over 75 years or with a body weight lower than 60 kg.⁶¹ The results of ISAR-REACT 5 trial should be interpreted considering its open-label rather than double-dummy design, incomplete observance at hospital discharge and 1 year of follow-up, and an appreciable number of patients lost to follow-up. A recent network meta-analysis of 12 RCTs comprising a total of 52,816 patients, including ISAR-REACT 5, found prasugrel to be associated with a lower risk of definite or probable stent

thrombosis compared with ticagrelor (HR: 0.68, 95% CI: 0.50–0.93)⁶².

There may also be some pharmacodynamic differences between prasugrel and ticagrelor. In fact, another study recently reported prasugrel to better prevent the endothelial dysfunction and inflammation associated with coronary stenting and NSTEMI, as compared with clopidogrel or ticagrelor.⁶³ Following these results, the 2020 ESC guidelines have granted a class IIb evidence favoring prasugrel over ticagrelor in patients with NSTEMI undergoing PCI, and for whom use of potent P2Y₁₂ inhibitors is indicated. The loading dose of P2Y₁₂ inhibitors may be administered as soon as the coronary angiogram is performed and prior to PCI.^{61,64}

Future Developments

Oral Anticoagulation

Considering the risk of early ischemic events following PCI for an ACS, and the fact that coagulation factors may remain activated long after the acute phase of the thrombosis formation, the addition of a non-vitamin K oral anticoagulant (NOAC) to a background antiplatelet therapy has been evaluated in several phase II RCTs.⁶⁵ Such a dual antithrombotic therapy strategy, in patients who would not otherwise require oral anticoagulants, should first demonstrate its safety profile, as bleeding complications following ACS are strongly associated with subsequent ischemic events and mortality.⁶⁶ In fact, the first trials evaluating a full dosage of NOAC in addition to DAPT initially reported a significant increase of the risk of bleeding events in high-risk patients, outweighing any potential gain in terms of ischemic event prevention.^{67–70} Subsequent trials, evaluating lower dosages of NOAC, in addition to DAPT, have reported a lower risk of ischemic events with such a strategy. In the Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46 (ATLAS ACS–TIMI 46) trial, the twice-daily 2.5 mg dose of rivaroxaban, in addition to DAPT (mostly aspirin and clopidogrel), reduced the risk of the composite of CV death, MI, or stroke (HR: 0.84, 95% CI: 0.72–0.97) and even all-cause mortality (HR: 0.68, 95% CI: 0.53–0.87). However, this gain in ischemic event prevention was once again offset by a significant increase in the risk of intracranial hemorrhage (HR: 2.83, 95% CI: 1.02–7.86). Finally, the optimal balance between ischemic prevention and bleeding complication may have been found in the GEMINI-ACS-1 trial, where a strategy of low-dose rivaroxaban (i.e., 2.5 mg twice daily) in association with clopidogrel or ticagrelor was compared with the current gold standard of DAPT with aspirin and clopidogrel or ticagrelor, in high-risk patients presenting with ACS, without leading to a significant increase of the risk of TIMI non-coronary artery bypass surgery clinically significant bleeding.⁷¹ Adequately powered RCTs are warranted to evaluate if such a dual pathway antithrombotic inhibition strategy could lead to a reduction of ischemic event, following PCI for ACS.

Accelerating the onset of action of P2Y₁₂ inhibitors: The pharmacodynamics of potent P2Y₁₂ inhibitors may be delayed in the setting of ACS. In fact, the Rapid Activity of Platelet Inhibitor Drugs (RAPID) study, which evaluated the residual

platelet reactivity following a loading dose of prasugrel and ticagrelor in patients with STEMI, reported that high residual platelet reactivity was present in approximately half of the patients at 2, while a 4-hour delay was required to observe an effective platelet inhibition overall.⁷² Crushing or chewing tablet of prasugrel or ticagrelor may lead to improved pharmacokinetics and a lower rate of high on-treatment platelet reactivity.^{73–78} The Platelet Inhibition With Cangrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention (CANTIC) study also demonstrated that an association of intravenous cangrelor and crushed ticagrelor could be used to bridge the gap in platelet inhibition compared with crushed oral P2Y₁₂ alone, without any sign of drug–drug interaction.⁷⁹ Recently, the Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over Prasugrel: A Multicenter Randomized Open-Label Trial in Patients with ST-Elevation Myocardial Infarction Referred for Primary Percutaneous Intervention (FABOLUS-FASTER) trial found cangrelor to provide with inferior inhibition of platelet aggregation compared with tirofiban but higher inhibition of platelet aggregation than chewed prasugrel in patients with STEMI undergoing PCI. The recently published COMPARISON of pre-hospital CRUSHed versus uncrushed prasugrel tablets in patients with STEMI undergoing primary PCIs (COMPARE CRUSH) trial investigated the impact of prehospital administration of crushed tablet prasugrel loading doses compared with integral tablet prasugrel loading doses in 727 patients presenting with STEMI and planned for primary PCI.⁸⁰ In this study, prehospital administration of crushed prasugrel tablets did not result in a significant difference of the two independent primary endpoints, which were the percentage of patients reaching the TIMI flow grade 3 in the infarct-related artery at initial angiography and achieving $\geq 70\%$ ST-segment elevation resolution assessed at 1 hour after PCI. No significant differences were observed with respect to ischemic events at 30 days. It should be noted, however, that these pharmacodynamics and pharmacokinetic studies have not been powered to evaluate the clinical impact of such strategies. Patients with sudden cardiac arrest-related cardiac arrest or cardiogenic shock may present with further impairment of the pharmacodynamics and pharmacokinetics of oral P2Y₁₂ inhibitors due to slower absorption and metabolism.^{81–83} Cangrelor with its quasi-immediate onset of action could be an interesting therapeutic alternative in this setting and is being currently investigated in the ongoing DAPT-SHOCK-AMI (NCT03551964), which will include 304 patients presenting with infarct-related cardiogenic shock.⁸⁴ Finally, selatogrel (ACT-246475) is a novel class of reversible, nonthienopyridine, P2Y₁₂ receptor inhibitors administered subcutaneously. This agent, which can be self-administered by the patients, may induce a profound and rapid platelet inhibition in the setting of both acute MI and chronic coronary syndromes, opening interesting therapeutic perspectives.^{85–88}

Maintenance Treatment

Current evidence: Based on the CURE trial, a 12-month duration of DAPT has remained the gold standard following

an ACS.^{25,26,34,89,90} Such minimal duration of DAPT is meant to prevent the risk of stent thrombosis in the culprit lesion as well as events from noninfarct-related coronary artery which equally contribute to the incidence of major adverse CV events following the index event.⁹¹ Considering the improvement of stent device technology and the widespread use of lipid-lowering therapy, which has led to a reduction of the risk of stent thrombosis and nonstent-related MI, the principle of 12-month DAPT duration has been recently challenged.^{7,92,93} In particular, the SMART-DATE trial compared a strategy of DAPT duration of 6-month versus 12-month DAPT in 2,712 patients undergoing PCI for an ACS.⁹⁴ Although the 6-month DAPT duration strategy was associated with a significantly noninferior risk of the primary composite endpoint of death, MI, or stroke at 18 months (with a relatively wide predefined noninferiority margin of 2.0%), it came at the cost of a significantly increased risk of MI (HR: 2.41, 95% CI: 1.15–5.05), and without significant difference in the risk of type 2 to 5 BARC bleeding. The DAPT-STEMI trial compared a 6-month to a 12-month duration of DAPT in 1,100 patients with STEMI treated with PCI and event free at 6 months of follow-up.⁹⁵ This trial also found the 6-month DAPT duration to be noninferior to the 12-month strategy on the composite endpoint of death, MI, any revascularization, stroke, or TIMI major bleeding at 18 months, without any significant differences for the individual endpoint. Overall, these results confirmed that the 12-month duration of DAPT

should remain the preferred strategy, in the absence of excessive risk of bleeding. Conversely, in the case of PRECISE-DAPT score ≥ 25 or in the case of high-bleeding risk as defined by the Academic Research Consortium for High Bleeding Risk criteria (**► Table 1**), the recent ESC guidelines recommend to consider (class IIA) P2Y₁₂ discontinuation after 3 months of treatment (**► Fig. 2**).^{27,96}

Platelet function test- or genotype-based individualized antiplatelet therapy: Several large RCTs have evaluated the role of platelet function testing (PFT) or genotyping to tailor the antiplatelet therapy following an ACS.²¹ The Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting (ARCTIC) and the ANTARTIC trials demonstrated that a PFT-based P2Y₁₂ inhibitor upgrading strategy did not result in improved outcomes in patients undergoing PCI.^{97,98} Conversely, strategies of PFT- or genotyping-based P2Y₁₂ inhibitor de-escalation strategy following an ACS were evaluated in the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) and the Patient Outcome after Primary PCI (POPular Genetics) trials, respectively.^{99,100} Both trials found these de-escalation strategies to be noninferior to the current gold standard of systematic prolonged DAPT with potent P2Y₁₂ inhibitors in terms of ischemic risk prevention. In particular, the POPular Genetics

Table 1 ARC-defined high bleeding risk in patients undergoing PCI⁹⁶

High bleeding risk (≥ 1 major criteria or ≥ 2 minor criteria)
<i>Major criteria</i>
Chronic oral anticoagulation
Severe chronic kidney disease (eGFR < 30 mL/min)
Hemoglobin < 11 g/dL
Prior bleeding requiring hospitalization/transfusion within the last 6 months or recurrent
Thrombocytopenia
Liver cirrhosis with portal hypertension
Chronic bleeding diathesis
Neoplasia diagnosed within 12 months or undergoing treatment
History of spontaneous intracranial hemorrhage or traumatic hemorrhage within the last 12 months, or prior severe ischemic stroke within the last 6 months, or brain arteriovenous malformation
Recent major surgery or trauma within 30 days of the index PCI
Urgent major surgery on dual antiplatelet therapy
<i>Minor criteria</i>
Age ≥ 75 years
Moderate chronic kidney disease (30 < eGFR < 60 mL/min)
Hemoglobin between 11 and 12.9 g/dL for men and 11 and 11.9 g/dL for women
Prior bleeding requiring hospitalization or transfusion within the last 12 months ^a
History of ischemic stroke ^a
Chronic use of oral NSAID or steroids

Abbreviations: eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention.

^aNot meeting the major criteria.

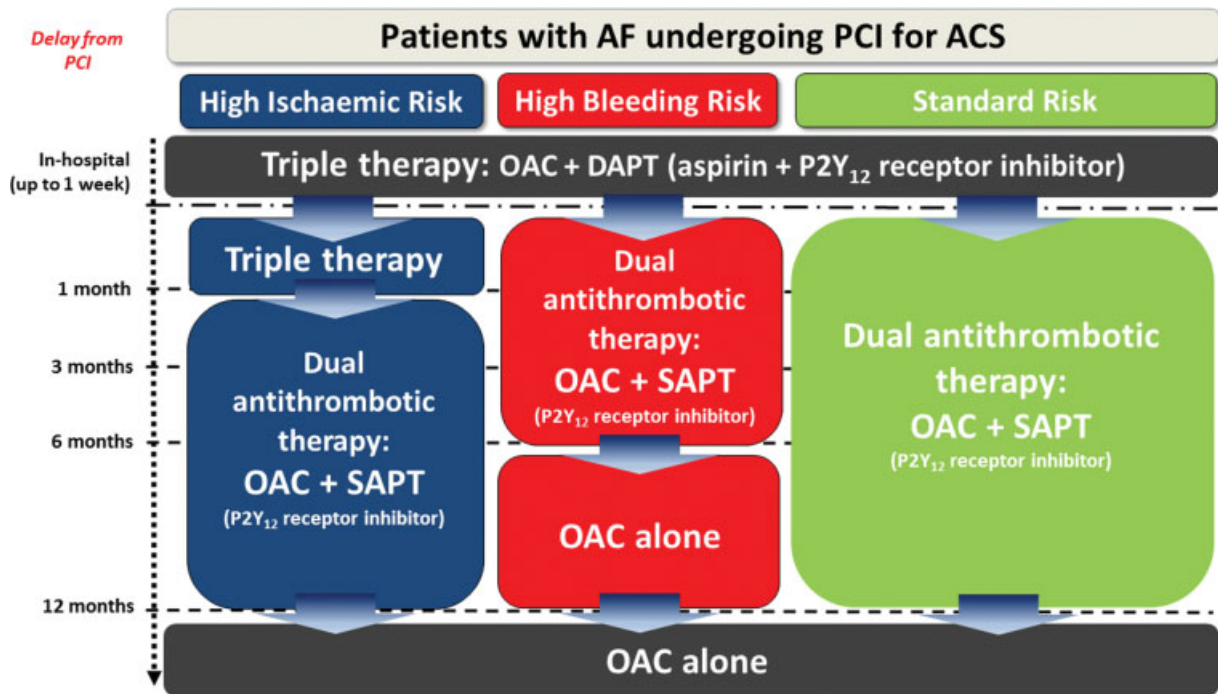


Fig. 2 Antithrombotic treatment for patients undergoing PCI for an ACS without chronic indication for oral anticoagulation, according to the 2020 ESC guidelines.²⁷ ACS, acute coronary syndrome; AF, atrial fibrillation; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

trial reported the CYP2C19 genotype-guided strategy for selection of oral P2Y₁₂ inhibitors to be associated with a lower risk of PLATO major or minor bleeding (HR: 0.78, 95% CI: 0.61–0.98). Rather than evaluating a de-escalation strategy, the Tailored Antiplatelet Therapy following PCI (TAILOR-PCI) primary analysis aimed at demonstrating the superiority of a genotype-based selection of P2Y₁₂ receptor inhibitor for the reduction of the composite of CV death, MI, stroke, definite or probable stent thrombosis, or severe recurrent ischemia at 12 months among patients presenting with a CYP2C19 loss-of-function variant.¹⁰¹ A total of 5,302 patients undergoing PCI were randomized, of whom 1,849 presented with CYP2C19 loss-of-function variants. Those patients were treated with clopidogrel in the conventional group and with ticagrelor in the genotype-guided group. No significant difference was observed with respect to the primary composite endpoint (HR: 0.66 95% CI: 0.43–1.02, $p=0.06$) between the two strategies.

The recent ESC guidelines have acknowledged the possibility of the de-escalation of P2Y₁₂ inhibitors in patients deemed unsuitable for potent platelet inhibition, based on PFT or genotyping, according to the availability of such assays.²⁷

Ongoing Issues and Future Developments

Several strategies for maintenance of antithrombotic treatment following ACS have been evaluated in large RCTs focusing on specific subgroups presenting with high ischemic and/or bleeding risk during the last decade. Overall, these trials have demonstrated that a personalization of the treatment in accordance with the specific features of the patients was more efficient than a one-size-fits-all strategy.

Pairing Oral Anticoagulation with Antiplatelet Therapy

Aspirin treatment exposes patients to a significantly increased risk of bleeding, notably from the gastrointestinal track, as the cyclooxygenase inhibition it induces may enhance the risk of acid-related lesion and ulcers. Moreover, in the era of strong P2Y₁₂ inhibitors, aspirin may only provide little additional platelet inhibition, questioning its place as a cornerstone of contemporary antithrombotic therapy for patients presenting with ACS.^{102,103} This may be particularly true among patient presenting with a chronic indication for oral anticoagulation such as atrial fibrillation. The What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST) trial was the first RCT to evaluate a strategy of early aspirin discontinuation in such patients treated with clopidogrel and vitamin K antagonist (VKA).¹⁰⁴ This dual pathway inhibition strategy was associated with a significant reduction of not only the risk of bleeding, but also the risk of the composite of death, MI, stroke, target-vessel revascularization, or stent thrombosis (HR: 0.60, 95% CI: 0.38–0.94), and even all-cause mortality (HR: 0.39, 95% CI: 0.16–0.93). The benefit of this strategy was further confirmed by more recent RCTs, based on the use of commercially available NOACs.^{105–108} A network meta-analysis of these RCTs comprising 11,532 patients also evaluated the various antithrombotic strategies (i.e., VKA or NOAC in association with DAPT or P2Y₁₂ inhibitor) and found a strategy of NOAC plus P2Y₁₂ inhibitors, with early aspirin discontinuation to be associated with the highest reduction of the risk of bleeding, without any significant offset in terms of ischemic risk, including stent thrombosis.¹⁰⁹ The recent ESC guidelines confirmed the validity of this strategy by granting a class I

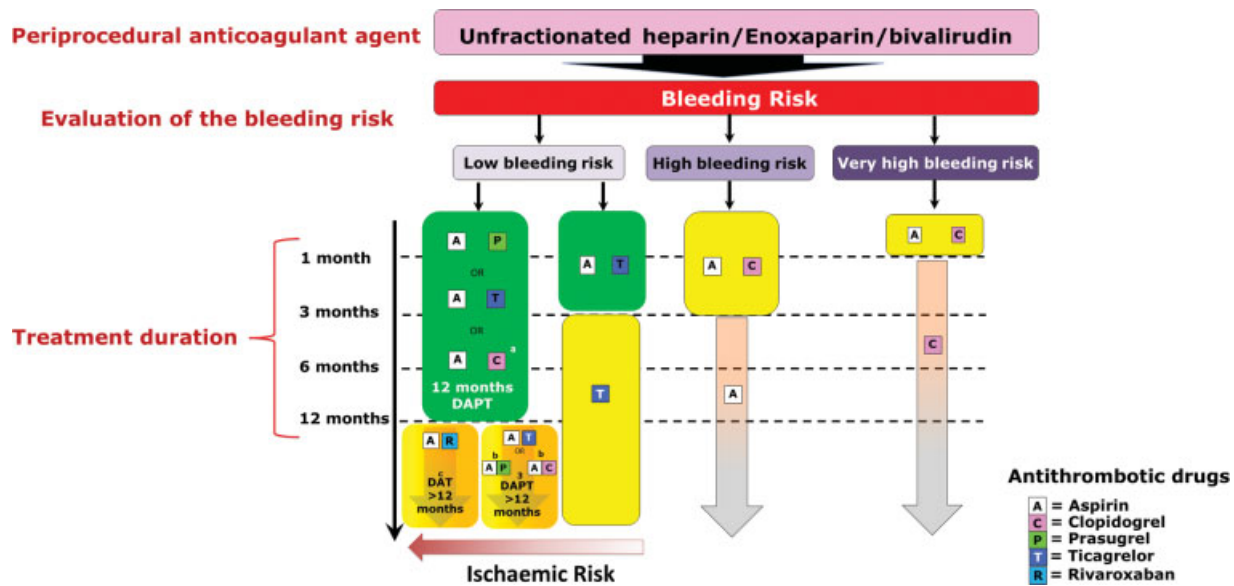


Fig. 3 Antithrombotic treatment for patients undergoing PCI for an ACS with chronic indication for oral anticoagulation, according to the 2020 ESC guidelines.²⁷ ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention.

recommendation favoring the use of a short (i.e., up to 1 week) triple therapy in such patients followed by a dual antithrombotic treatment comprising NOAC at the recommended dose for stroke prevention and a single antiplatelet agent, preferably clopidogrel (→ Fig. 3).²⁷ In the case of ischemic risk outweighing the bleeding risk, the triple therapy should be prolonged up to 1 month following PCI. In any case, discontinuation of antiplatelet agent after 12 months is recommended with the continuation of the NOAC.

Early Aspirin Discontinuation Following an ACS: The Twilight Approach

This strategy of early aspirin discontinuation with P2Y₁₂ inhibitor prolongation in patients undergoing PCI without an indication for chronic oral anticoagulation was also evaluated in several large RCTs.^{110–113} A meta-analysis of these trials reported this strategy to be associated with a lower risk of all bleeding (risk ratio [RR]: 0.61, 95% CI: 0.39–0.96), a trend toward a lower risk of major adverse cardiac or cerebrovascular events (RR: 0.89, 95% CI: 0.78–1.01), without any significant difference with respect to the risk of reinfarction (RR: 0.89, 95% CI: 0.74–1.08) or definite stent thrombosis (RR: 1.02, 95% CI: 0.72–1.43).¹¹⁴ The Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial randomized 7,119 patients undergoing PCI, a majority of whom for NSTEMI or unstable angina, and presenting with at least one clinical feature of high ischemic or bleeding risk and one angiographic feature of high-risk lesion.¹¹³ After 3 months of treatment with aspirin and ticagrelor without major bleeding or ischemic events, those patients were randomized to ticagrelor monotherapy or the pursuit of DAPT. The former was associated with a significant reduction of the risk of BARC type 2, 3, or 5 bleeding (4.0% vs. 7.1%; HR: 0.56, 95% CI: 0.45–0.68), without any significant difference with respect to

ischemic event and without a significant interaction according to the indication of the index PCI.

Post-ACS Maintenance Antithrombotic Therapy

Several trials have tested various strategies of prolonged DAPT to prevent thrombotic recurrence in patients undergoing PCI.¹¹⁵ The DAPT trial randomized 9,961 patients treated with PCI and 12-month DAPT with clopidogrel and aspirin, without any ischemic or bleeding event, to an additional 18 months or to placebo.¹¹⁶ The prolonged DAPT strategy was associated with a lower risk of the composite of death, MI, or stroke (HR: 0.71, 95% CI: 0.59–0.85), mitigated by a significantly increased risk of moderate or severe GUSTO bleeding (2.5 vs. 1.6%, *p* = 0.001) and a dubious impact of death (HR: 1.36, 95% CI: 1.00–1.85, *p* = 0.05). Consistently, the ARTIC-Interruption trial confirmed that a strategy of prolonged DAPT in a low-risk population is associated with a significantly increased risk of bleeding.¹¹⁷ Conversely, the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS–TIMI 54) trial evaluated a strategy of prolonged DAPT with two different dosages of ticagrelor (i.e., 90 or 60 mg twice a day) in association with aspirin in high-risk patients with a history of MI 1 or 3 years prior to randomization and at least one other high-risk feature among age of 65 years or older, diabetes mellitus, chronic kidney disease, multivessel CAD, or a history of a second MI.¹¹⁸ The trial reported prolonged DAPT with ticagrelor to be associated with a significant reduction of the risk of CV death, MI, or stroke, as well as numerically lower rates of CV death, once again at the cost of increased risk of bleeding, albeit without significant difference in terms fatal or intracranial bleeding. Finally, a prespecified subanalysis of the Cardiovascular Outcomes for People Using Anticoagulation

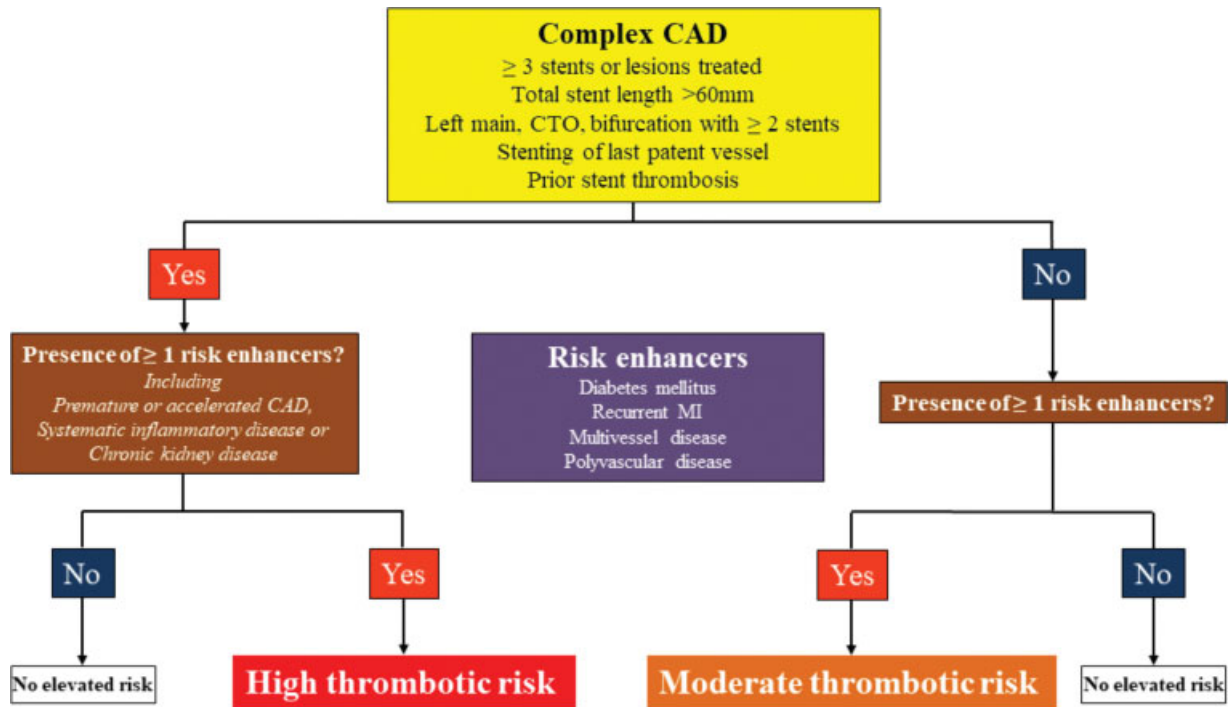


Fig. 4 Evaluation of the ischemic risk. CAD, coronary artery disease; CTO, chronic total occlusion; MI, myocardial infarction.

Strategies (COMPASS) trial evaluated the impact of dual pathway inhibition with rivaroxaban 2.5 mg twice daily plus aspirin 100 mg versus aspirin alone in 9,862 high-risk patients with prior PCI, a vast majority of whom had a history of MI, and reported the former to be associated with a

significant reduction of the composite of CV death, MI, or stroke (HR: 0.74, 95% CI: 0.61–0.88) and even all-cause death (HR: 0.73, 95% CI: 0.58–0.92), despite the significant increase of the risk of major bleeding (HR: 1.72, 95% CI: 1.34–2.21).¹¹⁹ The recent ESC guidelines have granted class IIa and IIb

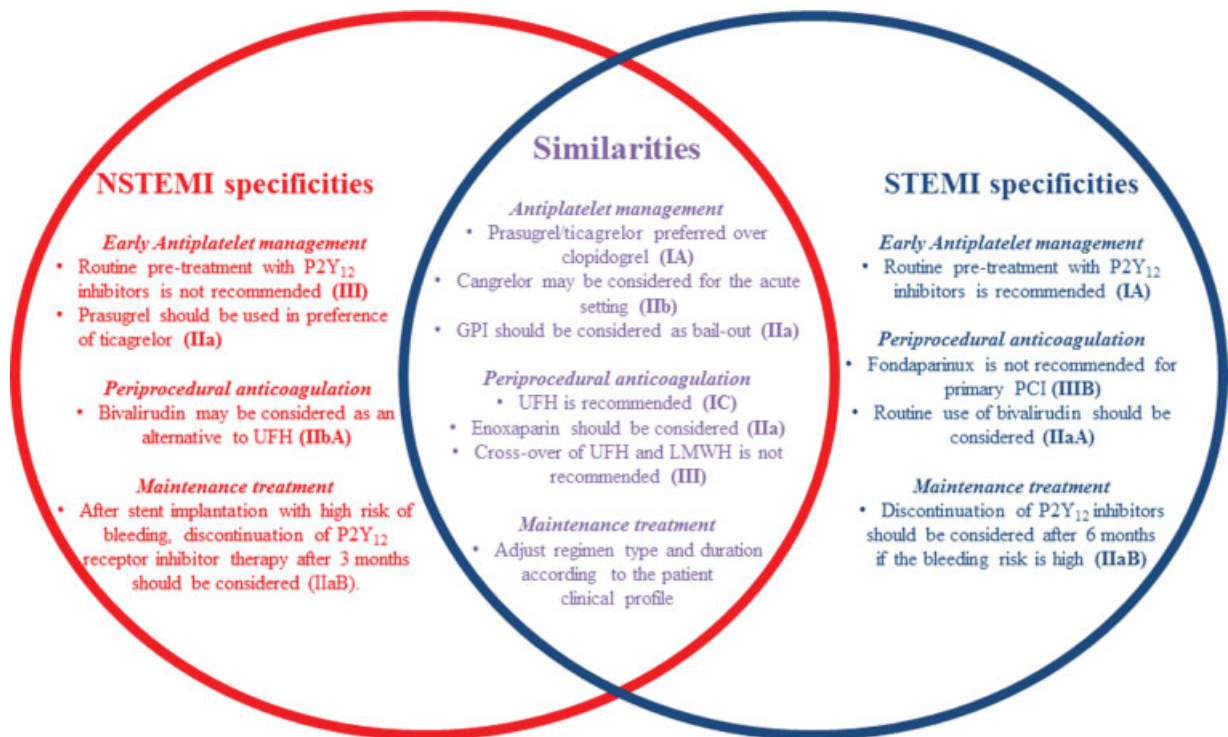


Fig. 5 Similarities and specificities of antithrombotic management of myocardial infarction with and without persistent ST-segment elevation. GPI, glycoprotein inhibitor; LMWH, low-molecular-weight heparin; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; UFH, unfractionated heparin.

recommendations favoring the addition of a second antithrombotic agent such as low-dose rivaroxaban in patients at high risk and moderate risk of ischemic events, respectively (►Fig. 4), and without increased bleeding risk.²⁷

Similarities and Specificities in the Management of STEMI and NSTEMI

MI, with or without persistent ST-segment elevation, represents the most severe clinical presentation of CAD. The antithrombotic management of these two entities, though mainly similar, presents some specificities, which are detailed in ►Fig. 5.

Conclusion

The issue of the optimal antithrombotic therapy for an ACS has seen considerable development in the last few decades. Current guidelines, which recommend primary PCI with transient anticoagulation and prolonged DAPT with aspirin and a potent P2Y₁₂ inhibitor, are based on solid accumulation of evidence and have resulted in lower morbidity and mortality. This topic continues to evolve as emerging concepts such as early aspirin discontinuation with potent P2Y₁₂ inhibitor prolongation or prolonged dual pathway inhibition with antiplatelet and low-dose direct oral anticoagulant are progressively being implemented in clinical practice.

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Conflict of Interest

J.-P.C. has received research grants or honoraria from AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Fédération Française de Cardiologie, Lead-Up, Medtronic, Merck Sharp & Dohme, Sanofi, Servier, and WebMD.

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