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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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, $P2Y_{12}$, 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 prothrombogenic 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors prasugrel and ticagrelor both were proven superior to

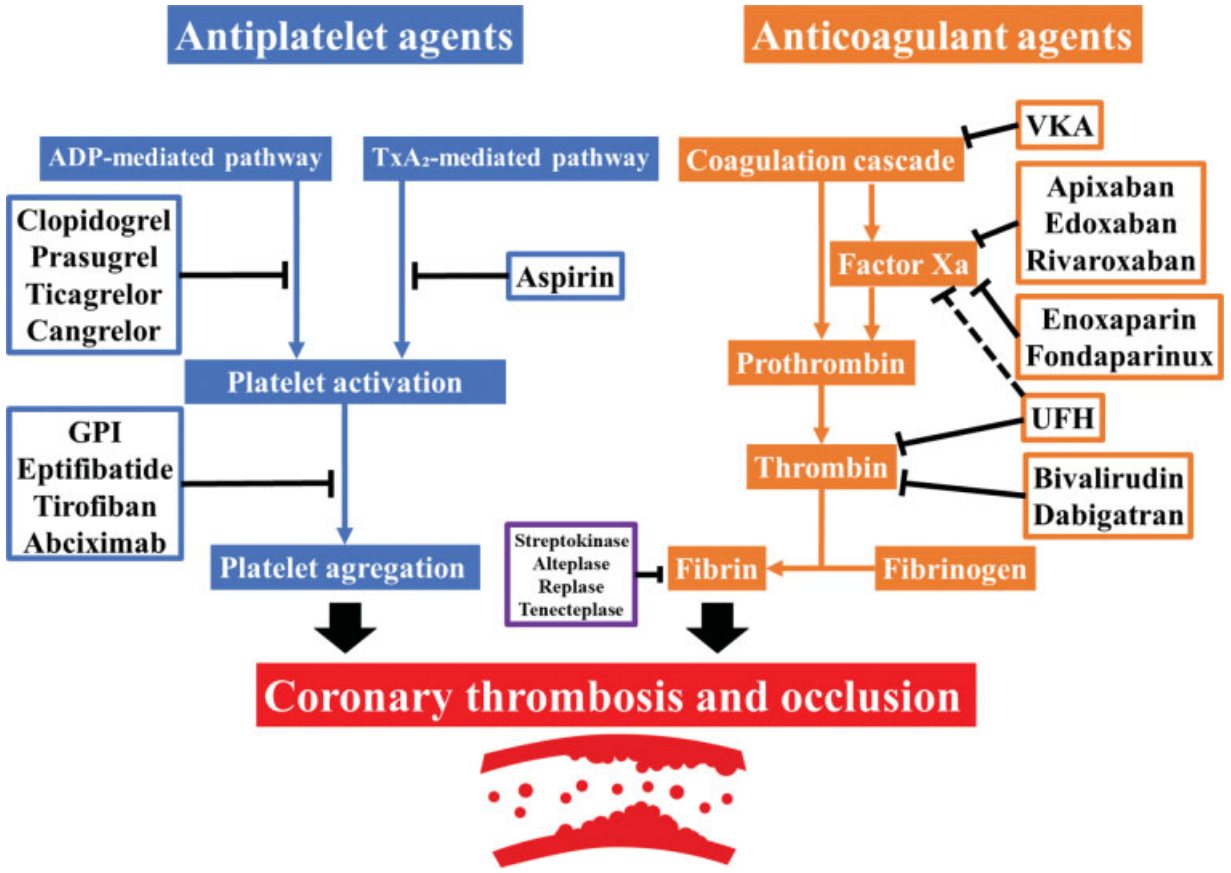

Fig. 1 Available antithrombotic agents for the management of acute coronary syndrome. GPI, glycoprotein IIb/IIIa inhibitor; UFH, unfractionated heparin; VKA, vitamin K antagonist.

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 $P2Y_{12}$ 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 PY12 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 $P2Y_{12}$, 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 predicable 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 $P2Y_{12}$ 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, $p = 0006$). Consistent results were reported by the ACCOAST-PCI subanalysis, 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 ≥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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors: The pharmacodynamics of potent $P2Y_{12}$ 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 $P2Y_{12}$ 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 prehospital 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 $P2Y_{12}$ 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, $P2Y_{12}$ 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 the12-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 $\geq$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) $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor upgrading strategy did not result in improved outcomes in patients undergoing PCI.[97,98] Conversely, strategies of PFT- or genotyping-based $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors in terms of ischemic risk prevention. In particular, the POPular Genetics

Table 1 ARC-defined high bleeding risk in patients undergoing PCI[96]

High bleeding risk ($\geq$1 major criteria or $\geq$2 minor criteria)
Major criteria
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
Minor criteria
Age $\geq$ 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.
[a]Not meeting the major criteria.

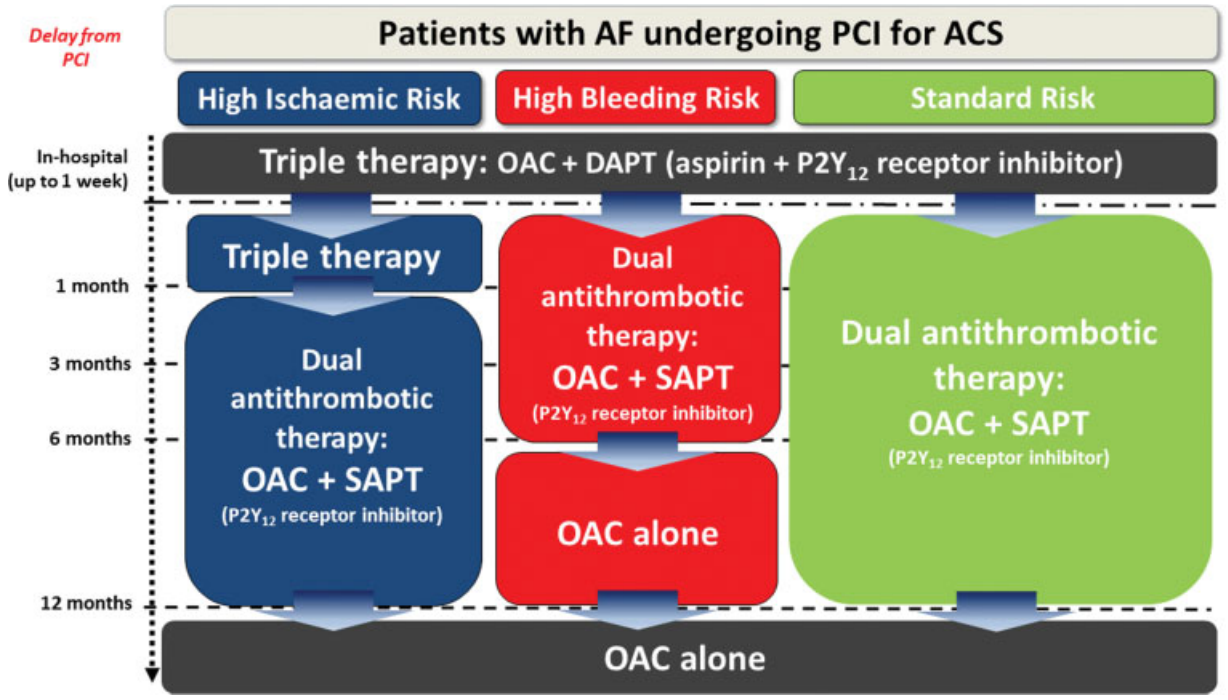

Fig. 2 Antithrombotic treatment for patients undergoing PCI for an ACS without chronic indication for oral anticoagulation, according to the 2020 ESC guidelines.[27] ACS, acute coronary syndrome; AF, atrial fibrillation; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; OAC, oral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

trial reported the CYP2C19 genotype-guided strategy for selection of oral $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor) and found a strategy of NOAC plus $P2Y_{12}$ 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

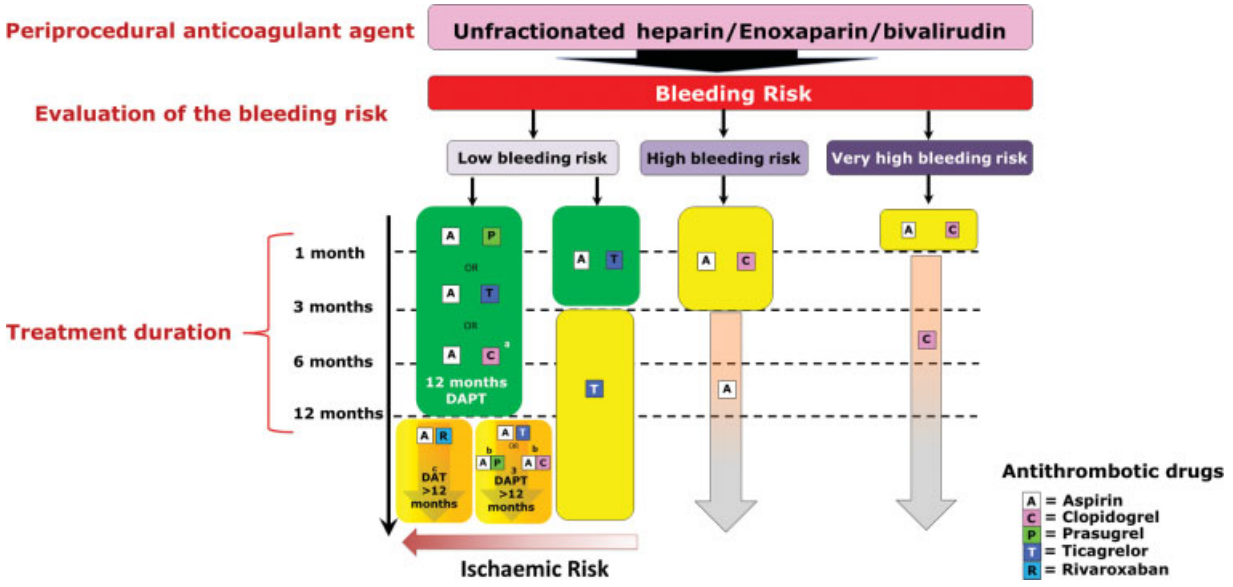

Fig. 3 Antithrombotic treatment for patients undergoing PCI for an ACS with chronic indication for oral anticoagulation, according to the 2020 ESC guidelines.[27] ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention.

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 $P2Y_{12}$ 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

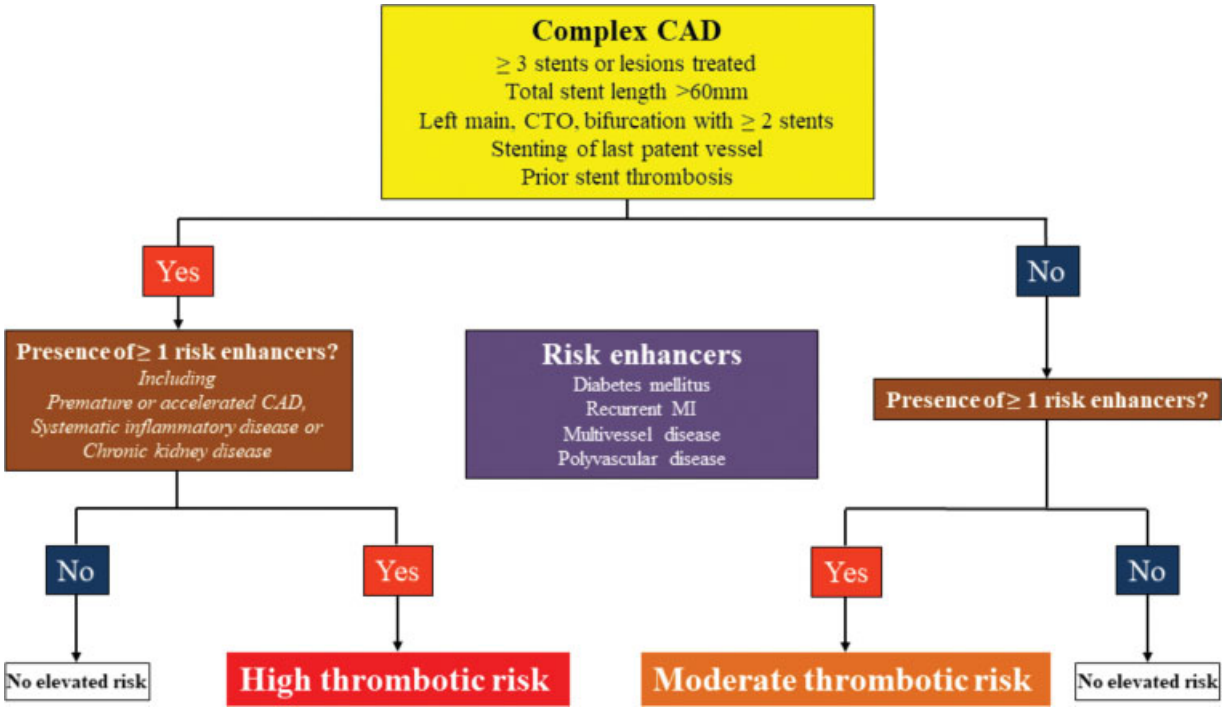

Fig. 4 Evaluation of the ischemic risk. CAD, coronary artery disease; CTO, chronic total occlusion; MI, myocardial infarction.

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

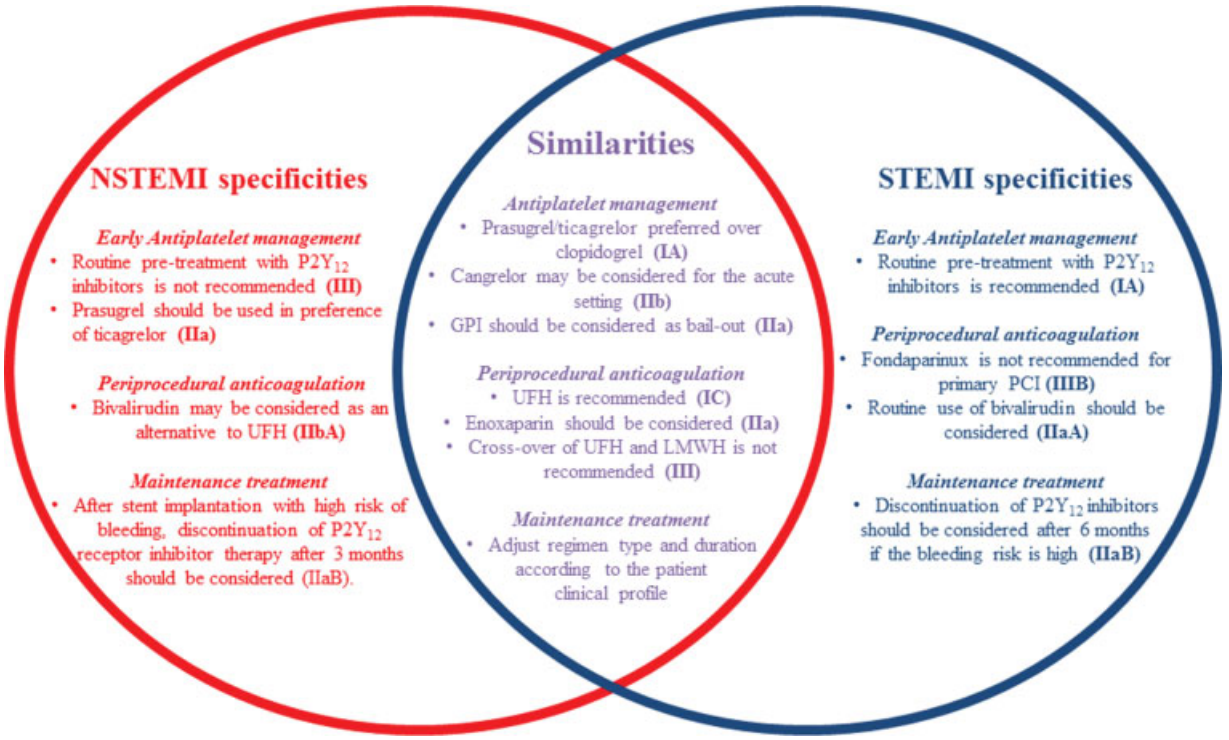

Fig. 5 Similarities and specificities of antithrombotic management of myocardial infarction with and without persistent ST-segment elevation. GPI, glycoprotein inhibitor; LMWH, low-molecular-weight heparin; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention;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

References

1 Szummer K, Jernberg T, Wallentin L. From early pharmacology to recent pharmacology interventions in acute coronary syndromes: JACC state-of-the-art review. J Am Coll Cardiol 2019; 74(12):1618–1636
2 Sibbing D, Angiolillo DJ, Huber K. Antithrombotic therapy for acute coronary syndrome: past, present and future. Thromb Haemost 2017;117(07):1240–1248
3 Silvain J, Collet J-P, Nagaswami C, et al. Composition of coronary thrombus in acute myocardial infarction. J Am Coll Cardiol 2011; 57(12):1359–1367
4 Silvain J, Collet J-P, Guedeney P, et al. Thrombus composition in sudden cardiac death from acute myocardial infarction. Resuscitation 2017;113:108–114
5 Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol 2017;70(01):1–25
6 Guedeney P, Aboyans V, Dalon F, et al. Epidemiology, treatment patterns and outcomes in patients with coronary or lower extremity artery disease in France. Arch Cardiovasc Dis 2019; 112(11):670–679
7 Guedeney P, Montalescot G. GLOBAL LEADERS: looking now at the bigger picture. EuroIntervention 2019;15(12):e1030–e1032
8 Guedeney P, Collet J-P. Diagnosis and management of acute coronary syndrome: what is new and why? Insight from the 2020 European Society of Cardiology guidelines. J Clin Med 2020;9(11):3474
9 Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368(21):2004–2013
10 Spronk HMH, Padro T, Siland JE, et al. Atherothrombosis and thromboembolism: position paper from the Second Maastricht Consensus Conference on Thrombosis. Thromb Haemost 2018; 118(02):229–250
11 Trenk D, Hille L, Leggewie S, et al. Antagonizing P2Y12 receptor inhibitors: current and future options. Thromb Haemost 2019; 119(10):1606–1616
12 Gorog DA, Geisler T. Platelet inhibition in acute coronary syndrome and percutaneous coronary intervention: insights from the past and present. Thromb Haemost 2020;120(04):565–578
13 Zeitouni M, Kerneis M, Nafee T, Collet JP, Silvain J, Montalescot G. Anticoagulation in acute coronary syndrome-state of the art. Prog Cardiovasc Dis 2018;60(4–5):508–513
14 Geddings JE, Mackman N. Recently identified factors that regulate hemostasis and thrombosis. Thromb Haemost 2014;111 (04):570–574
15 Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988;2(8607):349–360
16 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KKClopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345(07):494–502
17 Collet J-P, Hulot J-S, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet 2009;373(9660):309–317
18 Bonello L, Tantry US, Marcucci R, et al;Working Group on High On-Treatment Platelet Reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010;56(12):919–933
19 Silvain J, Cayla G, Hulot J-S, et al. High on-thienopyridine platelet reactivity in elderly coronary patients: the SENIOR-PLATELET study. Eur Heart J 2012;33(10):1241–1249
20 Hulot J-S, Collet J-P, Silvain J, et al. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. J Am Coll Cardiol 2010;56(02):134–143
21 Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment in percutaneous coronary intervention. JACC Cardiovasc Interv 2019;12(16):1521–1537
22 Wiviott SD, Braunwald E, McCabe CH, et al;TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357(20):2001–2015
23 Wallentin L, Becker RC, Budaj A, et al;PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361(11):1045–1057
24 Montalescot G, Wiviott SD, Braunwald E, et al;TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373(9665):723–731
25 Roffi M, Patrono C, Collet J-P, et al;ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37(03):267–315

26 Ibanez B, James S, Agewall S, et al;ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39 (02):119–177

27 Collet J-P, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020. Doi: 10.1093/eurheartj/ehaa575

28 Montalescot G, Bolognese L, Dudek D, et al;ACCOAST Investigators. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 2013;369(11): 999–1010

29 Steg PG, Bhatt DL, Hamm CW, et al;CHAMPION Investigators. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. Lancet 2013;382(9909):1981–1992

30 Grimfjärd P, Lagerqvist B, Erlinge D, Varenhorst C, James S. Clinical use of cangrelor: nationwide experience from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Eur Heart J Cardiovasc Pharmacother 2019;5(03):151–157

31 Montalescot G, Barragan P, Wittenberg O, et al;ADMIRAL Investigators. Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344(25): 1895–1903

32 De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. Eur Heart J 2009;30 (22):2705–2713

33 Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. JACC Cardiovasc Interv 2011;4(06):654–664

34 Neumann F-J, Sousa-Uva M, Ahlsson A, et al;ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40(02):87–165

35 Montalescot G, Collet JP, Tanguy ML, et al. Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. Circulation 2004;110(04):392–398

36 Montalescot G, White HD, Gallo R, et al;STEEPLE Investigators. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. N Engl J Med 2006;355(10): 1006–1017

37 Guedeney P, Hammoudi N, Duthoit G, et al. Intravenous enoxaparin anticoagulation in percutaneous left atrial cardiac procedures. EuroIntervention 2017;13(10):1226–1233

38 Collet J-P, Huber K, Cohen M, et al;ATOLL Investigators. A direct comparison of intravenous enoxaparin with unfractionated heparin in primary percutaneous coronary intervention (from the ATOLL trial). Am J Cardiol 2013;112(09):1367–1372

39 Silvain J, Beygui F, Barthélémy O, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ 2012;344:e553

40 Kastrati A, Neumann F-J, Schulz S, et al;ISAR-REACT 4 Trial Investigators. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. N Engl J Med 2011; 365(21):1980–1989

41 Stone GW, Witzenbichler B, Guagliumi G, et al;HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358(21):2218–2230

42 Capodanno D, De Caterina R. Bivalirudin for acute coronary syndromes: premises, promises and doubts. Thromb Haemost 2015;113(04):698–707

43 Valgimigli M, Frigoli E, Leonardi S, et al;MATRIX Investigators. Bivalirudin or unfractionated heparin in acute coronary syndromes. N Engl J Med 2015;373(11):997–1009

44 Erlinge D, Omerovic E, Fröbert O, et al. Bivalirudin versus heparin monotherapy in myocardial infarction. N Engl J Med 2017;377 (12):1132–1142

45 Bikdeli B, McAndrew T, Crowley A, et al. Individual patient data pooled analysis of randomized trials of bivalirudin versus heparin in acute myocardial infarction: rationale and methodology. Thromb Haemost 2020;120(02):348–362

46 Stone GW. Individual patient data pooled analysis of randomized trials of bivalirudin versus heparin in acute myocardial infarction. TCT connect 2020. Accessed December 7, 20202020. Available at: https://www.tctmd.com/slide/individual-patient-data-pooled-analysis-randomized-trials-bivalirudin-versus-heparin-acute

47 Mehta SR, Yusuf S, Peters RJ, et al;Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358 (9281):527–533

48 Montalescot G, Collet J-P, Ecollan P, et al;ACCOAST Investigators. Effect of prasugrel pre-treatment strategy in patients undergoing percutaneous coronary intervention for NSTEMI: the ACCOAST-PCI study. J Am Coll Cardiol 2014;64(24):2563–2571

49 Bellemain-Appaix A, Kerneis M, O'Connor SA, et al;ACTION Study Group. Reappraisal of thienopyridine pretreatment in patients with non-ST elevation acute coronary syndrome: a systematic review and meta-analysis. BMJ 2014;349:g6269

50 Almendro-Delia M, Gonzalez-Torres L, Garcia-Alcantara Á, et al; ARIAM-Andalucía Group. Prognostic impact of clopidogrel pretreatment in patients with acute coronary syndrome managed invasively. Am J Cardiol 2015;115(08):1019–1026

51 Dworeck C, Redfors B, Angerås O, et al. Association of pretreatment with P2Y12 receptor antagonists preceding percutaneous coronary intervention in non-ST-segment elevation acute coronary syndromes with outcomes. JAMA Netw Open 2020;3(10): e2018735

52 Lindholm D, Varenhorst C, Cannon CP, et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. Eur Heart J 2014;35(31):2083–2093

53 Tarantini G, Mojoli M, Varbella F, et al. Timing of oral P2Y12 inhibitor administration in patients with non-ST-segment elevation acute coronary syndrome. J Am Coll Cardiol 2020;76(21): 2450–2459

54 Montalescot G. Non-ST-segment elevation acute coronary syndrome: the last nail in the coffin of pre-treatment. J Am Coll Cardiol 2020;76(21):2460–2462

55 Montalescot G, van 't Hof AW, Lapostolle F, et al;ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014;371(11):1016–1027

56 Tavenier AH, Hermanides RS, Fabris E, et al;ATLANTIC investigators. Efficacy and safety of glycoprotein IIb/IIIa inhibitors on top of ticagrelor in STEMI: a subanalysis of the ATLANTIC trial. Thromb Haemost 2020;120(01):65–74

57 Motovska Z, Hlinomaz O, Miklik R, et al;PRAGUE-18 Study Group. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: multicenter randomized PRAGUE-18 study. Circulation 2016;134(21):1603–1612

58 Basra SS, Wang TY, Simon DN, et al. Ticagrelor use in acute myocardial infarction: insights from the national cardiovascular data registry. J Am Heart Assoc 2018;7(12):7

59 Jneid H. Ticagrelor or prasugrel in acute coronary syndromes - the winner takes it all? N Engl J Med 2019;381(16):1582–1585

60 Schüpke S, Neumann F-J, Menichelli M, et al;ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019;381(16):1524–1534

61 Menichelli M, Neumann F-J, Ndrepepa G, et al. Age- and weight-adapted dose of prasugrel versus standard dose of ticagrelor in patients with acute coronary syndromes : results from a randomized trial. Ann Intern Med 2020;173(06):436–444

62 Navarese EP, Khan SU, Kołodziejczak M, et al. Comparative efficacy and safety of oral $P2Y_{12}$ inhibitors in acute coronary syndrome: network meta-analysis of 52 816 patients from 12 randomized trials. Circulation 2020;142(02):150–160

63 Schnorbus B, Daiber A, Jurk K, et al. Effects of clopidogrel vs. prasugrel vs. ticagrelor on endothelial function, inflammatory parameters, and platelet function in patients with acute coronary syndrome undergoing coronary artery stenting: a randomized, blinded, parallel study. Eur Heart J 2020;41(33):3144–3152

64 Valina C, Neumann FJ, Menichelli M. Ticagrelor or prasugrel in patients with non-ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2020;76(21):2436–2446; In press

65 Guedeney P, Vogel B, Mehran R. Non-vitamin K antagonist oral anticoagulant after acute coronary syndrome: is there a role? Interv Cardiol (Lond) 2018;13(02):93–98

66 Sharma A, Hagström E, Wojdyla DM, et al;Apixaban for Prevention of Acute Ischemic Safety Events APPRAISE-2 Steering Committee and Investigators. Clinical consequences of bleeding among individuals with a recent acute coronary syndrome: Insights from the APPRAISE-2 trial. Am Heart J 2019;215:106–113

67 Oldgren J, Budaj A, Granger CB, et al;RE-DEEM Investigators. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J 2011;32(22):2781–2789

68 Alexander JH, Becker RC, Bhatt DL, et al;APPRAISE Steering Committee and Investigators. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation 2009;119(22):2877–2885

69 Alexander JH, Lopes RD, James S, et al;APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 2011;365(08):699–708

70 Mega JL, Braunwald E, Mohanavelu S, et al;ATLAS ACS-TIMI 46 study group. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet 2009;374(9683):29–38

71 Ohman EM, Roe MT, Steg PG, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. Lancet 2017;389 (10081):1799–1808

72 Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013;61(15):1601–1606

73 Rollini F, Franchi F, Hu J, et al. Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: the CRUSH study. J Am Coll Cardiol 2016;67 (17):1994–2004

74 Alexopoulos D, Dragasis S, Kafkas N. Loading with oral P2Y12 receptor inhibitors: to crush or not to crush? Thromb Haemost 2019;119(07):1037–1047

75 Niezgoda P, Sikora J, Barańska M, et al. Crushed sublingual versus oral ticagrelor administration strategies in patients with unstable angina. A pharmacokinetic/pharmacodynamic study. Thromb Haemost 2017;117(04):718–726

76 Parodi G, Xanthopoulou I, Bellandi B, et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. J Am Coll Cardiol 2015;65(05):511–512

77 Asher E, Tal S, Mazin I, et al. Effect of chewing vs swallowing ticagrelor on platelet inhibition in patients with ST-segment elevation myocardial infarction: a randomized clinical trial. JAMA Cardiol 2017;2(12):1380–1384

78 Asher E, Frydman S, Katz M, et al;For The PLATIS (Platelets and Thrombosis in Sheba) Study Group. Chewing versus swallowing ticagrelor to accelerate platelet inhibition in acute coronary syndrome - the CHEERS study. Thromb Haemost 2017;117 (04):727–733

79 Franchi F, Rollini F, Rivas A, et al. Platelet inhibition with cangrelor and crushed ticagrelor in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Circulation 2019;139(14):1661–1670

80 Vlachojannis George J, Wilschut Jeroen M, Vogel Rosanne F, et al. Effect of pre-hospital crushed prasugrel tablets in patients with STEMI planned for primary percutaneous coronary intervention: the randomized COMPARE CRUSH trial. Circulation 2020; 142(24):2316–2328

81 Ibrahim K, Christoph M, Schmeinck S, et al. High rates of prasugrel and ticagrelor non-responder in patients treated with therapeutic hypothermia after cardiac arrest. Resuscitation 2014;85(05):649–656

82 Weeks PA, Sieg A, Paruthi C, Rajapreyar I. Antiplatelet therapy considerations in ischemic cardiogenic shock: implications of metabolic bioactivation. J Cardiovasc Pharmacol Ther 2015;20 (04):370–377

83 Schoergenhofer C, Hobl E-L, Staudinger T, et al. Prasugrel in critically ill patients. Thromb Haemost 2017;117(08): 1582–1587

84 Prüller F, Bis L, Milke OL, et al. Cangrelor induces more potent platelet inhibition without increasing bleeding in resuscitated patients. J Clin Med 2018;7(11):442

85 Storey RF, Gurbel PA, Ten Berg J, et al. Pharmacodynamics, pharmacokinetics, and safety of single-dose subcutaneous administration of selatogrel, a novel P2Y12 receptor antagonist, in patients with chronic coronary syndromes. Eur Heart J 2020;41 (33):3132–3140

86 Hulot J-S, Montalescot G. Do we need a new P2Y12 receptor antagonist? Eur Heart J 2020;41(33):3141–3143

87 Sinnaeve P, Fahrni G, Schelfaut D, et al. Subcutaneous selatogrel inhibits platelet aggregation in patients with acute myocardial infarction. J Am Coll Cardiol 2020;75(20):2588–2597

88 Silvain J, Zeitouni M, Kerneis M. Selatogrel for acute myocardial infarction: the promise and challenges of self-medication. J Am Coll Cardiol 2020;75(20):2598–2601

89 Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68(10): 1082–1115

90 Valgimigli M, Bueno H, Byrne RA, et al;ESC Scientific Document Group ESC Committee for Practice Guidelines (CPG) ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39(03):213–260

91 Stone GW, Maehara A, Lansky AJ, et al;PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364(03):226–235

92 Guedeney P, Giustino G, Sorrentino S, et al. Efficacy and safety of alirocumab and evolocumab: a systematic review and meta-analysis of randomized controlled trials. Eur Heart J 2019. Doi: 10.1093/eurheartj/ehz430
93 Guedeney P, Sorrentino S, Giustino G, et al. Indirect comparison of the efficacy and safety of alirocumab and evolocumab: a systematic review and network meta-analysis. Eur Heart J Cardiovasc Pharmacother 2020. Doi: 10.1093/ehjcvp/pvaa024
94 Hahn J-Y, Song YB, Oh J-H, et al;SMART-DATE investigators. 6-Month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. Lancet 2018;391(10127):1274–1284
95 Kedhi E, Fabris E, van der Ent M, et al. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. BMJ 2018;363:k3793
96 Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. Eur Heart J 2019;40(31):2632–2653
97 Collet J-P, Cuisset T, Rangé G, et al;ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012;367(22):2100–2109
98 Cayla G, Cuisset T, Silvain J, et al;ANTARCTIC investigators. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet 2016;388(10055):2015–2022
99 Sibbing D, Aradi D, Jacobshagen C, et al;TROPICAL-ACS Investigators. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017;390(10104):1747–1757
100 Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. N Engl J Med 2019;381(17):1621–1631
101 Pereira NL, Farkouh ME, So D, et al. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. JAMA 2020;324(08):761–771
102 Armstrong PCJ, Leadbeater PD, Chan MV, et al. In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation. J Thromb Haemost 2011;9(03):552–561
103 Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol 2018;15(08):480–496
104 Dewilde WJM, Oirbans T, Verheugt FWA, et al;WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013;381(9872):1107–1115
105 Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375(25):2423–2434
106 Cannon CP, Bhatt DL, Oldgren J, et al;RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377(16):1513–1524
107 Lopes RD, Heizer G, Aronson R, et al;AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380(16):1509–1524
108 Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet 2019;394(10206):1335–1343
109 Lopes RD, Hong H, Harskamp RE, et al. Optimal antithrombotic regimens for patients with atrial fibrillation undergoing percutaneous coronary intervention: an updated network meta-analysis. JAMA Cardiol 2020;5(05):582–589
110 Watanabe H, Domei T, Morimoto T, et al;STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. JAMA 2019;321(24):2414–2427
111 Hahn J-Y, Song YB, Oh J-H, et al;SMART-CHOICE Investigators. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. JAMA 2019;321(24):2428–2437
112 Vranckx P, Valgimigli M, Jüni P, et al;GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392(10151):940–949
113 Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381(21):2032–2042
114 Guedeney P, Mesnier J, Sorrentino S, et al. Early aspirin discontinuation following acute coronary syndrome or percutaneous coronary intervention: a systematic review and meta-analysis of randomized controlled trials. J Clin Med 2020;9(03):9
115 Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol 2015;65(13):1298–1310
116 Mauri L, Kereiakes DJ, Yeh RW, et al;DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371(23):2155–2166
117 Collet J-P, Silvain J, Barthélémy O, et al;ARCTIC investigators. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. Lancet 2014;384(9954):1577–1585
118 Bonaca MP, Bhatt DL, Cohen M, et al;PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372(19):1791–1800
119 Bainey KR, Welsh RC, Connolly SJ, et al;COMPASS Investigators. Rivaroxaban plus aspirin versus aspirin alone in patients with prior percutaneous coronary intervention (COMPASS-PCI). Circulation 2020;141(14):1141–1151