Carciotto *et al. Vessel Plus* 2024;8:33
DOI: 10.20517/2574-1209.2024.01

Vessel Plus

Review

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De-escalating antiplatelet therapy in patients with acute coronary syndrome

Gabriele Carciotto[1,2], Mattia Galli[3], Victoria Garcia-Ruiz[4], Emmanuele Soraci[5], Alberto Magliarditi[5], Paolo Liotta[2], Lucio Teresi[1,2], Marco Franzino[1,2], Simone Zecchino[6], Deborah Bonfiglio[1], Italo Porto[7,8], Rocco Vergallo[7,8], Antonio Giovanni Versace[9], Fabrizio Oliva[10], Claudio Montalto[10,11], Giorgio Quadri[12], Giampiero Vizzari[1,2], Fausto Castriota[3], Piera Capranzano[13], Ferdinando Varbella[6], Giuseppe Musumeci[11], Antonio Micari[1,2], Francesco Costa[2-14]

[1]Division of Cardiology, University Hospital Policlinico G Martino, Messina 98124, Italy.
[2]Department of Biomedical and Dental Sciences and of Morphological and Functional Images, University of Messina, Messina 98122, Italy.
[3]Maria Cecilia Hospital, GVM Care & Research, Cotignola 48033, Italy.
[4]Division of Cardiology, GIOMI Hospital, Messina 98165, Italy.
[5]Dipartimento Funzionale di Medicina, U.O.S. Emodinamica, Ospedale Barone Romeo di Patti, Messina 98066, Italy.
[6]Interventional Cardiology Unit, Degli Infermi Hospital, Turin 10098, Italy.
[7]Cardiothoracic and Vascular Department, IRCCS Ospedale Policlinico San Martino, Genova 16132, Italy.
[8]Department of Internal Medicine and Medical Specialties, Università di Genova, Genova 16132, Italy.
[9]Emergency Medicine Unit, Papardo Hospital, Messina 98166, Italy.
[10]Interventional Cardiology, De Gasperis Cardio Center, Niguarda Hospital, Milan 20162, Italy.
[11]Department of Medicine and Surgery, University of Milano Bicocca, Milan 20126, Italy.
[12]S.C.Cardiologia, AO Ordine Mauriziano, Torino 10128, Italy.
[13]Azienda Ospedaliero-Universitaria Policlinico G. Rodolico-San Marco, University of Catania, Catania 95123, Italy.
[14]Área del Corazón, Hospital Universitario Virgen de la Victoria, CIBERCV, IBIMA Plataforma BIONAND, Departamento de Medicina UMA, Malaga, Spain, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV).

Correspondence to: Prof. Antonio Micari, Department of Biomedical and Dental Sciences and of Morphological and Functional Images, University of Messina, Piazza Pugliatti 1, Messina 98122, Italy. E-mail: micariantonio@gmail.com

How to cite this article: Carciotto G, Galli M, Garcia-Ruiz V, Soraci E, Magliarditi A, Liotta P, Teresi L, Franzino M, Zecchino S, Bonfiglio D, Porto I, Vergallo R, Versace AG, Oliva F, Montalto C, Quadri G, Vizzari G, Castriota F, Capranzano P, Varbella F, Musumeci G, Micari A, Costa F. De-escalating antiplatelet therapy in patients with acute coronary syndrome. *Vessel Plus* 2024;8:33. https://dx.doi.org/10.20517/2574-1209.2024.01

Received: 27 Jan 2024 **First Decision:** 22 May 2024 **Revised:** 20 Jul 2024 **Accepted:** 13 Sep 2024 **Published:** 27 Sep 2024

Academic Editors: Frank W. Sellke, Annie Laurie W. Shroyer **Copy Editor:** Yu-Fei Wang **Production Editor:** Yu-Fei Wang

Abstract

Dual antiplatelet therapy (DAPT), combining aspirin and a P2Y12 receptor inhibitor, is the basis of acute coronary syndrome (ACS) treatment, demonstrating efficacy in reducing ischemic complications while being linked to increased bleeding. Recent interest has emerged in bleeding reduction strategies, specifically de-escalation strategies involving P2Y12 inhibitor potency and dosage modulation that can be achieved in two different ways: the

unguided de-escalation, where P2Y12 inhibitors are adjusted based on clinical judgment, and the guided de-escalation, incorporating genetic or platelet function tests to tailor the therapy. Several randomized controlled trials (RCTs) demonstrated that both unguided and guided de-escalation strategies can reduce bleeding without compromising ischemic outcomes. However, some gaps in evidence are still present and further investigation is needed. Ongoing and upcoming RCTs aim to address uncertainties, including direct comparisons between de-escalation strategies, optimal timing for intervention, and personalized approaches guided by genetic testing. Furthermore, the review emphasizes the need for standardization in implementing de-escalation strategies in routine clinical practice.

Keywords: Dual antiplatelet therapy, P2Y12 inhibitors, acute coronary syndrome, percutaneous coronary intervention, de-escalation, bleeding

INTRODUCTION

Dual antiplatelet therapy (DAPT), the combination of acetylsalicylic acid and a $P2Y_{12}$ receptor inhibiting agent, represents the backbone of pharmacological management in acute coronary syndrome (ACS) patients[1-3]. Indeed, compared with aspirin alone, DAPT improves outcomes in ACS patients[4,5], preventing procedure-related thrombotic complications, such as peri-procedural myocardial infarction (MI) or stent thrombosis (ST)[6,7], as well as long-term spontaneous ischemic events both in the coronary and extra-coronary vasculature[8,9]. However, this benefit is counterbalanced by an increase in bleeding, which is more evident when potent P2Y12 inhibitors, prasugrel and ticagrelor, are used[3]. Because ACS patients are considered by definition at elevated likelihood risk of ischemic events, current international guidelines recommend a default 12-month DAPT strategy with either ticagrelor or prasugrel in patients with ACS, unless contraindicated[10]. Nevertheless, the growing recognition of the prognostic significance of bleeding events in individuals with ACS or those treated with percutaneous coronary interventions (PCI)[11], combined with the introduction of new stent platforms associated with low rates of adverse events such as ST, has led to questions about the use of 12-month DAPT as a default strategy and has stimulated interest in the use of antithrombotic strategies that could reduce bleeding without hampering the ischemic benefits. These are known as bleeding reduction strategies[12,13]. Moreover, increasing evidence supporting the difference in temporal trends of ischemic and bleeding risks after ACS/PCI has suggested that modulation of antithrombotic therapy 1-3 months after the index may be beneficial[8,12]. Certainly, the likelihood of ischemic/thrombotic events is most pronounced in the initial months following PCI and tends to diminish subsequently, whereas the bleeding risk tends to remain relatively constant over time [Figure 1][8]. Hence, various bleeding reduction strategies have been proposed in recent years, including shortening the course of DAPT, and other de-escalation strategies to modulate P2Y12i potency. In this manuscript, we will focus on describing de-escalation strategies for P2Y12i switching from a potent P2Y12i to clopidogrel or potent P2Y12i dose reduction. Different from other DAPT modulation strategies, de-escalation by switching or dose-reduction may enable a more nuanced reduction of antiplatelet potency on the P2Y12 inhibitor pathway, unlike shortening DAPT which can either result in no action (if ASA alone is chosen) or excessive action (if a potent P2Y12 inhibitor alone is chosen)[14].

De-escalation of prasugrel or ticagrelor to clopidogrel may be either guided or unguided, either if the therapy selection is based on the use or not of platelet function (PFT) or genetic testing to lead clopidogrel administration based on individual patient's responsiveness. In fact, the superior effectiveness and lower security of both prasugrel and ticagrelor compared with clopidogrel is in part attributable to their more predictable pharmacodynamic effects[15]. On the contrary, clopidogrel is characterized by a significant variability in response among patients, due to both acquired and genetic factors, including the polymorphisms of the gene that transcribes the CYP2C19 enzyme. The latter is accountable for the two-step

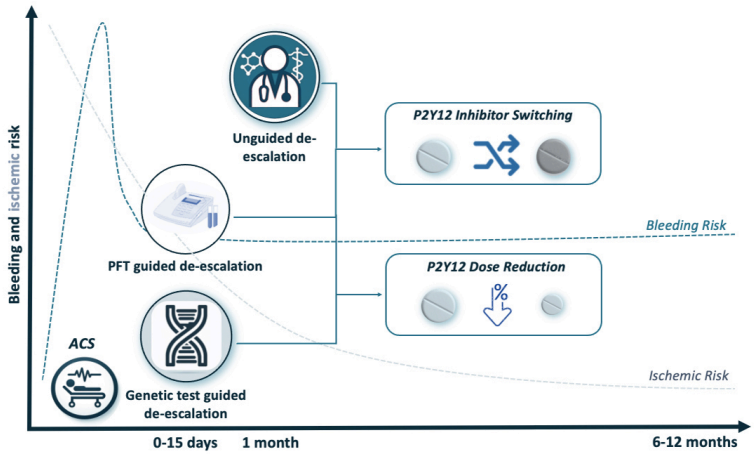

Figure 1. $P2Y_{12}$ inhibitor de-escalation in patients with ACS. Estimated risk of ischemic and bleeding events. While ischemic risk progressively weans off after the ACS, bleeding risk remains higher when patient is treated with dual antiplatelet therapy. ACS: Acute coronary syndrome.

oxidation of clopidogrel's pro-drug into its active metabolite[15,16]. Therefore, individuals carrying one or two loss-of-function (LoF) alleles, identified as intermediate metabolizer and poor metabolizer, respectively, exhibit reduced CYP2C19 enzyme activity. This leads to lower concentrations of clopidogrel's active metabolism product and higher platelet reactivity (HPR), serving as an indicator of increased thrombotic risk. Up to 30% of patients undergoing PCI may be poor or non-responders. Two tools can be used to identify poor responders: genetic tests that detect patients carrying CYP2C19 LoF alleles and platelet function tests (PFT) that directly assess platelet reactivity phenotype in response to clopidogrel[17]. The application of these instruments in patients with ACS allows for a guided de-escalation of $P2Y_{12}$ inhibiting therapy, consisting of the selective administration of clopidogrel among patients deemed to be responder to clopidogrel, with prasugrel or ticagrelor being used only in clopidogrel poor or non-responders[15].

This review critically appraises the available evidence supporting the de-escalation of antiplatelet therapy in ACS [Table 1]. It discusses the future perspective and possible implications of using this strategy as the new standard of care for ACS patients. It also considers other bleeding reduction strategies that have been investigated, such as DAPT shortening.

RANDOMIZED CONTROLLED TRIALS ON DE-ESCALATION STRATEGIES

Unguided de-escalation

Unguided de-escalation is a practical approach consisting of the modulation of $P2Y_{12}$ receptor inhibition after the period associated with the highest rates of thrombotic complications has weaned off, such as the first 1-3 months post-ACS/PCI. In this setting, the modulation of $P2Y_{12}$ receptor inhibition is based on the clinical judgment of the physician and does not take into account the individual responsiveness to clopidogrel.

The effectiveness and security of changing from powerful $P2Y12_i$ to clopidogrel 30 days after an ACS was first validated in the TOPIC trial[18], a randomized, controlled trial conducted in France. The study enrolled 646 patients with ACS who were over 18 years old and were treated with aspirin and a potent $P2Y_{12}i$ after PCI. The patients were free from major adverse events at one month. Patients who suffered major bleeding in the last 12 months, as per the Bleeding Academic Research Consortium (BARC) criteria, and those with indications for long-term anticoagulation, or thrombocytopenia were excluded. After one month from the

Table 1. Current large randomized controlled trials testing a de-escalation strategy

Study title	Patients enrolled (*n*)	Target population	Experimental treatment	Control treatment	Primary endpoint (experimental group *vs.* control group, *P*-value)
TOPIC[18]	646	ACS patients treated with ASA and a potent P2Y12 inhibitor, free from major adverse events at 1 month after PCI	Unguided de-escalation to clopidogrel	Continuation of ticagrelor or prasugrel	Composite of CV death, urgent coronary revascularization, stroke, BARC ≥ 2 bleedings at 12 months (13.4% *vs.* 26.3%, $P < 0.01$)
HOST-REDUCE-POLYTECH-ACS[19]	2,338	ACS patients who underwent PCI treated with prasugrel 10 mg	Unguided de-escalation to prasugrel 5 mg	Continuation of prasugrel 10 mg	Net adverse clinical events: all-cause death, nonfatal MI, ST, revascularization, stroke, BARC ≥ 2 bleedings at 12 months (7.2% *vs.* 10.1%, $P_{non\text{-}inferiority} < 0.0001$)
TALOS-AMI[20]	2,697	Stabilized patients with acute MI treated with PCI and DAPT (ASA + Ticagrelor), free from major ischemic or bleeding events in the first month after PCI	Unguided de-escalation from ticagrelor to clopidogrel	Continuation of ticagrelor	Composite of CV death, MI, stroke or BARC ≥ 2 type bleeding at 12 months (4.6% *vs.* 8.4%, $P < 0.001$)
ANTARCTIC[26]	877	Elderly patients who underwent PCI for ACS	Prasugrel 5 mg with PFT dose or drug adjustment	Prasugrel 5 mg with no PFT	Composite of CV death, MI, stroke, ST, urgent revascularization, BARC 2, 3 or 5 bleeding complications (28% *vs.* 28%, $P = 0.98$)
TROPICAL-ACS[27]	2,610	ACS patients who underwent successful PCI and indication for 1 year DAPT	PFT guided de-escalation to clopidogrel	Standard DAPT (ASA + Prasugrel 10 mg)	Net clinical benefit: CV death, MI, stroke or BARC 2 or higher bleeding events (7% *vs.* 9%, $P_{non\text{-}inferiority} = 0.0004$)
POPULAR GENETICS[28]	2,488	STEMI patients who underwent PCI with stent implantation	Genetic test guided de-escalation to clopidogrel	Continuation of ticagrelor or prasugrel	Net adverse clinical events: death from any cause, MI, definite ST, cerebrovascular events or PLATO major bleeding at 12 months (5.1% *vs.* 5.9%, $P_{non\text{-}inferiority} < 0.001$)

ACS: Acute coronary syndrome; PCI: percutaneous coronary interventions; DAPT: dual antiplatelet therapy; PFT: platelet function tests; CV: cardiovascular; BARC: bleeding academic research consortium; MI: myocardial infarction; ST: stent thrombosis.

index event, patients were randomized in a 1:1 fashion to continue their prior $P2Y_{12}i$ or to switch to clopidogrel. The rate of the primary composite endpoint of death from cardiovascular (CV) causes, urgent PCI or CABG, cerebrovascular events, and BARC type 2 or more serious bleeding at 12 months after the ACS was reduced by clopidogrel compared to the potent $P2Y_{12}i$, with a statistically significant difference (13.4% *vs.* 26.3%). This result was consistent across ACS presentation, presence of diabetes and $P2Y_{12}$ inhibitor used. However, BARC 2 or higher bleeding events were less frequent in the clopidogrel group (4% *vs.* 14.9%). The rate of ST was very low in both groups, with only 4 and 3 patients experiencing it, respectively. Additionally, the rate of ischemic complications did not differ in the two groups[18].

The HOST-REDUCE-POLYTECH-ACS trial assessed the non-inferiority of a DAPT de-escalation strategy based on the reduction of the prasugrel dose[19]. This randomized, multicenter trial enrolled 2,338 ACS patients who underwent PCI and met the core indication for treatment with prasugrel-based DAPT[19]. Patients were randomly divided in a 1:1 fashion to 5 mg prasugrel or 10 mg prasugrel after the initial 30 days of 10 mg prasugrel treatment. The non-inferiority was met. Indeed, the de-escalation group had a lower rate of the composite primary endpoint of net adverse clinical events at 1 year (7.2% *vs.* 10.1%). Additionally, no increase in the secondary endpoints (death from CV causes, MI, ST, and ischemic cerebrovascular events) was registered and a significant reduction in the risk of bleeding was observed[19]. This approach was safe, irrespective of PCI complexity. Indeed, 705 patients received complex PCI, and a

post-hoc analysis of PCI complexity of the trial showed that in this subset of patients, de-escalating the prasugrel dose did not elevate the risk of major adverse cardiovascular events (MACE) and led to a reduction in bleeding events classified as BARC class 2 or higher[16].

The TALOS-AMI trial aimed to investigate the non-inferiority of unguided de-escalation from ticagrelor to clopidogrel after 30 days of standard DAPT in individuals experiencing acute MI treated with PCI[20]. It was an open-label, multicenter, randomized trial that included 2,697 individuals with AMI who received DAPT with aspirin and ticagrelor and were free from major ischemic or bleeding events in the first month after percutaneous revascularization. They were randomized in a 1:1 ratio to either switch to clopidogrel, or to continue their prior treatment. At 12 months, the primary endpoint - a composite of death from CV causes, acute MI, cerebrovascular events, or BARC ≥ 2 type bleeding - was registered in 4.6% of patients treated with clopidogrel and 8.4% in the control group. The rate of ischemic events in the two groups was similar and bleeding was less frequent in the de-escalation group (3.0% *vs.* 5.6%)[20].

A recent meta-analysis that included these three trials has shown that unguided de-escalation lowers bleeding without increasing the ischemic events[21].

Further limitations of current evidence on unguided de-escalation arise from the fact that the trials predominantly involved non-complex PCI procedures and were conducted mostly (~86%) on East Asians, which limits the applicability of the evidence from these trials to other ethnic groups due to the unique bleeding and ischemic risk profiles exhibited by East Asians. Finally, it is crucial to acknowledge that this approach does not consider the individual variations in response to clopidogrel. As a result, nearly 30% of treated patients are expected to experience incomplete or no platelet inhibition when de-escalated to clopidogrel.

Recently, the PLINY THE ELDER trial, a randomized, crossover, non-inferiority study that enrolled 50 elderly ACS patients (mean age 79.6 ± 4.0 years) undergoing PCI, evaluated the pharmacodynamic and pharmacokinetic profiles of ticagrelor 60 mg versus 90 mg. The primary endpoint was P2Y12 inhibition, measured by pre-dose P2Y12 reaction units (PRU) using the VerifyNow-P2Y12 assay. Ticagrelor 60 mg was found to be non-inferior to the 90 mg dose in terms of platelet inhibition (PRU 26.4 ± 32.1 *vs.* 30.4 ± 39.0, confidence interval: -16.27 to 8.06; $P = 0.002$ for non-inferiority), suggesting that the lower dose could be a viable option for this population[22].

Guided de-escalation

PFT can identify patients with HPR while on clopidogrel treatment[15,23]. These tests may take place in a laboratory setting or be conducted as near-patient tests. The latter is often preferred as it can be performed at the patient's bedside by non-expert personnel and provide results more quickly (0.5-2 h). Although PFTs have the key advantage of directly assessing platelet reactivity associated with increased event rates, they have several limitations. These include intra- and inter-patient variability and the need to perform them while the patient is on treatment with clopidogrel after reaching the steady-state phase[23].

The use of genetic testing to identify carriers of CYP2C19 LoF alleles may overcome these limitations. As previously mentioned, genetic testing evaluates CYP2C19 polymorphisms, identifying LoF alleles that are linked to intermediate or poor metabolism of clopidogrel. However, genotyping is only one of the factors that influence platelet reactivity in patients who assume clopidogrel[23]. Multiple clinical and demographic factors also contribute to the overall picture[24]. Scores such as the ABCD-GENE score, incorporating genetic data alongside clinical characteristics like weight, age, chronic renal disease, and diabetes mellitus, have the

potential to improve the precision of these tests[25].

There are three major RCTs that tested a PFT-guided de-escalation therapy in ACS patients[26-28].

The ANTARCTIC, a multicenter, randomized controlled superiority study, enrolled 877 elderly patients who underwent coronary stenting for ACS. The patients were randomly assigned in a 1:1 ratio to receive either 5 mg of prasugrel with dose adjustment or drug switching in case of insufficient response, or 5 mg of prasugrel without monitoring[26]. PFT was performed 2 weeks after randomization. Patients were maintained on prasugrel 5 mg if the results of the VerifyNow assay results showed normal platelet reactivity (PRU 85-208). If PFT showed high platelet reactivity, the dosage was escalated to prasugrel 10 mg. If the patient had low platelet reactivity, the dosage was de-escalated to clopidogrel 75 mg. The primary endpoint, a composite of CV death, MI, stroke, ST, urgent revascularization, and bleeding complications BARC 2, 3 or 5, at 12 months occurred in 120 patients in the de-escalation group and 123 patients in the standard group (28% *vs.* 28%). There was no significant difference in terms of the rate of bleeding events[26].

The TROPICAL-ACS is another RCT that evaluated PFT-guided de-escalation therapy. This larger randomized, multicenter trial enrolled 2,610 ACS patients who underwent successful PCI and had an indication for 12 months of DAPT[27]. The study randomly assigned patients (1:1) to either standard DAPT with prasugrel 10 mg or to a PFT-guided de-escalation therapy. The de-escalation group was administered prasugrel for 1 week, followed by 1 week of clopidogrel. Subsequently, the patients underwent PFT to decide whether to maintain therapy with clopidogrel or to switch again to prasugrel, 14 days after the hospital discharge. The de-escalation strategy was found to be non-inferior for the primary composite endpoint of net clinical benefit at 12 months (7% *vs.* 9%), with no differences in the combined risk of CV death, MI, or stroke and no differences in terms of bleeding[27].

The POPular Genetics randomized trial studied a de-escalation strategy based on genetic tests in 2,488 patients with STEMI who underwent coronary stenting. The patients were randomly assigned in a 1:1 ratio to either genotype-guided-descalation, receiving clopidogrel when CYP2C19 LoF alleles were not found, or DAPT with potent $P2Y_{12}$ inhibitors (mainly ticagrelor), within 48 h after PCI, for 12 months[28]. The de-escalation strategy proved to be non-inferior for the primary endpoints of net adverse clinical events at 1 year (with rates of 5.1% in the genotype-guided group and 5.9% in the standard treatment group). PLATO major or minor bleeding at 12 months occurred less often in the genotype-guided group, with no apparent increase in the rate of ischemic events[28].

A recent comprehensive meta-analysis, which included 11 RCTs and 3 observational studies with data for 20,743 patients, improved statistical power for hard ischemic and bleeding outcomes. The analysis showed that guided de-escalation therapy reduced the rate of bleeding by 19% without increasing the incidence of ischemic events[29].

Another network meta-analysis was conducted on 61,898 patients from 15 different RCTs comparing various oral P2Y12 inhibitors recommended for patients with ACS. Trials testing a guided versus a standard approach were also included. This analysis concluded that, compared to clopidogrel, the only strategy that reduced MACE without a significant difference in terms of all bleeding was the guided de-escalation approach[30].

HOW DE-ESCALATION FITS IN THE NOVEL PARADIGM OF DAPT SHORTENING AND $P2Y_{12}$ INHIBITOR MONOTHERAPY?

Several bleeding reduction strategies have demonstrated promising outcomes compared to the standard 12-month DAPT in the context of ACS patients treated with PCI[12,17].

The initial bleeding reduction strategies tested in the setting of ACS undergoing PCI involved shortening DAPT by discontinuing the $P2Y_{12}$ inhibitor 3-6 months after ACS[31-33]. However, due to a numerical increase in MI and ST in the short DAPT followed by aspirin group, this strategy was only recommended for ACS patients at high bleeding risk who cannot undergo standard 12-month DAPT with potent $P2Y_{12}$ inhibitors[31,32,34,35]. Therefore, the focus has shifted to shortening DAPT by interrupting aspirin and maintaining a $P2Y_{12}$ inhibitor[36,37]. In this setting, a strategy of clopidogrel monotherapy for 1-2 months (median of 39 days) after standard DAPT did not succeed in reaching non-inferiority to standard 12 months of DAPT in terms of net clinical benefit with a numerical increase in CV events despite a decrease in bleeding complications[38]. On the other hand, two RCTs showed that a strategy of ticagrelor monotherapy for 1 or 3 months after standard DAPT is safer and equally effective compared to a standard 12-month DAPT with ticagrelor[39,40]. Collectively, although some residual concern exists due to the inclusion of low-ischemic risk and East Asian patients in many of these trials, it seems that a strategy of short DAPT followed by ticagrelor monotherapy may represent a successful strategy in ACS patients, being also possibly advantageous compared with a de-escalation strategy.

However, it is important to note that there is currently no direct comparison of these strategies available. Therefore, it is crucial to recognize both the strengths and limitations of each approach when providing guidance for their use in clinical practice. Notably, shortening or modulating the standard 12-month DAPT with a potent $P2Y_{12}$ inhibitor is expected to decrease bleeding risk, but there is a potential trade-off in efficacy[41]. This concern should be addressed through adequately powered RCTs.

Currently, three recent network meta-analyses have evaluated an indirect comparison among multiple bleeding reduction strategies in ACS patients, and two of them concluded that while a short DAPT strategy is safer in terms of bleeding, a DAPT de-escalation strategy reduces the risk for NACE[42-44]. The one conducted by Laudani *et al.* included twenty-nine studies with a total of 50,602 participants[42]. The study compared short DAPT, characterized by halting the $P2Y_{12}$i or aspirin within 1-6 months, with DAPT de-escalation, which involves switching to clopidogrel or a lower dose of potent $P2Y_{12}$i. The study found that short DAPT strategies and de-escalation strategies did not differ in a significant way in terms of risk of death and death from CV causes. Short DAPT guaranteed a lower risk of major bleeding but increased the rate of NACE. Conversely, de-escalation was associated with a higher risk of major bleeding but reduced the risk of NACE, mainly due to the reduction of MACE, MI, cerebrovascular events, and ST (resulting in a reduction of these events)[42]. The study results indicate that using two antiplatelet drugs throughout the study period, rather than discontinuing one of them, has a synergistic effect. This suggests that a short DAPT strategy may be safer for patients with a high PRECISE-DAPT score or who meet the HBR criteria. Current guidelines recommend a short DAPT strategy as a class IIa recommendation and a de-escalation strategy as a class IIb recommendation when the primary concern is preventing bleeding risk[42]. However, the authors concluded that based on network meta-analyses, a DAPT de-escalation strategy was linked to a similar risk of death and reduced risk of NACE compared to short-term DAPT. Therefore, the class of recommendation should be at least the same[42].

Kuno *et al.* conducted a network meta-analysis that included 32 RCTs with 103,497 ACS patients treated with 12 months of DAPT (clopidogrel, ticagrelor or prasugrel), prolonged DAPT, short DAPT pursued by

either aspirin or $P2Y_{12}$i monotherapy, unguided de-escalation, and guided (PFT or genetic tests) de-escalation[43]. The study found no differences in efficacy between the strategies. However, unguided de-escalation was associated with the lowest risk of MACE and major or minor bleeding. On the other hand, short DAPT followed by $P2Y_{12}$ inhibitor reduced the risk of major bleeding and all-cause death[43].

De Filippo *et al.* conducted a systematic review and network meta-analysis to compare different de-escalation strategies[44]. Six strategies were assessed: ASA and prasugrel for 12 months; ASA and low-dose prasugrel for 12 months; ASA and ticagrelor for 12 months; ASA + P2Y12 inhibitor for 1-3 months, then single antiplatelet therapy with potent P2Y12 inhibitor or DAPT with clopidogrel; ASA and clopidogrel for 12 months; ASA and clopidogrel for 3-6 months. A total of 75,064 patients with ACS from 23 different RCTs were included. The study showed that short DAPT and DAPT with clopidogrel regimens may reduce bleeding events compared with standard DAPT with potent P2Y12 inhibitors. However, any regimen that includes clopidogrel may potentially increase ST risk, while this risk may be mitigated especially during the initial period with potent P2Y12i. In addition, it is important to highlight that some specific de-escalation strategies, such as a dose de-escalation to ticagrelor 60 mg as recently studied in the PLINY THE ELDER trial, were still not present in the current meta-analysis and may merit further evaluation in the future[44]. On top of differences in study design and strategy, small differences in these meta-analyses regarding the study safety endpoint may also be justified by varying definitions of bleeding. Taken together, it can be concluded that a short-term DAPT followed by $P2Y_{12}$ inhibitor monotherapy may represent the bleeding reduction strategy associated with the best performance in ACS. However, it should be noted that these network meta-analyses rely on indirect comparisons, providing hypothesis-generating evidence that, considering their limitations such as wider confidence intervals than direct comparisons and the wide array of potential sources of heterogeneity in the experimental arms, has to be taken with a grain of salt while waiting for confirmation by RCTs. Moreover, the generic definition of "$P2Y_{12}$ inhibitor monotherapy" should be interpreted in light of the profound variability in the pharmacodynamic and clinical response to different $P2Y_{12}$ inhibitors (i.e., clopidogrel versus ticagrelor). Finally, there are practical considerations that should be considered. Although ticagrelor monotherapy may be effective for up to 12 months after ACS, there is uncertainty about the appropriate course of action thereafter. This is because ticagrelor 90 mg bid is not recommended for secondary prevention beyond 12 months after ACS. Likewise, a de-escalation antiplatelet strategy, which involves the adjustment of $P2Y_{12}$ inhibitor intensity by reducing the dose of a potent $P2Y_{12}$ inhibitor, faces the same limitation after 12 months post-ACS. Currently, there is no approved reduced dose of prasugrel or ticagrelor monotherapy for secondary prevention. Additionally, individuals with a history of ACS are likely to undergo subsequent PCI in their lifetime, requiring the use of DAPT with clopidogrel. This is because prasugrel or ticagrelor is not recommended in patients with CCS, except for those at very high ischemic risk[10]. As studies supporting the use of a reduced dose of prasugrel or ticagrelor are lacking, clopidogrel, the currently most commonly prescribed $P2Y_{12}$ inhibitor, is likely to remain a crucial antiplatelet agent in the near future. Administering a drug known to be ineffective in nearly 30% of patients as a single antiplatelet therapy is problematic, particularly in an era where precision medicine is consistently emphasized. Against this backdrop, the application of instruments that allow for a guided choice of antiplatelet therapy may represent a practical and valuable strategy that deserves increasing consideration for ACS patients undergoing PCI.

GAPS IN EVIDENCE AND FUTURE PERSPECTIVES

Over the last two decades, extensive research has focused on modulating antiplatelet therapy, primarily concerning therapy duration. Recently, however, other modulation strategies for effective de-escalation have been explored, such as P2Y12 inhibitor (P2Y12i) switching or dose reduction. Nonetheless, substantial gaps in evidence remain in this area, and multiple randomized trials are expected [Table 2]. While

Table 2. Future randomized controlled trials testing a de-escalation strategy

Study title	NCT number	Estimated enrollment	Primary objective	Target population	Experimental treatment	Control treatment	Primary outcomes	Expected completion year
VERONICA	NCT04654052	634	Optimize platelet inhibition therapy in ACS patients using PFT	ACS patients with VerifyNow PRU ≤ 30 at 30 days after PCI	De-escalation to clopidogrel	Continuation of ticagrelor or prasugrel	Combined net clinical benefit (CV death, nonfatal AMI, nonfatal stroke, bleeding BARC ≥ 2)	2023
TAILOR BLEED	NCT05681702	90	Compare the pharmacodynamic effects of two bleeding reduction strategies in patients undergoing PCI	ACS and CCS patients who have undergone PCI and have been on DAPT	DAPT de-escalation (switching from prasugrel or ticagrelor to clopidogrel while maintaining aspirin)	Potent P2Y12 inhibitor monotherapy (maintaining prasugrel or ticagrelor and dropping aspirin)	Thrombus formation as measured by T-TAS	2024
Dan-DAPT	NCT05262803	2,808	Evaluate a reduced antithrombotic strategy in high bleeding risk patients post-MI	Type 1 MI patients treated with PCI and at high bleeding risk	Shorter, individualized antithrombotic therapy after genetic testing	Standard DAPT	BARC type 2-5 bleeding and NACE	2025
DESC-HBR	NCT05277987	200	Assess the impact of de-escalating P2Y12 inhibitor therapy in high bleeding risk patients post-ACS	High bleeding risk patients treated with PCI due to recent ACS	De-escalation to clopidogrel 75 mg, ticagrelor 60 mg bid, or prasugrel 5 mg	Continuation of full-dose potent P2Y12 inhibitors (Ticagrelor 90 mg bid or prasugrel 10 mg)	Proportion of patients at optimal platelet reactivity (PRU 85-208)	2025
GUARANTEE	NCT05277987	4,009	Evaluate effectiveness and security of CYP2C19 genotype-guided antiplatelet therapy	ACS or CCS patients treated with PCI with DES	Genotype-guided antiplatelet therapy (clopidogrel or ticagrelor)	Standard antiplatelet therapy without genotyping	MACCE	2025
ADEN	NCT05577988	2,468	Compare early de-escalation to low-potency single antiplatelet therapy guided by genetics *vs.* high-potency therapy in high bleeding risk patients	Patients with type 1 MI classified as high bleeding risk	Low-potency single antiplatelet therapy (aspirin or clopidogrel) guided by genetic testing	High-potency single antiplatelet therapy (ticagrelor or prasugrel)	BARC type 2-5	2026

ACS: Acute coronary syndrome; PCI: percutaneous coronary interventions; DAPT: dual antiplatelet therapy; PFT: platelet function tests; CV: cardiovascular; BARC: bleeding academic research consortium; MI: myocardial infarction; ST: stent thrombosis; MACCE: major adverse cardiovascular and cerebrovascular events; PRU: P2Y12 reaction units; T-TAS: total thrombus-formation analysis system.

comparisons between P2Y12i switching, dose reduction, or interruption and standard of care (typically 12 months of dual antiplatelet therapy) have been conducted, there are no randomized studies that directly compare these strategies against each other. Currently, no studies have compared a de-escalation strategy based on switching antiplatelet therapy (e.g., from a potent P2Y12 inhibitor to clopidogrel) or dose reduction (e.g., from a full to a reduced dose of a potent P2Y12 inhibitor) against short-term DAPT followed by single antiplatelet monotherapy. The TAILOR BLEED study aims to compare the pharmacodynamic effects of two bleeding reduction strategies: DAPT de-escalation (changing from prasugrel or ticagrelor to clopidogrel, alongside aspirin) versus potent P2Y12 inhibitor monotherapy (continuing prasugrel or ticagrelor, excluding aspirin in a short-term DAPT approach). Including 90 patients with both CCS and ACS, the primary outcome is thrombus formation, measured by the Total Thrombus-Formation Analysis System (T-TAS).

Future research should also directly compare different de-escalation strategies, including unguided de-escalation, PFT-guided de-escalation, and genetic testing-guided de-escalation. These comparisons could focus on clinical endpoints and the cost-effectiveness of implementing PFT and genetic testing technologies. Additionally, determining the optimal timing for treatment de-escalation is crucial for future studies. Current research often uses an arbitrary one-month post-PCI period for unguided de-escalation. It is unclear whether this timeframe could be adjusted earlier or later. Antiplatelet therapy de-escalation aims to optimize outcomes by reducing bleeding risk while maintaining ischemic protection. However, studies focusing on specific patient subgroups, particularly those at high bleeding risk with a greater baseline risk of hemorrhagic complications, are currently lacking. De-escalation strategies may be particularly beneficial for this subgroup.

The Dan-DAPT clinical trial focuses on optimizing antithrombotic therapy for myocardial infarction patients at high bleeding risk. This phase 4 study, conducted across multiple hospitals in Denmark, uses a randomized, parallel assignment design with single masking. It targets patients treated with PCI and drug-eluting stents, identified as HBR using the PRECISE-DAPT score[45], excluding those with a long-term indication to oral anticoagulants (OAC). A total of 2,808 participants are randomized to either standard dual antiplatelet therapy (DAPT) with prasugrel/ticagrelor and aspirin for 6 months followed by aspirin monotherapy, or an experimental strategy involving genetic testing-guided de-escalation of P2Y12 inhibitors in CYP2C19*2/3 loss-of-function allele carriers and a short-term DAPT for 3 months followed by aspirin monotherapy. The study's primary outcomes are BARC type 2-5 bleedings over a one-year period and a composite of net adverse clinical events (NACE).

The ADEN study will include HBR patients after experiencing ACS. In this multicenter trial, 2,468 HBR patients, as per HBR-ARC criteria, will be randomized 1 to 3 months post-ACS into two arms: a control arm continuing high-potency antiplatelet therapy (ticagrelor or prasugrel) and an intervention arm switching to low-potency antiplatelets (aspirin or clopidogrel) guided by genetic testing. The primary outcome is the rate of BARC 2-5 bleeding at 1 year. Secondary outcomes include major adverse cardiovascular events (MACE).

Finally, the DESC-HBR trial will assess the impact of treatment de-escalation in HBR patients post-ACS. It will randomize 200 HBR patients, identified by PRECISE-DAPT or HBR-ARC criteria, at 1 month post-ACS to four treatment arms: a control group continuing full-dose potent P2Y12 inhibition with ticagrelor or prasugrel, and three experimental arms de-escalated to clopidogrel 75 mg, ticagrelor 60 mg bid, or prasugrel 5 mg. The primary outcome is the proportion of patients in the optimal platelet reactivity (OPR) range, measured by the VerifyNow system. A key secondary outcome is the incidence of major, minor, and nuisance bleeding according to the BARC definition within a 5-month period.

There is also a current gap in long-term data on the effects of treatment de-escalation in larger populations. The VERONICA study will assess a platelet function test (PFT)-guided de-escalation strategy in patients recently experiencing ACS. It will involve 634 patients one month post-ACS, using the VerifyNow system to measure platelet reactivity units (PRU). Patients with PRU ≤ 30 will be randomized 1:1 to either continue with potent $P2Y12_i$ for up to 12 months or switch to clopidogrel. The primary endpoint is the combined net clinical benefit at 12 months, including death from CV causes, nonfatal AMI, nonfatal cerebrovascular events, and bleeding BARC ≥ 2.

The GUARANTEE study aims to determine whether personalized therapy based on CYP2C19 genetic profiling can improve patient outcomes. This trial will include 4,009 patients and use a randomized, open-

label, parallel assignment design. Patients in the genotyping arm will receive antiplatelet therapy (clopidogrel or ticagrelor) based on their CYP2C19 genotype, which will be identified through blood tests within 48 h of randomization. The control group will receive treatment based on clinical and procedural characteristics, without genotyping. The primary outcome measures at the one-year follow-up will include major adverse cardiovascular and cerebrovascular events (MACCE), such as death from all causes, nonfatal stroke, nonfatal MI, and ischemia-driven revascularization.

Finally, standardizing the implementation of treatment de-escalation in routine clinical practice is necessary. Clinical practice guidelines and investigators should focus more on defining patient profiles and standardized treatment strategies based on individual patient risk for both ischemic and bleeding events. Even the so-called "unguided" de-escalation strategy, despite its introduction in the literature and widespread use, is never truly unguided. It is always grounded in clinical judgment and physician discretion. Including a patient in a study of "unguided" de-escalation involves a deliberate decision to select that patient for treatment - a choice that would not be made if the patient were deemed ineligible for the strategy. Many bleeding or ischemic risk scores are currently available to inform decision making for DAPT duration, but aside from the previously mentioned genetic testing or PFT, no risk score or specific decision-making criteria have been proposed to guide other de-escalation strategies. Additionally, no studies have thoroughly evaluated clinical markers that inform the decision-making process for patient selection or the timing of de-escalation. Considering that risk factors for both ischemic and bleeding events often overlap, further evidence is needed to better understand the potential barriers and facilitators for implementing de-escalation in routine clinical practice.

CONCLUSION

In conclusion, DAPT de-escalation strategies represent a promising approach to minimizing the risk of bleeding complications without hampering the ischemic benefits of DAPT, in ACS patients treated with prasugrel or ticagrelor; however, further evidence is needed to compare different types of antiplatelet agent modulation. Furthermore, a standardized approach based on individual patient risk needs to be investigated to implement these strategies in routine clinical practice.

DECLARATIONS

Authors' contributions

Made substantial contributions to conceive the review, draft and critically revise the text: Carciotto G, Galli M, Costa F, Garcia-Ruiz V, Soraci E, Magliarditi A, Liotta P, Teresi L, Franzino M, Zecchino S, Bonfiglio D, Porto I, Vergallo R, Versace AG, Oliva F, Montalto C, Quadri G, Musumeci G, Vizzari G, Capranzano P, Varbella F, Castriota F, Micari A

Availability of data and materials

Not applicable.

Financial support and sponsorship

Costa F, Vizzari G and Quadri G declare institutional support with research funding from the Italian Ministry of Health (RFGR-2021-12374500).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA versus ESC guidelines on dual antiplatelet therapy. *J Am Coll Cardiol* 2018;72:2915-31. DOI PubMed
2. Cao D, Chandiramani R, Chiarito M, Claessen BE, Mehran R. Evolution of antithrombotic therapy in patients undergoing percutaneous coronary intervention: a 40-year journey. *Eur Heart J* 2021;42:339-51. DOI PubMed
3. Costa F, Windecker S, Valgimigli M. Dual antiplatelet therapy duration: reconciling the inconsistencies. *Drugs* 2017;77:1733-54. DOI PubMed
4. Giustino G, Costa F. Characterization of the individual patient risk after percutaneous coronary intervention. *JACC Cardiovasc Interv* 2019;12:831-4. DOI PubMed
5. Patrono C, Morais J, Baigent C, et al. Antiplatelet agents for the treatment and prevention of coronary atherothrombosis. *J Am Coll Cardiol* 2017;70:1760-76. DOI PubMed
6. Cavender MA, Bhatt DL, et al. Consistent reduction in periprocedural myocardial infarction with cangrelor as assessed by multiple definitions: findings from CHAMPION PHOENIX (cangrelor versus standard therapy to achieve optimal management of platelet inhibition). *Circulation* 2016;134:723-33. DOI PubMed PMC
7. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013;368:1303-13. DOI PubMed
8. Angiolillo DA, Galli M, Collet JP, Kastrati A, O'Donoghue MO. Antiplatelet therapy after percutaneous coronary intervention. *EuroIntervention* 2022;17:e1371-96. DOI PubMed PMC
9. Collet JP, Roffi M, Byrne RA, et al. Case-based implementation of the 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease. *Eur Heart J* 2018;39:e1-33. DOI
10. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2024;13:55-161. DOI
11. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the thrombin receptor antagonist for clinical event reduction in acute coronary syndrome (TRACER) randomized trial. *Eur Heart J* 2017;38:804-10. DOI PubMed PMC
12. Capodanno D, Mehran R, Krucoff MW, et al. Defining strategies of modulation of antiplatelet therapy in patients with coronary artery disease: a consensus document from the academic research consortium. *Circulation* 2023;147:1933-44. DOI
13. Galli M, Laborante R, Andreotti F, et al. Bleeding complications in patients undergoing percutaneous coronary intervention. *Rev Cardiovasc Med* 2022;23:286. DOI PubMed PMC
14. Patrono C. Low-dose aspirin for the prevention of atherosclerotic cardiovascular disease. *Eur Heart J* 2024;45:2362-76. DOI PubMed PMC
15. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv* 2019;12:1521-37. DOI PubMed
16. Hwang D, Lim YH, Park KW, et al. Prasugrel dose de-escalation therapy after complex percutaneous coronary intervention in patients with acute coronary syndrome: a post hoc analysis from the HOST-REDUCE-POLYTECH-ACS trial. *JAMA Cardiol* 2022;7:418. DOI PubMed PMC
17. Galli M, Angiolillo DJ. De-escalation of antiplatelet therapy in acute coronary syndromes: why, how and when? *Front Cardiovasc Med* 2022;9:975969. DOI PubMed PMC
18. Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J* 2017;38:3070-8. DOI PubMed
19. Kim HS, Kang J, Hwang D, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *The Lancet* 2020;396:1079-89. DOI
20. Kim CJ, Park MW, Kim MC, et al. Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. *The Lancet* 2021;398:1305-16. DOI
21. Tavenier AH, Mehran R, Chiarito M, et al. Guided and unguided de-escalation from potent P2Y12 inhibitors among patients with acute coronary syndrome: a meta-analysis. *Eur Heart J* 2022;8:492-502. DOI

22. Piccolo R, Simonetti F, Avvedimento M, et al. Ticagrelor 60 versus 90 mg in elderly ACS patients undergoing PCI: a randomized, crossover trial. *Eur Heart J* 2024:pvae054. DOI
23. Galli M, Franchi F, Rollini F, Angiolillo DJ. Role of platelet function and genetic testing in patients undergoing percutaneous coronary intervention. *Trends Cardiovasc Med* 2023;33:133-8. DOI PubMed
24. Gurbel PA, Tantry US, Shuldiner AR, Kereiakes DJ. Genotyping. *J Am Coll Cardiol* 2010;56:112-6. DOI PubMed
25. Capodanno D, Angiolillo DJ, Lennon RJ, et al. ABCD-GENE score and clinical outcomes following percutaneous coronary intervention: insights from the TAILOR-PCI Trial. *J Am Heart Assoc* 2022;11:e024156. DOI PubMed PMC
26. Cayla G, Cuisset T, Silvain J, et al. 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. *The Lancet* 2016;388:2015-22. DOI
27. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *The Lancet* 2017;390:1747-57. DOI PubMed
28. 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;381:1621-31. DOI PubMed
29. Galli M, Benenati S, Capodanno D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *The Lancet* 2021;397:1470-83. DOI
30. Galli M, Benenati S, Franchi F, et al. Comparative effects of guided versus potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. *Eur Heart J* 2022;43:959-67. DOI PubMed PMC
31. De Luca G, Damen SA, Camaro C, et al. Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). *EuroIntervention* 2019;15:e990-8. DOI PubMed
32. Hahn JY, Song YB, Oh JH, et al. 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. *The Lancet* 2018;391:1274-84. DOI PubMed
33. 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:k3793. DOI PubMed PMC
34. Costa F, Montalto C, Branca M, et al. Dual antiplatelet therapy duration after percutaneous coronary intervention in high bleeding risk: a meta-analysis of randomized trials. *Eur Heart J* 2023;44:954-68. DOI
35. Collet JP, 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* 2021;42:1289-367. DOI
36. Capodanno D, Baber U, Bhatt DL, et al. P2Y12 inhibitor monotherapy in patients undergoing percutaneous coronary intervention. *Nat Rev Cardiol* 2022;19:829-44. DOI PubMed
37. Galli M, Capodanno D, Andreotti F, Crea F, Angiolillo DJ. Safety and efficacy of P2Y 12 inhibitor monotherapy in patients undergoing percutaneous coronary interventions. *Expert Opin Drug Saf* 2021;20:9-21. DOI PubMed
38. Watanabe H, Morimoto T, Natsuaki M, et al. Comparison of clopidogrel monotherapy after 1 to 2 months of dual antiplatelet therapy with 12 months of dual antiplatelet therapy in patients with acute coronary syndrome: The STOPDAPT-2 ACS randomized clinical trial. *JAMA Cardiol* 2022;7:407. DOI PubMed PMC
39. Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA* 2020;323:2407. DOI PubMed PMC
40. Hong SJ, Lee SJ, Suh Y, et al. Stopping aspirin within 1 month after stenting for ticagrelor monotherapy in acute coronary syndrome: the T-PASS randomized noninferiority trial. *Circulation* 2024;149:562-73. DOI
41. De Caterina R, Agewall S, Andreotti F, et al. Great debate: triple antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting should be limited to 1 week. *Eur Heart J* 2022;43:3512-27. DOI PubMed
42. Laudani C, Greco A, Occhipinti G, et al. Short duration of DAPT versus de-escalation after percutaneous coronary intervention for acute coronary syndromes. *JACC Cardiovasc Interv* 2022;15:268-77. DOI PubMed
43. Kuno T, Watanabe A, Shoji S, et al. Short-term DAPT and DAPT de-escalation strategies for patients with acute coronary syndromes: a systematic review and network meta-analysis. *Circ Cardiovasc Interv* 2023;16:e013242. DOI PubMed
44. De Filippo O, Piroli F, Bruno F, et al. De-escalation of dual antiplatelet therapy for patients with acute coronary syndrome after percutaneous coronary intervention: a systematic review and network meta-analysis. *BMJ Evid-Based Med* 2024;29:171-86. DOI PubMed
45. Costa F, Van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *The Lancet* 2017;389:1025-34. DOI