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Defining Strategies of Modulation of Antiplatelet Therapy in Patients with Coronary Artery Disease: A Consensus Document from the Academic Research Consortium

Davide Capodanno[1], Roxana Mehran[2], Mitchell W. Krucoff[3], Usman Baber[4], Deepak L. Bhatt[5], Piera Capranzano[1], Jean-Philippe Collet[6], Thomas Cuisset[7], Giuseppe De Luca[8], Leonardo De Luca[9], Andrew Farb[10], Francesco Franchi[11], C. Michael Gibson[12], Joo-Yong Hahn[13], Myeong-Ki Hong[14], Stefan James[15], Adnan Kastrati[16], Takeshi Kimura[17], Pedro A. Lemos[18], Renato D. Lopes[3], Adrian Magee[10], Ryosuke Matsumura[19], Shuichi Mochizuki[19], Michelle L. O'Donoghue[20], Naveen L. Pereira[21], Sunil V. Rao[22], Fabiana Rollini[11], Yuko Shirai[19], Dirk Sibbing[23], Peter C Smits[24], Gabriel Steg[25], Robert Storey[26], Jurien ten Berg[27], Marco Valgimigli[28], Pascal Vranckx[29], Hirotoshi Watanabe[30], Stephan Windecker[31], Patrick W. Serruys[32], Robert W. Yeh[33], Marie-Claude Morice[34], Dominick J. Angiolillo[11]

Affiliations

[1] Azienda Ospedaliero-Universitaria Policlinico "G. Rodolico-San Marco", University of Catania, Italy.
[2] Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, United States.
[3] Duke University Medical Center, Durham, North Carolina, United States.
[4] University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States.
[5] Mount Sinai Heart, Icahn School of Medicine at Mount Sinai Health System, New York, NY, United States.
[6] Sorbonne Université, ACTION Study Group, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, Paris, France.
[7] Department of Cardiology, Marseille, France.
[8] Azienda Ospedaliero-Universitaria Policlinico "G Martino", University of Messina, Messina, Italy.
[9] Department of Cardio-Thoracic and Vascular Medicine and Surgery, Division of Cardiology, Azienda Ospedaliera San Camillo-Forlanini, Rome, and UniCamillus-Saint Camillus International University of Health Sciences, Roma, Italy.
[10] US Food and Drug Administration, Silver Spring, Maryland, United States.
[11] Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida, United States.
[12] Baim Institute for Clinical Research, Boston, Massachusetts, United States.
[13] Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.
[14] Division of Cardiology, Severance Hospital, Yonsei University College of Medicine.
[15] Department of Medical Sciences and Uppsala Clinical research center, Uppsala University, Uppsala, Sweden.
[16] Deutsches Herzzentrum München, Technische Universität München, Munich, and DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany.
[17] Department of Cardiology, Hirakata Kohsai Hospital, Osaka, Japan.
[18] Hospital Israelita Albert Einstein, São Paulo-SP, Brazil.
[19] Pharmaceuticals and Medical Devices Agency, Tokyo, Japan
[20] TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts, United States.
[21] Department of Cardiovascular Medicine, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, Minnesota, United States.
[22] NYU Langone Health System, New York, United States.
[23] Ludwig-Maximilians University München, Munich, Germany, Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), partner site Munich Heart Alliance, München, Germany and Privatklinik Lauterbacher Mühle am Ostsee, Seeshaupt, Germany.
[24] Department of Cardiology, Maasstad Hospital, Rotterdam, The Netherlands.
[25] Université Paris-Cité, AP-HP and INSERM U-1148/LVTS Paris, France. Institut Universitaire de France, Paris, France.
[26] Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, United Kingdom.
[27] Cardiovascular Research Institute Maastricht (CARIM), School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, The Netherlands; and Department of Cardiology, St. Antonius Hospital, Nieuwegein, The Netherlands; Department of Cardiology, University Medical Center Maastricht, Maastricht, The Netherlands.
[28] Cardiocentro Institute, Ente Ospedaliero Cantonale, Università della Svizzera Italiana (USI), Lugano, Switzerland and University of Bern, Bern Switzerland.
[29] Department of cardiology and critical care medicine, Jessa Ziekenhuis, Hasselt, & Faculty of Medicine and Life Sciences, University of Hasselt, Hasselt, Belgium.
[30] Department of Cardiology, Hirakata Kohsai Hospital, Osaka, Japan.
[31] Department of Cardiology, Bern University Hospital, Inselspital, University of Bern, Switzerland

[32] Department of Cardiology, University of Galway, Galway, Ireland.
[33] Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[34] ICPS and CERC, Massy, Paris, France.

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ABSTRACT

Antiplatelet therapy is the mainstay of pharmacological treatment to prevent thrombotic or ischemic events in patients with coronary artery disease treated with percutaneous coronary intervention and those treated medically for an acute coronary syndrome. However, the use of antiplatelet therapy comes at the expense of an increased risk of bleeding complications. Defining the optimal intensity of platelet inhibition according to the clinical presentation of atherosclerotic cardiovascular disease and individual patient factors is a clinical challenge. Modulation of antiplatelet therapy is a medical action that is frequently performed to balance the risk of thrombotic or ischemic events and the risk of bleeding. This aim may be achieved by reducing (i.e., de-escalation) or increasing (i.e., escalation) the intensity of platelet inhibition by changing the type, dose or number of antiplatelet drugs. Because de-escalation or escalation can be achieved in different ways, with a number of emerging approaches, confusion arises with terminologies that are often used interchangeably. To address this issue, this Academic Research Consortium (ARC) collaboration provides an overview and definitions of different strategies of antiplatelet therapy modulation for patients with coronary artery disease, including but not limited to those undergoing percutaneous coronary intervention, and a consensus statement on standardized definitions.

INTRODUCTION

An initial treatment with dual antiplatelet therapy (DAPT) including aspirin and a platelet receptor $P2Y_{12}$ inhibitor is the current standard of care for the prevention of atherothrombotic events in all patients undergoing percutaneous coronary intervention (PCI) as well as those treated medically for an acute coronary syndrome (ACS)[1,2]. In ACS patients undergoing PCI, current guidelines from Europe and the United States recommend that, in the absence of contraindications, the more potent prasugrel or ticagrelor be the $P2Y_{12}$ inhibitors of choice for DAPT combinations, in preference to clopidogrel[3–5]. Conversely, it is recommended that PCI patients with a chronic coronary syndrome (CCS) receive aspirin in combination with clopidogrel[5,6]. DAPT is known to reduce the incidence of atherothrombotic events at the expense of increased bleeding, and therefore its duration must be carefully determined. The traditional approach recommended by current guidelines for PCI is that DAPT be maintained for at least 12 months after an ACS, and 6 months for CCS, unless concerns over bleeding prevail[3–6]. At the end of the minimum required DAPT period, all PCI patients may be transitioned to a chronic regimen of single antiplatelet therapy (SAPT), usually aspirin[3–6]. Aspirin is the perceived standard of care for thrombotic prevention in patients with coronary artery disease in general, regardless of whether revascularization is performed[7]. Current recommendations for DAPT or SAPT after PCI are well-defined and represent an effective treatment strategy for most patients. Nevertheless, there are clinical circumstances in which physicians are particularly concerned about the risk of thrombotic events, the risk of bleeding events, or both. Bleeding and/or high thrombotic risk characteristics may lead a physician to prefer one among several potential types and durations of DAPT and SAPT for an individual patient.

When antiplatelet therapy after PCI is modified, the timing and antiplatelet strategy selected will reflect physician concern with relative bleeding versus thrombotic risk[8]. This practice has led to proliferation of terms (e.g., “short DAPT”, “de-escalation”, “escalation”, and “switch” among others) that lack standardization and are sometimes used interchangeably. Lack of precision in terminology has resulted in confusion and misunderstanding on the use of antiplatelet medications post PCI[9]. Current guidelines have not clarified the terminology that should be used when changing post-PCI antiplatelet therapy, leaving physicians without a common understanding of which terms should be used to describe antiplatelet changes and clouding our communication around clinical practice decisions and the corresponding evidence used to guide them.

The Academic Research Consortium (ARC) is an academic partnership created to help create consensus definitions and endpoints to help standardize the language around clinical care and evidence generation. In response to these antiplatelet use guidance gap, the ARC came together to develop a consensus initiative to homogenize the language for antiplatelet therapy definitions. This initiative was undertaken by key leaders from North America, South America, Europe and Asia with recognized expertise in the field of antiplatelet therapy. These experts, identified by the document chairs (D.C. and D.J.A.), reviewed the scientific literature on antiplatelet therapy modulation with input from representatives from the US Food and Drug Administration (FDA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). All participants agreed to participate in the development of this document, and approve its contents.

With regard to methodology, a blinded survey consisting of 14 statements grouped into four categories was first sent to the invited experts, who were asked whether they agreed or disagreed with each statement and provided comments or advice. A virtual consensus meeting, coordinated by the Cardiovascular European Research Center (Massy, France), was held on November 21, 2022, to discuss the results of the survey, reach consensus on disagreements, and define the scope of the present document. The document is free from any type of industry support and represents the output of an academic collaboration between the identified experts who provided an overview and critique of different strategies of post-PCI antiplatelet therapy modulation resulting in consensus statements on standardized definitions for each potential antiplatelet strategy. Patients with a baseline indication to oral anticoagulation are not addressed in this document. Moreover, the document does not refer to those situations where modulation of antithrombotic therapy is achieved by addition of an approved (e.g., rivaroxaban 2.5 mg) or investigational (e.g., activated factor XI inhibitors asundexian, milvexian) anticoagulant in the absence of a pre-existing reason for oral anticoagulation (e.g., for venous thromboembolism, mechanical valve prosthesis, atrial fibrillation). This consensus document is not intended to provide treatment recommendations for clinical practice. The consensus definitions in this document are intended to create a commonly understood lexicon to help the clinical and research communities to more precisely describe antiplatelet strategies.

DEFINITIONS, GUIDELINES AND SUPPORTING EVIDENCE

Antiplatelet therapy can be modulated in two ways: by reducing (i.e., *de-escalation*) or increasing (i.e., *escalation*) the intensity of platelet inhibition. These terms refer to the actions of reducing or

increasing the antiplatelet effect by means of changes in the type, dose or number of drugs used to inhibit platelets. For those treated with PCI or admitted with ACS, these actions may occur acutely (i.e., within 24 hours), early (i.e., within 30 days), late (i.e., between 30 days and 1 year) and/or very late (i.e., after 1 year). In the following paragraphs, de-escalation and escalation are discussed and further categorized (**Figure 1**). For each strategy, we briefly summarize the available guidelines and supporting evidence, and we provide the ARC consensus statements.

Consensus statements

- **Modulation of antiplatelet therapy** consists of changes in the antiplatelet effect by modification of the type, dose or number of drugs aimed at decreasing or increasing the intensity of platelet inhibition.
- Strategies of modulation of antiplatelet therapy include **de-escalation** or **escalation**.

[L2] De-escalation

De-escalation is intended to decrease bleeding complications of antiplatelet therapy at a time when their risk is perceived to be greater than the risk of thrombotic complications. Reduced bleeding risk may be achieved by a) switching to a drug with less anticipated antiplatelet effect (*de-escalation by switching*), b) reducing the dose (*de-escalation by dose reduction*), or c) removing an antiplatelet agent (*de-escalation by discontinuation*) (**Figure 2**). For DAPT, switching and dose reduction are usually confined to the $P2Y_{12}$ inhibitor, although they are theoretically possible with aspirin (e.g., switch to a better tolerated aspirin formulation, or dose decrease from 325 mg to 81 mg). Switch and dose reduction are also possible for $P2Y_{12}$ inhibitor monotherapy. By discontinuation, which is also typically performed in the context of DAPT, we will refer to the cessation by physician indication. Interruption due to surgery or disruption due to bleeding or non-adherence are other forms of treatment cessation that go beyond the scope of this document.

De-escalation by switching

De-escalation by switching typically refers to changing from a $P2Y_{12}$ antagonist with more potent platelet inhibition (i.e., prasugrel or ticagrelor) to z $P2Y_{12}$ antagonist with less expected potent effects (i.e., clopidogrel). This is most likely to occur in ACS patients treated initially with a

guideline-recommended DAPT regimen with prasugrel or ticagrelor. Because prasugrel and ticagrelor are known to increase the risk of major spontaneous bleeding compared with clopidogrel[10,11], the objective of switching is to improve safety (i.e., less bleeding) at a time when there is perceived minimal trade-off in efficacy (i.e., antithrombotic effects). De-escalation by switching may occur with (i.e., guided) or without (i.e., clinical judgement) using tests to evaluate or predict responses to clopidogrel. Clopidogrel response is subject to broad interindividual response variability. The ~30% of subjects with impaired clopidogrel-induced platelet inhibition and persistent high platelet reactivity are at an increased the risk of major adverse cardiac events (MACE) and stent thrombosis[12]. Tests to guide de-escalation by switching include platelet function testing (to identify patients with high residual platelet reactivity) and genotyping (to identify patients with *CYP2C19* loss-of-function alleles that predispose to high residual platelet reactivity). DAPT switching studies in ACS patients include switching guided by clinical judgement alone (known as "unguided" switching), switching guided by platelet function testing and switching guided by genotyping. The optimal time for switching is not standardized. However, in unguided (i.e., clinical judgement) switching studies, the change of $P2Y_{12}$ inhibitor mostly occurred at 1 month (i.e., when the bleeding risk was believed to surpass the thrombotic complication risk). In contrast, the change typically occurred at earlier time points, including immediately after PCI, in switching studies guided by platelet function and genetic testing. Of note, de-escalation by switching in the immediate peri-PCI period has been associated with an increase in thrombotic complications[13–15].

The strategy of DAPT de-escalation was first introduced in the 2018 ESC/EACTS guidelines on myocardial revascularization (guided de-escalation, class IIb)[16]. The 2020 European Society of Cardiology (ESC) guidelines for ACS refined and expanded the recommendation by stating that de-escalation by switching is considered for an individual patient, especially for ACS patients deemed unsuitable for potent platelet inhibition, based on clinical judgment or guided by platelet function testing or *CYP2C19* genotyping depending on patient's risk profile and availability of respective assays (class IIb)[3]. Conversely, the 2021 joint guidelines from the American College of Cardiology (ACC), American Heart Association (AHA) and Society for Cardiovascular Angiography and Interventions (SCAI) do not mention de-escalation by switching among the options to reduce bleeding after PCI[5].

Two trials investigated strategies of unguided switching in ACS: i) in TOPIC (n=646), switching from prasugrel or ticagrelor to clopidogrel at 1 month was superior to standard DAPT with

prasugrel or ticagrelor for the 1-year composite of cardiovascular events or major bleeding (i.e., net adverse cardiac events [NACE])[17]; ii) in TALOS-AMI (n=2,697), switching at 1 month from ticagrelor to clopidogrel was superior to standard DAPT for NACE between 1 and 12 months[18]. In both trials, the findings were driven by reduction in bleeding with switching. Two other trials investigated strategies of switching guided by platelet function testing: i) in ANTARCTIC (n=877), switching was the most common strategy prompted by platelet function testing; treatment adjustment at 2 weeks and 1 month did not reduce 1-year NACE[19]; ii) in TROPICAL-ACS (n=2,610), switching at 1 week was noninferior but not superior to standard DAPT for 1-year NACE[20]. Finally, two trials investigated strategies including switching guided by genotyping at the time of the ACS diagnosis or PCI procedure: i) in PHARMCLO (n=888, prematurely stopped), switching was one of the potential adjustment strategies, and treatment adjustment reduced 1-year NACE[21]; ii) in POPULAR-GENETICS (n=2,488), switch was noninferior to standard DAPT for 1-year NACE and superior for bleeding[22].

Consensus statements

- De-escalation by switching consists of changing an antiplatelet drug with another one with the intention to decrease the intensity of platelet inhibitory effect.
- $P2Y_{12}$-specific de-escalation of DAPT by switching, generally in patients who experienced an ACS, consists of switching the $P2Y_{12}$ inhibitors prasugrel or ticagrelor to the $P2Y_{12}$ inhibitor clopidogrel.
- De-escalation by switching may be guided by clinical judgment or by the results of platelet function testing or genotyping.
- More data are needed on i) the comparative effectiveness and safety of guided versus unguided $P2Y_{12}$-specific de-escalation by switching; ii) the specific subgroups that may or may not derive a clinical benefit from a $P2Y_{12}$-specific de-escalation strategy by switching; and iii) the optimal timing of $P2Y_{12}$-specific de-escalation by switching.

[L3] ***De-escalation by dose reduction***

Pharmacokinetic data support the concept that reducing the dose of prasugrel or ticagrelor is associated with less systemic exposure of a drug, leading to reduced platelet inhibitory effects and thus reduced bleeding[23,24]. Reducing the dose of prasugrel or ticagrelor in DAPT combinations (e.g.,

by using prasugrel doses of 3.75 or 5 mg once daily, or ticagrelor 60 mg twice daily) is a $P2Y_{12}$-specific de-escalation strategy that may be desired when concerns exist regarding high exposure to the active metabolite of more potent $P2Y_{12}$ inhibitors (e.g., in ethnicities such as East Asian patients). However, there are only limited effectiveness and safety data on these de-escalation strategies during the first year after ACS. In the HOST-REDUCE-POLYTECH-ACS trial (n=2,338), use of a halved dose of prasugrel (i.e., 5 mg once daily) at 1 month reduced 1-year NACE[25]. While during the first year after an ACS event, the recommended maintenance dose of ticagrelor is 90 mg twice daily, after 1-year a dosing regimen of 60 mg twice daily can be used based on the PEGASUS-TIMI 54 trial[47]. In PEGASUS-TIMI 54, the 60 mg dosing regimen showed similar efficacy to the 90 mg but had an overall more favorable safety (bleeding and non-bleeding side effects).

Consensus statements

- De-escalation by dose reduction consists of diminishing the dose of an antiplatelet drug with the intention to decrease the intensity of platelet inhibitory effects.
- $P2Y_{12}$-specific de-escalation of DAPT by dose reduction consists of reducing the dose of the $P2Y_{12}$ inhibitor compared with the standard dose.
- More data are needed on the comparative effectiveness and safety of $P2Y_{12}$-specific de-escalation by switching versus de-escalation by dose reduction.

[L3] ***De-escalation by discontinuation***

Discontinuation refers to the practice of stopping one of the two DAPT antiplatelet agents and transitioning to SAPT (aspirin or a $P2Y_{12}$ inhibitor). This practice is typically physician-recommended and consistent with practice guidelines, and therefore is distinguished from other types of DAPT cessations. For example, discontinuation planned at the time of surgery, or due to non-adherence[26] or because of bleeding carry different prognostic consequences and are more properly termed interruption or disruption, respectively[27]. With current generation coronary stents, the time for discontinuation has been moved earlier after PCI than in the past. In the following paragraphs, we refer to discontinuation of $P2Y_{12}$ inhibitors or aspirin that occurs before the period initially planned (i.e., 6 months in CCS and 12 months in ACS). Current investigations of DAPT discontinuation in CCS include studies where the $P2Y_{12}$ inhibitor was stopped at 1 month or aspirin was stopped at 1 months or at the time of PCI. Investigations of DAPT discontinuation in

ACS currently include studies where the $P2Y_{12}$ inhibitor was stopped at 3-6 months or aspirin was stopped at 1-3 months. It is of note that all these studies generally had a follow up of 1 to 2 years, and therefore the best SAPT strategy for chronic therapy after this timeframe remains undefined.

[L4] $P2Y_{12}$ inhibitor discontinuation – The 2019 guidelines from the ESC for patients with CCS and sinus rhythm undergoing PCI recommend the $P2Y_{12}$ inhibitor (usually clopidogrel) discontinuation at 3 months (class IIa) or 1 month (class IIb) in patients at high bleeding risk (HBR)[6]. The definition of HBR has been standardized as part of a dedicated ARC initiative[28]. In patients at HBR, the 2020 ESC guidelines for patients with an ACS without ST-segment elevation recommend the $P2Y_{12}$ inhibitor (usually prasugrel or ticagrelor) discontinuation at 3 months (class IIa)[3]. Conversely, the 2021 ACC/AHA/SCAI guidelines recommend the $P2Y_{12}$ inhibitor discontinuation at 3 months (class 2b) in HBR patients with CCS, and at 6 months in HBR patients with ACS (class 2b)[5].

There is a paucity of randomized controlled trials that compared early $P2Y_{12}$ inhibitor discontinuation versus discontinuation at the later times post-PCI set by current European and United States guidelines. In the ONE-MONTH DAPT trial (n=3,020), DAPT discontinuation at 1 month was noninferior to discontinuation at 6 to 12 months for 1-year NACE in patients with CCS or ACS (HBR and non-HBR) who underwent PCI for noncomplex lesions[29]. Three trials were conducted in ACS patients (HBR and non-HBR): i) in SMART-DATE (n=2,712), discontinuation at 6 months was noninferior to discontinuation at 12 months for 1-year MACE but there was an increase in myocardial infarction[30]; ii) in REDUCE-ACS (n=1,496), discontinuation at 3 months was noninferior to discontinuation at 12 months for 1-year NACE[31]; iii) in DAPT-STEMI (n=870), discontinuation at 6 months was noninferior to discontinuation at 12 months for 2-year NACE in patients with STEMI[32]. The results of these trials, which used wide noninferiority margins, did not lead to a change in current ACS guidelines.

[L4] Aspirin discontinuation – The 2019 ESC guidelines for CCS do not include recommendation for aspirin discontinuation in HBR patients[6]. The 2020 ESC guidelines for ACS recommend that aspirin be discontinued at 3-6 months, and the $P2Y_{12}$ inhibitor continued, depending on ischemic versus bleeding risks (class IIa)[3]. The 2021 ACC/AHA/SCAI guidelines for coronary revascularization recommend that aspirin be discontinued at 1-3 months (class 2a), and the $P2Y_{12}$ inhibitor continued, regardless of bleeding risk and clinical presentation with ACS or CCS[5].

There are no randomized controlled trials that compared early aspirin discontinuation versus the 6-month standard DAPT regimen recommended by current guidelines for CCS. ASET was a

single-arm trial with a stopping rule based on the occurrence of definite stent thrombosis, where aspirin discontinuation at the time of PCI with transition to prasugrel monotherapy was feasible and safe without stent thrombosis at 3 months[33]. Two trials compared early aspirin discontinuation versus the 12 months of DAPT recommended by current guidelines for ACS: i) in TICO (n=3,056), discontinuation at 3 months with transition to ticagrelor monotherapy was superior for 1-year NACE[34]; ii) in STOPDAPT-2 ACS, (n=4,169), discontinuation at 1-2 months with transition to clopidogrel monotherapy was not noninferior for 1-year NACE[35].

[L4] $P2Y_{12}$ inhibitor or aspirin discontinuation – In recent trials, the decision to discontinue the $P2Y_{12}$ inhibitor or aspirin has been left at the discretion of the treating physician. DAPT discontinuation with transition to SAPT is now receiving greater attention than more precise characterization of $P2Y_{12}$ inhibitor or aspirin discontinuation with transition to $P2Y_{12}$ inhibitor or aspirin monotherapy. In the MASTER DAPT trial (n=4,573), among patients at HBR, discontinuation of the $P2Y_{12}$ inhibitor or aspirin (at the physician's discretion) at 1 month was noninferior to their continuation for at least two additional months with respect to 1-year NACE or MACE, and it was associated with reduced bleeding[36].

Consensus statements

- Discontinuation of DAPT consists of stopping the $P2Y_{12}$ inhibitor or aspirin based on physician's recommendation.
- More data are needed on i) the impact and timing of $P2Y_{12}$ inhibitor or aspirin discontinuation in CCS and ACS; ii) the comparative effectiveness and safety of $P2Y_{12}$ inhibitor or aspirin discontinuation leading to SAPT; iii) the best SAPT strategy for chronic management beyond the 1- to 2- year period investigated in trials of aspirin or $P2Y_{12}$ inhibitor monotherapy.

[L2] Escalation

Antiplatelet therapy escalation is meant to decrease thrombotic or ischemic complications by increasing the intensity of platelet inhibition at a time when this risk considered greater than the risk of bleeding complications. Escalation may be achieved by a) switching to a drug with higher anticipated platelet inhibitory effects (*escalation by switching*), b) increasing the dose (*escalation by dose increase*), or c) adding an antiplatelet drug (*add-on escalation*) (**Figure 3**). In DAPT, switching and dose increase are usually confined to the $P2Y_{12}$ inhibitor but can be applied aspirin

as well (e.g., dose increase from 81 mg to 325 mg). Switching and dose increase are also theoretically possible in the context of $P2Y_{12}$ inhibitor monotherapy (e.g., clopidogrel dose increase from 75 mg to 150 mg). By add-on escalation, we refer to escalation over the strategy initially planned by the physician.

[L3] ***Escalation by switching***

Escalation by switching typically refers to the practice of changing from a platelet $P2Y_{12}$ receptor inhibitor with modest platelet inhibitory effects (i.e., clopidogrel) to one with more potent platelet inhibitory effects (i.e., prasugrel or ticagrelor). This is most likely to occur in CCS patients undergoing elective PCI and treated with a guideline-recommended clopidogrel-based DAPT regimen. Prasugrel and ticagrelor were not shown to be more effective than clopidogrel among patients undergoing elective PCI in two trials that were not specific to de-escalation: SASSICAIA, which was prematurely terminated, and ALPHEUS, which was powered for periprocedural myocardial injury[37,38]. Therefore, the rationale for routine $P2Y_{12}$ inhibitor-specific escalation is currently unproven. However, switching from clopidogrel to prasugrel or ticagrelor may be desired in selected CCS patients due to several circumstances, including but not restricted to concern of low antithrombotic protection following complex PCI, evidence of on-clopidogrel high platelet reactivity, or known *CYP2C19* loss-of-function genotype. Investigations of DAPT escalation by switching in CCS are mostly confined to this last category, and therefore include switching studies guided by platelet function and genetic testing. The optimal time for switching is not standardized, although in most of the available studies switching guided by platelet function testing and *CYP2C19* loss-of-function genotype have changed the $P2Y_{12}$ inhibitor as soon as the results of the test was available (typically close to the PCI procedure), because the risk of thrombotic or ischemic complications is believed to surpass the bleeding risk. Switching may also be considered a modification of the default strategy underscoring clopidogrel as a standard component of DAPT for CCS, rather than a true switching from clopidogrel to prasugrel or ticagrelor.

The 2019 ESC guidelines for CCS recommend switching to prasugrel or ticagrelor to be selectively considered as an alternative DAPT strategy, at least as initial therapy, in specific high-risk situations of elective stenting (e.g., suboptimal stent deployment or other procedural characteristics associated with a high risk of stent thrombosis, complex left main stem PCI, or multivessel stenting), with no comment on whether this practice should be based on clinical

judgment or guided by platelet function testing or *CYP2C19* genotyping (class IIb). Conversely, the 2021 ACC/AHA/SCAI guidelines do not mention escalation by switching among the options to reduce thrombotic or ischemic events after elective PCI[5].

One trial (PATH-PCI) investigated a strategy of switching from clopidogrel to ticagrelor, guided by platelet function testing in 2,337 participants undergoing elective PCI for CCS. The study showed superiority for 6-month MACE associated with platelet function adjustment compared to standard treatment[39]. Another trial (TAILOR-PCI) investigated a strategy of ticagrelor versus clopidogrel in 1,849 patients undergoing PCI for ACS or stable CAD with *CYP2C19* loss-of-function variants based on point-of-care genotyping; the study showed a non-statistically significant numerical reduction in 1-year MACE[40].

Consensus statements

- Escalation by switching consists of changing an antiplatelet drug to another drug with the intention of increasing the intensity of platelet inhibitory effect compared with the initially planned treatment strategy.
- $P2Y_{12}$-specific DAPT escalation by switching consists of switching the $P2Y_{12}$ inhibitor clopidogrel to the $P2Y_{12}$ inhibitor prasugrel or ticagrelor.
- $P2Y_{12}$-specific DAPT escalation by switching may be guided by clinical judgment or by the results of platelet function testing or genotyping.
- More data are needed on i) the comparative effectiveness and safety of guided versus unguided $P2Y_{12}$-specific escalation by switching; ii) the optimal timing of $P2Y_{12}$-specific escalation by switching.

[L3] ***Escalation by dose increase***

Increasing the clopidogrel or aspirin dose in DAPT combinations is a strategy that is not currently supported by clinical guidelines for CCS. Doubling the maintenance dose of aspirin did not prove to be effective in the CURRENT-OASIS 7 trial[41,42]. In the ARCTIC trial (n=2,440), including patients with ACS or CCS, platelet function testing used to guide the doubling of clopidogrel dose or the switch to prasugrel did not significantly reduce 1-year MACE[43]. In the GRAVITAS trial (n=2,214), among patients with high on-treatment platelet reactivity after PCI, the use of a doubled clopidogrel dose compared with standard-dose clopidogrel also did not reduce the incidence of MACE[44]. In the

ADAPTABLE trial (n=15,076), there were no significant differences in cardiovascular events or major bleeding between patients assigned to 81 mg and those assigned to 325 mg of aspirin daily[45].

Consensus statements

- Escalation by dose increase consists of increasing the dose of an antiplatelet drug with the intention to increase the intensity of platelet inhibitory effect.
- More data are needed on the comparative effectiveness and safety of $P2Y_{12}$-specific escalation by switching versus dose increase.

[L3] ***Escalation by add-on***

Add-on escalation refers to the practice of adding a second antiplatelet agent to patients treated with SAPT. This strategy leads to DAPT when a second antiplatelet agent is added. DAPT was superior to SAPT with aspirin in reducing ischemic events in randomized trials including patients with prior PCI (in both ACS and CCS patients after an event-free period of DAPT)[46], prior myocardial infarction[47] and diabetes[48].

In 2019, the ESC guidelines for CCS introduced a recommendation for the addition of clopidogrel, ticagrelor or prasugrel to aspirin in patients with CCS at high (class IIa) or moderate (IIb) risk of thrombotic or ischemic events and without HBR[6]. The 2020 ESC guidelines for ACS without ST-segment elevation included these recommendations as DAPT extension after the first year following the ACS and provided criteria for identifying optimal candidates[3]. The 2021 ACC/AHA/SCAI guidelines do not have add-on specific recommendations but recommend that DAPT be continued beyond 6 months in CCS and 12 months in ACS in selected patients who are not at HBR (class 2b)[5].

Add-on of an antiplatelet agent to aspirin has been investigated in two trials: i) in PEGASUS-TIMI 54 (n=21,162), in patients with prior myocardial infarction, DAPT with aspirin and ticagrelor (60 mg or 90 mg twice daily) was superior for MACE[47] at 3 years; iii) in THEMIS (n=19,220), in patients with type 2 diabetes without a prior acute cardiovascular event (prior myocardial infarction or cerebrovascular event), DAPT with aspirin and ticagrelor was superior for MACE at a median of 39.9 months[48].

Consensus statements

- Add-on escalation consists of adding a $P2Y_{12}$ inhibitor to aspirin (resulting in transitioning from SAPT to DAPT).
- More data are needed on the effectiveness and safety of aspirin add-on in patients on chronic $P2Y_{12}$ inhibitor monotherapy.

[L1] CONCLUSIONS

In patients with coronary artery disease without baseline indication for oral anticoagulation, particularly those undergoing PCI, modulation of antiplatelet therapy is a medical action that is frequently performed considering the risk of thrombotic or ischemic events and the risk of bleeding, with the optimal intensity of platelet inhibition varying according to the the stage and presentation of coronary artery disease and individual patient factors. This aim may be achieved by reducing (i.e., de-escalation) or increasing (i.e., escalation) the intensity of platelet inhibition in a number of different ways, including by changing the type, dose or number of antiplatelet drugs.

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FIGURES

Figure 1 – Strategies of modulation of dual antiplatelet therapy. Modulation of dual antiplatelet therapy (DAPT) consists of changes in the type, dose or number antiplatelet agents aimed at decreasing or increasing the intensity of platelet inhibition.

Figure 2 – Strategies of de-escalation of antiplatelet therapy. There are three strategies of de-escalation of antiplatelet therapy. A) De-escalation of DAPT by switch consists of switching type of drug, e.g., the $P2Y_{12}$ inhibitors prasugrel or ticagrelor with the $P2Y_{12}$ inhibitor clopidogrel. B) De-escalation of DAPT by dose reduction consists of reducing, e.g., the dose of the $P2Y_{12}$ inhibitors prasugrel or ticagrelor as an alternative to the dose regimen initially planned. C) Discontinuation of DAPT, based on physician's recommendation, consists of stopping a drug, e.g., the $P2Y_{12}$ inhibitor or aspirin with transition to SAPT with aspirin or a $P2Y_{12}$ inhibitor at a time that precedes the duration of DAPT initially planned. ACS, acute coronary syndromes; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.

Figure 3 – Strategies of escalation of antiplatelet therapy. There are three strategies of de-escalation of antiplatelet therapy. A) Escalation of DAPT by switch consists of switching type of drug, e.g., the $P2Y_{12}$ inhibitor clopidogrel with the $P2Y_{12}$ inhibitors prasugrel or ticagrelor. B) Escalation of DAPT by dose increase conceptually consists of increasing, e.g., the dose of the $P2Y_{12}$ inhibitor or aspirin, but such action has no currently approved recommendations. C) Add-on escalation consists of adding a drug, e.g., the $P2Y_{12}$ inhibitor or aspirin with transition to DAPT at a time when the patients is on SAPT. DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.

Figure 1

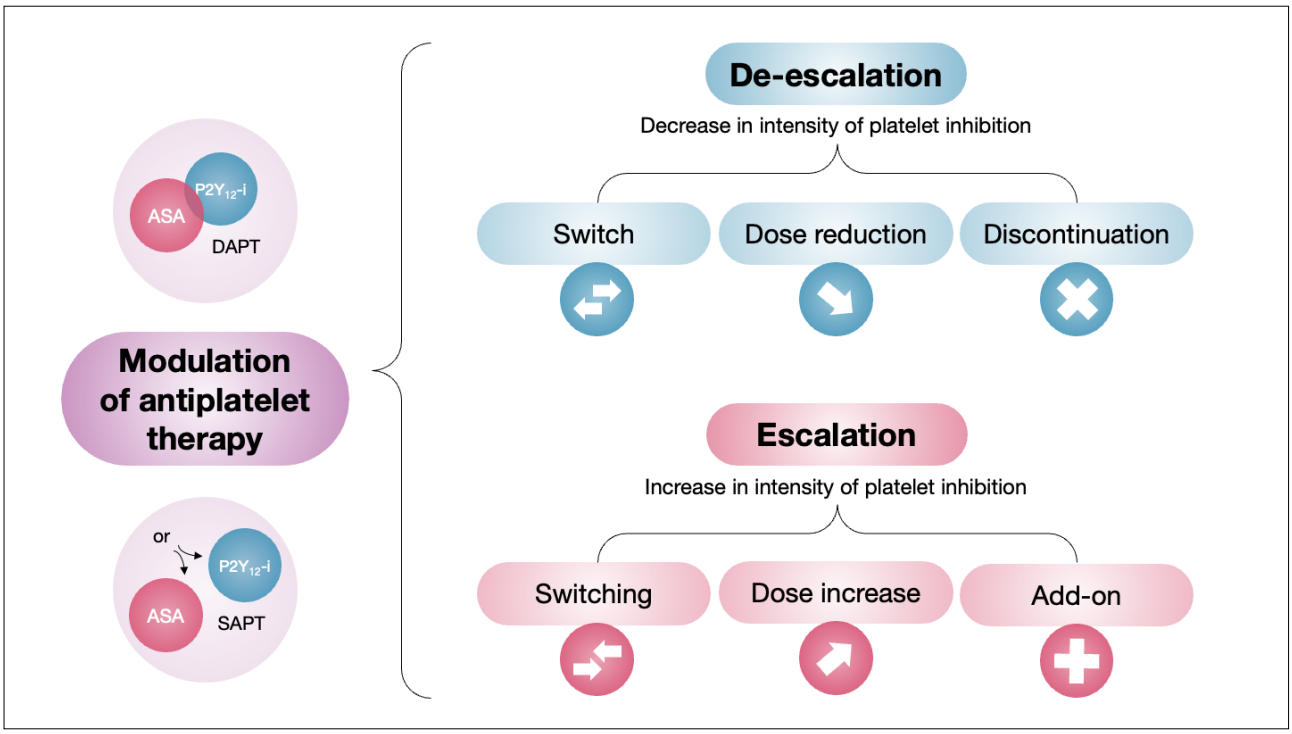

ASA
P2Y12-i
DAPT
Modulation of antiplatelet therapy
or
ASA
P2Y12-i
SAPT
De-escalation
Decrease in intensity of platelet inhibition
Switch
Dose reduction
Discontinuation
Escalation
Increase in intensity of platelet inhibition
Switching
Dose increase
Add-on

Figure 2

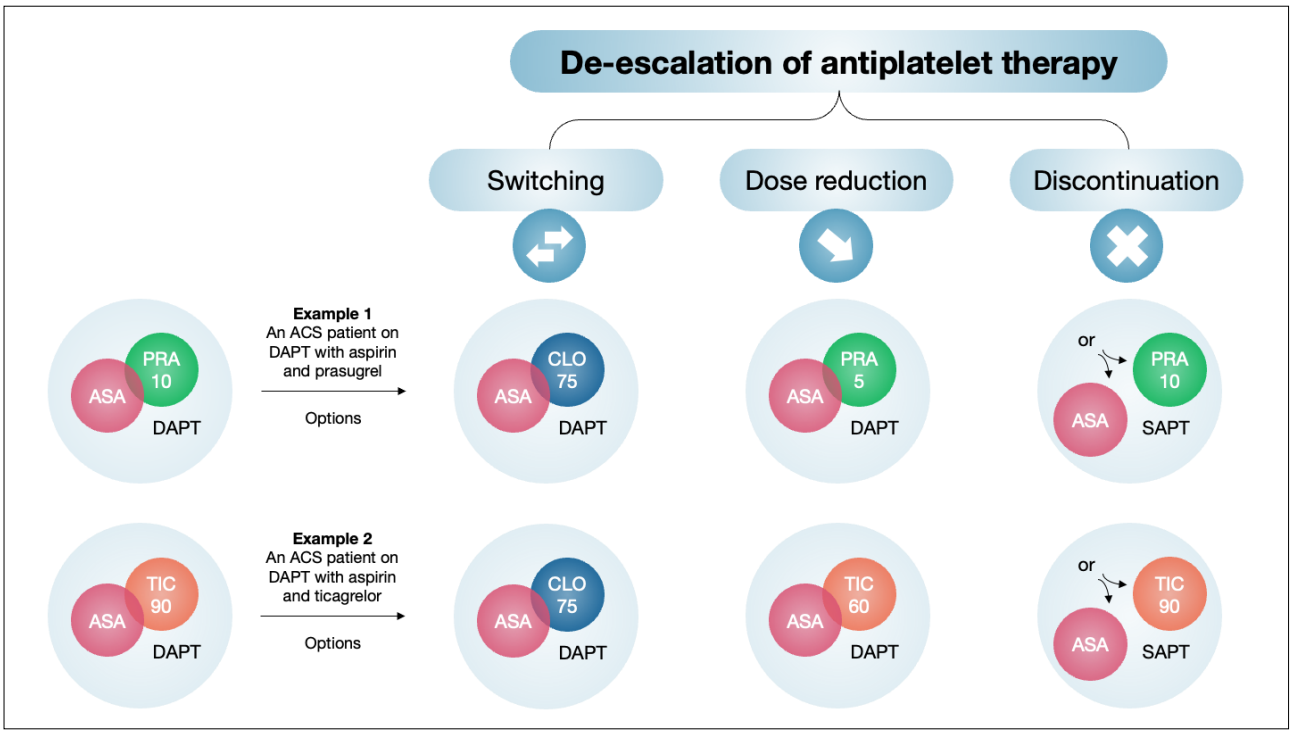
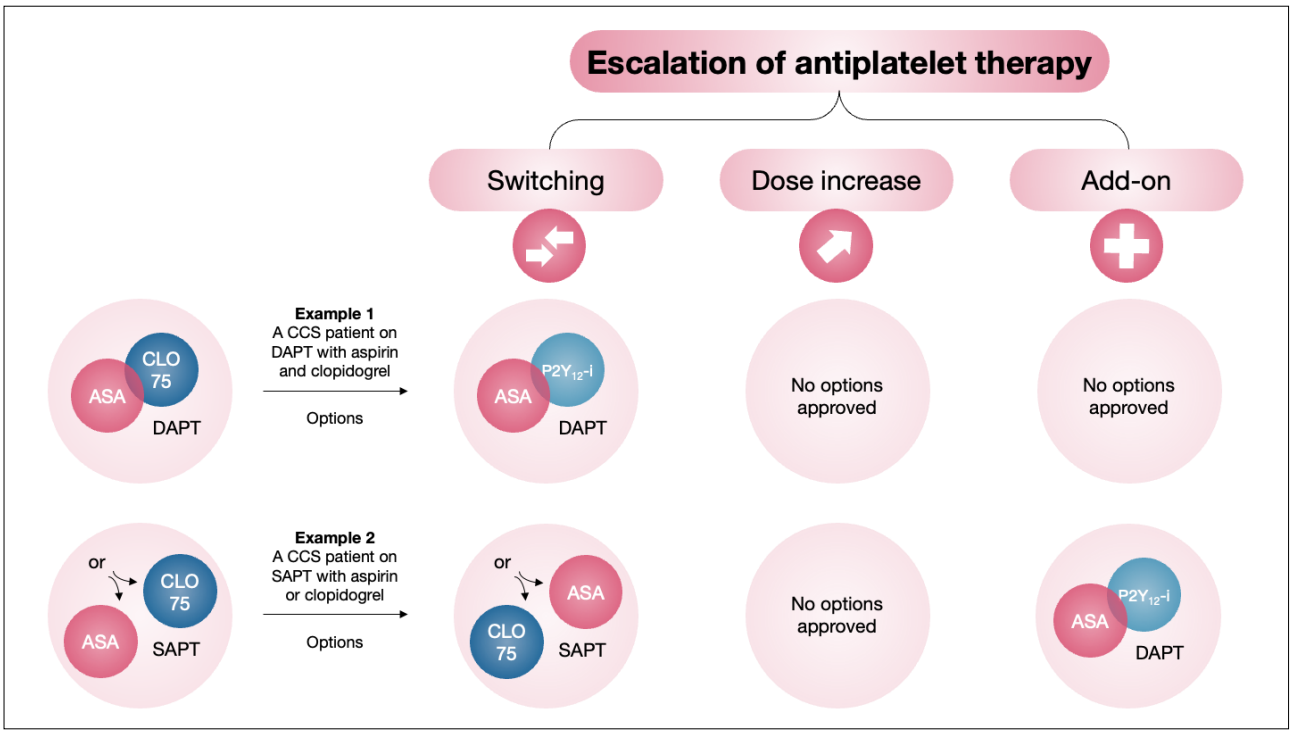

De-escalation of antiplatelet therapy
Switching
Dose reduction
Discontinuation
Example 1
An ACS patient on DAPT with aspirin and prasugrel
Options
ASA
PRA 10
DAPT
CLO 75
PRA 5
or
SAPT
Example 2
An ACS patient on DAPT with aspirin and ticagrelor
TIC 90
TIC 60

Figure 3


Escalation of antiplatelet therapy
Switching
Dose increase
Add-on
Example 1
A CCS patient on DAPT with aspirin and clopidogrel
Options
ASA
CLO 75
DAPT
ASA
P2Y12-i
DAPT
No options approved
No options approved
Example 2
A CCS patient on SAPT with aspirin or clopidogrel
Options
or
ASA
CLO 75
SAPT
or
CLO 75
ASA
SAPT
No options approved
ASA
P2Y12-i
DAPT