

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

Peer-reviewed author version

Capodanno, Davide; Mehran, Roxana; Krucoff, Mitchell W.; Baber, Usman; Bhatt, Deepak L.; Capranzano, Piera; Collet, Jean-Philippe; Cuisset, Thomas; De Luca, Giuseppe; De Luca, Leonardo; Farb, Andrew; Franchi, Francesco; Gibson, C. Michael; Hahn, Joo-Yong; Hong, Myeong-Ki; James, Stefan; Kastrati, Adnan; Kimura, Takeshi; Lemos, Pedro A.; Lopes, Renato D.; Magee, Adrian; Matsumura, Ryosuke; Mochizuki, Shuichi; O'Donoghue, Michelle L.; Pereira, Naveen L.; Rao, Sunil V.; Rollini, Fabiana; Shirai, Yuko; Sibbing, Dirk; Smits, Peter C.; Steg, P. Gabriel; Storey, Robert F.; ten Berg, Jurrien; Valgimigli, Marco; VRANCKX, Pascal; Watanabe, Hiroto; Windecker, Stephan; Serruys, Patrick W.; Yeh, Robert W.; Morice, Marie-Claude & Angiolillo, Dominick J. (2023) Defining Strategies of Modulation of Antiplatelet Therapy in Patients With Coronary Artery Disease: A Consensus Document from the Academic Research Consortium. In: CIRCULATION, 147 (25) , p. 1933 -1944.

DOI: 10.1161/CIRCULATIONAHA.123.064473

Handle: <http://hdl.handle.net/1942/41675>

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

Davide Capodanno¹, Roxana Mehran², Mitchell W. Krucoff³, Usman Baber⁴, Deepak L. Bhatt⁵, Piera Capranzano¹, Jean-Philippe Collet⁶, Thomas Cuisset⁷, Giuseppe De Luca⁸, Leonardo De Luca⁹, Andrew Farb¹⁰, Francesco Franchi¹¹, C. Michael Gibson¹², Joo-Yong Hahn¹³, Myeong-Ki Hong¹⁴, Stefan James¹⁵, Adnan Kastrati¹⁶, Takeshi Kimura¹⁷, Pedro A. Lemos¹⁸, Renato D. Lopes³, Adrian Magee¹⁰, Ryosuke Matsumura¹⁹, Shuichi Mochizuki¹⁹, Michelle L. O'Donoghue²⁰, Naveen L. Pereira²¹, Sunil V. Rao²², Fabiana Rollini¹¹, Yuko Shirai¹⁹, Dirk Sibbing²³, Peter C Smits²⁴, Gabriel Steg²⁵, Robert Storey²⁶, Jurien ten Berg²⁷, Marco Valgimigli²⁸, Pascal Vranckx²⁹, Hirotohi Watanabe³⁰, Stephan Windecker³¹, Patrick W. Serruys³², Robert W. Yeh³³, Marie-Claude Morice³⁴, Dominick J. Angiolillo¹¹

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.

Disclosures

DC reports speaker's or consulting fees from Amgen, Arena, Daiichi Sankyo, Sanofi, Terumo, and institutional fees from Medtronic. RM reports institutional research payments from Abbott, Abiomed, Alleviant Medical, Amgen, AM-Pharma, Arena, AstraZeneca, Atricure, Bayer, Biosensors, Biotronik, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CeloNova, Chiesi, Concept Medical, CSL Behring, Cytosorbents, Daiichi Sankyo, Element Science, Faraday, Filterlex Medical, Humacyte, Idorsia Pharmaceuticals, Janssen, Mediasphere, Medtelligence, Medtronic, Novartis, OrbusNeich, Penumbra, PhaseBio, Philips, Pi-Cardia, PLx Pharma, Protembis, RenalPro, RM Global, Shockwave, Vivasure, Zoll; personal fees from Cine-Med Research, Ionis Pharmaceuticals, Novartis, Novo Nordisk, Vectura, WebMD; Equity <1% in Applied Therapeutics, Elixir Medical, Stel, ControlRad (spouse); AMA (Scientific Advisory Board, JAMA Cardiology Associate Editor), ACC (BOT Member, SC Member CTR Program), SCAI (Women in Innovations Committee Member; Faculty CRF (no fee). UB discloses honoraria from Amgen, AstraZeneca, Boston scientific and Abbott Vascular. DLB discloses the following relationships - Advisory Board: Angiowave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: Angiowave (stock options), Boston VA Research Institute, Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock), Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Consultant: Broadview Ventures, Hims; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees), Wiley (steering committee); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither I nor Brigham and Women's Hospital receive any income from this patent); Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, Cleerly, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, 89Bio; Royalties: Elsevier (Editor, Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solutions; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Takeda. PC reports speaker fees from Daiichi-Sankyo, Amgen and Bayer. JPC reports grants for the institution, honoraria, or research fees from BMS Pfizer, Medtronic, Boston Scientific, AstraZeneca. TC reports consulting and lecture fees from Abbott Vascular, Boston Scientific, Edwards, Europa Organisation, Medtronic, Terumo, Sanofi, and shares from CERC, a healthcare company; LDL declares that he has received consulting fees or honoraria from Amgen, Aspen, AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, Daiichi Sankyo, Eli Lilly, Menarini, Pfizer/Bristol-Myers Squibb, Sanofi, Servier, and The Medicines Company, outside the present work; FF declares that

he has received payment as an individual for consulting fee or honoraria from AstraZeneca, Bayer and Sanofi; and institutional payments for grants from PLx Pharma and The Scott R. MacKenzie Foundation; CMG reports grant support paid to the institution and consulting fees from Johnson & Johnson, Bristol-Myers Squibb, CeleCor, Daiichi Sankyo, and Merck; JYH reports an Institutional Research Grant from the National Evidence-based Healthcare Collaborating Agency, Ministry of Health & Welfare, Korea, and from Abbott Vascular, Biosensors, Boston Scientific, Daiichi Sankyo, Donga-ST, Hanmi Pharmaceutical, and Medtronic Inc. SJ reports grants to the institution from Amgen, Novartis, Janssen, AstraZeneca. PL reports: i) institutional research funding, and/or unpaid advisory board member, and/or unpaid member of the steering/executive/data safety and monitoring group of trials, and/or unpaid interventional proctor by Abbott, Corindus, Scitech, Boston Scientific, and Flouit but has not received personal payments by pharmaceutical companies or device manufacturers; ii) being part of Argonauts, an innovation facilitator; iii) partially supported by a grant from The National Council for Scientific and Technological Development (CNPq) – Brazil (grant number 306677/2019-9). RDL reports research support from Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer; Consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Medtronic, Merck, Pfizer, Portola. MCM reports being CEO and shareholder of CERC and minor shareholder of Electroducer. MOD reports grants via hospital from Amgen, Novartis, Janssen, Merck, AstraZeneca. Honoraria from Amgen, Novartis, AstraZeneca, Janssen. PWS reports consultancy fees from SMT, Philips, Novartis, Merillife, Xeltis. PS reports institutional research grants from Abbott Vascular and SMT, and speaker or consulting honoraria from Abbott Vascular, Microport, Terumo. PGS reports research grants: Amarin, Bayer, Sanofi, Servier; he is speaker or consultant: Amarin, Amgen, AstraZeneca, Bayer, Bristol-Myers-Squibb, Janssen, Kowa, Idorsia, Lexicon, Merck, Novartis, Novo-Nordisk, PhaseBio, Pfizer, Regeneron, Sanofi, Servier; he is Senior Associate Editor of Circulation. RFS reports institutional research grants/support and personal fees from AstraZeneca, Cytosorbents, GlyCardial Diagnostics and Thromboserin; and personal fees from Alnylam, Bayer, Bristol Myers Squibb/Pfizer, Chiesi, CSL Behring, Daiichi Sankyo, Hengrui, Idorsia, Intas Pharmaceuticals, Novartis, PhaseBio, and Sanofi Aventis; MV reports grants and personal fees from Terumo, and personal fees from Astra Zeneca, Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Bayer, CoreFLOW, IDORSIA PHARMACEUTICALS LTD, Universität Basel, Dept. Klinische Forschung, Vifor, Bristol Myers Squib SA, Biotronik, Boston scientific, Medscape, Medtronic, Vesalio, Novartis, Chiesi, ECRI, and PhaseBio. PW received personal fees from Daiichi Sankyo, Bayer AG, CSL Behring, Novartis, Pfizer-Bristol Meyers Squibb alliance. SW reports research, travel or educational grants to the institution from Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardinal Health, CardioValve, Corflow Therapeutics, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Janssen-Cilag, Johnson & Johnson, Medicure, Medtronic, Merck Sharp & Dohm, Miracor Medical, Novartis, Novo Nordisk, Organon, OrPha Suisse, Pfizer, Polares, Regeneron, Sanofi-Aventis, Servier, Sinomed, Terumo, Vifor, V-Wave; he serves as advisory board member and/or member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, Boston Scientific, Biotronik, Bristol Myers Squibb, Edwards Lifesciences, Janssen, MedAlliance, Medtronic, Novartis, Polares, Recardio, Sinomed, Terumo, V-Wave and Xeltis with payments to the institution but no personal payments; he is also member of the steering/executive committee group of several investigator-initiated trials that receive funding by industry without impact on his personal remuneration. RYH reports research grants or Consulting fees from Abbott Vascular, Boston Scientific, Medtronic, and consulting fees from Cathworks, Elixir Medical, Shockwave, Zoll; D.J.A. declares that he has received consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx Pharma, Pfizer, Sanofi and Ventura, outside the present work; D.J.A. also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions and Scott R. MacKenzie Foundation. All the other authors have nothing to disclose.

Disclaimer

This article reflects the views of the authors and does not necessarily represent the practices, policies, requirements, or recommendations of the US Food and Drug Administration or the Japanese Pharmaceuticals and Medical Devices Agency. Furthermore, the use of the word “required,” “must,” or “should” in the document is not intended to indicate a US Food and Drug Administration or the Japanese Pharmaceuticals and Medical Devices Agency requirement.

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 P2Y₁₂ 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 P2Y₁₂ inhibitors of choice for DAPT combinations, in preference to clopidogrel³⁻⁵. 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 prevail³⁻⁶. 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 aspirin³⁻⁶. Aspirin is the perceived standard of care for thrombotic prevention in patients with coronary artery disease in general, regardless of whether revascularization is performed⁷. 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 risk⁸. 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 PCI⁹. 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ antagonist with more potent platelet inhibition (i.e., prasugrel or ticagrelor) to a P2Y₁₂ 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 thrombosis¹². 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 P2Y₁₂ 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 PCI⁵.

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 months¹⁸. 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 NACE¹⁹; ii) in TROPICAL-ACS (n=2,610), switching at 1 week was noninferior but not superior to standard DAPT for 1-year NACE²⁰. 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 NACE²¹; ii) in POPULAR-GENETICS (n=2,488), switch was noninferior to standard DAPT for 1-year NACE and superior for bleeding²².

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.
- P2Y₁₂-specific de-escalation of DAPT by switching, generally in patients who experienced an ACS, consists of switching the P2Y₁₂ inhibitors prasugrel or ticagrelor to the P2Y₁₂ 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 P2Y₁₂-specific de-escalation by switching; ii) the specific subgroups that may or may not derive a clinical benefit from a P2Y₁₂-specific de-escalation strategy by switching; and iii) the optimal timing of P2Y₁₂-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 P2Y₁₂-specific de-escalation strategy that may be desired when concerns exist regarding high exposure to the active metabolite of more potent P2Y₁₂ 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 NACE²⁵. 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 trial⁴⁷. 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.
- P2Y₁₂-specific de-escalation of DAPT by dose reduction consists of reducing the dose of the P2Y₁₂ inhibitor compared with the standard dose.
- More data are needed on the comparative effectiveness and safety of P2Y₁₂-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 P2Y₁₂ 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-adherence²⁶ or because of bleeding carry different prognostic consequences and are more properly termed interruption or disruption, respectively²⁷. 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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] P2Y₁₂ inhibitor discontinuation – The 2019 guidelines from the ESC for patients with CCS and sinus rhythm undergoing PCI recommend the P2Y₁₂ 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 initiative²⁸. In patients at HBR, the 2020 ESC guidelines for patients with an ACS without ST-segment elevation recommend the P2Y₁₂ inhibitor (usually prasugrel or ticagrelor) discontinuation at 3 months (class IIa)³. Conversely, the 2021 ACC/AHA/SCAI guidelines recommend the P2Y₁₂ 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 P2Y₁₂ 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 lesions²⁹. 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 infarction³⁰; ii) in REDUCE-ACS (n=1,496), discontinuation at 3 months was noninferior to discontinuation at 12 months for 1-year NACE³¹; iii) in DAPT-STEMI (n=870), discontinuation at 6 months was noninferior to discontinuation at 12 months for 2-year NACE in patients with STEMI³². 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 patients⁶. The 2020 ESC guidelines for ACS recommend that aspirin be discontinued at 3-6 months, and the P2Y₁₂ 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 P2Y₁₂ inhibitor continued, regardless of bleeding risk and clinical presentation with ACS or CCS⁵.

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 months³³. 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 NACE³⁴; ii) in STOPDAPT-2 ACS, (n=4,169), discontinuation at 1-2 months with transition to clopidogrel monotherapy was not noninferior for 1-year NACE³⁵.

[L4] P2Y₁₂ inhibitor or aspirin discontinuation – In recent trials, the decision to discontinue the P2Y₁₂ 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 P2Y₁₂ inhibitor or aspirin discontinuation with transition to P2Y₁₂ inhibitor or aspirin monotherapy. In the MASTER DAPT trial (n=4,573), among patients at HBR, discontinuation of the P2Y₁₂ 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 bleeding³⁶.

Consensus statements

- Discontinuation of DAPT consists of stopping the P2Y₁₂ inhibitor or aspirin based on physician’s recommendation.
- More data are needed on i) the impact and timing of P2Y₁₂ inhibitor or aspirin discontinuation in CCS and ACS; ii) the comparative effectiveness and safety of P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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 PCI⁵.

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 treatment³⁹. 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 MACE⁴⁰.

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.
- P2Y₁₂-specific DAPT escalation by switching consists of switching the P2Y₁₂ inhibitor clopidogrel to the P2Y₁₂ inhibitor prasugrel or ticagrelor.
- P2Y₁₂-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 P2Y₁₂-specific escalation by switching; ii) the optimal timing of P2Y₁₂-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 MACE⁴³. 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 MACE⁴⁴. 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 daily⁴⁵.

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 P2Y₁₂-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 infarction⁴⁷ and diabetes⁴⁸.

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 HBR⁶. 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 candidates³. 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 MACE⁴⁷ 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 months⁴⁸.

Consensus statements

- Add-on escalation consists of adding a P2Y₁₂ 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 P2Y₁₂ 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.

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* [Internet]. 2018;72:2915–2931. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/30522654>
2. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML. Antiplatelet therapy after percutaneous coronary intervention. *EuroIntervention* [Internet]. 2022 [cited 2023 Jan 3];17:E1371–E1396. Available from: <https://pubmed.ncbi.nlm.nih.gov/35354550/>
3. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, Kastrati A, Mamas MA, Aboyans V, Angiolillo DJ, Bueno H, Bugiardini R, Byrne RA, Castelletti S, Chieffo A, Cornelissen V, Crea F, Delgado V, Drexel H, Gierlotka M, Halvorsen S, Haugaa KH, Jankowska EA, Katus HA, Kinnaird T, Kluin J, Kunadian V, Landmesser U, Leclercq C, Lettino M, Meinila L, Mylotte D, Ndrepepa G, Omerovic E, Pedretti RFE, Petersen SE, Petronio AS, Pontone G, Popescu BA, Potpara T, Ray KK, Luciano F, Richter DJ, Shlyakhto E, Simpson IA, Sousa-Uva M, Storey RF, Touyz RM, Valgimigli M, Vranckx P, Yeh RW, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* [Internet]. 2021;42:1289–1367. Available from: <https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa575/5898842>
4. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW,

- Zieman SJ, ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* [Internet]. 2014 [cited 2017 Dec 28];130:e344–e426. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25249585>
5. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, Fremes SE, Gaudino MF, Goldberger ZD, Grant MC, Jaswal JB, Kurlansky PA, Mehran R, Metkus TS, Nnacheta LC, Rao S v., Sellke FW, Sharma G, Yong CM, Zwischenberger BA. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* [Internet]. 2021; Available from: <https://www.ahajournals.org/doi/10.1161/CIR.0000000000001038>
 6. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes The Task Force for the diagnosis and management of chronic. *Eur Heart J*. 2019;00:1–71.
 7. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B, ESC National Cardiac Societies, ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42:3227–3337.
 8. Capodanno D, Angiolillo DJ. Timing, Selection, Modulation, and Duration of P2Y12 Inhibitors for Patients With Acute Coronary Syndromes Undergoing PCI. *JACC Cardiovasc Interv* [Internet]. 2023 [cited 2023 Feb 4];16:1–18. Available from: <https://pubmed.ncbi.nlm.nih.gov/36599574/>
 9. Ferro EG, Capodanno D, Yeh RW. The Need to Standardize Our Language Around Dual Antiplatelet Therapy-A Call to Action. *JAMA Cardiol* [Internet]. 2022 [cited 2023 Jan 30];7:995–996. Available from: <https://pubmed.ncbi.nlm.nih.gov/36001332/>
 10. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F-JF-JF-J, Ardissino D, de Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, TRITON-TIMI 38 Investigators. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. *New England Journal of Medicine* [Internet]. 2007;357:2001–2015. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa0706482>
 11. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson HHH, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators, Freij A, Thorsén M, for the PLATO Investigators. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* [Internet]. 2009;361:1045–57. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa0904327>
 12. Stone GW, Witzencbichler B, Weisz G, Rinaldi MJ, Neumann F-J, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD, ADAPT-DES Investigators. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* [Internet]. 2013;382:614–23. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23890998>
 13. Sibbing D, Aradi D, Alexopoulos D, ten Berg J, Bhatt DL, Bonello L, Collet JP, Cuisset T, Franchi F, Gross L, Gurbel P, Jeong YH, Mehran R, Moliterno DJ, Neumann FJ, Pereira NL, Price MJ, Sabatine MS, So DYF, Stone GW, Storey RF, Tantry U, Trenk D, Valgimigli M, Waksman R, Angiolillo DJ. Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y12

- Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* [Internet]. 2019 [cited 2023 Jan 3];12:1521–1537. Available from: <https://pubmed.ncbi.nlm.nih.gov/31202949/>
14. Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, Sibbing D, So DYF, Trenk D, Alexopoulos D, Gurbel PA, Hochholzer W, de Luca L, Bonello L, Aradi D, Cuisset T, Tantry US, Wang TY, Valgimigli M, Waksman R, Mehran R, Montalescot G, Franchi F, Price MJ. International Expert Consensus on Switching Platelet P2Y₁₂ Receptor-Inhibiting Therapies. *Circulation* [Internet]. 2017 [cited 2023 Jan 3];136:1955–1975. Available from: <https://pubmed.ncbi.nlm.nih.gov/29084738/>
 15. de Luca L, D'Ascenzo F, Musumeci G, Saia F, Parodi G, Varbella F, Marchese A, de Servi S, Berti S, Bolognese L. Incidence and outcome of switching of oral platelet P2Y₁₂ receptor inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: the SCOPE registry. *EuroIntervention* [Internet]. 2017 [cited 2023 Feb 4];13:459–466. Available from: <https://pubmed.ncbi.nlm.nih.gov/28374678/>
 16. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, Wijns W, Glineur D, Aboyans V, Achenbach S, Agewall S, Andreotti F, Barbato E, Baumbach A, Brophy J, Bueno H, Calvert PA, Capodanno D, Davierwala PM, Delgado V, Dudek D, Freemantle N, Funck-Brentano C, Gaemperli O, Gielen S, Gilard M, Gorenek B, Haasenritter J, Haude M, Ibanez B, Jung B, Jeppsson A, Katritsis D, Knuuti J, Kolh P, Leite-Moreira A, Lund LH, Maisano F, Mehilli J, Metzler B, Montalescot G, Pagano D, Petronio AS, Piepoli MF, Popescu BA, Sádaba R, Shlyakhto E, Silber S, Simpson IA, Sparv D, Tavilla G, Thiele H, Tousek P, van Belle E, Vranckx P, Witkowski A, Zamorano JL, Roffi M. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* [Internet]. 2019 [cited 2023 Jan 30];40:87–165. Available from: <https://pubmed.ncbi.nlm.nih.gov/30165437/>
 17. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, Bonnet G, Fourcade L, Mouret JP, Lambert M, Verdier V, Morange PE, Alessi MC, Bonnet JL. 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* [Internet]. 2017 [cited 2017 Jul 11];38:3070–3078. Available from: <https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehx175>
 18. Kim CJ, Park M-W, Kim MC, Choo E-H, Hwang B-H, Lee KY, Choi YS, Kim H-Y, Yoo K-D, Jeon D-S, Shin E-S, Jeong Y-H, Seung K-B, Jeong MH, Yim HW, Ahn Y, Chang K, Kim CJ, Park M-W, Kim MC, Choo E-H, Hwang B-H, Lee KY, Choi YS, Kim H-Y, Yoo K-D, Jeon D-S, Shin E-S, Jeong Y-H, Seung K-B, Jeon MH, Ahn Y, Chang K, Oh J-H, Ha SJ, Baek JY, Jung KT, Doh J-H, Kim W, Kim D-B, Cha KS, Yoon M-H, Hur S-H, Lee S-H, Cho B-R, Park J-S, Koh JS, Kim S-H, Cho JH, Shim BJ, Kim SW, Jang J-S, Kim K-S, Shin W-Y, Sung K-C. 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* [Internet]. 2021;398:1305–1316. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0140673621014458>
 19. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, Delarche N, Bellemain-Appaix A, Range G, el Mahmoud R, Carrié D, Belle L, Souteyrand G, Aubry P, Sabouret P, du Fretay XH, Beygui F, Bonnet J-L, Lattuca B, Pouillot C, Varenne O, Boueri Z, van Belle E, Henry P, Motreff P, Elhadad S, Salem J-E, Abtan J, Rousseau H, Collet J-P, Vicaut E, Montalescot G. 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* [Internet]. 2016 [cited 2018 Mar 25];388:2015–2022. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S014067361631323X>

20. Sibbing D, Aradi DD, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban MMM, Hadamitzky M, Merkely B, Kiss RG, Komócsi A, Dézsi CA, Holdt L, Felix SB, Parma R, Klopotoski M, Schwinger RHGG, Rieber J, Huber K, Neumann F-JJ, Koltowski L, Mehilli J, Huczek Z, Massberg S, Parma R, Parma Z, Lesiak M, Komosa A, Huczek Z, Koltowski L, Kowara M, Rymuza B, Klopotoski M, Malek L, Aradi DD, Veress G, Dézsi AD, Merkely B, Lux Á, Kiss RG, Papp J, Kovács A, Dézsi CA, Amer S, Ruzsa Z, Róna S, Komócsi A, Ili R, Ungi I, Nagy F, Zweiker R, Tóth-Gayor G, Huber K, Haller P, von Scheidt W, Blüthgen A, Neumann F-JJ, Trenk D, Leggewie S, Kreider-Stempfle HU, Remp T, Kara K, Mügge A, Wutzler A, Fichtlscherer S, Zeiher AM, Seeger F, Hinterseer M, König A, Lederle S, Jacobshagen C, Czepluch F, Maier L, Schillinger W, Sossalla S, Hummel A, Felix SB, Karakas M, Sydow K, Rudolph T, Halbach M, Gori T, Münzel T, May A, Gerstenberg C-MM, Pilecky D, Rieber J, Deichstetter M, Sibbing D, Mehilli J, Gross L, Käab S, Löw A, Orban MMM, Orban MMM, Sattler S, Deuschl S, Teupser D, 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* [Internet]. 2017 [cited 2018 Mar 25];390:1747–1757. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28855078>
21. Notarangelo FM, Maglietta G, Bevilacqua P, Cereda M, Merlini PA, Villani GQ, Moruzzi P, Patrizi G, Malagoli Tagliazucchi G, Crocama A, Guidorossi A, Pigazzani F, Nicosia E, Paoli G, Bianchessi M, Comelli MA, Caminiti C, Ardissino D. Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Patients With Acute Coronary Syndromes. *J Am Coll Cardiol* [Internet]. 2018 [cited 2018 Mar 25];71:1869–1877. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29540324>
22. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, Barbato E, Morisco C, Tjon Joe Gin RM, Asselbergs FW, Mosterd A, Herrman J-PR, Dewilde WJM, Janssen PWA, Kelder JC, Postma MJ, de Boer A, Boersma C, Deneer VHM, ten Berg JM. A Genotype-Guided Strategy for Oral P2Y₁₂ Inhibitors in Primary PCI. *New England Journal of Medicine* [Internet]. 2019;381:1621–1631. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/31479209>
23. Jakubowski JA, Erlinge D, Alexopoulos D, Small DS, Winters KJ, Gurbel PA, Angiolillo DJ. The Rationale for and Clinical Pharmacology of Prasugrel 5 mg. *Am J Cardiovasc Drugs* [Internet]. 2017 [cited 2023 Jan 2];17:109–121. Available from: <https://pubmed.ncbi.nlm.nih.gov/27854064/>
24. Teng R. Ticagrelor: Pharmacokinetic, Pharmacodynamic and Pharmacogenetic Profile: An Update. *Clin Pharmacokinet* [Internet]. 2015 [cited 2023 Jan 2];54:1125–1138. Available from: <https://pubmed.ncbi.nlm.nih.gov/26063049/>
25. Kim H-S, Kang J, Hwang D, Han J-K, Yang H-M, Kang H-J, Koo B-K, Rhew JY, Chun K-J, Lim Y-H, Bong JM, Bae J-W, Lee BK, Park KW. 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* [Internet]. 2020;396:1079–1089. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0140673620317918>
26. Valgimigli M, Garcia-Garcia HM, Vrijens B, Vranckx P, McFadden EP, Costa F, Pieper K, Vock DM, Zhang M, van Es GA, Tricoci P, Baber U, Steg G, Montalescot G, Angiolillo DJ, Serruys PW, Farb A, Windecker S, Kastrati A, Colombo A, Feres F, Jüni P, Stone GW, Bhatt DL, Mehran R, Tijssen JGP. Standardized classification and framework for reporting, interpreting, and analysing medication non-adherence in cardiovascular clinical trials: a consensus report from the Non-adherence Academic Research Consortium (NARC). *Eur Heart J* [Internet]. 2019 [cited 2023 Jan 30];40:2070–2085. Available from: <https://pubmed.ncbi.nlm.nih.gov/29992264/>
27. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Berger PB, Iakovou I, Dangas G, Waksman R, Antoniucci D, Sartori S, Krucoff MW, Hermiller JB, Shawl F, Gibson CM, Chieffo A, Alu M, Moliterno DJ, Colombo A, Pocock S. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2

- year results from a prospective observational study. *Lancet* [Internet]. 2013;382:1714–22. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24004642>
28. Urban P, Mehran R, Collieran R, Angiolillo DJDJ, Byrne RARA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CMM, Gregson J, Haude M, James SKSK, Kim H-SH-S, Kimura T, Konishi A, Laschinger J, Leon MBMB, Magee PFAFA, Mitsutake Y, Mylotte D, Pocock S, Price MJMJ, Rao SVSV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RWRW, Krucoff MWMW, Morice M-CM-C. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Circulation* [Internet]. 2019;140:240–261. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/31116395>
 29. Hong S-J, Kim J-S, Hong SJ, Lim D-S, Lee S-Y, Yun KH, Park J-K, Kang WC, Kim YH, Yoon H-J, Won H, Nam C-M, Ahn C-M, Kim B-K, Ko Y-G, Choi D, Jang Y, Hong M-K. 1-Month Dual-Antiplatelet Therapy Followed by Aspirin Monotherapy After Polymer-Free Drug-Coated Stent Implantation. *JACC Cardiovasc Interv* [Internet]. 2021;14:1801–1811. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1936879821010451>
 30. Hahn J-Y, Song Y bin, Oh J-H, Cho D-K, Lee JBJMJ-Y, Doh J-H, Kim S-H, Jeong J-O, Bae J-H, Kim B-O, Cho JH, Suh I-W, Kim D, Park H-KHS, Park J-S, Choi WG, Lee WS, Kim J, Choi KH, Park TK, Lee JBJMJ-Y, Yang JH, Choi JWJ-H, Choi S-H, Gwon H-C, Gwon H-C, Hahn J-Y, Song Y bin, Park TK, Lee JBJMJ-Y, Yang JH, Choi JWJ-H, Choi S-H, Lee JBJMJ-Y, Choi WG, Bae J-H, Park H-KHS, Hwang J-Y, Hur S-H, Rha S-W, Cho D-K, Cho SC, Kang WY, Lim S-H, Lee JBJMJ-Y, Kim MH, Cha KS, Choi RK, Chae I-H, Oh J-H, Jang WJ, Park YH, Chun WJ, Kim S-H, Cho JH, Suh I-W, Park J-S, Choi JWJ-H, Kim B-O, Doh J-H, Kim D, Jeong MH, Kang SH, Lee WS, Park H-KHS, Jeong J-O, Ahn K-J. 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* [Internet]. 2018 [cited 2018 Apr 2];391:1274–1284. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29544699>
 31. de Luca G, Damen SA, Camaro C, Benit E, Verdoia M, Rasoul S, Liew HB, Polad J, Ahmad WA, Zambahari R, Postma S, Kedhi E, Suryapranata H, Collaborators. 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* [Internet]. 2019; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/31422929>
 32. Kedhi E, Fabris E, van der Ent M, Buszman P, von Birgelen C, Roolvink V, Zurakowski A, Schotborgh CE, Hoorntje JCA, Eek CH, Cook S, Togni M, Meuwissen M, van Royen N, van Vliet R, Wedel H, Delewi R, Zijlstra F. 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* [Internet]. 2018;363:k3793. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/30279197>
 33. Kogame N, Guimarães PO, Modolo R, de Martino F, Tinoco J, Ribeiro EE, Kawashima H, Ono M, Hara H, Wang R, Cavalcante R, Moulin B, Falcão BAA, Leite RS, de Almeida Sampaio FB, Morais GR, Meireles GC, Campos CM, Onuma Y, Serruys PW, Lemos PA. Aspirin-Free Prasugrel Monotherapy Following Coronary Artery Stenting in Patients With Stable CAD. *JACC Cardiovasc Interv* [Internet]. 2020;13:2251–2262. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1936879820313698>
 34. Kim B-K, Hong S-J, Cho Y-H, Yun KH, Kim YH, Suh Y, Cho JY, Her A-Y, Cho S, Jeon DW, Yoo S-Y, Cho D-K, Hong B-K, Kwon H, Ahn C-M, Shin D-H, Nam C-M, Kim J-S, Ko Y-G, Choi D, Hong M-K, Jang Y. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome. *JAMA* [Internet]. 2020;323:2407. Available from: <https://jamanetwork.com/journals/jama/fullarticle/2767161>

35. Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Ogita M, Suwa S, Isawa T, Domei T, Yamaji K, Tatsushima S, Watanabe H, Ohya M, Tokuyama H, Tada T, Sakamoto H, Mori H, Suzuki H, Nishikura T, Wakabayashi K, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Morino Y, Kadota K, Furukawa Y, Nakagawa Y, Kimura T, Kozuma K, Hanaoka K, Tezuka S, Fujino Y, Kato R, Kitamura M, Tsumori M, Hanazawa M, Yamauchi M, Yamazaki I, Hirokami M, Makiguchi N, Nozaki Y, Tomita H, Yagi M, Komaru T, Higuchi M, Isshiki T, Kodama T, Tosaka A, Takamisawa I, Tanaka H, Hata Y, Kato R, Akashi Y, Yumoto K, Tsukahara K, Ako J, Onishi Y, Uzui H, Noda T, Morishima I, Yamada M, Yoshida R, Suzuki S, Maeda T, Tanigawa T, Kaitani K, Matsuoka S, Akao M, Yokomatsu T, Inoko M, Inada T, Morita T, Nakazawa G, Ishihara S, Kinoshita M, Kusuyama T, Togi K, Tamura T, Akasaka T, Tabuchi I, Kihara Y, Ueda H, Katayama Y, Wakeyama T, Kaneko T, Wakatsuki T, Kishi K, Doi M, Okayama H, Suematsu N, Inoue S, Natsuaki M, Tsujita K, Sakamoto T, 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. *JAMA Cardiol* [Internet]. 2022; Available from: <https://jamanetwork.com/journals/jamacardiology/fullarticle/2789701>
36. Valgimigli M, Frigoli E, Heg D, Tijssen J, Jüni P, Vranckx P, Ozaki Y, Morice M-C, Chevalier B, Onuma Y, Windecker S, Tonino PAL, Roffi M, Lesiak M, Mahfoud F, Bartunek J, Hildick-Smith D, Colombo A, Stanković G, Iñiguez A, Schultz C, Kornowski R, Ong P, Alasnag M, Rodriguez AE, Moschovitis A, Laanmets P, Donahue M, Leonardi S, Smits PC. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. *New England Journal of Medicine* [Internet]. 2021;385:1643–1655. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/34449185>
37. Mehilli J, Baquet M, Hochholzer W, Mayer K, Tesche C, Aradi D, Xu Y, Thienel M, Gschwendtner S, Zadrozny M, Jochheim D, Sibbing D, Schüpke S, Mansmann U, Hoffmann E, Kastrati A, Neumann F-J, Massberg S. Randomized Comparison of Intensified and Standard P2Y12-Receptor-Inhibition Before Elective Percutaneous Coronary Intervention: The SASSICAIA Trial. *Circ Cardiovasc Interv*. 2020;13:e008649.
38. Silvain J, Lattuca B, Beygui F, Rangé G, Motovska Z, Dillinger J-G, Boueri Z, Brunel P, Lhermusier T, Pouillot C, Larrieu-Ardilouze E, Boccara F, Labeque J-N, Guedeney P, el Kasty M, Laredo M, Dumaine R, Ducrocq G, Collet J-P, Cayla G, Blanchart K, Kala P, Vicaut E, Montalescot G, ALPHEUS investigators. Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3b trial. *Lancet*. 2020;396:1737–1744.
39. Zheng Y-Y, Wu T-T, Yang Y, Hou X-G, Gao Y, Chen Y, Yang Y-N, Li X-M, Ma X, Ma Y-T, Xie X. Personalized antiplatelet therapy guided by a novel detection of platelet aggregation function in stable coronary artery disease patients undergoing percutaneous coronary intervention: a randomized controlled clinical trial. *Eur Heart J Cardiovasc Pharmacother*. 2020;6:211–221.
40. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, Bell M, Bae J-H, Jeong MH, Chavez I, Gordon P, Abbott JD, Cagin C, Baudhuin L, Fu Y-P, Goodman SG, Hasan A, Iturriaga E, Lerman A, Sidhu M, Tanguay J-F, Wang L, Weinshilboum R, Welsh R, Rosenberg Y, Bailey K, Rihal C. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. *JAMA* [Internet]. 2020;324:761–771. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/32840598>
41. Mehta SR, Tanguay J-F, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, Faxon DP, Rupprecht H-J, Budaj A, Avezum A, Widimsky P, Steg PG, Bassand J-P, Montalescot G, Macaya C, di Pasquale G, Niemela K, Ajani AE, White HD, Chrolavicius S, Gao P, Fox KA, Yusuf S, CURRENT-OASIS 7 trial investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *The Lancet* [Internet]. 2010 [cited 2018 Jan 22];376:1233–1243. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20817281>

42. CURRENT-OASIS 7 Investigators, Mehta SR, Bassand J-PP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KAA, Granger CB, Jolly S, Joyner CD, Rupprecht H-JJ, Widimsky P, Afzal R, Pogue J, Yusuf S. Dose Comparisons of Clopidogrel and Aspirin in Acute Coronary Syndromes. *New England Journal of Medicine* [Internet]. 2010 [cited 2018 Jan 1];363:930–942. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20818903>
43. Collet J-P, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrié D, Boueri Z, Belle L, van Belle E, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthélémy O, Beygui F, Silvain J, Vicaut E, Montalescot G, ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* [Internet]. 2012 [cited 2018 Mar 25];367:2100–9. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa1209979>
44. Price MJ, Berger PB, Teirstein PS, Tanguay J-F, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillabower ME, Stillablower ME, Aragon JR, Kandzari DE, Stinis CT, Lee MS, Manoukian S v, Cannon CP, Schork NJ, Topol EJ, GRAVITAS Investigators. Standard- vs High-Dose Clopidogrel Based on Platelet Function Testing After Percutaneous Coronary Intervention. *JAMA* [Internet]. 2011 [cited 2018 Mar 25];305:1097. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21406646>
45. Jones WS, Mulder H, Wruck LM, Pencina MJ, Kripalani S, Muñoz D, Crenshaw DL, Effron MB, Re RN, Gupta K, Anderson RD, Pepine CJ, Handberg EM, Manning BR, Jain SK, Girotra S, Riley D, DeWalt DA, Whittle J, Goldberg YH, Roger VL, Hess R, Benziger CP, Farrehi P, Zhou L, Ford DE, Haynes K, VanWormer JJ, Knowlton KU, Kraschnewski JL, Polonsky TS, Fintel DJ, Ahmad FS, McClay JC, Campbell JR, Bell DS, Fonarow GC, Bradley SM, Paranjape A, Roe MT, Robertson HR, Curtis LH, Sharlow AG, Berdan LG, Hammill BG, Harris DF, Qualls LG, Marquis-Gravel G, Modrow MF, Marcus GM, Carton TW, Nauman E, Waitman LR, Kho AN, Shenkman EA, McTigue KM, Kaushal R, Masoudi FA, Antman EM, Davidson DR, Edgley K, Merritt JG, Brown LS, Zemon DN, McCormick TE, Alikhaani JD, Gregoire KC, Rothman RL, Harrington RA, Hernandez AF. Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease. *New England Journal of Medicine* [Internet]. 2021 [cited 2023 Jan 2];384:1981–1990. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa2102137>
46. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand S-LT, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, ver Lee P, Rinaldi MJ, Massaro JM, DAPT Study Investigators. [DAPT] Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. *New England Journal of Medicine* [Internet]. 2014;371:2155–2166. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa1409312>
47. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Ophuis TO, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. *New England Journal of Medicine* [Internet]. 2015 [cited 2017 Dec 17];372:1791–1800. Available from: <http://www.nejm.org/doi/10.1056/NEJMoa1500857>
48. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, Held C, Andersson M, Himmelmann A, Ridderstråle W, Leonsson-Zachrisson M, Liu Y, Opolski G, Zateyshchikov D, Ge J, Nicolau JC, Corbalán R, Cornel JH, Widimský P, Leiter LA. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. *New England Journal of Medicine*. 2019;381:1309–1320.

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 P2Y₁₂ inhibitors prasugrel or ticagrelor with the P2Y₁₂ inhibitor clopidogrel. B) De-escalation of DAPT by dose reduction consists of reducing, e.g., the dose of the P2Y₁₂ 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 P2Y₁₂ inhibitor or aspirin with transition to SAPT with aspirin or a P2Y₁₂ 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 P2Y₁₂ inhibitor clopidogrel with the P2Y₁₂ inhibitors prasugrel or ticagrelor. B) Escalation of DAPT by dose increase conceptually consists of increasing, e.g., the dose of the P2Y₁₂ inhibitor or aspirin, but such action has no currently approved recommendations. C) Add-on escalation consists of adding a drug, e.g., the P2Y₁₂ 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

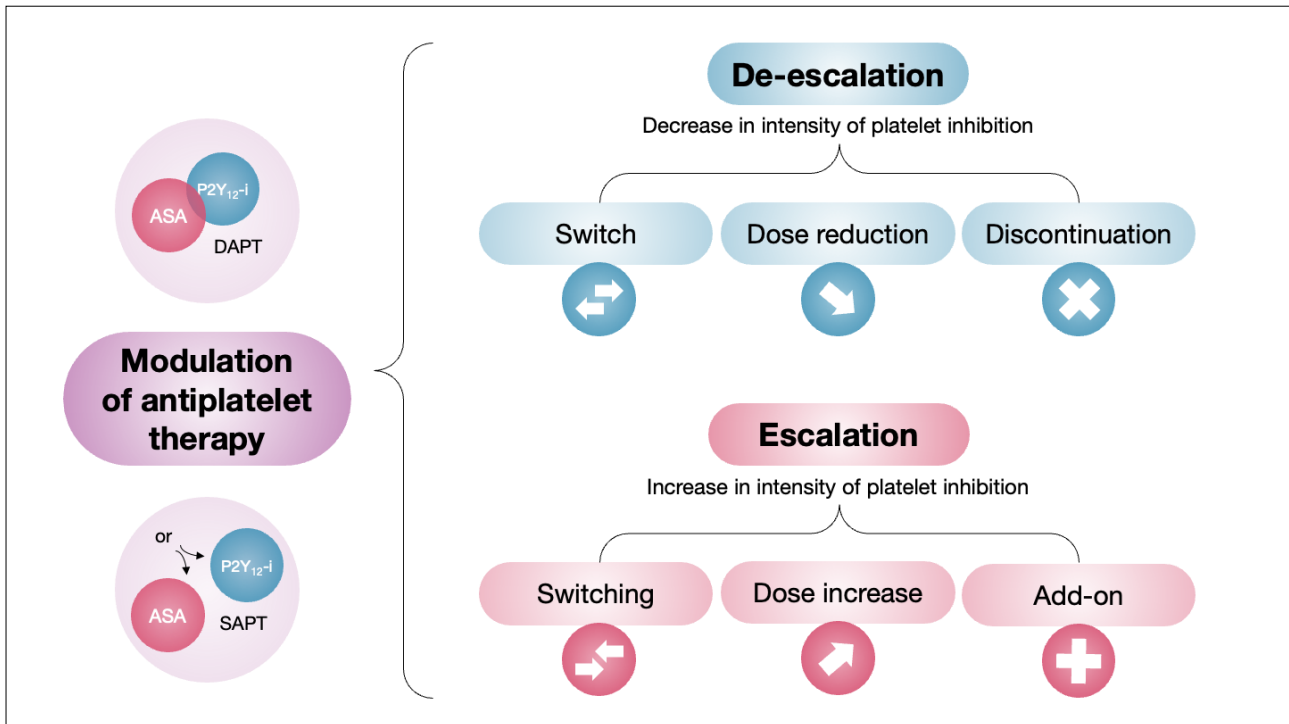


Figure 2

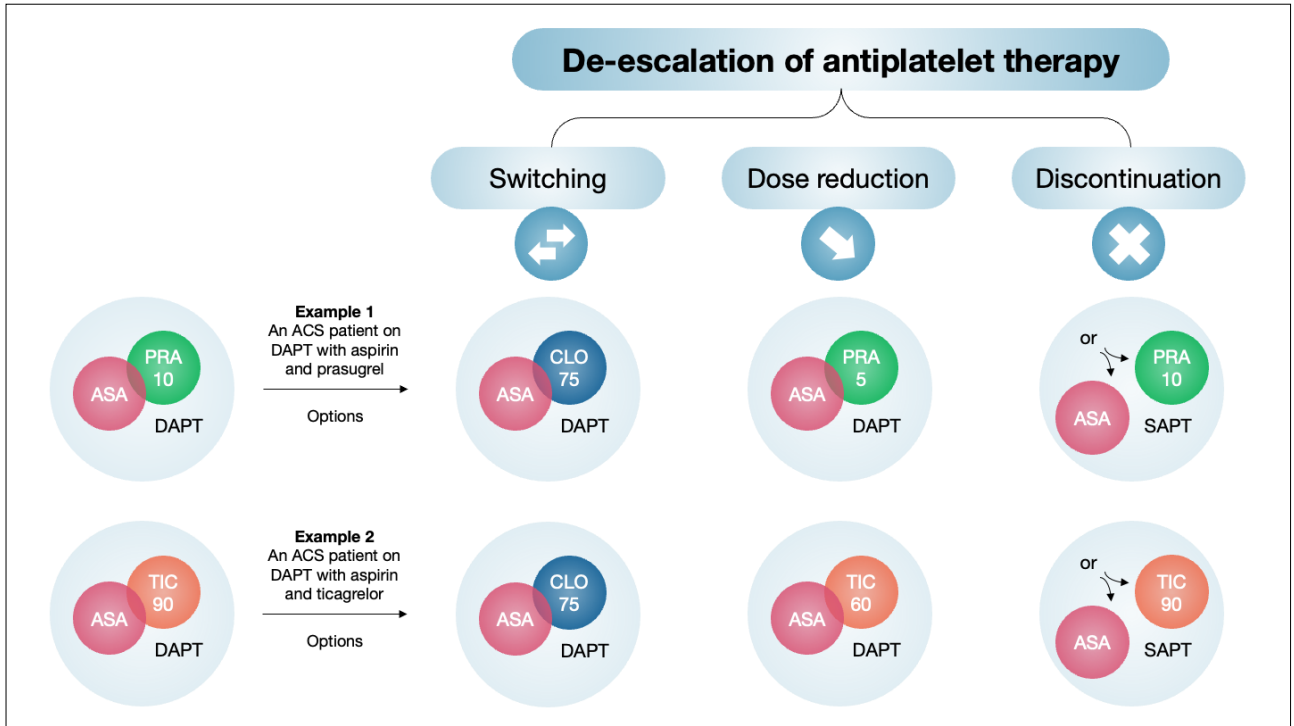


Figure 3

