nature REVIEWS

Nature Reviews referee guidelines

Consensus Statement

Nature Reviews publishes timely, authoritative articles that are of broad interest and exceptional quality. Thank you for taking the time to help us to ensure that our articles meet these high standards.

Consensus Statements provide a comprehensive analysis by a panel of experts of a scientific or medical issue.

Please submit your report in narrative form and provide detailed justifications for all statements. Confidential comments to the editor are welcome, but it is helpful if the main points are stated in the comments for transmission to the authors.

Please note that all *Nature Reviews* articles will be thoroughly edited before publication and all figures will be redrawn by our in-house art editors. We therefore request that you concentrate on the scientific content of the article, rather than any minor errors in language or grammar.

Please consider and comment on the following points when reviewing this manuscript:

- Is the article timely and are the recommendations likely to improve research approaches, clinical practice and/or patient outcomes?
- Will this Consensus Statement be of use to medical practitioners and guide decision-making, or does it conflict with previous recommendations from other organisations? Are the statements and guidelines sufficiently robust to warrant publication?
- Are the scope, aims and methodology of the article clear?
- Are the claims and/ or recommendations convincing and well supported? If not, what further evidence or analysis is needed?
- Are the concepts and statements logically presented and adequately discussed? Is there sufficient detail as to how the statements were constructed and the methodology used for the generation of the document?
- Are the criteria used to base each recommendation on clear and representative of all available information? If the recommendations are graded, is the approach used to grade satisfactory?
- Is the article balanced, or are certain areas given too much weight? Although authors are entitled and encouraged to be opinionated, they should not ignore relevant, published data.
- Do the figures, boxes and tables provide clear and accurate information?
- Are the references appropriate and up-to-date? Do they reflect the scope of the article?
- Are you aware of any conflicts of interest that might affect the balance of the recommendations?

De-escalation or Abbreviation of Dual Antiplatelet Therapy in Acute Coronary Syndromes and PCI – Consensus Statements from an International Expert Panel on Coronary Thrombosis

Diana A Gorog,[1]* Jose Luis Ferreiro,[2]* Ingo Ahrens,[3] Junya Ako,[4] Tobias Geisler,[5] Sigrun Halvorsen,[6] Kurt Huber,[7] Young-Hoon Jeong,[8] Eliano P Navarese,[9] Andrea Rubboli,[10] Dirk Sibbing,[11] Jolanta M Siller-Matula,[12] Robert F Storey,[13] Jack W C Tan,[14] Jurrien M ten Berg,[15] Marco Valgimigli,[16] Christophe Vandenbriele,[17] Gregory Y H Lip[18]

*Joint first authors

1. [a]Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom and [b] Centre for Health Services Research, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Hertfordshire, United Kingdom
2. [a]Department of Cardiology, Hospital Universitario de Bellvitge; CIBERCV; L'Hospitalet de Llobregat, Spain and [b]Bio-Heart Cardiovascular Diseases Research Group, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Spain
3. Department of Cardiology and Medical Intensive Care, Augustinerinnen Hospital Cologne, Academic Teaching Hospital University of Cologne, Cologne, Germany and Faculty of Medicine, University of Freiburg, Freiburg, Germany
4. Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan
5. Department of Cardiology and Angiology, University Hospital, Eberhard-Karls-University Tuebingen, Tuebingen, Germany
6. [a]Department of Cardiology, Oslo University Hospital Ulleval, University of Oslo, Oslo, Norway and [b]University of Oslo, Oslo, Norway
7. 3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminenhospital and Sigmund Freud University, Medical Faculty, Vienna, Austria
8. [a]CAU Thrombosis and Biomarker Center, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Republic of Korea and [b]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Republic of Korea
9. [a]Interventional Cardiology and Cardiovascular Medicine Research, Department of Cardiology and Internal Medicine, Nicolaus Copernicus University, Bydgoszcz, Poland and [b]Faculty of Medicine, University of Alberta, Edmonton, Canada
10. Department of Emergency, Internal Medicine and Cardiology, Division of Cardiology, S. Maria delle Croci Hospital, Ravenna, Italy.
11. 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
12. Department of Cardiology, Austria Medical University of Vienna, Vienna, Austria
13. Cardiovascular Research Unit, Department of Infection, Immunity & Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom
14. National Heart Centre Singapore and Sengkang General Hospital, Singapore
15. [a]St. Antonius Hospital, Nieuwegein, The Netherlands and [b]Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands
16. [a]Cardiocentro Institute, Ente Ospedaliero Cantonale, Università della Svizzera Italiana (USI), Lugano, Switzerland and [b]University of Bern, Bern Switzerland
17. Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium
18. [a]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom and [b]Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

Text word count: 5291. Tables: 4; Figures: 2

***Correspondence to:**

Diana A. Gorog
Faculty of Medicine
Dovehouse Street
National Heart and Lung Institute
Imperial College
London
United Kingdom
d.gorog@imperial.ac.uk
Tel: +442070348934

Abstract

Conventional dual antiplatelet therapy (DAPT) for patients with acute coronary syndromes (ACS) undergoing percutaneous cardiovascular intervention comprises of aspirin with a potent $P2Y_{12}$ inhibitor (ticagrelor or prasugrel) for 12 months. Whilst reducing ischaemic risk, this exposes patients to a significant risk of bleeding. Strategies to reduce bleeding include de-escalation of DAPT intensity (downgrading from potent $P2Y_{12}$ inhibitors prasugrel or ticagrelor at conventional doses to either clopidogrel or reduced-dose prasugrel) or abbreviation of DAPT duration, and the two approaches have not been compared in a head-to-head trial.

Nevertheless, use of either strategy requires an assessment of the individual's ischaemic and bleeding risks. De-escalation of DAPT intensity can reduce bleeding without increasing ischaemic events and may be guided by platelet function testing or genotyping. Abbreviation of DAPT after 1-6 months, followed by monotherapy with aspirin or a $P2Y_{12}$ inhibitor, reduces bleeding without an increase in ischaemic events in patients at high bleeding risk, particularly those without high ischaemic risk.

Herein, we summarise the evidence base for these treatment approaches, provide guidance on the assessment of ischaemic and bleeding risk, and provide consensus statements, from an international panel, to help guide clinicians to optimise these DAPT approaches for individual patients to improve outcomes.

Word count: 200

Keywords: DAPT, ACS, de-escalation, abbreviation, bleeding

Abbreviations

ACS = acute coronary syndrome

ARC = Academic Research Consortium

BARC = Bleeding Academic Research Consortium

CCS = chronic coronary syndrome

CKD = chronic kidney disease

DAPT = dual antiplatelet therapy

GFR = glomerular filtration rate

HBR = high bleeding risk

MI = myocardial infarction

NSTE-ACS = non-ST-segment elevation

PCI = percutaneous coronary intervention

PFT = platelet function test

STEMI = ST-segment elevation myocardial infarction

Introduction

Antiplatelet therapy is central to the management of acute coronary syndromes (ACS) and in patients undergoing percutaneous cardiovascular intervention (PCI).

Current "standard-of-care" dual antiplatelet therapy (DAPT) for patients with ACS undergoing PCI, as recommended by international guidelines, comprises of aspirin combined with a potent $P2Y_{12}$ inhibitor, namely ticagrelor or prasugrel[1-3].

Whilst DAPT reduces the risk of ischaemic events following ACS, it significantly increases the risk of bleeding[4,5]. Increased awareness of the prognostic importance of bleeding has prompted investigation of strategies to de-escalate DAPT, to identify a strategy balancing thrombotic and bleeding risks.

Whilst there are guidelines on the management of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation ACS (NSTE-ACS) and PCI, these only loosely cover options for antithrombotic therapy and do not make clear all the possible options for de-escalation, nor the evidence base supporting the different possible strategies.

Currently, there is no position document or guideline available for clinicians that summarizes the available options for de-escalation of DAPT or the evidence base supporting the various de-escalation strategies.
Therefore, we convened an expert panel to produce consensus statements to help guide clinicians to identify suitable patients for de-escalation, to improve clinical outcomes, by maintaining efficacy whilst reducing bleeding. We excluded patients who require oral anticoagulation following ACS, since there represent a very specific cohort, for which the evidence base for de-escalation is less robust, and includes different medications when de-escalation is done.
For the purposes of this document, we will refer to:

(i) Shortening or abbreviating DAPT duration (also known as de-escalation of DAPT duration), meaning abbreviation of standard 12-months' DAPT duration and continuing with single antiplatelet therapy, either aspirin or a $P2Y_{12}$ inhibitor.
(ii) De-escalation of DAPT intensity, meaning switching or downgrading from the more potent $P2Y_{12}$ inhibitors prasugrel or ticagrelor at conventional doses to either clopidogrel or reduced-dose prasugrel.

Methods for consensus recommendations

We conducted a literature search to identify studies that assessed de-escalation of DAPT intensity or abbreviation of DAPT duration in patients with ACS treated with PCI, from PubMed, Embase and Cochrane library databases, with no restriction on language. Authors worked on allocated sections in pairs, with literature review to November 2022. All the authors reviewed all sections of the manuscript, and participated in a series of 'rounds', where the manuscript was shared with all authors at each round and comments at each round used to inform and evolve the manuscript in

response to earlier comments in the next round, as well as by video discussion. All authors judged the available evidence leading to the consensus recommendations.

Risk of bleeding with DAPT in ACS patients undergoing PCI in contemporary clinical trials

In clinical trials of DAPT, the incidence of major bleeding in the 12 months post-PCI is 1-10%, depending on the bleeding definition, as well as the type and dose of $P2Y_{12}$ inhibitor used[6-8], bleeding risk category and patient ethnicity[9,10], with observational studies reporting incidences of 2.8-11%[8,11]. Major bleeding in ACS patients increases the risk of mortality by nearly threefold in the first 12 months after hospital discharge[11], as well as increasing the adjusted hazard of 30-day death or MI up to 5-fold, with risk increasing in proportion to the severity of the bleeding[12].

The risk of bleeding with DAPT relates not only to the combined effects of aspirin and $P2Y_{12}$ inhibitor on haemostasis, but also to the potency of the $P2Y_{12}$ inhibitor used (i.e. ticagrelor or prasugrel > clopidogrel).

In a systematic review including 53 studies (36 observational studies and 17 randomized clinical trials; 714,458 ACS participants) focusing on the post-discharge period, the 12-month incidence of bleeding ranged from 0.2% to 37.5% in observational studies and 0.96% to 39.4% in randomised trials, varying with the classification of bleeding used[11]. In contrast to the thrombotic risk, which is higher early after an ACS (see below), the risk of bleeding appears more constant (despite being most common in the first month) and substantial over time (after the first month)[11,13,14].

Bruising is the most common bleeding event, followed by gastrointestinal bleeding and epistaxis, whereas intracranial bleeding is relatively rare[13]. Nuisance bleeding (Bleeding Academic Research Consortium [BARC] type 1) is very common in the first year after ACS (up to 37.5%)[15] and can lead to DAPT discontinuation, worse reported quality-of-life, repeat hospitalization and increased risk of subsequent serious bleeding[15]. In addition, the degree of platelet inhibition achieved by the $P2Y_{12}$ inhibitor, as measured by platelet function testing (PFT), is directly related to the risk of mild bleeding (BARC type 1 or 2)[16,17] and likelihood of DAPT discontinuation.

Clinical risk factors for bleeding in patients with ACS undergoing PCI

Older age, prior bleeding and chronic kidney disease (CKD) are well known risk factors for bleeding, but other clinical factors also contribute (Table 1). Bleeding risk is usually the interaction of non-modifiable and modifiable bleeding risk factors. Multiple clinical scores have been developed to predict the risk of bleeding in patients on antiplatelet therapy[4,18,19]. The PRECISE-DAPT Risk Calculator was developed to predict the risk of bleeding in patients treated with coronary stenting receiving subsequent DAPT. The score included five-items (age, creatinine clearance, haemoglobin, white-blood-cell

count and previous spontaneous bleeding) and predicted the risk of out-of-hospital bleeding during DAPT.

In 2019, the Academic Research Consortium (ARC) for High Bleeding Risk (HBR) developed a consensus definition of patients at HBR, focusing on patients undergoing PCI[20]. Twenty clinical criteria were identified as major or minor by consensus, supported by published evidence. Patients were considered at HBR (annual BARC type 3-5 bleeding rate of ≥4%) if at least 1 major or 2 minor criteria were present. Although the ARC-HBR criteria can be adequately applied to real-world cohorts, several important clinical risk factors for bleeding were not covered by this score (e.g. low body weight, frailty, heart failure and peripheral artery disease) and bleeding risk may be under-estimated in such patients[21].

Differences between antiplatelet agents with respect to the incidence of bleeding

The bleeding risk relating to the different oral $P2Y_{12}$ inhibitors largely reflects the extent of platelet $P2Y_{12}$ inhibition achieved. Currently approved regimens of prasugrel and ticagrelor achieve a higher mean level of platelet inhibition than clopidogrel[22-24] and are associated with higher rates of minor and major bleeding[6,7,17] (Table 2)[6,7,25-27]. Consistently high levels of $P2Y_{12}$ inhibition with standard prasugrel (10 mg daily) and ticagrelor (90 mg twice daily) translate to similar rates of bleeding with each[26,28]. However, the wide interindividual pharmacodynamic response to clopidogrel is associated with variation in individual bleeding risk such that those with greater $P2Y_{12}$ inhibition have higher rates of bleeding[28,29]. The risk of bleeding related to cardiac surgery and major non-cardiac surgery depends on the timing of $P2Y_{12}$ inhibitor cessation prior to surgery, the mean level of platelet $P2Y_{12}$ inhibition during treatment, and whether the inhibitory effect is reversible (ticagrelor) or irreversible (prasugrel and clopidogrel)[30].

Aspirin, even at low daily maintenance doses of ≤100 mg, achieves consistently high levels of platelet cyclooxygenase-1 inhibition, resulting in a predictable compromise between haemostasis and increased bleeding risk with standard regimens[31], both as monotherapy and as part of DAPT[27] (Table 2). Furthermore, aspirin treatment is associated with dose-dependent increase in the risk of gastroduodenal erosion or ulceration, which then further increases the risk of gastrointestinal haemorrhage beyond the risk attributable to platelet inhibition[32]. Indeed, aspirin *per se* is not benign from the bleeding perspective, with major bleeding and intracranial bleeding risks with aspirin being broadly similar to warfarin, when stratified by the HAS-BLED score, in patients with atrial fibrillation (AF)[33].

The assessment and mitigation of bleeding risk in AF and venous thromboembolism, and the ethnic differences in bleeding risk with antithrombotic drugs, have been the topics of recent consensus documents[34,35].

Clinical risk factors for recurrent ischaemic events in patients with ACS undergoing PCI

Patients with ACS are at risk of subsequent ischaemic events with a rate of nearly 5% in the first year after the index event, increasing to 15% by the fourth year[36]. Clinical risk factors associated with increased ischaemic events include age, frailty, diabetes mellitus, polyvascular disease, complex coronary artery disease and CKD (Table 1)[37,38]. Technical aspects of PCI that increase ischaemic risk include: (i) at least 3 stents implanted; (ii) at least 3 lesions treated; (iii) total stent length >60mm; (iv) bifurcation with 2 stent implanted; (v) history of complex revascularization (left main stem, chronic total occlusion, etc.); and (vi) history of stent thrombosis on antiplatelet treatment.

In patients with ACS undergoing PCI, definite or probable stent thrombosis occurs in 0.4-1.8% of patients in the first year[39,40] and is more frequent than in patients with chronic coronary syndromes (CCS), especially within the first 6 months[41]. The major risk with premature DAPT discontinuation is stent thrombosis, which has a 20-45% mortality rate[42], being highest with acute (<24 h) and subacute (1-30 days) stent thrombosis. In a real-world registry of patients receiving DES, including NSE-ACS, but excluding STEMI patients, the incidence of stent thrombosis at 9-months was 1.3%, substantially higher than rates reported in major clinical trials (0.4-0.6%), and stent thrombosis occurred in 29% of patients who prematurely discontinued DAPT, with a case-fatality rate of 45%[43]. In another large registry, among MI patients receiving DES, those who stopped thienopyridine therapy by 30 days were at 9-fold increased risk of death over the next 11 months (7.5% versus 0.7%, P<0.0001)[44]. Two other registries have shown that amongst ACS patients, stent thrombosis is increased 3-fold following premature clopidogrel or DAPT cessation, and three times higher when clopidogrel was discontinued within the first month, compared to 1-6 months[45,46]. There is a suggestion that the increased risk of stent thrombosis with abbreviated DAPT may be significantly attenuated with the use of second-generation, compared to first generation DES[47].

~~Ischaemic events predominate over bleeding events in the first year after ACS when patients are not fully revascularized~~. In two large registries of 19,826 unselected ACS patients undergoing PCI, the ischemic and bleeding risks were overall similar in the first 1 year, with ischemic risk exceeding bleeding risk within the first 2 weeks, especially in STEMI patients and those with incomplete revascularization[48]. Use of risk scores to assess bleeding risk is gaining popularity, but ischaemic and bleeding risk scores often have overlapping clinical features. However, it has been shown that HBR patients do not clearly derive ischaemic benefit from prolonged DAPT, therefore, ischaemic risk should guide a more prolonged DAPT regimen mainly in non-HBR patients[9,49].

Importance of balancing ischaemic and bleeding risks, considering specific factors that may tip the balance towards either

The principle of balancing ischaemic and bleeding risks is important when reducing the intensity or duration of DAPT. Bleeding risk can be assessed using the ARC-HBR

criteria[3] or the PRECISE-DAPT, CRUSADE or ACUITY risk scores[50], although PRECISE-DAPT is the only one validated for selecting DAPT duration. The definition of high ischaemic risk has undergone several changes over time (Table 1), with the current definition based on the 2020 European Society of Cardiology (ESC) Guidelines for the Management of ACS in Patients Presenting without Persistent ST-segment Elevation[1].

A systematic review and meta-analysis of studies validating the DAPT score in 88,563 patients undergoing PCI electively or for ACS, the DAPT score was able to separate the risks of ischemia and bleeding[51]. Patients with a DAPT score ≥2 were at higher ischemic risk and lower bleeding risk, compared to patients with a DAPT score <2, who were at higher bleeding and lower ischemic risk. Thus, application of the DAPT score could help identify those patients who may benefit from standard or prolonged DAPT.

A recent paper reporting on the long-term outcomes of patients enrolled in the PEGASUS-TIMI 54 trial indicates that a single factor defining an increased ischaemic risk is insufficient to recommend prolonged DAPT[52] and that 2 or more risk factors define a patient who is truly high ischaemic risk. Especially in the elderly, bleeding and ischaemic risks are often combined and depend frequently on the same variables.

Timelines of ischaemic vs. bleeding risk

The incidence of ischaemic events is highest during the first month after PCI and tends to decrease thereafter[53]. Registry data on 19,826 patients with ACS treated with PCI suggest that ischaemic risk is highest in the first 30 days, especially the first 2 weeks post-ACS[54], and may be stent-related (e.g. stent thrombosis), due to progression or destabilisation of non-culprit lesions (e.g. new myocardial infarction [MI]) or vascular events in other areas affected by atherosclerotic disease (e.g. stroke).

On the other hand, the risk of bleeding with DAPT, despite being relatively high in the first days after PCI (due to the use of an arterial access site and periprocedural antithrombotic therapy), does not diminish over time as long as antiplatelet therapy is continued[53,55].

In ACS patients undergoing PCI, the ischaemic risk may surpass the bleeding risk especially in the first month[48] but then declines over the subsequent 1-3 months. On the other hand, risk of bleeding with maintenance DAPT persists, and so the net benefit of DAPT may diminish, depending on the clinical circumstances of the patient[53].

Therefore, the rationale for de-escalation of DAPT in the setting of ACS lies in the concept that ischaemic risk clusters within the first months, while bleeding risk remains stable and may exceed ischaemic risk beyond the first few months after the ACS.

Identifying suitable patients for de-escalation of DAPT

Multiple strategies that vary the intensity and/or the duration of DAPT have been investigated in an effort to mitigate bleeding hazard without a trade-off in ischaemic risk (Figure 1). The basic construct of DAPT de-escalation is the switching from ticagrelor or prasugrel to a reduced dosing regimen or to clopidogrel. The decision to de-escalate depends on individual clinical judgement, driven by the perceived balance between the patient's ischaemic and bleeding risks, the occurrence of adverse events, comorbidities, co-medications, and the availability of the respective drugs. DAPT de-escalation might be tailored to the patient's risk profile (which may be dynamic, requiring reassessment as circumstances change), PFT or genetics. Overall, many patients with ACS undergoing PCI, especially those at HBR, may be suitable for de-escalation.

Consensus-based criteria and statistical tools can assist in guiding clinical judgment and decision making to implement this strategy. The ARC-HBR classification can help identify HBR patients[20] and the PRECISE-DAPT score can aid bleeding risk prediction, with a score ≥ 25 identifying subjects at HBR[4,56], although an additional risk factor should be considered if age is the only underlying factor for this score.

De-escalation may be unguided, based purely on clinical judgment, or based on clinical judgement and additionally guided, either by PFT or *CYP2C19* genotyping, depending on the patient's risk profile and availability of respective assays (ESC Class of Recommendation IIb, LOE A)[1]. Use of PFT allows the direct determination of the degree of platelet inhibition, which in turn can identify patients at increased thrombotic (high on-treatment platelet reactivity) or bleeding (low on-treatment platelet reactivity) risk, and further allows the modulation of $P2Y_{12}$ therapy to achieve the desired platelet response. The benefit of genetic testing over PFT is that the results of the former remain unchanged while the results of the latter are subject to intra- and inter-individual variability, but genetic factors should be integrated with knowledge of clinical phenotype such as obesity, BMI, diabetes and kidney dysfunction that impair antithrombotic efficacy. Both guided and unguided de-escalation were associated with a reduction in bleeding without an increase in ischaemic events in a recent meta-analysis[57,58].

Future tools integrating clinical and laboratory knowledge to optimize patient selection for DAPT de-escalation are warranted.

Clinical trial evidence base for abbreviation of DAPT duration

Several studies have investigated the risks and benefits of 6-month or shorter regimens of DAPT followed by aspirin monotherapy, in comparison to standard 12 months of DAPT, in patients undergoing PCI with DES implantation; however, few have focused on ACS patients (Table 3)[9,59-70]. Amongst those focusing on ACS, there was significant heterogeneity amongst the trials in terms of the type of DES used, with some studies mandating only biodegradable polymer and others durable polymer DES. Drugs eluted

included sirolimus, everolimus, zotarolimus, tacrolimus and biolimus. Whilst in some studies patients only received one type of stent, others enrolled patients with 3 or more types of DES. We therefore think, on the whole, the data can be extrapolated to daily clinical practice with most modern types of stent.

In the SMART DATE trial, 1,357 ACS patients were assigned to the 6-month DAPT group and 1,355 to the 12-month or longer DAPT group[62]. The trial showed non-inferiority of the 6-month DAPT regimen for the composite of all cause death, MI and stroke, however MI occurred more frequently with 6 months of DAPT than with DAPT of 12-month or longer, whilst there was no significant difference in BARC type 2-5 bleeding[62].

A subsequent individual patient-level analysis of 14,963 patients from 8 randomized trials comparing 3-6 months of DAPT followed by aspirin with at least 12 months of DAPT, showed that patients with ACS benefitted from prolonged DAPT with reduction in ischaemic events if HBR features (PRECISE DAPT score ≥25) were not present, whereas HBR patients did not benefit, irrespective of the ischaemic risk[49].

Seven studies have assessed the comparative effectiveness and safety of abbreviated DAPT regimens followed by $P2Y_{12}$ inhibitor monotherapy (rather than aspirin continuation), compared with standard DAPT. Prior aggregate data from direct or network meta-analyses have not conclusively quantified the risks and benefits of aspirin withdrawal in comparison with DAPT after PCI, because they included events occurring during the initial DAPT phase, which was identical in both experimental and control regimens and might have biased treatment estimates towards the null, hence underestimating the potential benefit of aspirin withdrawal.

The Single Versus Dual Antiplatelet Therapy (Sidney) Collaboration first gathered individual patient data from two ticagrelor monotherapy studies[71], and, in a second iteration, from 6 studies assessing either ticagrelor or clopidogrel after 1-3 months of DAPT compared with DAPT continuation[72]. The rate of the primary outcome of all-cause death, MI and stroke was similar in patients with $P2Y_{12}$ inhibitor monotherapy (mainly ticagrelor) and in patients on DAPT, with $P2Y_{12}$ inhibitor monotherapy meeting the criteria for non-inferiority to DAPT. The treatment effect was consistent across use of clopidogrel or ticagrelor, and in patients with or without HBR or ACS; whereas $P2Y_{12}$ inhibitor monotherapy strategy was associated with reduced major bleeding[72].

More recently, the STOPDAPT-2 ACS extension study recruited ACS patients undergoing PCI, who were randomized to 1-2 months of DAPT followed by clopidogrel monotherapy versus standard DAPT for 12 months comprising of aspirin and clopidogrel[70]. Analysed in combination with the previous 1,161 ACS patients included in a prior trial, clopidogrel monotherapy after 1-2 months of DAPT failed to attest non-inferiority to conventional DAPT for net clinical benefit and was associated with a substantial increase in the rate of MI. Hence, the use of clopidogrel monotherapy might be reserved for ACS patients in whom bleeding risk outweighs ischaemic risk.

The MASTER DAPT trial recruited patients exclusively at HBR undergoing PCI (both CCS and ACS) and, among those without need for oral anticoagulation (64% of the patients enrolled), compared a 1-month DAPT regimen followed by single antiplatelet therapy (either aspirin or in two-thirds of patients, a $P2Y_{12}$ inhibitor) with standard DAPT for at least 6 months[9]. The trial demonstrated the non-inferiority of 1-month DAPT regimen, both for net adverse events and major adverse cardiac and cerebral events, together with a lower rate of bleeding, with consistent results in patients with ACS, including those undergoing complex interventions[73,74].

Clinical trial evidence base for unguided de-escalation of DAPT intensity

There have been three randomized trials testing an unguided de-escalation approach after ACS (Table 4)[75-80]. In the TOPIC trial, ACS patients were randomized to clopidogrel-based DAPT versus standard DAPT[75]. All patients were pre-treated with either ticagrelor or prasugrel for one month before randomization. The primary composite endpoint of cardiovascular death, urgent revascularization, stroke and BARC bleeding grade ≥2 at 1-year post-ACS was significantly lower in the de-escalation arm compared to the standard DAPT arm, driven by a reduction in BARC ≥2 bleeding, while ischaemic events were similar in the two arms[75].

The non-inferiority of a dose reduction (from 10mg to 5mg) of prasugrel one month after ACS was tested in East Asian patients in the HOST-REDUCE-POLYTECH-ACS randomized trial. The primary endpoint, the rate of net adverse clinical events (all-cause death, non-fatal MI, stent thrombosis, repeat revascularization, stroke and BARC ≥2 bleeding) was lower with the prasugrel-based dose de-escalation strategy, driven by a reduction in minor bleeding without an increase in ischaemia. Ischaemic events were similar and bleeding events were significantly lower in the de-escalation arm[76], irrespective of PCI complexity[81].

Finally, the TALOS-AMI, an open-label, non-inferiority trial randomized 2,697 East-Asian patients one month after ACS to clopidogrel-based DAPT or continuation of ticagrelor-based DAPT. The de-escalation strategy met the criteria of non-inferiority for the primary composite endpoint of cardiovascular death, MI, stroke or BARC ≥2 bleeding, with reduced BARC ≥2 bleeding in the de-escalation group[77].

Clinical trial evidence base for guided de-escalation of DAPT intensity

While both genetic and platelet function tests have been used to guide DAPT de-escalation, access to these tests is not uniform across all practice settings. Many clinicians may have access to neither test, and even when available, results may not be available in a suitable timeframe to guide clinical decision making during the acute ACS admission.

Genetics

The response to drugs can be variable, which is to some extent due to genetic variations, as well as differing patient characteristics, including body weight, CKD and diabetes

mellitus[82]. Of the antiplatelet drugs, only clopidogrel is subject to large inter-individual variability in antiplatelet effect, partly due to genetic polymorphism (i.e., *CYP2C19* gene), resulting in some 30% of patients not adequately responding to treatment[83]. To reduce the risk of bleeding when treating ACS patients with ticagrelor or prasugrel as part of DAPT, it may be useful to de-escalate to clopidogrel based on genetic testing.

The ABCD-GENE risk score, comprising 4 clinical (Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus) and 1 genetic (*CYP2C19* loss-of-function alleles) variables, which when assessed to give a risk-weighted score, can aid clinicians identify those patients who are most likely to have high-on-treatment platelet reactivity on clopidogrel[82].

The Popular Genetics trial tested this genotype-guided de-escalation strategy in 2,488 STEMI patients undergoing primary PCI[80]. All patients received aspirin and were randomised within 48 hours to a genotype-guided or to standard-of-care $P2Y_{12}$ inhibitor strategy (ticagrelor or prasugrel). In the genotype-guided group, carriers of loss-of-function *CYP2C19* alleles (39%) were treated with ticagrelor, while noncarriers (61%) received clopidogrel. Genotype-guided $P2Y_{12}$ inhibitor treatment resulted in a lower rate of bleeding compared to the standard-treatment group (9.8% vs. 12.5%, HR 0.78, 95% CI 0.61-0.98, p=0.04), without an increase in ischaemic events.

Platelet function tests

The antiplatelet effect of oral $P2Y_{12}$ inhibitors can be assessed *in vitro* by PFT[84]. Studies have consistently shown that PCI-treated patients with high on-treatment platelet reactivity are at increased risk of ischaemic events including stent thrombosis, while bleeding risk is significantly higher in patients with an enhanced antiplatelet drug response (low on-treatment platelet reactivity)[84]. These observations led to the concept of a therapeutic window or "sweet-spot" of platelet inhibition[29], which could enable tailoring of antiplatelet treatment, including guiding DAPT de-escalation in ACS patients post-PCI. The TROPICAL-ACS trial[79] showed that PFT-guided de-escalation met the criteria for noninferiority, compared to standard prasugrel treatment, for a net clinical benefit endpoint, with a similar rate of ischaemic events in the two arms, with a trend toward less bleeding with guided treatment. Specific sub-groups (e.g. younger patients) derived a net clinical benefit from a guided treatment approach[85].

A recent meta-analysis (19,855 patients, 11 randomized and 3 observational studies including ACS and CCS patients)[86] showed that patients receiving guided (genotyping or PFT) de-escalation strategy experienced fewer bleeding events (RR 0.81, 95% CI 0.68-0.96) than those receiving standard DAPT. Reflecting the available evidence, recent practice guidelines[1,3] have updated their recommendations by including a Class IIb (Level of Evidence: A) recommendation on a DAPT de-escalation strategy (including but not restricted to a PFT-guided approach), which may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for 12 months of potent platelet inhibition.

Comparison of abbreviated DAPT versus de-escalation of DAPT intensity

The number of patients enrolled in trials assessing abbreviated DAPT (n=41,093) is three times more than the patients enrolled in trials assessing de-escalation of DAPT intensity (n=12,707). Although there have been no head-to-head comparisons of the two strategies, a recent network meta-analysis of 29 trials in patients with ACS undergoing PCI, showed that there was no difference in all-cause death between abbreviated DAPT and de-escalation of DAPT intensity[87]. Abbreviated DAPT reduced the occurrence of major bleeding, whilst de-escalation of DAPT intensity reduced the rate of net adverse cardiovascular events[87]. Furthermore, whilst several studies of DAPT abbreviation specifically enrolled patients at high bleeding risk, the same cannot be said about trials assessing de-escalation of DAPT intensity, so that the latter approach has less supporting evidence in HBR patients.

Optimal timing of de-escalation

De-escalation strategies may be instituted at different timepoints. De-escalation of intensity may be instituted within one week post-PCI if guided by PFT or genotyping[55] and at 1 month if unguided[75-77].

Most studies of DAPT abbreviation switched to aspirin monotherapy at 6 months, but the RESET and the REDUCE trials abbreviated DAPT after 3 months, and showed non-inferiority of 3 months of DAPT compared with 12 months DAPT with regards to the primary composite endpoint of ischemic and bleeding events[60,65]. On the other hand, most trials abbreviating DAPT and switching to P2Y12 inhibitor monotherapy, de-escalated earlier at 1-3 months. Based on the available evidence, abbreviation of DAPT duration may be considered after 1–3 months of DAPT if switching to monotherapy with ticagrelor or clopidogrel, or after 3–6 months of DAPT if switching to aspirin monotherapy.

For example, the 2020 ESC guidelines on NSTEMI recommend the use of ticagrelor monotherapy after 3 months of standard DAPT as an alternative to a standard 12-month DAPT[1].

Procedural characteristics (e.g. double stenting of coronary bifurcations, stenting of chronic total occlusion or long lesions requiring multiple stents) are associated with an increased risk of ischaemic events[1,55,88]. In such patients, standard 12-months of DAPT with prasugrel or ticagrelor or even prolongation of antiplatelet therapy beyond 12 months should be considered among low bleeding risk patients, in whom lower dose ticagrelor would be the agent of choice[89]. Overall, the duration and intensity of DAPT should be tailored to the individual's ischaemic and bleeding risks (Figure 2).

Specific evidence for de-escalation in special populations

The elderly

Elderly patients are conventionally regarded as those aged 75 years or older and represent over one third of the population with ACS[90,91]. They are at higher ischaemic as well as bleeding risk, owing to increased frailty and most frequently associated comorbidities[91]. There are few randomized trials testing de-escalation strategies or shortening of DAPT in elderly patients with ACS. Acute, periprocedural and long-term antithrombotic therapy in the elderly has been recently addressed in a consensus paper from the ESC Working Group on Thrombosis[92].

Shortening of DAPT duration

In a prespecified analysis of elderly patients enrolled in the GLOBAL LEADERS trial (>75 years; n=2,565), comparing 23-months ticagrelor monotherapy (after one month of DAPT) with 12-months DAPT followed by 12 months of aspirin, there were no significant differences between the two strategies with respect to the primary endpoint of all-cause death or new Q-wave MI[93]. Among the over 7,000 ACS-patients randomized into the TWILIGHT trial, ticagrelor monotherapy (after 3 months of DAPT) was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, without increased risk of death, MI or stroke[27]. These results were confirmed when restricted to older patients (≥65 years of age). In contrast, in the recent STOPDAPT-2 ACS study including >4,000 patients (29%: ≥75 years of age), clopidogrel monotherapy after 1-2 months of DAPT failed to achieve noninferiority to standard 12 months of DAPT for the net clinical benefit, with a numerical increase in cardiovascular events[70]. No treatment interaction by age was observed.

De-escalation of DAPT intensity

In a pre-specified analysis of the TROPICAL-ACS study, no significant differences in net clinical outcome were found between guided de-escalation and the control group in patients >70 years of age (15.5% vs. 13.6%; HR 1.17, 95% CI 0.69–2.01; p=0.56)[85]. In the TALOS-AMI trial investigating an unguided de-escalation strategy in ACS patients, only 12% of patients were ≥75 years of age, but the HRs for the primary endpoint were consistent across the prespecified age-subgroups (<75 or ≥75 years of age) showing a significant reduction in net clinical events[77]. Other studies assessing switching from potent $P2Y_{12}$ inhibitors to clopidogrel included very few elderly patients. An alternative strategy was assessed in the ANTARCTIC trial, randomly assigning elderly ACS patients to prasugrel 5 mg daily with dose or drug adjustment in case of inadequate response (including up-titration to 10 mg or down-grading to clopidogrel according to PFT results) or oral prasugrel 5 mg daily with no monitoring. The study showed comparable results with the two strategies[78].

Patients with renal impairment

Renal impairment is an important risk factor for the development of complex coronary artery disease. Although historically less likely to undergo coronary angiography and PCI, recent advancements have led to an uptrend in coronary intervention among CKD patients[94]. Patients with CKD represent a challenging group of patients for PCI, with

greater coronary calcification burden, and a higher prevalence of cardiovascular risk factors such as hypertension, hyperlipidaemia and diabetes mellitus. They are also at higher risk of in-hospital complications including death and bleeding following PCI, especially if transfemoral access is used[95,96]. Importantly, CKD is a risk factor for both long-term ischaemic and bleeding events in patients after PCI.

The ESC guidelines list baseline CKD (glomerular filtration rate [GFR] 15-59 mL/min/1.73 m^2) as a factor for DAPT extension beyond one year to reduce the risk of ischaemic events[1]. On the other hand, CKD represents a major (eGFR <30 mL/min) or minor criterion (eGFR 30-59 mL/min) to shorten the DAPT duration or de-escalate the potency of $P2Y_{12}$ inhibitor according to the ARC-HBR score[1]. Trials investigating shortening of DAPT duration or de-escalation[97] and providing a subgroup analysis for baseline CKD have shown the benefit of short DAPT in patients with CKD[9,27,80]. Although patients with CKD tend to have high coronary calcium burden and often undergo more complex PCI, sub-analyses of trials assessing shortened DAPT duration in patients undergoing complex PCI at HBR confirm the safety and efficacy of this approach in this population[74,98].

East Asian patients

East Asian patients are considered to be at lower ischaemic risk and at higher bleeding (including intracranial haemorrhage) with DAPT, referred to as the "East Asian paradox", including enhanced pharmacokinetic and pharmacodynamic profiles with ticagrelor and prasugrel in East Asian versus Caucasian subjects, and despite *CYP2C19* loss-of-function alleles being more frequent in those with East Asian ancestry[35]. Hence, when prasugrel is used, lower than conventional doses are prescribed in some East Asian countries such as Japan and Taiwan.

A recent systematic review and meta-analysis specifically assessed the safety and effectiveness of DAPT "de-escalation strategies" in East Asian versus non-East Asian patients with ACS undergoing PCI[99]. The net benefit and safety of reduction in either DAPT intensity or duration appears to be greater in East Asian that in non-East Asian patients.

The 2021 Asia Pacific Society of Cardiology Consensus Recommendations on the Use of $P2Y_{12}$ Receptor Antagonists in the Asia-Pacific Region: Special Populations[100] indicates that following a period of DAPT, use of ticagrelor monotherapy appears reasonable in patients at high ischaemic and low bleeding risk. On the other hand, clopidogrel monotherapy may be used for patients with low ischaemic risk or patients at high ischaemic and HBR. The recommendations also support the use of abbreviated DAPT in elderly patients at HBR or in patients with CKD on dialysis. For patients with diabetes undergoing complex PCI who are at HBR, ticagrelor monotherapy can be considered after 3 months of DAPT[101].

Short-Term DAPT with Early Discontinuation of Aspirin

The TICO trial showed that ticagrelor monotherapy following 3 months of DAPT, compared with 12 months of DAPT, had clinical benefit in ACS patients, mostly driven by a reduction in major bleeding[69]. Compared with 12 months of DAPT, use of $P2Y_{12}$ inhibitor monotherapy following an initial 1-3 months of DAPT has been shown to reduce the risk of clinically serious bleeding in East Asians undergoing PCI[67,102].

De-escalation of Potent $P2Y_{12}$ Inhibitors

The HOST-REDUCE-POLYTECH ACS trial found that in ACS patients treated with DAPT including 10-mg prasugrel for 1 month, the subsequent reduction to 5-mg prasugrel significantly reduced the risk of bleeding (HR 0.48; 95% CI 0.32–0.73, p=0.0007) without increasing ischaemic risk (HR 0.76; 95% CI 0.40–1.45; p=0.40) compared with continuation of the conventional dose of 10 mg.

Use of Risk Scoring to guide DAPT

The Korea Acute Myocardial Infarction Registry-National Institutes of Health combined ischaemic and bleeding models to establish a simple clinical prediction score for the use of DAPT. Patients with a high score (≥3 points) showed an overall benefit from potent $P2Y_{12}$ inhibitor versus clopidogrel in reducing 1-year ischaemic events without significant increase in bleeding, whereas in patients with a low score, the bleeding risk due to potent $P2Y_{12}$ inhibitors exceeded ischaemic benefit[103].

Current gaps in evidence

- Clarity regarding specific subsets of ACS patients that may derive the greatest net clinical benefit from DAPT de-escalation or abbreviation.
- The comparative safety and benefit of de-escalation of DAPT intensity or abbreviation of DAPT, have not been compared in head-to-head trials.
- The clinical trial evidence base for de-escalation of DAPT intensity or abbreviated DAPT in non-East Asians is not as robust as in East Asian patients.
- The optimal timepoint post-ACS (e.g. 1-3 months) for abbreviation or de-escalation of DAPT intensity, remains to be determined.
- Whether monotherapy, following abbreviated DAPT, should consist of aspirin or a $P2Y_{12}$ inhibitor, is not clear.
- Guided or unguided de-escalation of DAPT intensity have not been compared in head-to-head trials.
- DAPT de-escalation guided by genotyping or PFT have not been compared in head-to-head trials.
- Whether potent $P2Y_{12}$ inhibitor alone, from the onset of ACS, without aspirin, may be non-inferior to DAPT, is unknown. Pilot data using ticagrelor or prasugrel monotherapy in 70 ACS patients suggests this may be a feasible strategy[104], and is the subject of ongoing trials.
- Whether sex-related differences in the clinical benefit of de-escalation of DAPT intensity or abbreviation of DAPT may exist, remains to be determined.

Conclusions

The duration and intensity of DAPT should be tailored to the individual's ischaemic and bleeding risks. Both risks are highest in the early period post-ACS, then bleeding risk falls but stays constant over time while DAPT is continued. Strategies available to reduce the risk of bleeding include de-escalation of DAPT intensity or abbreviation of DAPT duration, and the two approaches have not been compared in head-to-head randomised trials. Trials have shown that de-escalation of DAPT intensity can reduce bleeding without an increase in ischaemic events in patients without high long-term ischaemic risk and may be guided by PFT or genotyping. Abbreviation of DAPT after 1-6 months reduces bleeding without an increase in ischaemic events in patients with HBR features, particularly in those without high long-term ischaemic risk. Our consensus statements should serve to guide clinicians to optimise these DAPT approaches for individual patients to improve outcomes.

Consensus statements regarding de-escalation or abbreviation of DAPT in patients with ACS undergoing PCI

1. Patients should be stratified for high ischaemic and high bleeding risk
2. Ischaemic risk is highest early after an ACS, especially within the first 30 days
3. Bleeding risk is highest during the first days (in particularly, peri-PCI), then falls and subsequently stays constant over time while DAPT is continued
4. Common risk factors for bleeding include age, CKD, anaemia, thrombocytopenia, prior spontaneous bleeding, recent surgery and active malignancy.
5. The PRECISE-DAPT and ARC-HBR scores can help risk stratify patients for bleeding whereas the DAPT score may help risk stratify patients for recurrent ischaemic events.
6. Risk factors for ischaemic risk include age, diabetes mellitus, suboptimal cardiovascular risk factor control, polyvascular disease, complex coronary artery disease, incomplete revascularization and CKD. In addition, technical aspects of PCI including longer lesion length, greater number stents, 2 stents bifurcation or treatment of a chronic total occlusion increase subsequent thrombosis risk
7. Strategies available to reduce the risk of bleeding include:
    - De-escalation of DAPT intensity (unguided, or guided by PFT or genotyping)
    - Abbreviation of DAPT duration
8. De-escalation of DAPT intensity (whether guided or unguided) appears to reduce bleeding without an increase in ischaemic events. These studies were mostly conducted in East Asian patients. In Westerners, de-escalation of DAPT intensity, from ticagrelor or prasugrel to clopidogrel, was only evaluated in two relatively small studies, one of which used PFT to guide de-escalation
9. Both genotype- and PFT-guided de-escalation of DAPT intensity, which can be started within a week of PCI, can reduce bleeding without an increase in thrombotic events, particularly in those without high long-term ischaemic risk
10. Overall, shortening of DAPT duration reduces bleeding without an increase in ischaemic events in patients with HBR features, particularly in those without high long-term ischaemic risk
11. DAPT duration may be abbreviated after 1-3 months continuing with $P2Y_{12}$ inhibitor monotherapy, in patients with HBR or in those without HBR features and without high long-term ischaemic risk
12. DAPT duration may be abbreviated after 3-6 months post-ACS, continuing with aspirin monotherapy, ideally only if HBR features are present
13. In East Asian patients, reduction in the duration or the intensity of DAPT after the acute phase appear safe strategies to reduce bleeding without an ischaemic penalty, particularly in those at high bleeding risk or low long-term ischaemic risk.

599

References

1 Collet, J. P. *et al.* 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* **42**, 1289-1367, doi:10.1093/eurheartj/ehaa575 (2021).

2 Ibanez, B. *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* **39**, 119-177, doi:10.1093/eurheartj/ehx393 (2018).

3 Neumann, F. J. *et al.* 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* **40**, 87-165, doi:10.1093/eurheartj/ehy394 (2019).

4 Costa, F. *et al.* Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* **389**, 1025-1034, doi:10.1016/S0140-6736(17)30397-5 (2017).

5 Navarese, E. P. *et al.* Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. *BMJ* **350**, h1618, doi:10.1136/bmj.h1618 (2015).

6 Wallentin, L. *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* **361**, 1045-1057, doi:10.1056/NEJMoa0904327 (2009).

7 Wiviott, S. D. *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* **357**, 2001-2015, doi:10.1056/NEJMoa0706482 (2007).

8 Pufulete, M. *et al.* Real-world bleeding in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) and prescribed different combinations of dual antiplatelet therapy (DAPT) in England: a population-based cohort study emulating a 'target trial'. *Open Heart* **9**, doi:10.1136/openhrt-2022-001999 (2022).

9 Valgimigli, M. *et al.* Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. *N Engl J Med* **385**, 1643-1655, doi:10.1056/NEJMoa2108749 (2021).

10 Kang, J. *et al.* Racial Differences in Ischaemia/Bleeding Risk Trade-Off during Anti-Platelet Therapy: Individual Patient Level Landmark Meta-Analysis from Seven RCTs. *Thromb Haemost* **119**, 149-162, doi:10.1055/s-0038-1676545 (2019).

11 Ismail, N. *et al.* Incidence and prognostic impact of post discharge bleeding post acute coronary syndrome within an outpatient setting: a systematic review. *BMJ Open* **9**, e023337, doi:10.1136/bmjopen-2018-023337 (2019).

12 Eikelboom, J. W. *et al.* Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* **114**, 774-782, doi:10.1161/CIRCULATIONAHA.106.612812 (2006).

13 Ismail, N. *et al.* Bleeding After Hospital Discharge Following Acute Coronary Syndrome: Incidence, Types, Timing, and Predictors. *J Am Heart Assoc* **8**, e013679, doi:10.1161/JAHA.119.013679 (2019).

14 Crimi, G. *et al.* Time Course of Ischemic and Bleeding Burden in Elderly Patients With Acute Coronary Syndromes Randomized to Low-Dose Prasugrel or Clopidogrel. *J Am Heart Assoc* **8**, e010956, doi:10.1161/JAHA.118.010956 (2019).

15 Amin, A. P. *et al.* Nuisance bleeding with prolonged dual antiplatelet therapy after acute myocardial infarction and its impact on health status. *J Am Coll Cardiol* **61**, 2130-2138, doi:10.1016/j.jacc.2013.02.044 (2013).

16 Jeong, Y. H. *et al.* Pharmacodynamic Profile and Prevalence of Bleeding Episode in East Asian Patients with Acute Coronary Syndromes Treated with Prasugrel Standard-Dose versus De-escalation Strategy: A Randomized A-MATCH Trial. *Thromb Haemost* **121**, 1376-1386, doi:10.1055/a-1346-3300 (2021).

17 Aradi, D. *et al.* Platelet reactivity and clinical outcomes in acute coronary syndrome patients treated with prasugrel and clopidogrel: a pre-specified exploratory analysis from the TROPICAL-ACS trial. *Eur Heart J* **40**, 1942-1951, doi:10.1093/eurheartj/ehz202 (2019).

18 Baber, U. *et al.* Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. *J Am Coll Cardiol* **67**, 2224-2234, doi:10.1016/j.jacc.2016.02.064 (2016).

19 Yeh, R. W. *et al.* Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. *JAMA* **315**, 1735-1749, doi:10.1001/jama.2016.3775 (2016).

20 Urban, P. *et al.* Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J* **40**, 2632-2653, doi:10.1093/eurheartj/ehz372 (2019).

21 Nakamura, M. *et al.* JCS 2020 Guideline Focused Update on Antithrombotic Therapy in Patients With Coronary Artery Disease. *Circ J* **84**, 831-865, doi:10.1253/circj.CJ-19-1109 (2020).

22 Wiviott, S. D. *et al.* Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* **116**, 2923-2932, doi:10.1161/CIRCULATIONAHA.107.740324 (2007).

23 Storey, R. F. *et al.* Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATelet inhibition and patient Outcomes) PLATELET substudy. *J Am Coll Cardiol* **56**, 1456-1462, doi:10.1016/j.jacc.2010.03.100 (2010).

24 Orme, R. C. *et al.* Study of Two Dose Regimens of Ticagrelor Compared with Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention for Stable

679 Coronary Artery Disease (STEEL-PCI). *Circulation* **138**, 1290-1300,
680 doi:10.1161/CIRCULATIONAHA.118.034790 (2018).

681 25 Yusuf, S. *et al.* Effects of clopidogrel in addition to aspirin in patients with acute
682 coronary syndromes without ST-segment elevation. *N Engl J Med* **345**, 494-502,
683 doi:10.1056/NEJMoa010746 (2001).

684 26 Schupke, S. *et al.* Ticagrelor or Prasugrel in Patients with Acute Coronary
685 Syndromes. *N Engl J Med* **381**, 1524-1534, doi:10.1056/NEJMoa1908973 (2019).

686 27 Mehran, R. *et al.* Ticagrelor with or without Aspirin in High-Risk Patients after PCI.
687 *N Engl J Med* **381**, 2032-2042, doi:10.1056/NEJMoa1908419 (2019).

688 28 Kang, M. G. *et al.* Prevalence of adverse events during ticagrelor versus clopidogrel
689 treatment and its association with premature discontinuation of dual antiplatelet therapy
690 in East Asian patients with acute coronary syndrome. *Front Cardiovasc Med* **9**,
691 1053867, doi:10.3389/fcvm.2022.1053867 (2022).

692 29 Sibbing, D., Steinhubl, S. R., Schulz, S., Schomig, A. & Kastrati, A. Platelet
693 aggregation and its association with stent thrombosis and bleeding in clopidogrel-
694 treated patients: initial evidence of a therapeutic window. *J Am Coll Cardiol* **56**, 317-
695 318, doi:10.1016/j.jacc.2010.03.048 (2010).

696 30 Sousa-Uva, M. *et al.* Expert position paper on the management of antiplatelet
697 therapy in patients undergoing coronary artery bypass graft surgery. *Eur Heart J* **35**,
698 1510-1514, doi:10.1093/eurheartj/ehu158 (2014).

699 31 Jones, W. S. *et al.* Comparative Effectiveness of Aspirin Dosing in Cardiovascular
700 Disease. *N Engl J Med* **384**, 1981-1990, doi:10.1056/NEJMoa2102137 (2021).

701 32 Investigators, C.-O. *et al.* Dose comparisons of clopidogrel and aspirin in acute
702 coronary syndromes. *N Engl J Med* **363**, 930-942, doi:10.1056/NEJMoa0909475
703 (2010).

704 33 Friberg, L., Rosenqvist, M. & Lip, G. Y. Evaluation of risk stratification schemes
705 for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the
706 Swedish Atrial Fibrillation cohort study. *Eur Heart J* **33**, 1500-1510,
707 doi:10.1093/eurheartj/ehr488 (2012).

708 34 Gorog, D. A. *et al.* Assessment and Mitigation of Bleeding Risk in Atrial
709 Fibrillation and Venous Thromboembolism: Executive Summary of a European and
710 Asia-Pacific Expert Consensus Paper. *Thromb Haemost* **122**, 1625-1652, doi:10.1055/s-
711 0042-1750385 (2022).

712 35 Kim, H. K. *et al.* The East Asian Paradox: An Updated Position Statement on the
713 Challenges to the Current Antithrombotic Strategy in Patients with Cardiovascular
714 Disease. *Thromb Haemost* **121**, 422-432, doi:10.1055/s-0040-1718729 (2021).

715 36 Abtan, J. *et al.* Residual Ischemic Risk and Its Determinants in Patients With
716 Previous Myocardial Infarction and Without Prior Stroke or TIA: Insights From the
717 REACH Registry. *Clin Cardiol* **39**, 670-677, doi:10.1002/clc.22583 (2016).

37 Lafitte, M. *et al.* After acute coronary syndrome, diabetic patients with peripheral vascular disease remain at high risk of cardiovascular events despite secondary prevention measures. *Arch Cardiovasc Dis* **103**, 97-105, doi:10.1016/j.acvd.2009.12.003 (2010).

38 Leonardi, S. *et al.* Optimised care of elderly patients with acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care* **7**, 287-295, doi:10.1177/2048872618761621 (2018).

39 D'Ascenzo, F. *et al.* Incidence and predictors of coronary stent thrombosis: evidence from an international collaborative meta-analysis including 30 studies, 221,066 patients, and 4276 thromboses. *Int J Cardiol* **167**, 575-584, doi:10.1016/j.ijcard.2012.01.080 (2013).

40 Gosling, R. *et al.* Comparison of P2Y(12) inhibitors for mortality and stent thrombosis in patients with acute coronary syndromes: Single center study of 10 793 consecutive 'real-world' patients. *Platelets* **28**, 767-773, doi:10.1080/09537104.2017.1280601 (2017).

41 Palmerini, T. *et al.* Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. *Eur Heart J* **38**, 1034-1043, doi:10.1093/eurheartj/ehw627 (2017).

42 Grines, C. L. *et al.* Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* **115**, 813-818, doi:10.1161/CIRCULATIONAHA.106.180944 (2007).

43 Iakovou, I. *et al.* Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* **293**, 2126-2130, doi:10.1001/jama.293.17.2126 (2005).

44 Spertus, J. A. *et al.* Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* **113**, 2803-2809, doi:10.1161/CIRCULATIONAHA.106.618066 (2006).

45 Zwart, B., Godschalk, T. C., Kelder, J. C. & Ten Berg, J. M. High risk of stent thrombosis in the first 6 months after coronary stenting: Do not discontinue clopidogrel early after ACS. *J Interv Cardiol* **30**, 421-426, doi:10.1111/joic.12413 (2017).

46 Schoos, M. *et al.* Patterns and Impact of Dual Antiplatelet Cessation on Cardiovascular Risk After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndromes. *Am J Cardiol* **123**, 709-716, doi:10.1016/j.amjcard.2018.11.051 (2019).

47 Giustino, G. *et al.* Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol* **65**, 1298-1310, doi:10.1016/j.jacc.2015.01.039 (2015).

48 D'Ascenzo, F. *et al.* Average daily ischemic versus bleeding risk in patients with ACS undergoing PCI: Insights from the BleeMACS and RENAMI registries. *Am Heart J* **220**, 108-115, doi:10.1016/j.ahj.2019.10.001 (2020).

49 Costa, F. *et al.* Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. *J Am Coll Cardiol* **73**, 741-754, doi:10.1016/j.jacc.2018.11.048 (2019).

50 Kawashima, H. *et al.* Comparative Assessment of Predictive Performance of PRECISE-DAPT, CRUSADE, and ACUITY Scores in Risk Stratifying 30-Day Bleeding Events. *Thromb Haemost* **120**, 1087-1095, doi:10.1055/s-0040-1712449 (2020).

51 Mihatov, N. *et al.* Utility of the dual antiplatelet therapy score to guide antiplatelet therapy: A systematic review and meta-analysis. *Catheter Cardiovasc Interv* **97**, 569-578, doi:10.1002/ccd.29352 (2021).

52 Bonaca, M. P. *et al.* Patient selection for long-term secondary prevention with ticagrelor: insights from PEGASUS-TIMI 54. *Eur Heart J* **43**, 5037-5044, doi:10.1093/eurheartj/ehac402 (2022).

53 Angiolillo, D. J., Galli, M., Collet, J. P., Kastrati, A. & O'Donoghue, M. L. Antiplatelet therapy after percutaneous coronary intervention. *EuroIntervention* **17**, e1371-e1396, doi:10.4244/EIJ-D-21-00904 (2022).

54 Chau, K. H. *et al.* Stent Thrombosis Risk Over Time on the Basis of Clinical Presentation and Platelet Reactivity: Analysis From ADAPT-DES. *JACC Cardiovasc Interv* **14**, 417-427, doi:10.1016/j.jcin.2020.12.005 (2021).

55 Galli, M. & Angiolillo, D. J. De-escalation of antiplatelet therapy in acute coronary syndromes: Why, how and when? *Front Cardiovasc Med* **9**, 975969, doi:10.3389/fcvm.2022.975969 (2022).

56 Costa, F. *et al.* A 4-item PRECISE-DAPT score for dual antiplatelet therapy duration decision-making. *Am Heart J* **223**, 44-47, doi:10.1016/j.ahj.2020.01.014 (2020).

57 Tavenier, A. H. *et al.* Guided and unguided de-escalation from potent P2Y12 inhibitors among patients with acute coronary syndrome: a meta-analysis. *Eur Heart J Cardiovasc Pharmacother* **8**, 492-502, doi:10.1093/ehjcvp/pvab068 (2022).

58 Kang, J. *et al.* Dual antiplatelet therapy de-escalation in acute coronary syndrome: an individual patient meta-analysis. *Eur Heart J*, doi:10.1093/eurheartj/ehac829 (2023).

59 Gwon, H. C. *et al.* Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* **125**, 505-513, doi:10.1161/CIRCULATIONAHA.111.059022 (2012).

60 Kim, B. K. *et al.* A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following

Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* **60**, 1340-1348, doi:10.1016/j.jacc.2012.06.043 (2012).

61 Han, Y. *et al.* Six Versus 12 Months of Dual Antiplatelet Therapy After Implantation of Biodegradable Polymer Sirolimus-Eluting Stent: Randomized Substudy of the I-LOVE-IT 2 Trial. *Circ Cardiovasc Interv* **9**, e003145, doi:10.1161/CIRCINTERVENTIONS.115.003145 (2016).

62 Hahn, J. Y. *et al.* 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet* **391**, 1274-1284, doi:10.1016/S0140-6736(18)30493-8 (2018).

63 Kedhi, E. *et al.* Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. *BMJ* **363**, k3793, doi:10.1136/bmj.k3793 (2018).

64 Lee, B. K. *et al.* Safety of six-month dual antiplatelet therapy after second-generation drug-eluting stent implantation: OPTIMA-C Randomised Clinical Trial and OCT Substudy. *EuroIntervention* **13**, 1923-1930, doi:10.4244/EIJ-D-17-00792 (2018).

65 De Luca, G. *et al.* Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). *EuroIntervention* **15**, e990-e998, doi:10.4244/EIJ-D-19-00539 (2019).

66 Vranckx, P. *et al.* Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* **392**, 940-949, doi:10.1016/S0140-6736(18)31858-0 (2018).

67 Hahn, J. Y. *et al.* Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. *JAMA* **321**, 2428-2437, doi:10.1001/jama.2019.8146 (2019).

68 Baber, U. *et al.* Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. *Eur Heart J* **41**, 3533-3545, doi:10.1093/eurheartj/ehaa670 (2020).

69 Kim, B. K. *et al.* Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. *JAMA* **323**, 2407-2416, doi:10.1001/jama.2020.7580 (2020).

70 Watanabe, H. *et al.* Comparison of Clopidogrel Monotherapy After 1 to 2 Months of Dual Antiplatelet Therapy With 12 Months of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome: The STOPDAPT-2 ACS Randomized Clinical Trial. *JAMA Cardiol* **7**, 407-417, doi:10.1001/jamacardio.2021.5244 (2022).

71 Valgimigli, M. *et al.* Ticagrelor Monotherapy Versus Dual-Antiplatelet Therapy After PCI: An Individual Patient-Level Meta-Analysis. *JACC Cardiovasc Interv* **14**, 444-456, doi:10.1016/j.jcin.2020.11.046 (2021).

72 Valgimigli, M. *et al.* P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *BMJ* **373**, n1332, doi:10.1136/bmj.n1332 (2021).

73 Smits, P. C. *et al.* Abbreviated Antiplatelet Therapy After Coronary Stenting in Patients With Myocardial Infarction at High Bleeding Risk. *J Am Coll Cardiol* **80**, 1220-1237, doi:10.1016/j.jacc.2022.07.016 (2022).

74 Valgimigli, M. *et al.* Duration of antiplatelet therapy after complex percutaneous coronary intervention in patients at high bleeding risk: a MASTER DAPT trial sub-analysis. *Eur Heart J* **43**, 3100-3114, doi:10.1093/eurheartj/ehac284 (2022).

75 Cuisset, T. *et al.* Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J* **38**, 3070-3078, doi:10.1093/eurheartj/ehx175 (2017).

76 Kim, H. S. *et al.* Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet* **396**, 1079-1089, doi:10.1016/S0140-6736(20)31791-8 (2020).

77 Kim, C. J. *et al.* Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. *Lancet* **398**, 1305-1316, doi:10.1016/S0140-6736(21)01445-8 (2021).

78 Cayla, G. *et al.* Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet* **388**, 2015-2022, doi:10.1016/S0140-6736(16)31323-X (2016).

79 Sibbing, 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. *Lancet* **390**, 1747-1757, doi:10.1016/S0140-6736(17)32155-4 (2017).

80 Claassens, D. M. F. *et al.* A Genotype-Guided Strategy for Oral P2Y(12) Inhibitors in Primary PCI. *N Engl J Med* **381**, 1621-1631, doi:10.1056/NEJMoa1907096 (2019).

81 Hwang, D. *et al.* Prasugrel Dose De-escalation Therapy After Complex Percutaneous Coronary Intervention in Patients With Acute Coronary Syndrome: A Post Hoc Analysis From the HOST-REDUCE-POLYTECH-ACS Trial. *JAMA Cardiol* **7**, 418-426, doi:10.1001/jamacardio.2022.0052 (2022).

82 Angiolillo, D. J. *et al.* Derivation, Validation, and Prognostic Utility of a Prediction Rule for Nonresponse to Clopidogrel: The ABCD-GENE Score. *JACC Cardiovasc Interv* **13**, 606-617, doi:10.1016/j.jcin.2020.01.226 (2020).

83 Roberts, J. D. *et al.* Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet* **379**, 1705-1711, doi:10.1016/S0140-6736(12)60161-5 (2012).

84 Sibbing, D. *et al.* Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y(12) Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* **12**, 1521-1537, doi:10.1016/j.jcin.2019.03.034 (2019).

85 Sibbing, D. *et al.* Age and outcomes following guided de-escalation of antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: results from the randomized TROPICAL-ACS trial. *Eur Heart J* **39**, 2749-2758, doi:10.1093/eurheartj/ehy332 (2018).

86 Galli, M. *et al.* Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Lancet* **397**, 1470-1483, doi:10.1016/S0140-6736(21)00533-X (2021).

87 Laudani, C. *et al.* Short Duration of DAPT Versus De-Escalation After Percutaneous Coronary Intervention for Acute Coronary Syndromes. *JACC Cardiovasc Interv* **15**, 268-277, doi:10.1016/j.jcin.2021.11.028 (2022).

88 Giustino, G. *et al.* Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. *J Am Coll Cardiol* **68**, 1851-1864, doi:10.1016/j.jacc.2016.07.760 (2016).

89 Bonaca, M. P. *et al.* Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* **372**, 1791-1800, doi:10.1056/NEJMoa1500857 (2015).

90 Garcia-Blas, S. *et al.* Acute Coronary Syndrome in the Older Patient. *J Clin Med* **10**, doi:10.3390/jcm10184132 (2021).

91 Kayani, W. T., Khan, M. R., Deshotels, M. R. & Jneid, H. Challenges and Controversies in the Management of ACS in Elderly Patients. *Curr Cardiol Rep* **22**, 51, doi:10.1007/s11886-020-01298-x (2020).

92 Andreotti, F. *et al.* Acute, periprocedural and longterm antithrombotic therapy in older adults. *Eur Heart J* **44**, 262-279, doi:10.1093/eurheartj/ehac515 (2023).

93 Tomaniak, M. *et al.* Ticagrelor monotherapy beyond one month after PCI in ACS or stable CAD in elderly patients: a pre-specified analysis of the GLOBAL LEADERS trial. *EuroIntervention* **15**, e1605-e1614, doi:10.4244/EIJ-D-19-00699 (2020).

94 Patel, B., Shah, M., Dusaj, R., Maynard, S. & Patel, N. Percutaneous coronary intervention and inpatient mortality in patients with advanced chronic kidney disease presenting with acute coronary syndrome. *Proc (Bayl Univ Med Cent)* **30**, 400-403, doi:10.1080/08998280.2017.11930205 (2017).

95 Gupta, T. *et al.* Association of chronic renal insufficiency with in-hospital outcomes after percutaneous coronary intervention. *J Am Heart Assoc* **4**, e002069, doi:10.1161/JAHA.115.002069 (2015).

96 Latif, A. *et al.* Meta-Analysis of Transradial Versus Transfemoral Access for Percutaneous Coronary Intervention in Patients With Chronic Kidney Disease. *Am J Cardiol* **157**, 8-14, doi:10.1016/j.amjcard.2021.07.018 (2021).

97 Gelbenegger, G. *et al.* Optimal duration and combination of antiplatelet therapies following percutaneous coronary intervention: a meta-analysis. *Vascul Pharmacol* **138**, 106858, doi:10.1016/j.vph.2021.106858 (2021).

98 Dangas, G. *et al.* Ticagrelor With or Without Aspirin After Complex PCI. *J Am Coll Cardiol* **75**, 2414-2424, doi:10.1016/j.jacc.2020.03.011 (2020).

99 Gorog, D. A. *et al.* Comparison of de-escalation of DAPT intensity or duration in East Asian and Western patients with ACS undergoing PCI: a systematic review and meta-analysis. *Thrombosis and Haemostasis* **In press** (2023).

100 Tan, J. W. *et al.* 2020 Asian Pacific Society of Cardiology Consensus Recommendations on the Use of P2Y(12) Receptor Antagonists in the Asia-Pacific Region. *Eur Cardiol* **16**, e02, doi:10.15420/ecr.2020.40 (2021).

101 Tan, J. W. C. *et al.* 2021 Asian Pacific Society of Cardiology Consensus Recommendations on the Use of P2Y1(2) Receptor Antagonists in the Asia-Pacific Region: Special Populations. *Eur Cardiol* **16**, e43, doi:10.15420/ecr.2021.35 (2021).

102 Watanabe, H. *et al.* Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. *JAMA* **321**, 2414-2427, doi:10.1001/jama.2019.8145 (2019).

103 Lee, S. H. *et al.* Practical guidance for P2Y12 inhibitors in acute myocardial infarction undergoing percutaneous coronary intervention. *Eur Heart J Cardiovasc Pharmacother* **7**, 112-124, doi:10.1093/ehjcvp/pvaa005 (2021).

104 van der Sangen, N. M. R. *et al.* Single antiplatelet therapy directly after percutaneous coronary intervention in non-ST-segment elevation acute coronary syndrome patients: the OPTICA study. *EuroIntervention*, doi:10.4244/EIJ-D-22-00886 (2023).

Disclosures

J Ako reports speaking honoraria from Astra Zeneca, Daiichi-Sankyo, and Bayer

JL Ferreiro reports: a) speaker fees from Eli Lilly Co, Daiichi Sankyo, Inc., AstraZeneca, Roche Diagnostics, Pfizer, Abbott, Ferrer, Rovi, Boehringer Ingelheim, Bristol-Myers Squibb and Terumo; b) consulting fees from AstraZeneca, Eli Lilly Co., Ferrer, Boston Scientific, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Bristol-Myers Squibb and Biotronik; c) research grant from AstraZeneca.

T Geisler reports speaker, consultant fees or research grants from Astra Zeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Edwards Lifescience, Ferrer/Chiesi, Medtronic not related to the submitted work.

DA Gorog reports institutional research grants from AstraZeenca, Werfen, Medtronic, Bayer and Alpha MD, and speaker frees from AstraZeneca.

S Halvorsen has received speaker fees from Astra Zeneca, BMS/Pfizer, Sanofi and Novartis. No fees are received personally.

GYH Lip reports consultant and speaker activities for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo and Anthos. No fees are received personally.

EP Navarese reports research grants from Abbott, Amgen, and lecture fees/honoraria from Amgen, AstraZeneca, Bayer, Pfizer, and Sanofi-Regeneron, outside the submitted work.

RF Storey reports institutional research grants/support from AstraZeneca, Cytosorbents, GlyCardial Diagnostics and Thromboserin; and personal fees from Alnylam, AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, Chiesi, CSL Behring, Cytosorbents, Daiichi Sankyo, GlyCardial Diagnostics, Hengrui, Idorsia, Intas Pharmaceuticals, Medscape, Novartis, PhaseBio, Sanofi Aventis and Thromboserin.

JM Siller-Matula has received speaker or consultant fees from Chiesi, Biosensors, Boston Scientific, P&F, Boehringer Ingelheim and Daiichi Sankyo not related to the submitted work.

YH Jeong reports: a) speaker fees from Daiichi Sankyo, Sanofi-Aventis, Han-mi Pharmaceutical, and JW Pharmaceutical; b) research grants from Yuhan Pharmaceuticals, Han-mi Pharmaceuticals, Sam-jin Pharmaceuticals, Biotronik, and U&I Corporation.

D Sibbing reports speaker fees and fees for advisory board activities from Sanofi Aventis and Bayer

JWC Tan reports honoraria from AstraZeneca, Bayer, Amgen, Medtronic, Abbott Vascular, Biosensors, Alvimedica, Boehringer Ingelheim and Pfizer; research and educational grants from Medtronic, Biosensors, Biotronik, Philips, Amgen, AstraZeneca, Roche, Otsuka, Terumo and Abbott Vascular; and consulting fees from Elixir and CSL Behring.

JM ten Berg received advisory/consulting/speakers fees from AstraZeneca, Eli Lilly, Daiichi Sankyo, Boehringer Ingelheim, BMS, Pfizer, Bayer, Ferrer, CeleCOR and Institutional Research grants: ZonMw (Dutch Government), AstraZeneca, Daiichi-Sankyo

M Valgimigli 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.

C Vandenbriele reports speaker fees from Bayer, Boehringer Ingelheim and Daiichi-Sankyo not related to the submitted work.

The other authors have no disclosures to declare.

Figure legends

Figure 1. Standard and alternative antithrombotic strategies to reduce bleeding risk in acute coronary syndrome patients.

Abbreviations: ASA: aspirin; DAPT: dual antiplatelet therapy; HBR: high bleeding risk; SAPT: single antiplatelet therapy

Figure 2. Algorithm to select dual antithrombotic therapy strategies in ACS patients undergoing PCI.

Abbreviations: ASA: aspirin; DAPT: dual antiplatelet therapy; DAT: dual antithrombotic therapy; HBR: high bleeding risk; HIR: high ischaemic risk; SAPT: single antiplatelet therapy

*Clopidogrel is the most studied $P2Y_{12}$ inhibitor in this setting.

**Ticagrelor is the most studied $P2Y_{12}$ inhibitor in this setting.

Tables

Table 1. Factors that increase the risk of bleeding and/or ischaemic events

Table 2. Bleeding hazard associated with oral antiplatelet drugs

Table 3. Randomized clinical trials evaluating abbreviated DAPT in patients with ACS undergoing PCI

Table 4. Randomized clinical trials evaluating de-escalation of DAPT intensity in patients with ACS undergoing PCI