

2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA)

Gregory Y.H. Lip (Chair)^{1,2,3*}, Jean-Phillippe Collet (Co-Chair)⁴, Michael Haude (Co-Chair)⁵, Robert Byrne^{6,7}, Eugene H. Chung⁸, Laurent Fauchier⁹, Sigrun Halvorsen¹⁰, Dennis Lau¹¹, Nestor Lopez-Cabanillas¹², Maddalena Lettino¹³, Francisco Marin¹⁴, Israel Obel¹⁵, Andrea Rubboli¹⁶, Robert F. Storey¹⁷, Marco Valgimigli¹⁸, and Kurt Huber (Co-Chair)¹⁹

* Corresponding author. Tel: +44 121 5075080. E-mail address: g.y.h.lip@bham.ac.uk

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ESC Scientific Document Group: Tatjana Potpara (Review Coordinator)²⁰, Carina Blomström Lundqvist²¹, Harry Crijns²², Jan Steffel²³, Hein Heidbüchel²⁴, Goran Stankovic²⁵, Juhani Airaksinen²⁶, Jurrien M. Ten Berg²⁷, Davide Capodanno²⁸, Stefan James²⁹, Hector Bueno^{30,31}, Joao Morais³², Dirk Sibbing³³, Bianca Rocca³⁴, Ming-Hsiung Hsieh³⁵, Nazem Akoum³⁶, Deborah J. Lockwood³⁷, Jorge Rafael Gomez Flores³⁸, Ronald Jardine³⁹

¹Institute of Cardiovascular Sciences, University of Birmingham, UK; ²Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; ³Department of Clinical Medicine, Aalborg Thrombosis Research Unit, Aalborg University, Aalborg, Denmark; ⁴Sorbonne Université Paris 6, ACTION Study Group (www.action-coeur.org), Institut de Cardiologie Hôpital Pitié-Salpêtrière (APHP), INSERM UMRS, Paris, France; ⁵Städtische Kliniken Neuss Lukaskrankenhaus GmbH Kardiologie, Nephrologie, Pneumologie, Neuss, Germany; ⁶Deutsches Herzzentrum München, Munich, Germany; ⁷DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany; ⁸University of North Carolina at Chapel Hill, Medicine, Cardiology, Electrophysiology, Chapel Hill, NC, USA; ⁹Centre Hospitalier Universitaire Trousseau et Faculté de Médecine—Université François Rabelais, Tours, France; ¹⁰Department of Cardiology, Oslo University Hospital Ullevål, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway; ¹¹Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia; ¹²Clinica Adventista Belgrano, Instituto Del Corazon, Buenos Aires, Argentina; ¹³Cardiology Department, Humanitas Research Hospital, Rozzano, MI, Italy; ¹⁴Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; ¹⁵Milpark Hospital, Cardiology Unit, Johannesburg, South Africa; ¹⁶Division of Cardiology, Laboratory of Interventional Cardiology, Ospedale Maggiore, Bologna, Italy; ¹⁷Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK; ¹⁸Inselspital, Cardiology, Bern, Switzerland; ¹⁹3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminenhospital Vienna, Vienna, Austria; ²⁰School of Medicine, Belgrade University, Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia; ²¹Department of Medical Science and Cardiology, Uppsala University, Uppsala, Sweden; ²²Cardiology Department, Maastricht UMC+, Maastricht, Netherlands; ²³University Heart Center Zurich, Zurich, Switzerland; ²⁴Antwerp University and University Hospital, Antwerp, Belgium; ²⁵Department of Cardiology, Clinical Center of Serbia, Belgrade, Serbia; ²⁶Turku University Hospital, Cardiology, Department of Internal Medicine, Turku, Finland; ²⁷St. Antonius Hospital, Cardiology Department, Nieuwegein, Netherlands; ²⁸Ferrarotto Hospital, Azienda Ospedaliero-Univ, Policlinico-Vittorio Emanuele, University of Catania, Cardiology Department, University of Catania, Catania, Italy; ²⁹Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University, Senior Interventional Cardiologist, Uppsala University Hospital, Uppsala, Sweden; ³⁰Centro Nacional de Investigaciones Cardiovasculares (CNIC), Melchor Fernandez Almagro, Madrid, Spain; ³¹Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain; ³²Department of Cardiology, Leiria Hospital Centre, Portugal; ³³Oberarzt, Medizinische Klinik und Poliklinik I, Ludwig-Maximilians-Universität (LMU), Campus Großhadern, München, Germany; ³⁴Department of Pharmacology, Catholic University School of Medicine, Rome, Italy; ³⁵Taipei Medical University, Taipei, Taiwan; ³⁶Cardiology Department, University of Washington, Seattle, USA; ³⁷OU Heart Rhythm Institute, OU Health Sciences Center, Oklahoma, USA; ³⁸Instituto Nacional de Cardiología I. Chavez, Electrofisiología, Mexico, DF Mexico; and ³⁹Linmed Hospital, Benoni, South Africa

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In 2014, a joint consensus document dealing with the management of antithrombotic therapy in atrial fibrillation (AF) patients presenting with acute coronary syndrome (ACS) and/or undergoing percutaneous coronary or valve interventions was published, which represented an effort of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Since publication of this document, additional data from observational cohorts, randomized controlled trials, and percutaneous interventions as well as new guidelines have been published. Moreover, new drugs and devices/interventions are also available, with an increasing evidence base. The approach to managing AF has also evolved towards a more integrated or holistic approach. In recognizing these advances since the last consensus document, EHRA, WG Thrombosis, EAPCI, and ACCA, with additional contributions from HRS, APHRS, Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA), proposed a focused update, to include the new data, with the remit of comprehensively reviewing the available evidence and publishing a focused update consensus document on the management of antithrombotic therapy in AF patients presenting with ACS and/or undergoing percutaneous coronary or valve interventions, and providing up-to-date consensus recommendations for use in clinical practice.

Keywords

European Heart Rhythm Association • Consensus document • Position paper • Atrial fibrillation • Acute coronary syndrome • Coronary artery disease • Myocardial infarction • Percutaneous coronary intervention • Stent • Antithrombotic therapy • Antiplatelet agents • Anticoagulation • Vitamin K antagonists • Non-vitamin K antagonist oral anticoagulants • Low molecular weight heparin • Parenteral anticoagulants • Left atrial appendage occlusion • Stroke • Thromboembolism • Thrombosis • Bleeding

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Introduction

In 2014, a joint consensus document dealing with the management of antithrombotic therapy in atrial fibrillation (AF) patients presenting with acute coronary syndrome (ACS) and/or undergoing percutaneous coronary (PCI) or valve interventions was published, which represented an effort of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS).¹ Since publication of this document, additional data from observational cohorts, randomized trials, and percutaneous interventions have been published. New guidelines on AF from the ESC² and APHRS,³ and European ST-elevation myocardial infarction (STEMI) management⁴ as well as a focused update on dual antiplatelet therapy (DAPT)⁵ have been published.

This year, we saw publication of the 2018 update of the EHRA practical guide on the use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with AF⁶ and we expect new AF guidelines from North America from the American College of Chest Physicians (ACCP) and American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS).

We also recognized that the approach to managing AF has evolved towards an integrated or holistic approach, with the three essential components of the patient management pathway as follows:⁷ (i) Avoid stroke with Anticoagulation therapy; (ii) Better symptom management, with a patient-centred, symptom-directed decision making with regard to rate or rhythm control; and (iii) Cardiovascular and comorbidity risk factor management, i.e. addressing lifestyle changes and associated risks including hypertension, sleep apnoea, cardiac ischaemia, etc. This has been referred to as the ABC (Atrial fibrillation Better Care) pathway.⁷

In recognizing these advances since the last consensus document, EHRA, WG Thrombosis, EAPCI, and ACCA, with additional contributions from HRS, APHRS, Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA), proposed a focused update to include the new data, with the remit of comprehensively reviewing the available evidence and publishing a focused update consensus document on the management of antithrombotic therapy in AF patients presenting with ACS and/or undergoing PCI or valve interventions (e.g. transcatheter aortic valve replacement), and providing up-to-date consensus recommendations for use in clinical practice. However, the ultimate

decision on management must be made between the healthcare provider and the patient in light of all individual factors presented.

Evidence review

This document was prepared by the Task Force with representation from EHRA, WG Thrombosis, EAPCI, and ACCA, with additional contributions from HRS, APHRS, LAHRS and CASSA, and peer-reviewed by official external reviewers representing all these bodies. Their members made a detailed literature review, weighing the strength of evidence for or against a specific treatment or procedure, and including estimates of expected health outcomes where data exist. In controversial areas, or with respect to issues without evidence other than usual clinical practice, a consensus was achieved by agreement of the expert panel after thorough deliberation.

We opted for an easier and user-friendly system of ranking using 'coloured hearts' that should allow physicians to easily assess the current status of the evidence and consequent guidance (Table 1). This EHRA grading of consensus statements does not have separate definitions of the level of evidence. This categorization, used for consensus statements, must not be considered as directly similar to that used for official society guideline recommendations, which apply a classification (Class I–III) and level of evidence (A, B, and C) to recommendations used in official guidelines.

Thus, a green heart indicates a 'should do this' consensus statement or indicated treatment or procedure that is based on at least one randomized trial, or is supported by strong observational evidence that it is beneficial and effective. A yellow heart indicates general agreement and/or scientific evidence favouring a 'may do this' statement or the usefulness/efficacy of a treatment or procedure. A 'yellow heart' symbol may be supported by randomized trials based on a small number of patients or which is not widely applicable. Treatment strategies for which there is scientific evidence of potential harm and should not be used ('do not do this') are indicated by a red heart.




An overview of new data since last version of the document

Observational cohorts

Since the publication of the previous consensus document, at least 30 observational reports on patients on oral anticoagulation (OAC) presenting with ACS and/or undergoing PCI have been published^{8–37} (Supplementary material online, Table Sw1).

A total of 171 026 patients have been included, with AF being the most frequent, albeit not the only, indication for OAC. For 29 418 patients, information on the different antithrombotic strategies was provided: 7656 (26%) received triple antithrombotic therapy (TAT) of OAC, aspirin and a P2Y₁₂-receptor inhibitor (generally clopidogrel), 21 279 (72%) DAPT of aspirin and P2Y₁₂-receptor inhibitor (generally clopidogrel), and 483 (2%) dual antithrombotic therapy (DAT) of OAC and either aspirin or clopidogrel. In all studies, except three^{14,15,21} where approximately 50%, 39%, and 8% of patients, respectively, received a NOAC as part of the antithrombotic regimen, OAC consisted of a vitamin K-antagonist (VKA), generally warfarin (Supplementary material online, Table Sw1). Indication for PCI

Table 1 Scientific rationale of recommendations^a

Definitions where related to a treatment or procedure	Consensus statement instruction	Symbol
Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial or is supported by strong observational evidence and authors' consensus (as indicated by an asterisk).	'Should do this'	
General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on a small number of patients or which is not widely applicable.	'May do this'	
Scientific evidence or general agreement not to use or recommend a treatment or procedure.	'Do not do this'	

^aThis categorization for our consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations.

included, in most cases, either ACS or stable coronary artery disease (CAD). The majority were retrospective analyses of either small-size databases or large, multicentre nationwide registries that had generally been set up for other purposes. In only a few cases, the data were derived from prospective, observational registries specifically designed to evaluate the management strategies and outcomes of OAC patients undergoing PCI. Length of follow-up was variable, ranging from in-hospital to 6 years (Supplementary material online, Table Sw1) between 1999 and 2015.

Overall, TAT was consistently associated with a significantly increased risk of total and/or major bleeding compared with other antithrombotic regimens. The risk of (major) bleeding may be inversely related to the quality of OAC, measured as time in therapeutic range (TTR) for patients receiving a VKA.⁸ The bleeding risk profile may impact on the occurrence of major bleeding more than the antithrombotic combination.¹⁰ The rates of major adverse cardiovascular and cerebrovascular events (MACCE) were similar irrespective of the antithrombotic regimen and/or use of OAC.

The limitations of these studies include the lack of randomization and associated selection bias in the prescription of the various antithrombotic regimens, as well as the lack of systematic bleeding risk assessment, incomplete information on adherence to treatment and TTR values, the independent contribution of periprocedural management on the occurrence of MACCE and bleeding, and the alterations in the prescribed antithrombotic therapy subsequent to an ischaemic or haemorrhagic event.

In patients with CHA₂DS₂-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female)] score 1 when compared with ≥2, the efficacy of TAT in the prevention of stroke and/or systemic embolism was not statistically superior to DAPT²² (Supplementary material online, Table Sw1). In general, these data

have to be interpreted with caution as this registry study was small and not randomized. The use of the newer, more potent P2Y₁₂-receptor inhibitors, prasugrel and ticagrelor as part of a TAT regime, has been associated with an increased risk of bleeding events. No specific information on the relative efficacy and safety of NOACs, either as a category or as individual agents, can be derived from available observational data. Further data are expected to come from the observational, multicentre AVIATOR 2 registry.³⁸ This study was capped after including 500 (of the originally planned 2500) AF patients undergoing PCI and evaluates MACCE and bleeding rates.

New randomized controlled trials on antithrombotic therapy

Oral anticoagulants

Since publication of the 2014 consensus document, two randomized controlled trials on NOAC vs. VKA in combination with antiplatelets for patients with AF undergoing PCI have been published primarily investigating safety,^{39,40} and at least two large trials are ongoing.

In the randomized PIONEER AF PCI trial (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban, and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), 2124 participants with non-valvular AF who had undergone PCI with stenting (about 30% of patients had a troponin-positive ACS and about 20% had unstable angina as index event) were randomly assigned to DAT with 'low-dose' rivaroxaban [15 mg od (once daily)] plus a P2Y₁₂ inhibitor for 12 months (Group 1), novel TAT with 'very-low-dose' rivaroxaban [2.5 mg bid (twice daily)] plus DAPT for 1, 6, or 12 months (Group 2), or standard therapy with a dose-adjusted VKA (od) plus DAPT for 1, 6, or 12 months (Group 3).³⁹

The primary endpoint of the trial was clinically-significant bleeding. The rates of clinically-significant bleeding were lower in the two groups receiving rivaroxaban than in the group receiving standard therapy (16.8% in Group 1, 18.0% in Group 2, and 26.7% in Group 3; $P < 0.001$ for both comparisons). There were no statistically significant differences in the rates of death from cardiovascular causes, myocardial infarction (MI), or stroke, although the study was not powered for efficacy and the observed broad confidence intervals (CIs) diminish the surety of any conclusions. No power calculation in this exploratory trial, recruitment was not event-driven, and that prior stroke was an exclusion criteria (which led to the selection of low risk patients).

In the Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) study,^{39,40} DAT with dabigatran etexilate (110 or 150 mg bid) and a P2Y₁₂ inhibitor (either clopidogrel or ticagrelor) was compared with TAT with warfarin, a P2Y₁₂ inhibitor (either clopidogrel or ticagrelor), and low-dose aspirin (for 1 or 3 months, depending on stent type) in 2725 non-valvular AF patients who had undergone PCI with stenting. The primary endpoint was major or clinically-relevant non-major bleeding during follow-up, as defined by the International Society on Thrombosis and Hemostasis (ISTH). The trial also tested for the non-inferiority of dual therapy with dabigatran (both doses combined) to TAT with warfarin with respect to the incidence of a composite efficacy Endpoint of thromboembolic events (MI, stroke, or systemic embolism), death, or unplanned revascularization. Approximately half of the patients had an ACS. Most of the patients received clopidogrel as the P2Y₁₂ inhibitor; only 12.0% received ticagrelor. Drug-eluting stents alone were used in 82.6% of the patients.

In RE-DUAL PCI, the incidence of the primary endpoint was 15.4% in the 110-mg DAT group when compared with 26.9% in the TAT group [hazard ratio (HR) 0.52, 95% CI 0.42–0.63; $P < 0.001$ for non-inferiority; $P < 0.001$ for superiority] and 20.2% in the 150-mg DAT group when compared with 25.7% in the corresponding TAT group, which did not include elderly patients outside the United States (HR 0.72, 95% CI 0.58–0.88; $P < 0.001$ for non-inferiority). The incidence of the composite efficacy endpoint was 13.7% in the two DAT groups combined when compared with 13.4% in the TAT group (HR 1.04, 95% CI 0.84–1.29; $P = 0.005$ for non-inferiority). When looking at the two dabigatran groups separately, there was a non-significant excess in the number of ischaemic events (i.e. stent thrombosis and MI) with the 110 mg bid dose compared with TAT.

Apixaban has been shown to have similar beneficial effects on stroke or systemic embolism and major bleeding compared with warfarin, irrespective of concomitant aspirin use.⁴¹ However, no completed trial has studied apixaban as part of dual or triple therapy in patients with AF and ACS or PCI. The ongoing AUGUSTUS study (NCT02415400) is an open-label, 2 × 2 factorial, randomized, controlled non-inferiority clinical trial to evaluate the safety of apixaban (standard dosing) vs. VKA and aspirin vs. aspirin placebo in patients with AF and ACS (the only trial including ACS patients treated conservatively or by PCI).⁴² The primary focus is a comparison of the bleeding risk of apixaban, with or without aspirin, vs. a VKA such as

warfarin, with or without aspirin. This study will include 4600 patients and enrolment was completed in April 2018 (Table 2). The Edoxaban Treatment vs. Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF-PCI, 1500 patients are planned) study is designed to evaluate the safety and to explore the efficacy of an edoxaban-based (standard dosing) antithrombotic regimen vs. a VKA-based antithrombotic regimen in subjects with AF following PCI with stent placement.⁴³ In both the AUGUSTUS and the ENTRUST-AF-PCI study (again, both being safety studies not sufficiently powered for ischaemic outcomes), standard dosing of NOAC is used in combination with antiplatelets, with dose reduction only in selected patients fulfilling NOAC specific dose reduction criteria.

In a systematic review and meta-analysis of four randomized clinical trials including 5317 patients [3039 (57%) received DAT], Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding showed a reduction by 47% in the DAT arm compared with the TAT arm (4.3% vs. 9.0%; HR 0.53, 95% CI 0.36–0.85).⁴⁴ There was no difference in the major adverse cardiac events (MACE) (10.4% vs. 10.0%, HR 0.85, 95% CI 0.48–1.29), or in individual outcomes of all-cause mortality, cardiac death, MI, stent thrombosis, or stroke between DAT and TAT.

Antiplatelet drugs

The WOEST study initially tested the concept of dropping aspirin after PCI and using a combination of clopidogrel and warfarin alone, suggesting that this approach is effective and safe in terms of thrombotic events, and reduced overall bleeding risk.⁴⁵ As discussed above, the PIONEER and RE-DUAL trials^{39,40} further reinforce the concept of potential redundancy of aspirin and its associated bleeding hazard in AF patients treated with anticoagulant and P2Y₁₂ inhibitor.

Although in a non-AF population, the GEMINI-ACS-1 study has reinforced the concept that oral anticoagulation may substitute for aspirin in patients who are stable early after PCI, showing that rivaroxaban combined with either clopidogrel or ticagrelor provided similar efficacy in prevention of ischaemic events compared with aspirin with either of these P2Y₁₂ inhibitors.⁴⁶ The COMPASS study demonstrated higher efficacy of rivaroxaban 2.5 mg bid plus aspirin 100 mg od in long-term prevention of ischaemic events vs. aspirin alone, in a non-AF vascular disease population. This was accompanied by higher bleeding complications when compared with aspirin alone, and does not support the suggestion that aspirin can be substituted by an OAC.⁴⁷ The GLOBAL-LEADERS study is assessing, amongst other concepts, whether ticagrelor monotherapy from 1 month after PCI is superior to standard DAPT and will further define the necessity of aspirin from this timepoint in a non-AF population.⁴⁸ TWILIGHT is the largest study to date that is designed and powered in order to demonstrate a lower bleeding rate with ticagrelor monotherapy vs. ticagrelor plus acetylsalicylic acid (ASA) beyond 3 months post-procedure in a high-risk patient population undergoing PCI with drug-eluting stents (DES).⁴⁹

Overall, limited numbers of patients have been studied with the combination of an anticoagulant and either prasugrel or ticagrelor.^{23,28,50} Because of the greater platelet inhibition with approved doses of prasugrel or ticagrelor compared with clopidogrel, the risk

Table 2 Randomized trials comparing NOAC vs. VKA in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting

Author, year	Study design	Size (n)	Comparison	Summary of findings	Comment
Published RCTs					
Gibson et al. ³⁹ (PIONEER AF PCI)	RCT Open-label (exploratory without statistical power calculation)	2124	15 mg rivaroxaban od plus a P2Y ₁₂ inhibitor for 12 months, very-low-dose rivaroxaban (2.5 mg bid) plus dual antiplatelet therapy (DAPT) for 1, 6, or 12 months, or standard therapy with a dose-adjusted vitamin K antagonist (od) plus DAPT for 1, 6, or 12 months	Rates of clinically significant bleeding were lower in the two groups receiving rivaroxaban than in the group receiving standard therapy with VKA (16.8% vs. 26.7% and 18.0% vs. 26.7%; $P < 0.001$ for both comparisons)	Not powered for efficacy
Cannon et al. ^{39,40} (RE-DUAL PCI)	RCT Open-label PROBE design	2725	Dual antithrombotic therapy with dabigatran etexilate (110 mg or 150 mg bid) plus clopidogrel or ticagrelor is compared with triple therapy with warfarin	ISTH major or CRNM bleeding was significantly lower in the two groups receiving dual therapy with dabigatran than in the group receiving triple therapy with warfarin (15.4% vs. 26.9% and 20.2% vs. 25.7%) (HR 0.52; 95% CI 0.42–0.63 and HR 0.72; 95% CI 0.58–0.88, respectively)	Not powered for efficacy
Ongoing RCTs					
AUGUSTUS ⁴² (NCT02415400)	RCT Open-label, 2 × 2 factorial design	4600 patients with ACS or PCI	Two randomization steps include (i) Apixaban (5 mg bid) vs. VKA based triple antithrombotic therapy and (ii) Aspirin vs. Aspirin Placebo	Primary outcome: ISTH major or CRNM bleeding during the treatment period	Enrolment completed April 2018
ENTRUST-AF-PCI ⁴³ (NCT02866175)	RCT	1500	Edoxaban-based regimen (60 mg od) is compared with a VKA based triple antithrombotic therapy	Primary outcome: ISTH major or CRNM bleeding during the treatment period	Estimated completion 2019

ACS, acute coronary syndrome; CRNM, clinically relevant non-major; CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; PCI, percutaneous coronary intervention; PROBE, prospective open-label blinded event adjudication; RCT, randomized clinical trial.

of spontaneous bleeding is higher when used in combination with aspirin.^{51,52}

The PEGASUS-TIMI 54 study assessed a lower dose of ticagrelor (60 mg bid) in addition to the 90 mg bid dose licensed for use in ACS in combination with aspirin (75–150 mg od) in non-AF patients within 1–3 years of MI and at higher risk of recurrent atherothrombotic events.⁵³ Both doses of ticagrelor had similar efficacy and safety although there were numerical trends suggesting less minor bleeding and better tolerability with ticagrelor 60 mg bid.⁵⁴ Interestingly, the extent of platelet inhibition with ticagrelor 60 mg bid was similar to that achieved with ticagrelor 90 mg bid.⁵⁵ The TROPICAL-ACS study suggested that guided de-escalation from prasugrel to clopidogrel (in clopidogrel responders) after PCI is non-inferior to continuing prasugrel in a DAPT strategy.⁵⁶ Another de-escalation trial (TOPIC) compared a switch from DAPT (aspirin plus a new P2Y₁₂-inhibitor) with conservative DAPT (aspirin plus clopidogrel) 1 month after ACS or to continue their initial drug regimen (unchanged DAPT).⁵⁷ These authors reported that switched DAPT is superior to an unchanged DAPT strategy to prevent bleeding complications without increase in ischaemic events following ACS, although these studies were not powered to compare ischaemic event rates. However, the implications of poor response to clopidogrel in patients treated with clopidogrel and an anticoagulant, rather than aspirin, are not well characterized.

Parenteral anticoagulants

Recent meta-analysis of 2325 VKA-treated AF patients undergoing coronary angiography with or without PCI showed that both bleeding and 30-day major adverse cardiovascular event rates were similar between those with interrupted or uninterrupted VKA.⁵⁸ However, those who received parenteral bridging anticoagulants on interruption of VKA had higher major bleeding rates.⁵⁸ The above data confirm recommendations of *uninterrupted anticoagulation* for elective PCI.¹ At present, little is known regarding the bleeding and MACCE rates with continuation or interruption of NOAC during PCI.

Limited data exists to guide the choice of and the dose of parenteral anticoagulants, whether unfractionated heparin (UFH), bivalirudin, or enoxaparin and their optimal dosages, specific to AF patients already taking OAC when undergoing PCI for ACS. Additional parenteral anticoagulants may not be needed, particularly if the international normalized ratio (INR) is more than 2.5 at the time of elective PCI.^{1,59} On the other hand, the usage of parenteral anticoagulants during PCI is recommended in AF patients on NOAC regardless of the timing of the last NOAC dose.⁵⁹

Stents in patients with increased bleeding risk

Drug-eluting and bare-metal stents

Since December 2014, three large-scale trials, comparing different stents, have enrolled relatively high proportions of patients with AF requiring treatment with OAC. One trial enrolled patients regarded as being uncertain candidates for DES at the time.⁶⁰ About 12% had OAC at discharge. This pre-specified *post hoc* analysis of the ZEUS trial demonstrated that the use of the Endeavor zotarolimus-eluting stent is superior to bare-metal stents in terms of the composite of

death, MI and target vessel revascularization (TVR) (HR 0.76, 95% CI 0.61–0.95; $P = 0.011$) in patients at high bleeding risk (mainly triggered by TVR).⁶⁰ The median duration of DAPT was 1 month.

Another prospective randomized trial enrolled patients at high bleeding risk and randomly allocated treatment with a polymer-free biolimus A9-DES vs. a bare-metal stent (LEADERS FREE trial).⁶¹ The main finding was that the primary safety endpoint of death, MI, and stent thrombosis was reduced with the biolimus A9-DES (HR 0.71, 95% CI 0.56–0.91; $P < 0.001$ for non-inferiority and $P = 0.005$ for superiority). In line with expectations, the primary efficacy endpoint of target lesion revascularization was reduced by half with the biolimus A9-DES (HR 0.50, 95% CI 0.37–0.69; $P < 0.001$), while death as single endpoint was not reduced. Treatment effects were consistent in patients with planned OAC therapy at discharge for efficacy and safety endpoints.

Subgroup analysis demonstrated similar outcome data for the biolimus A9-DES vs. bare-metal stents in elderly patients; there was evidence of interaction with regard to treatment effect and diagnosis of ACS at baseline in relation to the primary safety endpoint ($P = 0.04$) with greater benefit for patients treated with the biolimus A9-DES.⁶² Safety and efficacy were maintained during an extended follow-up out to 2 years, even amongst the subgroup of patients who were candidates for long term OAC.^{63,64}

A more recent clinical trial compared the outcomes of elderly patients (>75 years) undergoing PCI with a new generation DES (bio-degradable polymer everolimus-eluting stents) compared with bare-metal stents (SENIOR trial), where 17.6% had AF at enrolment.⁶⁵ DAPT was recommended in both groups for the same duration: 1 month in patients with stable angina and 6 months in patients with ACS. The composite of death, MI, stroke, or target lesion revascularization was significantly reduced in patients treated with DES (relative risk 0.71, 95% CI 0.52–0.94; $P = 0.02$). Bleeding was similar in both groups, in line with the identical recommendations for antithrombotic treatment in both groups.

Results with new-generation DES are generally excellent across the spectrum of patient and lesion subgroups. A recent systematic review of 158 trials—conducted as part of a ESC-EAPCI task force on the evaluation of coronary stents—reported low rates of both restenosis and stent thrombosis at 9–12 months with new-generation DES (less than 5% and 1%, respectively), with lower rates compared with both bare-metal stents and early-generation DES.⁶⁶ Large-scale registries support the generally high efficacy and safety of new-generation DES. Convincing data to support different durations of DAPT according to stent type are lacking and the general recommendation for 1-month DAPT after bare-metal stenting in stable patients is not well supported. More recently, drug-eluting balloons can be an alternative for stenting in special lesions (e.g. in patients with in-stent restenosis).


The 2017 ESC Focused Update on Antiplatelet Therapy recommends that choice of duration of DAPT in patients should no longer be differentiated on basis of device used, i.e. whether the stent implanted at time of PCI is a DES or bare-metal stent, or whether a drug eluting balloon is used.⁵ In view of the superior antirestenotic efficacy and no signal of higher thrombotic risks even after short term DAPT duration of new generation DES when compared with BMS, it is recommended that patients with AF undergoing PCI should be treated with new generation DES.

Bioresorbable scaffolds

Bioresorbable scaffolds (BRS) are rarely used in clinical practice at present,⁶⁷ due to an increased risk of target lesion failure and device thrombosis at 2–3 year follow-up and an excess of 1-year target vessel MI and stent thrombosis in comparison with conventional DES.⁶⁸

Consensus statements

- In view of the superior anti-restenotic efficacy and no signal of higher thrombotic risk of new-generation DES it is recommended that patients with AF undergoing PCI should be treated with new generation DES
- Choice of DAPT duration should not be differentiated based on whether the stent implanted at time of PCI is a DES or bare-metal stent
- Patients requiring oral anticoagulation should not receive BRS



References

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DES, drug-eluting stent; DAPT, dual antiplatelet therapy; BRS, biovascular scaffold.

Other data in structural interventions, i.e. valve interventions (TAVI, mitral), left atrial appendage closure

Transcatheter aortic valve implantation

Cerebral embolization is one of the major complications that might occur in the very early phase of valve placement. New periprocedural cerebral ischaemic defects have been reported in more than 60% of patients, and clinically-apparent stroke occurs in around 3% of cases on average (range 0–6%).⁶⁹

Despite a higher incidence of cerebrovascular events with the first devices in the PARTNERS trials,^{70,71} there seems to be a similar risk of stroke in patients undergoing TAVI compared with patients receiving the surgical aortic valve replacement (SAVR).^{72–75} Parenteral antithrombotic treatment during TAVI aims to prevent thromboembolic complications related to large catheter manipulation, guide-wire insertion, balloon aortic valvuloplasty, and valve prosthesis implantation, while minimizing the risk of bleeding, particularly at the vascular access site. Based on retrospective studies and randomized trials,^{72,73,76,77} the most commonly used anticoagulant is UFH at doses of 50–70 IU/kg with a target activated clotting time (ACT) of 250–300 s, although no optimal ACT has been defined, even in guidelines.^{78–82} Given the higher cost and similar efficacy of bivalirudin when compared with UFH, the latter should remain the standard of care for patients undergoing TAVI unless contra-indications to UFH, such as known heparin-induced thrombocytopenia, exist.⁸³

Subacute cerebrovascular events associated with TAVI occur between 24 h and 30 days, while all the episodes occurring after 30 days are defined as late. Stroke rate at 30 days reported by randomized clinical trials and registries ranges from 0% to 9%.⁸⁴ Factors potentially involved in such cerebrovascular events development are: thrombogenicity of the valve apparatus, exposure of the stent struts (expanded together with the valve), persistence of the perivalvular space occupied by the native valve and the development of paroxysmal atrial arrhythmias.^{69,82} Moreover, the baseline risk for ischaemic and thromboembolic complications is further increased by comorbidities including concomitant CAD, which is present in 20–70% of patients and requires PCI in 20–40% of patients. Furthermore, AF is found in about one-third of patients referred for TAVI.^{70,71,85–87}

Prospective data on antithrombotic therapy after TAVI are still scarce and recommendations regarding choice and optimal duration of antiplatelet or antithrombotic therapy are largely based on experience from PCI and open-heart aortic valve replacement.

Among patients without CAD and *without* AF, the current standard of care is still DAPT consisting of low-dose aspirin (75–100 mg per day) and clopidogrel 75 mg od (after loading dose of 300–600 mg), both started within 24 h prior to the intervention, and continued for 3–6 months followed by indefinite aspirin monotherapy. Patients receiving single antiplatelet therapy soon after TAVI tended to have a lower rate of major adverse events after the intervention when compared with patients on DAPT, with a significant reduction of major and life-threatening bleeding complications at three months follow-up.⁸⁸ A meta-analysis of the pooled results of this trial and other minor studies showed no benefit of DAPT in early stroke reduction with a trend towards an increase in major bleeding, thus suggesting the opportunity to adopt an antiplatelet monotherapy soon after the intervention for all patients without indication for anticoagulation.⁸⁹

Other clinical trials are currently ongoing. The Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular TAVI, $n = 1000$) trial is currently exploring whether it is possible to skip clopidogrel in a larger population of patients undergoing TAVI with or without an indication for OAC prior to the procedure. Patients are randomized to aspirin alone vs. aspirin plus clopidogrel for the first 3 months after the procedure and evaluated for the primary safety endpoint of freedom of non-procedure-related bleeding complications at 1 year follow-up. The cohort of patients for whom OAC is indicated (AF, mechanical valve prostheses) is randomized to clopidogrel plus OAC vs. OAC alone (NCT02247128).

The Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antiplatelet-based Strategy after Transcatheter aortic valve replacement to Optimize Clinical Outcome (Galileo, $n = 1520$) study is an open-label, multicentre, randomized controlled trial actively recruiting patients undergoing TAVI with no indication to permanent anticoagulant therapy. Patients assigned to the OAC arm are randomly assigned to receive 10 mg od rivaroxaban up to 25 months plus low-dose aspirin during the first 3 months in order to assess whether this strategy is superior to DAPT with aspirin plus clopidogrel (for 3 months) followed by aspirin alone in reducing death or first clinical thromboembolic events with no increase in bleeding complications (NCT02556203).⁹⁰

Third, the Anti-Thrombotic Strategy after Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS, $n = 1509$) trial is evaluating whether an anticoagulant-based strategy with apixaban 5 mg bid is superior to standard-of-care therapy in preventing death, MI, stroke, systemic embolism, intracardiac or bioprosthesis thrombus formation, or life-threatening/major bleeding complications at 1 year follow-up in patients successfully treated with a TAVI procedure. The ATLANTIS trial will include two different populations: patients with an indication for anticoagulation, where standard of care is represented by a VKA and patients for whom an antiplatelet regimen with aspirin plus clopidogrel is the first-choice antithrombotic treatment. Randomization is consequently stratified according to the need (or no need) for anticoagulation for clinical reasons other than TAVI itself (NCT02664649).

Finally, another study that aims at demonstrating the superiority of a single anticoagulant vs. the combination of an anticoagulation plus aspirin with respect to a net clinical benefit endpoint at 1 year (the AVATAR trial, NCT02735902) has been announced ($n = 170$).

Among TAVI patients with AF but without CAD, OAC is recommended in accordance with recommendations for AF alone.¹ Whether the addition of antiplatelet therapy to OAC is required in this context remains to be determined. The existing experience with patients receiving biological aortic valve replacement suggests that OAC alone may be sufficient to prevent thrombotic events.⁷⁹ Indeed, OAC (essentially VKA) use in surgically-implanted biological aortic valves is generally recommended for only 3 months and can be stopped thereafter, except where patients have other reasons for prolonged or life-long OAC.

The POPular TAVI trial, which is currently recruiting patients, will provide information regarding the safety and the net clinical benefit of a VKA alone vs. the combination of clopidogrel plus a VKA in patients undergoing TAVI who have an indication to permanent OAC.⁹¹ With reference to the life-long use of a NOAC compared with VKA, beyond the reported ATLANTIS trial, the Edoxaban Compared to Standard Care after Heart Valve Replacement Using a Catheter in Patients with Atrial Fibrillation (ENVISAGE-TAVI AF) trial recently started recruiting a planned population of 1400 AF patients undergoing TAVI. The study will compare the two anticoagulant drugs (warfarin vs. edoxaban) in terms of overall side effects and major bleeding during 3 years follow-up (NCT02943785).

In summary, TAVI patients taking OAC (e.g. for AF) and recent PCI should be treated similarly to patients receiving a stent without TAVI. While awaiting results of controlled randomized trials, patients undergoing TAVI without concomitant need for OAC should receive an antiplatelet regimen consisting of lifelong aspirin monotherapy or aspirin and clopidogrel for 3–6 months followed by aspirin monotherapy, depending on bleeding risk, and concomitant treated or untreated coronary artery disease. The use of prasugrel or ticagrelor in combination with aspirin or NOAC after TAVI has not been investigated and cannot be recommended at this time.

Mitral intervention

No study has addressed the optimal antithrombotic regimen after percutaneous edge-to-edge transcatheter mitral valve repair (e.g. MitraClip system, Abbott, Abbott Park, IL, USA⁹²). Pivotal studies have mandated the use of aspirin for at least 6 months in combination

with clopidogrel for 1–3 months in patients without AF while patients with AF are treated with OAC plus aspirin.⁹³

Transcatheter mitral valve implantation (TMVI) with a transcatheter mitral valve prosthesis has been performed in patients with surgical degenerated bioprostheses [valve-in-valve (ViV)] or with recurrent MR following mitral repair annuloplasty [valve-in-ring (ViR)].⁹⁴ There is currently limited evidence that adding a single antiplatelet therapy or DAPT to OACs further decreases the risk of symptomatic or asymptomatic valve thrombosis.

Left atrial appendage closure

The left atrial appendage (LAA) is implicated in approximately 90% of strokes in patients with AF.⁹⁵ Left atrial appendage occlusion, either percutaneous or surgical, is a rapidly-emerging option for patients who cannot take long-term OAC.⁹⁶ Of the percutaneous options, the WATCHMAN (Boston Scientific) device is so far the only tested LAA closure device in a randomized controlled fashion. It is currently the only percutaneous device approved in both Europe and the US.

In the PROTECT-AF trial, patients were treated with warfarin and aspirin 81 mg for 45 days post-procedure, then with aspirin and clopidogrel for 6 months, and then with aspirin indefinitely.⁹⁷ In the PREVAIL study, patients were on warfarin plus aspirin 81 mg for the first 45 days, then on aspirin 325 mg plus clopidogrel until post-operative month 6 (in the absence of any clot), then on aspirin 325 mg alone.⁹⁸ Thus, PROTECT and PREVAIL did not enroll patients unable to take OACs, but patients who were at least able to take warfarin for 45 days post-procedure. This contradicts the current suggested indication to use a LAA closure device in patients with contraindications against OACs. Moreover, the efficacy and safety of using a NOAC instead of warfarin was not assessed in these two major trials.

These trials have been subject to much debate,⁹⁹ with reports of device related thrombus that can lead to thromboembolism.¹⁰⁰ In the absence of clinically relevant LAA leaks, OAC can be discontinued and the patient treated with DAPT or a single antiplatelet therapy for at least 6 months after the procedure, although some cardiologists continue single antiplatelet therapy long term. There are also no data to suggest the optimal management of an AF patient with left atrial appendage occlusion who requires a cardioversion. A transoesophageal echocardiogram (TOE) assessment for thrombus may be performed, and a shortened duration of anticoagulation similar to TOE-guided cardioversion protocol may be considered.

Amplatzer

The data on Amplatzer Cardiac Plug (now Amulet), are largely based on registry studies.^{101,102} The most recent study had 18.9% patients on either a VKA or NOAC immediately post-procedure.¹⁰¹ In a study of 52 Canadian patients receiving this device, there was an only 1.9% rate of stroke when antiplatelets alone were used post-procedure during a mean follow-up of 20 ± 5 months.¹⁰³

Lariat

The LARIAT device (SentreHeart) ligates off the LAA via a combined trans-septal and epicardial approach. It received FDA approval for soft tissue closure but not specifically for LAA closure. It has not been tested in a randomized controlled trial, so efficacy data are

derived from prospective registries.¹⁰⁴ Since the US FDA released a safety alarm communication in July 2015 due to reports of adverse patient outcomes, the use of LARIAT in the US has dropped significantly (<https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm454501.htm>).

In summary, LAA occlusion may be considered in selected AF patients with absolute contraindications to any OAC. Trial data supporting use of shorter duration TAT or even DAT in these patients in general (as discussed above), as well as the recommendation for short duration OAC after the procedure in patients treated with Watchman device, makes the rationale for implanting these devices solely for the reason that the AF patient requires PCI unclear.

Assessing stroke and bleeding risks

The CHA₂DS₂-VASc has been widely used worldwide for stroke risk stratification in AF,¹⁰⁵ even in patients with coronary artery disease treated with coronary stenting.^{106,107} Other less established risk factors for stroke include unstable INR and low TTR in patients treated with a VKA; previous bleed or anaemia; alcohol excess and other markers for decreased therapy adherence; chronic kidney disease; elevated high-sensitivity troponin; and elevated N-terminal pro-B-type natriuretic peptide.² Some have been incorporated into more recent stroke scores proposed for AF, such as the ATRIA (Anticoagulation and Risk factors In Atrial fibrillation), QStroke, and ABC-stroke scores.^{108–110} Biomarker-based stroke risk scores (e.g. ABC score) do not appear to confer long-term benefit over simple clinical scores such as CHA₂DS₂-VASc.^{111,112} In addition, stroke risk is not static, and regular review and reassessment of risk is needed during follow-up.^{113,114}

In the CHA₂DS₂-VASc score, the V criterion for 'vascular disease' is defined as 'previous MI, peripheral artery disease, or aortic plaque', since these are factors, which are more validated to confer an excess of stroke risk in patients with AF. Patients with mild coronary atheroma alone, or simply a history of angina, have not been definitively shown to have an excess of stroke risk if no other CHA₂DS₂-VASc risk factors are present (hence do not score a point for the V criterion). Patients with a CHA₂DS₂-VASc score of ≥ 1 for men or ≥ 2 for women are likely to benefit from stroke prevention with specific treatment decisions for type and duration of associations of antithrombotic agents based on the clinical setting and patient profile (elective PCI or ACS, risk factor for CAD progression, and coronary events, risk of bleeding) possibly incorporating patient preferences.

Clinical risk scores for bleeding

Several bleeding risk scores have been developed, mainly in patients on VKAs. These include HAS-BLED [hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each)], ATRIA, ORBIT (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), and more recently, the ABC (age, biomarkers, clinical history) bleeding score, which includes selected biomarkers.^{115–118} While stroke and bleeding risks correlate with each other, the HAS-BLED score is a superior predictor of

bleeding risk compared with the CHADS₂ [congestive heart failure, hypertension, age, diabetes, stroke (doubled)] or CHA₂DS₂-VASc scores.^{119,120}

The simple HAS-BLED score has similar or a superior bleeding risk assessment to other proposed scores, some of which are more complex.^{121–123} This is particularly evident amongst VKA users, given that other scores (HEMORRH2AGES, ATRIA, ORBIT) do not consider quality of anticoagulation control, i.e. labile INR as a bleeding risk.^{124,125} In another trial cohort, the ORBIT score demonstrated the best discrimination and calibration when tested in the RE-LY (Randomized Evaluation of Long-term anticoagulant therapy with dabigatran etexilate) trial, whereby all the scores demonstrated, to a variable extent, an interaction with bleeding risk associated with dabigatran or warfarin.¹²⁶ On the other hand, the biomarker-based ABC bleeding risk score did not appear to confer long-term benefit over a more simple clinical score such as HAS-BLED.^{112,127} Similarly, the PRECISE DAPT score has been developed to assess the out-of-hospital bleeding risk in patients in whom DAPT but not OAC is indicated; however, this score currently does not provide useful information on the additional bleeding risk in patients in whom both OAC and DAPT are concomitantly indicated.¹²⁸

Of note, the HAS-BLED, ORBIT, and ABC scores have also been validated in patients on NOACs.^{126,129} The HAS-BLED score has been validated in patients with CAD treated with coronary stenting.^{130,131} A high bleeding risk score should generally not result in withholding OAC, and is appropriately used to 'flag up' patients at high risk of bleeding (HAS-BLED score ≥ 3) for more regular review and earlier follow-up.

Of importance, modifiable bleeding risk factors (e.g. uncontrolled blood pressure, concomitant antiplatelet or NSAID use, alcohol excess) should always be identified and corrected at every patient contact. In addition, bleeding risk is not static, and regular review and reassessment of risk is needed during follow-up, especially since an adverse change in (say) HAS-BLED score is associated with excessive bleeding risk particularly in the initial 3 months.¹³²

When managing patients with AF undergoing PCI/stenting, it is recommended to concomitantly assess stroke, bleeding, and ischaemic event risks (using validated tools such as the REACH, Syntax, and GRACE scores^{6,133–135}). A recent retrospective analysis confirmed the value of the Syntax and GRACE scores for identifying higher risks of coronary events and mortality, respectively, in AF patients with coronary stenting.¹⁰⁶

What is the practical application of formal bleeding risk assessment? An approach based only on modifiable bleeding risk factors alone is an inferior assessment compared with a formal bleeding risk score.^{119,136,137} A high (uncorrectable) bleeding risk may flag up the patient for earlier review and follow-up (e.g. 4 weeks rather than 4–6 months), as well as lead to shortening of TAT with earlier switch to DAT in case of estimated low atherothrombotic risk as calculated with the Syntax or REACH score, although prospective validation is missing in such combination scenarios. A similar clinical setting may lead to the decision to discontinue all antiplatelets and provide anticoagulation as monotherapy earlier (e.g. after 6 months instead of 1 year).^{2,6} In the small subset of AF patients undergoing PCI with elevated bleeding risk and a relatively low stroke risk (CHA₂DS₂-VASc of one in males or two in females), one option would be to treat with only DAPT, without OACs, from the onset (although in ACTIVE-W,

there were numerically more MIs with aspirin plus clopidogrel compared with warfarin).¹³⁸

The TIMI-AF score has recently been proposed in VKA-naïve patients with AF to assist in the prediction of a poor composite outcome and guide selection of anticoagulant therapy by identifying a differential clinical benefit with a NOAC or VKA.¹³⁹ This complex score includes 11 items (including a history of MI) with a maximum integer score of 17 and needs to be more specifically validated in AF patients with ACS and/or undergoing percutaneous coronary or valve interventions. In a 'real world' cohort of VKA-experienced AF patients, the TIMI-AF score was found to have limited usefulness in predicting net clinical outcomes over a long-term period of follow-up and was not superior to CHA₂DS₂-VASc and HAS-BLED for identifying low-risk AF patients.¹⁴⁰ Another simple score, the 2MACE [two points for Metabolic Syndrome and Age ≥ 75 ; one point for MI/revascularization, Congestive heart failure (ejection fraction $\leq 40\%$), thrombo-embolism (stroke/transient ischaemic attack)] score has also been proposed for the prediction of MACE, but has not been validated in AF patients undergoing PCI.^{141,142}

Optimizing management

Table 3 summarizes the key points outlined in major European and American guidelines in patients undergoing percutaneous coronary interventions when on oral anticoagulation.

From the OAC perspective, the main management aspects pertain to the introduction of the NOACs. The latter drugs have changed the landscape of stroke prevention management amongst patients with AF, although some regional differences are evident.¹⁴⁵

Table 4 provides a summary of the antithrombotic management differences between a VKA and NOAC in relation to management of AF patients presenting with an ACS and/or undergoing PCI/stenting.

Elective percutaneous cardiovascular intervention for stable coronary artery disease

Since the publication of the 2014 consensus document, several studies (mostly observational) have been published.^{8-32,34-37,39,146,147} As opposed to some studies where only patients with ACS have been included, none reported exclusively on AF patients undergoing PCI in the context of stable CAD. The proportion of patients with stable CAD included in the various studies was in the range of 20–0%.^{8-32,34-37,39,146,147}

Only extrapolation from the overall data can therefore be made when attempting to address the main issues in the management of AF patients undergoing PCI in the context of stable CAD, namely: periprocedural management of OAC, especially in the current era when both VKA and NOAC anticoagulants are available, and combination and duration of antithrombotic therapy during the medium to long-term after the procedure.

Periprocedural management

In patients receiving a VKA, an uninterrupted strategy is supported by various studies. In a meta-analysis of uninterrupted when compared with interrupted strategy,⁵⁸ uninterrupted OAC was found to be at least as safe as interrupted OAC, and seemed to be much safer than

interrupted OAC with bridging anticoagulation in patients undergoing coronary angiography with or without PCI.

In the WOEST study,¹⁴⁸ where 573 patients on OAC with VKA for various indications (mostly AF) underwent PCI, with stable CAD in approximately 70%, the procedure was carried out without OAC interruption in 241 (43%) and with OAC interruption plus low-molecular weight heparin (LMWH) bridging in the remaining 322 (57%). In most cases, the vascular approach was femoral and comparable in the two groups. At 30 days, as well as at 1 year follow-up, the occurrence of bleeding events was comparable in both groups (HR 0.83, 95% CI 0.50–1.37; $P = 0.46$ and HR 1.01, 95% CI 0.71–1.44; $P = 0.95$, respectively).¹⁴⁸ Also comparable was the occurrence of MACCE, including death, MI, stroke, target vessel revascularization, and stent thrombosis at both 30 days and 1 year (HR 0.48, 95% CI 0.15–1.51; $P = 0.21$ and HR 0.72, 95% CI 0.46–1.14; $P = 0.16$, respectively).¹⁴⁸

In the AFCAS registry, where 663 out of 929 patients with AF undergoing PCI (for stable CAD in approximately 50%), 498 (75%) had uninterrupted periprocedural OAC, whereas the remaining 165 (25%) had OAC interruption and LMWH bridging.¹⁴⁹ At 3 months, both unadjusted major bleeding and MACCE rates were significantly more frequent in the LMWH-bridging group, whereas at 12 months the difference remained statistically significant only for MACCE.¹⁴⁹ After propensity score matching, and subsequent comparison of 152 patients, in whom also the frequency of femoral access was similar, major bleeding was more frequent in the LMWH-bridging group at both 3 and 12 months, whereas MACCE rates were comparable.¹⁴⁹ The preferential role of radial access in patients on OAC with VKA undergoing PCI is corroborated by a retrospective, single-centre analysis of 97 patients undergoing PCI (proportion of stable CAD not reported) with INRs >2.0 , in whom total and major BARC bleeding and need for transfusions was significantly lower with radial when compared with femoral approach.¹⁵⁰

Limited data are available for AF patients undergoing PCI while on NOAC. In the phase IIa, multicentre D-fine clinical trial, 50 patients undergoing elective PCI were randomized to either pre-procedural dabigatran 110 or 150 mg bid or standard intra-procedural UFH.¹⁵¹ Following PCI, dabigatran appeared to provide insufficient anticoagulation, as shown by significantly higher values compared with UFH of prothrombin fragment 1 + 2 and thrombin-antithrombin complexes.¹⁵² Clinical outcomes tended to be higher in the dabigatran group, where 5 out of 40 (12.5%) required bail-out anticoagulation when compared with 1 out of 10 (10%) in the standard UFH group.¹⁵¹ No significant bleeding was observed in either group.¹⁵¹

In a phase IIa, multicentre trial (X-plorer), 108 patients undergoing elective PCI and on stable dual antiplatelet therapy of aspirin and clopidogrel were randomized to a single dose of either rivaroxaban 10 mg, rivaroxaban 20 mg, rivaroxaban 10 mg plus intravenous bolus of UFH, or standard UFH.¹⁵² Patients with an indication for OAC were excluded. Following PCI, in all groups receiving rivaroxaban coagulation was effectively suppressed, comparably to standard UFH, as shown by the low plasma levels of the fragment 1 + 2 and thrombin-antithrombin complex.¹⁵² No patients in the three rivaroxaban arms required bail-out antithrombotic medication and/or had clinical signs of catheter-related thrombosis.¹⁵² No significant bleeding was observed in either group up to 30 days after PCI.¹⁵²

Because of the inconsistency of the results reported with the two different NOACs (dabigatran and rivaroxaban), performing elective

Table 3 Summary of main recommendations in recent guidelines

	ESC myocardial revascularization 2017 ¹⁴³	ESC AF 2016 ²	ACC/AHA 2016 combined OAC/APT ¹⁴⁴	ESC 2017 DAPT update ⁵
Use of periprocedural aspirin and clopidogrel	—	—	—	++
Preferred use of DES	++	—	—	++
Recommendations according to the type of platform (DES vs. BMS)	n/a	—	++	n/a
Use of ticagrelor or prasugrel	—	—	—	—
Use of specific score for ischaemic or bleeding risks	++	n/a	n/a	n/a
DAPT as an alternative to TAT in CHA ₂ DS ₂ -VAsC score ≤1	++	n/a	n/a	n/a
DAT as an alternative to initial TAT	+	+	n/a	++
1–6 months as the default strategy in ACS patients	++	++	++	++
Use of NOAC	++	++	++	++
Stopping aspirin rather than clopidogrel	+	+	++	+
Stopping all antiplatelet therapy after 1 year	n/a	++	n/a	++

++, recommended; +, may be considered; —, not recommended by the relevant guideline; ACS, acute coronary syndrome; BMS, bare-metal stent; DAT, dual therapy; DES, drug-eluting stent; n/a, box means not stated; NOAC, non-vitamin K antagonist oral anticoagulant; TAT, triple therapy.

PCI in patients with stable CAD on ongoing uninterrupted NOAC monotherapy is currently not recommended. Also, uncertainty on the true level of anticoagulation with NOAC raises uncertainty when the treatment of a thrombotic complication is needed, e.g. administration of glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors¹⁵³ or the optimal use of additional UFH.

Whereas intra-procedural anticoagulation with UFH should be carried out as per usual practice in AF patients on NOAC, uncertainty exists on whether additional UFH should be given to patients on OAC with VKA undergoing PCI while the INR is >2.0. In a case-control study on 336 patients undergoing transradial coronary angiography either on therapeutic warfarin or standard, intra-procedural UFH, the incidence of both early (24-h) and late (30-day) radial artery occlusion was significantly higher in the ongoing warfarin group,¹⁵⁴ thereby supporting the addition of UFH also in VKA patients. Given that doses as low as 30–50 U/kg have been shown effective in preventing ischaemic complications related to PCI,¹⁵⁵ they should be preferred with the aim of limiting the risk of bleeding. When coronary angiography is performed through the femoral approach, (low-dose) UFH should likely be added only if PCI is carried out, given the uncertainty on the degree of protection provided by ongoing, therapeutic VKA.¹⁵⁶

Whether bivalirudin, which in both stable and ACS patients has been shown to be associated with a significantly lower rate of bleeding than UFH plus glycoprotein (GPI),¹⁵⁷ may be a preferable option for intra-procedural anticoagulation on ongoing effective VKA is uncertain. Limited, observational data suggest that bivalirudin may indeed be preferred, given that the 30-day occurrence of major bleeding and MACCE was shown to be lower in 51 patients receiving bivalirudin (stable CAD in 47%) when compared with 87 treated with UFH plus GPI (stable CAD in 15%), who were identified out of 1104 on warfarin undergoing PCI in two study protocols.¹⁵⁸

While there is a general agreement on the need for, at least initial, TAT of OAC plus DAPT of aspirin and clopidogrel in most AF patients undergoing PCI, the optimal timing and schedule for antiplatelet agents administration is not established. In patients not on OAC

and stable aspirin therapy, clopidogrel may be administered either prior to or during PCI with no apparent differences in outcomes with the two strategies.¹⁵⁹ Given that TAT is associated with an increased risk of bleeding, it may be considered to withhold the additional antiplatelet agent until indication for PCI arises from diagnostic coronary angiography.

The time required to reaching effective platelet inhibition with oral loading of clopidogrel is approximately 2 to 6–8 h, depending on whether a 600 or 300 mg dose, respectively, is given,¹⁶⁰ as opposed to either intravenous or oral aspirin, which has a nearly immediate antiplatelet effect.¹⁶¹ When carried out, pre-treatment with both aspirin and clopidogrel should preferably include loading with 300 mg, given that the slower and less intense platelet inhibition compared with 600 mg¹⁶² may reduce the initial risk of bleeding in patients naive to antiplatelet therapy and on ongoing OAC.

No additional data are available on GPI use in AF patients treated with OAC undergoing PCI. As for non-OAC patients with stable CAD, indication for GPI remains essentially limited to bail-out situations where however, further care is advised, given the previously reported substantial risk of major bleeding in the absence of a significant benefit on MACCE.¹⁵³ When abciximab is used, bolus only, either intracoronary or intravenous, may be considered because of possible superior safety compared with conventional intravenous bolus plus infusion strategy.¹⁶³ Use of GPI as per standard practice can be considered for patients on NOAC when timely discontinuation before PCI has been carried out.

Acute management

No randomized trials have specifically studied periprocedural management in anticoagulated patients developing an ACS and undergoing acute angiography with or without PCI. The following suggestions are based on observational studies and expert opinion and are in accordance with recent ESC guidelines.^{5,164,165} All AF patients taking OAC developing an ACS should receive aspirin immediately [150–300 mg oral loading dose or 75–150 mg i.v. (intravenous)].¹⁶⁴ To reduce the risk of bleeding, one option is to postpone the

Table 4 Summary of the antithrombotic management differences between a VKA and NOAC in patients undergoing elective PCI

	VKA	NOAC
Periprocedural management		
Anticoagulation (see Figure 1)	<p>Because of the reduced risk of bleeding, VKA should not be interrupted (or bridged with heparin):</p>	<p>Elective PCI</p> <ul style="list-style-type: none"> Because of the undefined intra-procedural protection against thrombotic events of NOAC, timely (12–24 h in advance, based on renal function and agent) interruption is preferred. Depending on renal function and agent used (e.g. Dabigatran has high renal dependency for its excretion), cessation for 24–48 h may be considered. No bridging is recommended. <p>Emergency PCI</p> <ul style="list-style-type: none"> NOACs need not to be interrupted.
Vascular access		
Additional intra-procedural UFH	<p>Because of the reduced risk of access-site bleeding complications, the radial approach should be preferred.</p> <p>To prevent radial artery occlusion, and possibly limit the occurrence of intra-procedural thrombotic complications, UFH should be administered.</p>	<p>Whether NOAC is interrupted or not, UFH should be administered as per usual practice</p>
Dose of additional intra-procedural UFH	To limit the risk of bleeding (in ongoing VKA), reduced dose (30–50 U/kg) should be given.	Standard dose UFH (70–100 U/kg) should be given
Use of bivalirudin	<p>Because of the observation of superior safety, and possibly also efficacy, it may be considered in accordance with prescribing label. Specific data in patients on OAC are limited.</p>	
P2Y ₁₂ -receptor inhibitor	<p>Because of potential increased risk of bleeding with prasugrel and ticagrelor in stable CAD patients on OAC, clopidogrel is generally recommended.</p> <ul style="list-style-type: none"> Consider pre-treatment with at least one antiplatelet agent in most cases. Where coronary anatomy is known or in emergency cases, whereby a decision for PCI is likely, pre-treatment with a P2Y₁₂-receptor inhibitor can be considered. Small numbers of prasugrel were used in the PIONEER-AF trial. In REDUAL-PCI, 12% were prescribed ticagrelor, which did not show excess bleeds when used with dabigatran as DAT. 	
Dose of P2Y ₁₂ -receptor inhibitor	Because clopidogrel should be given in advance of PCI, 300 mg loading should generally be preferred to limit the risk of bleeding (with ongoing VKA).	Whether NOAC is interrupted or not, 300 or 600 mg loading dose should be selected as per usual practice due to limited data.
Use of GPI	Because of the observed increase in major bleeding, with no benefit in ischemic outcomes, GPI should not be used, except for bail-out, in life-threatening situations.	Because of the observed increase in major bleeding, with no benefit in ischemic outcomes, GPI should not be used where NOACs are uninterrupted, except for bail out, in life-threatening situations.
Use of GPI as per standard practice can be made for patients on NOAC when timely discontinuation before PCI has been carried out.		

Continued

Table 4 Continued

	VKA	NOAC
Post-procedural management Antithrombotic regimen Intensity of OAC	<p>In patients on TAT, INR at the lower end of therapeutic range (2.0–2.5) should be targeted, with high TTR (>65–70%).</p> <p>With DAT, conventional therapeutic range (2.0–3.0) may be targeted, with high TTR (>65–70%).</p>	<p>Low dose dabigatran 110 mg bid and full dose apixaban 5 mg bid and edoxaban 60 mg od should be selected to optimize risk-benefit ratio, if part of a TAT regime.</p> <p>With DAT, dabigatran 150 mg plus P2Y₁₂ is preferred, unless dose reduction criteria for dabigatran are present in accordance with its label.</p> <p>Reduced Low dose rivaroxaban 15 mg od rather than full dose 20 mg od may be considered to reduce the risk of bleeding.</p> <p>Pending further data in the PCI setting, reduced dose apixaban and edoxaban are only used in accordance with their respective approved labels.</p> <p>After withdrawal of one antiplatelet agent, full dose apixaban 5 mg bid and edoxaban 60 mg od should be used, whereas reduced dose rivaroxaban 15 mg od should be replaced by full dose 20 mg od if Creatinine clearance is ≥ 50 mL/min.</p> <p>Decision on whether or not to increase ongoing dabigatran 110 mg bid to 150 mg bid should be left at the discretion of the attending physician, based on the individual risk of stroke and bleeding and the goal of antithrombotic therapy.</p>
Intensity of OAC during subsequent antithrombotic regimen after 12 months	Target INR should be 2.0–2.5 after withdrawal of one antiplatelet agent, with high TTR (>65–70%).	
Duration of TAT	Based on the risk of stent thrombosis/recurrent cardiac events and bleeding, 1 to 3–6 months should be selected.	
Dose of aspirin	Especially with ACS patients, ideally try to keep TAT to 6 months, but shorten to 3 months if high bleeding risk (e.g. HAS-BLED ≥ 3).	
Use of gastric protection	Low-dose 75–100 mg od should be used to reduce the risk of gastrointestinal bleeding.	
Subsequent antithrombotic regimen after triple therapy	Proton-pump inhibitors should be routinely administered throughout TAT. Upon completion of initial course of TAT, one antiplatelet agent, either aspirin (preferably), or clopidogrel should be withdrawn and DAT with OAC plus single antiplatelet therapy continued.	
Duration of subsequent antithrombotic regimen	Combined OAC plus single antiplatelet regimen should be continued up to 12 months after PCI.	
Long-term management Antithrombotic regimen	<ul style="list-style-type: none"> Approximately 6 months is the accepted risk period for stent thrombosis, although limited data are available for AF patients. 	

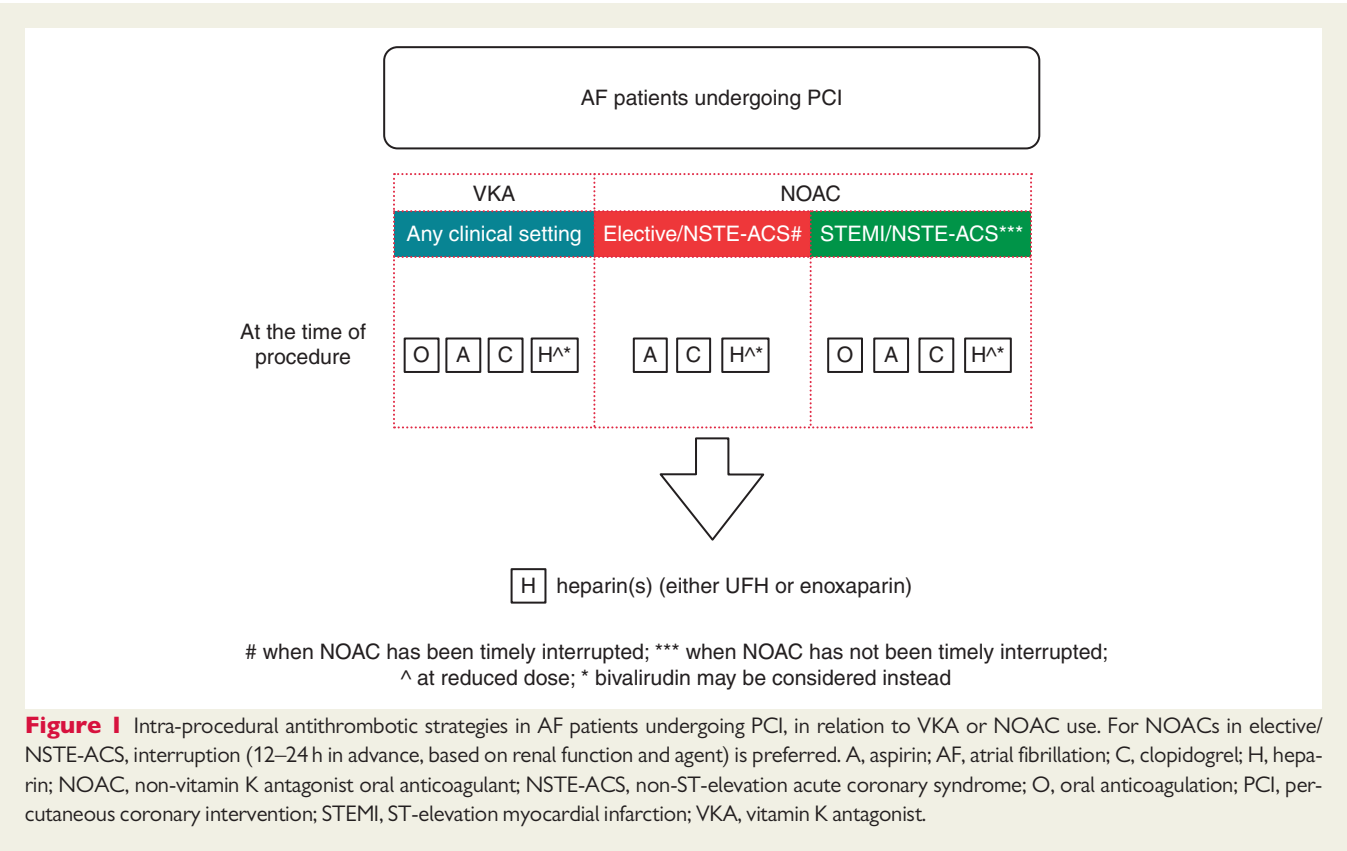
Continued

Table 4 *Continued*

	VKA	NOAC
	<ul style="list-style-type: none"> • Upon completion of 1-year of combined OAC plus (dual and single) anti-platelet therapy, OAC should be continued as monotherapy. • In patients at increased risk of stent thrombosis and/or recurrent cardiac events or of catastrophic consequences in the event this occurs continuation of combined OAC plus single antiplatelet agent (either aspirin or clopidogrel), may be considered, but has to be balanced against risk of serious bleeding. 	
Long-term management		<ul style="list-style-type: none"> • Full dose rivaroxaban 20 mg od, apixaban 5 mg bid, or edoxaban 60 mg od should be given, unless standard criteria for dose reduction are present. • Low (110 mg bid) or high (150 mg bid) dose of dabigatran should be selected based on the individual risks of stroke and bleeding and the goals of antithrombotic therapy.
Intensity of OAC during long-term management	Conventional INR target 2.0–3.0 should be prescribed, with TTR >65–70%.	

For details and references, see text.

bid, twice daily; CAD, coronary artery disease; DAT, dual antithrombotic therapy; GPI, glycoprotein IIb/IIIa inhibitor; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; od, once daily; PCI, percutaneous coronary intervention; TAT, triple antithrombotic therapy; TTR, time in therapeutic range; VKA, vitamin K antagonist.



administration of P2Y₁₂ inhibitors to the time of PCI, when the anatomy is known.¹⁶⁵

Oral anticoagulation is a relative contraindication for fibrinolysis. When anticoagulated patients present with a STEMI, they should be triaged for primary PCI regardless of the anticipated time to PCI-mediated reperfusion.¹⁶⁴ Primary PCI via a radial approach is strongly recommended¹⁶⁶ and clopidogrel is the P2Y₁₂ inhibitor of choice (600 mg loading dose given at the time of primary PCI).¹⁶⁴

The more potent P2Y₁₂ inhibitors prasugrel and ticagrelor are generally not routinely recommended in anticoagulated patients due to their increased bleeding risk in combination with aspirin.^{6,165,167} Anticoagulated patients undergoing primary PCI should receive additional low-dose parenteral anticoagulation regardless of the timing of the last dose of OAC (VKA or NOAC) (e.g. enoxaparin 0.5 mg/kg i.v. or UFH 60 IU/kg).¹⁶⁵

In NSTE-ACS patients undergoing an immediate invasive strategy (i.e. <2 h from symptom onset), periprocedural treatment should be as in STEMI patients. If invasive treatment is delayed, it is still suggested to perform PCI without interruption or discontinuation of VKAs or possibly, NOACs.^{58,165} As discussed above, an uninterrupted strategy was not associated with an increase in bleeding or major cardiovascular events compared with bridging therapy.^{58,168} In patients on VKAs, it is suggested either not to administer additional intraprocedural UFH if INR value is >2.5 or to consider a lower UFH dose regime.¹⁶⁵ In patients on NOACs, additional intraprocedural low-dose parenteral anticoagulation (e.g. enoxaparin 0.5 mg/kg i.v. or UFH 60 IU/kg) should be added irrespective of the time of the last administration of NOAC.¹⁶⁵ GPIs should be avoided unless for bail-out

situations. The new bioabsorbable vascular scaffolds should not be used in patients on OAC due to their higher thrombotic risk and need for a longer DAPT duration.¹⁶⁹

Post-procedural and post-discharge therapy

As regards the anti-thrombotic treatment to be prescribed at discharge, most of the additional evidence published since 2014 reports that TAT of OAC with either VKA or NOAC is consistently associated with an increased risk of major or total bleeding compared with other regimens with more heterogeneous effect on MACCE.^{8–32,34–37,39,146,147} The several limitations of observational studies, including lack of randomization, small size, insufficient information on treatment adherence, quality of OAC and limited absolute number of events, preclude definitive conclusions, especially regarding efficacy.

For most patients, TAT in the form of OAC, aspirin and clopidogrel should be considered for 1–6 months after an ACS.^{2,164,165} The optimal duration of such TAT depends on the patient's ischaemic and bleeding risks. Non-vitamin K antagonist oral anticoagulants as part of TAT or DAT are generally safer than VKA use, with respect to bleeding risk and is the preferred option in the absence of contraindications to these drugs.

Three randomized trials (WOEST, PIONEER AF PCI, and REDUAL PCI)^{39,40,148} showed that double therapy with a P2Y₁₂ inhibitor and either VKA (WOEST) or a NOAC (PIONEER, REDUAL PCI) was safer with respect to bleeding than TAT. However, none of these studies were sufficiently powered for efficacy and the populations studied were a mixture of stable CAD and ACS patients. Of

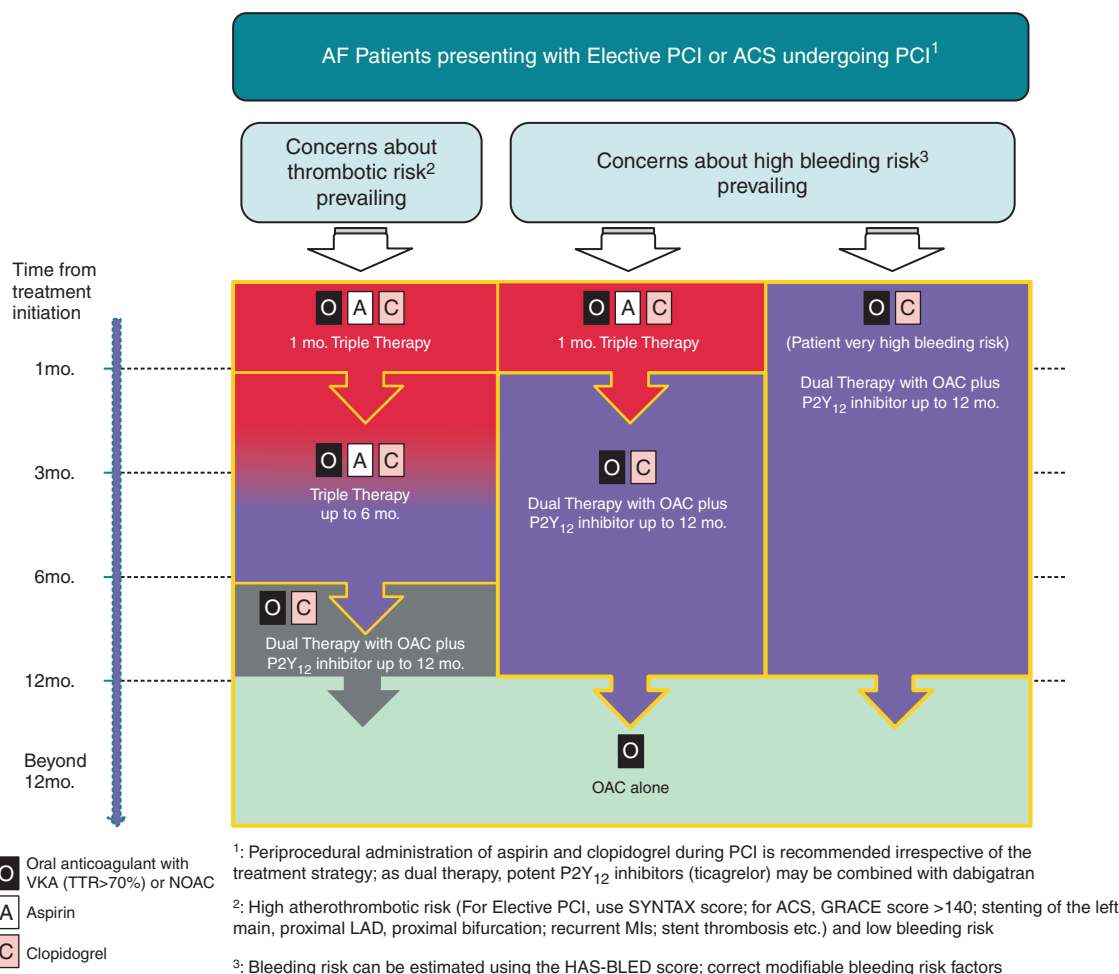


Figure 2 Management algorithm for AF patients presenting with elective PCI or ACS undergoing PCI.

note, a signal of increased harm in the risk of stroke was apparent in the very low dose, i.e. 2.5 mg bid, rivaroxaban arm compared with conventional TAT³⁹. In the RE-DUAL PCI trial, a numerical trend for more thrombotic endpoints was also seen with the dabigatran 110 mg bid arm.^{39,40} Until more data are available, TAT is still the recommended as the initial treatment for the first month after PCI or an ACS in patients with a high ischaemic risk and a low bleeding risk.⁵

Trials with apixaban and edoxaban are ongoing. Because full-dose apixaban 5 mg bid and edoxaban 60 mg od were associated with significantly less major bleeding than warfarin in the ARISTOTLE (Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation)¹⁷⁰ and ENGAGE AF-TIMI 48¹⁷¹ trials for stroke prevention in non-valvular AF, these doses should generally be selected for TAT. Whereas safety of reduced-dose apixaban 2.5 mg bid and edoxaban 30 mg bid is likely higher, true efficacy in stroke prevention is unknown when these doses are used in the absence of factors qualifying patients for dose reduction, and should therefore generally not be used, even when DAPT of aspirin and clopidogrel is given in conjunction.

In patients with a low risk of bleeding, TAT may be extended longer, for to 3–6 months depending on the clinical scenario. After this

period of TAT, OAC plus aspirin or (preferably) clopidogrel should be considered up to 12 months after PCI. After 1 year it is reasonable to maintain OAC alone.^{2,5}

In cases of high bleeding risk, DAT (OAC plus aspirin or preferably, clopidogrel) may be considered from the time of discharge and continued for 1 year, followed thereafter by OAC alone.^{2,5} When NOACs are used, in general, dose reduction below the approved doses for stroke prevention is not recommended. The dose intensity of VKA should be carefully monitored with an INR in the lower part of the recommended range, and to ensure good quality anticoagulation control, as reflected by high TTR (e.g. >65–70%). Gastric protection with a proton pump inhibitor (PPI) is recommended in patients on triple therapy and in high bleeding risk patients on double therapy.¹⁶⁵

As regards the optimal duration of TAT, especially with the aim of reducing the risk of bleeding, both the prospective, randomized ISAR-TRIPLE trial¹⁴⁷ and the observational data by Koskinas et al.²⁰ have provided additional information. In the ISAR-TRIPLE trial,¹⁴⁷ 614 patients receiving concomitant aspirin and VKA after PCI (for stable CAD in approximately 65%) with implantation of new-generation DES in about 80% of cases, were randomized to either 6-

week or 6-month clopidogrel therapy. At 9-month follow-up, the composite in incidence of death, MI, definite stent thrombosis or major bleeding was comparable in the two groups.¹⁴⁷ In the analysis by Koskinas et al.²⁰ of the prospective Bern PCI registry, out of the 568 patients with indication for VKA and discharged on TAT, 245 (43%) were prescribed 1-month duration of treatment whereas the remaining 323 (57%) were prescribed 6-month after PCI with implantation of new-generation DES in about 60% of cases.²⁰ At 1 year, the primary composite endpoint of cardiac death, MI, stroke, definite stent thrombosis, or major bleeding was comparable in the two groups.²⁰ In the current era of new-generation, less thrombogenic DES, it appears therefore that duration of TAT in OAC patients may be limited to 1–3 months only. No data were available on the quality of OAC, nor on the recommended INR range (commonly 2.0–2.5), but observational data suggest that freedom from major bleeding events may indeed be inversely related to TTR values.⁸

Additional evidence on the regimen to adopt or prolong after the initial course of TAT has been concluded, is not available. As per accepted recommendations, withdrawal of one of the two antiplatelet agents, either aspirin (preferably) or clopidogrel, should be performed, and combination of ongoing OAC (either VKA or NOAC) should be continued up to 1 year. If reduced dose rivaroxaban 15 mg od was ongoing, full dose 20 mg od could be started when one antiplatelet agent is withdrawn. The decision whether or not to increase the dose of dabigatran from 110 to 150 mg bid should be left at the discretion of the attending care provider based on the patient's overall risk of bleeding and stroke.

Post hoc analyses of the stroke prevention trials did not suggest reduced efficacy or increased harm when NOAC plus antiplatelet therapy was compared with VKA plus antiplatelet therapy.

Atrial fibrillation occurring early after percutaneous cardiovascular intervention in acute coronary syndrome patients

Approximately 10% of patients hospitalized for ACS and generally undergoing PCI plus stenting develop AF in the early phase.¹⁷² Although it is presently unclear whether new onset AF associated with ACS has the same risk as a prior history of paroxysmal AF,¹⁷³ OAC should be generally prescribed according to the individual risk of stroke, usually in combination, at least for some time, with antiplatelet agents. Initiation of warfarin in OAC-naïve patients, as generally are those developing AF in the context of an ACS, is associated with an increase risk of bleeding, which may result in the withdrawal of antithrombotic agents, therefore increasing the risk of thromboembolic events.¹⁷⁴ In the absence of established factors requiring dose reduction, the appropriate dose of NOAC should be given, as discussed above.¹⁷⁵

Long-term management

After 1 year of combined OAC and (dual and single) antiplatelet therapy has been completed, OAC monotherapy (either VKA or NOAC) should be continued long term. Based on historical data with warfarin,¹⁷⁶ the efficacy of OAC monotherapy in secondary prevention after a coronary event appears at least comparable to standard aspirin. VKA monotherapy has been associated with significantly

less major bleeding compared with combined VKA and antiplatelet therapy, with no difference in the risk of cardiovascular death, MI, or non-haemorrhagic stroke at 2 years.¹⁷⁷ Extrapolation of the VKA results has been made for NOAC.

Given the lack of specific data, combined OAC and single antiplatelet agent, either aspirin or clopidogrel, may be considered long-term only in highly selected cases with a very increased ongoing ischaemic risk, when clinical and/or anatomical circumstances indicate a high risk of thrombosis and/or major cardiovascular events if stent thrombosis occur.

Consensus statements for the management of atrial fibrillation patients presenting with an percutaneous cardiovascular intervention and/or undergoing percutaneous cardiovascular intervention/stenting

In general, the period of TAT should be as short as possible, followed by OAC plus a single antiplatelet agent (clopidogrel 75 mg od, or alternatively, aspirin 75–100 mg od). The duration of TAT is dependent on a number of considerations: acute vs. elective procedures, bleeding risk (as assessed by the HAS-BLED score), type of stent (with a preference for new-generation DES or BMS). Suboptimal stent placement might also increase the risk for ischaemic events and should be avoided in selected cases by use of intracoronary imaging techniques.

In case, we refer to OAC, this can be with well-controlled adjusted-dose VKA (with TTR >70%) or with a NOAC.

General management considerations

In AF patients, stroke risk must be assessed using the CHA₂DS₂-VASc score, and bleeding risk should be assessed using the HAS-BLED score.

- Stroke and bleeding risk stratification is a dynamic process, and must be performed at regular intervals.
- Every effort should be made to address modifiable bleeding risk factors at every patient contact.
- Established bleeding scores, e.g. HAS-BLED, should be used to draw attention to modifiable bleeding risk factors and to identify the patients for earlier review and followup.



106,107,113,122,
130,136,137

Continued

An initial period of triple therapy should be used in most AF patients undergoing PCI, depending on presentation (ACS vs. elective), stroke vs. bleeding risk, procedural considerations (e.g. disease severity) etc.

5



- Dual therapy with OAC plus one P2Y₁₂ inhibitor (usually clopidogrel) may be considered in patients who are predisposed to excessive bleeding risk and have low thrombotic risk.

In anticoagulated patients, pretreatment with antiplatelet therapy is appropriate if PCI planned.

51,52



- Clopidogrel is the P2Y₁₂ inhibitor of choice in anticoagulated patients; prasugrel and ticagrelor should be avoided in patients also receiving aspirin due to their higher bleeding risk if used in combination as part of a TAT regimen.

- In anticoagulated patients, postpone pretreatment with P2Y₁₂ inhibitors if the coronary anatomy is not known.



NOACs as part of TAT or DAT are safer than VKA (e.g. Warfarin) with respect to bleeding risk and is the preferred option in the absence of contraindications to use of these drugs.

39,40



- AF patients with CHA₂DS₂-VASC score ≥ 2 treated with a NOAC should continue their NOAC indefinitely, with addition of antiplatelets for up to 12 months after PCI/ACS.

DAT with rivaroxaban or dabigatran and a P2Y₁₂ inhibitor is associated with a lower risk of bleeding than TAT with warfarin.

39,40



- None have been sufficiently evaluated with respect to efficacy.

When dabigatran is used as part of DAT, the standard doses of 150 mg bid should be used to reduce the risk of ischaemic events.

39,40



Continued

- As per prescribing label, dabigatran 110 mg bid can be considered in elderly patients, concomitant when P_gP inhibitors (e.g. verapamil) are used, and in patients with high bleeding risk
- Both dabigatran 150 mg or 110 mg bid have been shown to be non-inferior (and in the case of 150 mg bid, superior) to warfarin for stroke prevention in AF.

When rivaroxaban is used as part of DAT, reduced dose 15 mg od should be considered.

39



- The efficacy with respect to stroke prevention of this reduced dose in this population has not been sufficiently evaluated.

When apixaban or edoxaban are used as part of TAT or DAT, the standard dose (5 mg bid and 60 mg od, respectively, unless label-guided dose reduction is indicated) should be selected pending results of ongoing trials.

Expert consensus



When VKA is given in combination with clopidogrel and/or low-dose aspirin, the dose intensity of VKA should be carefully regulated, with a target INR range of 2.0–2.5.

178



- Good quality anticoagulation is recommended, with a high time in therapeutic range (TTR >65–70%) aimed for.

In patients on VKA undergoing coronary angiography and/or PCI, an uninterrupted VKA strategy is at least as safe as interrupted VKA, and seems to be much safer than interrupted VKA with bridging anticoagulation.

1



Patients with AF and stable vascular disease (arbitrarily defined as being free from any acute ischaemic event or repeat revascularisation for >1 year) should be managed with OAC alone.

1



Continued

Radial access should be considered as the default approach for coronary angiography/intervention to minimize the risk of access-related bleeding depending on operator expertise and preference.

Gastric protection with PPIs should be considered in all patients with OAC plus antiplatelet therapy



1



1



1

Long-term antithrombotic therapy (beyond 12 months) is recommended with OAC in all patients.

- Combination OAC plus single antiplatelet therapy (i.e., aspirin) may sometimes be continued in very selected cases, e.g. stenting of the left main, proximal bifurcation, recurrent MIs etc.

Elective or stable CAD

For NOAC-treated patients undergoing elective PCI, timed cessation (e.g. >12–48 h) before intervention may be considered, depending on the agent and renal function (see text) and use of standard local anticoagulation practices periprocedurally.

- Early after PCI, such as the same evening or the next morning, NOAC therapy should be restarted.



5,6

In patients with stable CAD and AF undergoing PCI at low bleeding risk (HAS-BLED ≤ 2), TAT (OAC, aspirin 75–100 mg daily, clopidogrel 75 mg daily) should be given for a minimum of 4 weeks (and no longer than 6 months) after PCI following which DAT with OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) should be continued for up to 6–12 months.



5,6

In patients with stable CAD and AF undergoing PCI at high bleeding risk (HAS-BLED ≥ 3), TAT (OAC, aspirin 75–100 mg daily, clopidogrel 75 mg daily) or DAT consisting of OAC and clopidogrel 75 mg/day should be given for 1



5,6

Continued

month after PCI following which DAT with OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) should be continued for up to 6 months, beyond which patients would be managed on OAC alone.

- In patients at very high bleeding risk (e.g. recent bleeding event), aspirin may be omitted, and DAT with a NOAC and clopidogrel 75 mg/day continued for 3–6 months, beyond which patients would be managed on OAC alone.

Long-term antithrombotic therapy with OAC (beyond 12 months) is recommended in all patients.

- Combination OAC plus single antiplatelet therapy (i.e. aspirin) may be considered in only very selected cases with an increased ongoing ischaemic risk.



5,6

When the procedures require interruption of OAC for longer than 48 h in high-risk patients (i.e. TAVI or other non-PCI procedures at high bleeding risk), enoxaparin may be administered subcutaneously, although the efficacy of this strategy is uncertain.



Expert consensus

- Bridging is often considered in patients with mechanical heart valves, recent stroke/venous thromboembolism (<3 months).
- Pharmacodynamic data suggest that enoxaparin might be a better option than unfractionated heparin, because of the more predictable and stable level of anticoagulation.
- Such 'bridging' therapies may be associated with an excess bleeding risk, possibly due to dual modes of anticoagulation in the overlap periods.
- When NOACs are used, timing of any bridging therapy should be tailored based on renal function and the pharmacokinetics of the specific NOAC.

Continued

NSTE-ACS including unstable angina and NSTEMI

In patients on OAC developing a NSTE-ACS, aspirin loading should be as in STEMI, and clopidogrel is again the P2Y₁₂ inhibitor of choice.

5,6



- As clopidogrel takes considerable time to achieve its maximal antiplatelet effect in unstable patients, clopidogrel without aspirin cannot be recommended in the acute or periprocedural phase.
- Pretreatment with P2Y₁₂ receptor antagonists may be withheld until the time of coronary angiography in case of an early invasive strategy within 24 h.
- The use of ticagrelor or prasugrel in combination with OAC may only be considered under certain circumstances (e.g. definite stent thrombosis while on clopidogrel, aspirin, and OAC).

Administer unfractionated heparin or bivalirudin only as bailout (but avoiding GPIIb/IIIa inhibitors) or if INR ≤ 2 in a patient on VKA, balancing the acute need for additional antithrombotic therapy with the excess bleeding risk and the 'thrombus burden'.

Expert consensus



- Glycoprotein IIb/IIIa inhibitors should be avoided unless for bailout situations due to the increased risk of bleeding associated with their use.

TAT is still the recommended initial treatment for the first month after PCI or an ACS in AF patients with a high ischemic risk and a low bleeding risk.

1,5,6



An early invasive strategy (within 24 h) should be preferred among AF patients with moderate to high-risk NSTE-ACS in order to expedite treatment allocation (medical vs. PCI vs. coronary artery bypass grafting) and to determine the optimal antithrombotic regimen.

1,5



Continued

In AF patients with ACS at low risk of bleeding (HAS-BLED 0–2), the initial use of TAT (OAC, aspirin and clopidogrel) should be considered for 3–6 months following PCI irrespective of stent type; this should be followed by long term DAT (up to 12 months) with OAC and clopidogrel 75mg/day (or alternatively, aspirin 75–100 mg/day).

1,5,6



In patients with ACS and AF at high risk of bleeding (HAS-BLED ≥ 3), the initial use of TAT (OAC, aspirin, and clopidogrel) should be considered for 4 weeks following PCI irrespective of stent type; this should be followed by long term DAT (up to 12 months) with OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day).

5,6



- In patients at very high bleeding risk (e.g. recent bleeding event), aspirin may be omitted, and dual therapy with OAC and clopidogrel 75 mg/day continued for 3–6 months, beyond which patients would be managed with OAC alone.

Long-term antithrombotic therapy (beyond 12 months) with OAC, whether with VKA or NOAC, is recommended in all patients.

5,6



- Combination OAC plus single antiplatelet therapy (i.e. aspirin) may be considered in very selected cases, e.g. extensive multivessel CAD, last remaining patent coronary artery, stenting of the left main stem or a proximal bifurcation, recurrent MIs etc.

Primary PCI

When anticoagulated patients present with a STEMI, they should be triaged for primary PCI regardless of the anticipated time to PCI-mediated reperfusion.

1,4–6



Continued

In the setting of STEMI, radial access for primary PCI is the best option, when feasible, to avoid procedural bleeding depending on operator expertise and preference.

In patients with STEMI and AF at low risk of bleeding (HAS-BLED 0–2), the initial use of TAT (OAC, aspirin and clopidogrel) should be considered for 6 months following PCI irrespective of stent type; this should be followed by long term DAT (up to 12 months) with OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day).

In patients with STEMI and AF at high risk of bleeding (HAS-BLED ≥ 3), the initial use of TAT (OAC, aspirin, and clopidogrel) should be considered for 4 weeks following PCI irrespective of stent type; this should be followed by long term DAT (up to 12 months) with OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day).

- In patients at very high bleeding risk (e.g. recent bleeding event), aspirin may be omitted, and dual therapy with OAC and clopidogrel 75 mg/day continued for 3–6 months, beyond which patients would be managed on OAC alone.

Long-term antithrombotic therapy (beyond 12 months) is recommended with OAC in all patients.

- Combination OAC plus single antiplatelet therapy (i.e. aspirin) may sometimes be continued in very selected cases, e.g. stenting of the left main, proximal bifurcation, recurrent MIs etc.



1,4–6



1,5,6



1,5,6



5,6

Areas for future research

Dual antithrombotic therapy by omitting aspirin in secondary prevention after acute coronary syndrome in patients with atrial fibrillation

Although both the PIONEER-AF^{179,180} and RE-DUAL PCI⁴⁰ trials have shown a benefit of DAT (i.e. a NOAC in combination with clopidogrel) over TAT some questions still remain and need to be answered. Both studies miss a DAT comparator with VKA plus Clopidogrel. Moreover, 15 mg rivaroxaban in combination with clopidogrel does not reflect current guidelines that the NOAC should be used in the lowest dose that has been tested for stroke reduction.⁵

Finally, the use of potent P2Y₁₂-inhibitors (ticagrelor or prasugrel) in combination with a NOAC in this indication is still not sufficiently proven, given that only 12% of patients in RE-DUAL PCI and a minority in PIONEER-AF had these drugs. A particular patient group for further research with these newer agents includes those with high on clopidogrel platelet reactivity, especially in patients with a high prevalence of comorbidity.^{181,182} Such high on treatment platelet reactivity may have implications for prognosis, and optimal management remains uncertain.¹⁸³

New anticoagulants and new antiplatelet agents on the horizon

The search for the 'holy grail' of anticoagulation, an agent that combines optimal efficacy with minimal bleeding diathesis, continues. Also, novel antiplatelet drugs that selectively inhibit arterial thrombosis without interfering with normal haemostasis may yet occur. New antiplatelet drugs interfering with the interaction of von Willebrand factor (VWF) with glycoprotein (GP) Iba, and directed against GPIIb/IIIa (integrin $\alpha_{IIb}\beta_3$), the thrombin receptor PAR-1, and the ADP receptor P2Y₁₂ are on the horizon.¹⁸⁴

The development of new anticoagulant drugs is also rapidly expanding, targeting other factors in the coagulation cascade, such as Factor XI and XII.^{185,186} Factor XI has emerged as a particularly promising target for new anticoagulants that may be even safer than the NOACs, given the reduced thrombosis in factor XI-deficient mice, and that congenital factor XI deficiency is associated with only a mild bleeding diathesis.¹⁸⁷ A recent Phase II trial showed that, when compared with enoxaparin, factor XI inhibition by an antisense antibody reduced venous thromboembolism without increasing bleeding after elective knee arthroplasty.¹⁸⁸ Whether these new drugs can be translated to thromboprophylaxis for AF patients in the ACS or PCI setting requires further investigation.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: See [Supplementary material](#) online.

References

- Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM *et al*. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J* 2014;**35**:3155–79.
- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
- Chiang CE, Wang TD, Lin TH, Yeh HI, Liu PY, Cheng HM. The 2017 Focused Update of the Guidelines of the Taiwan Society of Cardiology (TSOC) and the Taiwan Hypertension Society (THS) for the Management of Hypertension. *Acta Cardiol Sin* 2017;**33**:213–25.
- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–77.
- Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–60.
- Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L *et al*. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace* 2018; doi:10.1093/europace/euy054 [Epub ahead of print].
- Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol* 2017;**14**:627–8.
- Proietti M, Airaksinen KEJ, Rubboli A, Schlitt A, Kiviniemi T, Karjalainen PP *et al*. Time in therapeutic range and major adverse outcomes in atrial fibrillation patients undergoing percutaneous coronary intervention: the Atrial Fibrillation Undergoing Coronary Artery Stenting (AFCAS) registry. *Am Heart J* 2017;**190**:86–93.
- Choi HI, Ahn JM, Kang SH, Lee PH, Kang SJ, Lee SW *et al*. Prevalence, management, and long-term (6-year) outcomes of atrial fibrillation among patients receiving drug-eluting coronary stents. *JACC Cardiovasc Interv* 2017;**10**:1075–85.
- Rubboli A, Saia F, Sciahbasi A, Leone AM, Palmieri C, Bacchi-Reggiani ML *et al*. Twelve-month outcome of patients with an established indication for oral anticoagulation undergoing coronary artery stenting and stratified by the baseline risk of bleeding: insights from the Warfarin and Coronary Stenting (War-Stent) Registry. *Cardiovasc Revasc Med* 2017;**18**:425–30.
- Verlinden NJ, Coons JC, Isella CJ, Kane-Gill SL. Triple antithrombotic therapy with aspirin, P2Y₁₂ inhibitor, and warfarin after percutaneous coronary intervention: an evaluation of prasugrel or ticagrelor versus clopidogrel. *J Cardiovasc Pharmacol Ther* 2017;**22**:546–51.
- Faza NN, Mentias A, Parashar A, Chaudhury P, Barakat AF, Agarwal S *et al*. Bleeding complications of triple antithrombotic therapy after percutaneous coronary interventions. *Catheter Cardiovasc Interv* 2017;**89**:E64–E74.
- Fauchier L, Ruiz-Nodar JM, Valdés M, Angoulvant D, Lip GYH, Marín F. Is oral anticoagulation needed in patients with atrial fibrillation and stent implantation at low-moderate risk of stroke? *Eur J Intern Med* 2016;**35**:e9–e10.
- Sra S, Tan MK, Mehta SR, Fisher HN, Déry J-P, Welsh RC *et al*. Ischemic and bleeding events in patients with myocardial infarction undergoing percutaneous coronary intervention who require oral anticoagulation: insights from the Canadian observational AntiPlatelet sTudy. *Am Heart J* 2016;**180**:82–9.
- Bogacki P, Kablak-Ziemicka A, Bryniarski K, Wrotniak L, Ostrowska-Kaim E, Żmudka K *et al*. Triple anticoagulation therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention—real life assessment. *Postępy Kardiologii Interwencyjnej* 2016;**4**:303–13.
- Fu A, Singh K, Abunassar J, Malhotra N, Le May M, Labinaz M *et al*. Ticagrelor in triple antithrombotic therapy: predictors of ischemic and bleeding complications. *Clin Cardiol* 2016;**39**:19–23.
- Sambola A, Mutuberria M, Garcia Del Blanco B, Alonso A, Barrabes JA, Bueno H *et al*. Impact of triple therapy in elderly patients with atrial fibrillation undergoing percutaneous coronary intervention. *PLoS One* 2016;**11**:e0147245.
- Lopes RD, Rao M, Simon DN, Thomas L, Ansell J, Fonarow GC *et al*. Triple vs dual antithrombotic therapy in patients with atrial fibrillation and coronary artery disease. *Am J Med* 2016;**129**:592–9.e1.
- De Vecchis R, Cantatrione C, Mazzei D. Clinical relevance of anticoagulation and dual antiplatelet therapy to the outcomes of patients with atrial fibrillation and recent percutaneous coronary intervention with stent. *J Clin Med Res* 2016;**8**:153–61.
- Koskinas KC, Raber L, Zanchin T, Pilgrim T, Stortecky S, Hunziker L *et al*. Duration of triple antithrombotic therapy and outcomes among patients undergoing percutaneous coronary intervention. *JACC Cardiovasc Interv* 2016;**9**:1473–83.
- Secemsky EA, Butala NM, Kartoun U, Mahmood S, Wasfy JH, Kennedy KF *et al*. Use of chronic oral anticoagulation and associated outcomes among patients undergoing percutaneous coronary intervention. *J Am Heart Assoc* 2016;**5**:e004310.
- Sambola A, Mutuberria M, Garcia Del Blanco B, Alonso A, Barrabes JA, Alfonso F *et al*. Effects of triple therapy in patients with non-valvular atrial fibrillation undergoing percutaneous coronary intervention regarding thromboembolic risk stratification. *Circ J* 2016;**80**:354–62.
- Braun OO, Bico B, Chaudhry U, Wagner H, Koul S, Tyden P *et al*. Concomitant use of warfarin and ticagrelor as an alternative to triple antithrombotic therapy after an acute coronary syndrome. *Thromb Res* 2015;**135**:26–30.
- Hess CN, Peterson ED, Peng SA, de Lemos JA, Fosbol EL, Thomas L *et al*. Use and outcomes of triple therapy among older patients with acute myocardial infarction and atrial fibrillation. *J Am Coll Cardiol* 2015;**66**:616–27.
- Mennuni MG, Halperin JL, Bansilal S, Schoos MM, Theodoropoulos KN, Meelu OA *et al*. Balancing the risk of bleeding and stroke in patients with atrial fibrillation after percutaneous coronary intervention (from the AVIATOR Registry). *Am J Cardiol* 2015;**116**:37–42.
- Staudacher DL, Kaiser M, Hehrlein C, Bode C, Ahrens I. Triple antithrombotic therapy after percutaneous coronary intervention (PCI) in patients with indication for oral anticoagulation: data from a single center registry. *PLoS One* 2015;**10**:e0140101.
- Kawai H, Watanabe E, Yamamoto M, Harigaya H, Sano K, Takatsu H *et al*. Major bleeding complications related to combined antithrombotic therapy in atrial fibrillation patients 12 months after coronary artery stenting. *J Cardiol* 2015;**65**:197–202.
- Jackson LR, Ju C, Zettler M, Messenger JC, Cohen DJ, Stone GW *et al*. Outcomes of patients with acute myocardial infarction undergoing percutaneous coronary intervention receiving an oral anticoagulant and dual antiplatelet therapy: a comparison of clopidogrel versus prasugrel from the TRANSLATE-ACS study. *JACC Cardiovasc Interv* 2015;**8**:1880–9.
- Karrowi W, Wang TY, Chen AY, Thomas L, Saucedo JF, El Accaoui RN. Chronic vitamin K antagonist therapy and bleeding risk in ST elevation myocardial infarction patients. *Heart (British Cardiac Society)* 2015;**101**:264–70.
- Enomoto Y, Iijima R, Tokue M, Ito N, Nagashima Y, Araki T *et al*. Bleeding risk with triple antithrombotic therapy in patients with atrial fibrillation and drug-eluting stents. *Cardiovasc Interv Ther* 2014;**29**:193–9.
- Rubboli A, Schlitt A, Kiviniemi T, Biancari F, Karjalainen PP, Valencia J *et al*. One-year outcome of patients with atrial fibrillation undergoing coronary artery stenting: an analysis of the AFCAS registry. *Clin Cardiol* 2014;**37**:357–64.
- Goto K, Nakai K, Shizuta S, Morimoto T, Shiomi H, Natsuaki M *et al*. Anticoagulant and antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention. *Am J Cardiol* 2014;**114**:70–8.
- Alonso A, Gore JM, Awad HH, Quill AL, Montalescot G, van de Werf F *et al*. Management and outcomes of patients presenting with STEMI by use of chronic oral anticoagulation: results from the GRACE registry. *Eur Heart J Acute Cardiovasc Care* 2013;**2**:280–91.
- Dąbrowska M, Ochala A, Cybulski W, Tendra M. Balancing between bleeding and thromboembolism after percutaneous coronary intervention in patients with atrial fibrillation. Could triple anticoagulant therapy be a solution? *Postępy Kardiologii Interwencyjnej* 2013;**3**:234–40.
- Fosbol EL, Wang TY, Li S, Piccini J, Lopes RD, Mills RM *et al*. Warfarin use among older atrial fibrillation patients with non-ST-segment elevation myocardial infarction managed with coronary stenting and dual antiplatelet therapy. *Am Heart J* 2013;**166**:864–70.
- Seivani Y, Abdel-Wahab M, Geist V, Richardt G, Sulimov DS, El-Mawady M *et al*. Long-term safety and efficacy of dual therapy with oral anticoagulation and clopidogrel in patients with atrial fibrillation treated with drug-eluting stents. *Clin Res Cardiol* 2013;**102**:799–806.
- Denas G, Padayattil Jose S, Greseli P, Erba N, Testa S, De Micheli V *et al*. Major bleeding in patients undergoing PCI and triple or dual antithrombotic therapy: a parallel-cohort study. *J Thromb Thrombolysis* 2013;**35**:178–84.
- Chandrasekhar J, Mastoris I, Baber U, Sartori S, Schoos M, Bansilal S *et al*. Antithrombotic strategy variability in Atrial fibrillation and obstructive coronary disease revascularized with PCI-rationale and study design of the prospective observational multicenter AVIATOR 2 registry. *Am Heart J* 2015;**170**:1234–42.

39. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;**375**:2423–34.
40. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;**377**:1513–24.
41. Alexander JH, Lopes RD, Thomas L, Alings M, Atar D, Aylward P et al. Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J* 2014;**35**:224–32.
42. Lopes RD, Vora AN, Liaw D, Granger CB, Darius H, Goodman SG et al. An open-Label, 2 × 2 factorial, randomized controlled trial to evaluate the safety of apixaban vs. vitamin K antagonist and aspirin vs. placebo in patients with atrial fibrillation and acute coronary syndrome and/or percutaneous coronary intervention: rationale and design of the AUGUSTUS trial. *Am Heart J* 2018;**200**:17–23.
43. Vranckx P, Lewalter T, Valgimigli M, Tijssen JG, Reimtz PE, Eckardt L et al. Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement: rationale and design of the ENTRUST-AF PCI trial. *Am Heart J* 2018;**196**:105–12.
44. Golwala HB, Cannon CP, Steg PG, Doros G, Qamar A, Ellis SG et al. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J* 2018;**39**:1726–35a.
45. Dewilde WJM, Oirbans T, Verheugt FWA, Kelder JC, De Smet BJGL, Herrman J-P et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;**381**:1107–15.
46. Ohman E, Roe M, Steg P, James S, Povsic T, White J et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. *Lancet* 2017;**389**:1799–808.
47. Eikelboom JWCS, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;**377**:1319–30.
48. Vranckx P, Valgimigli M, Windecker S, Steg P, Hamm C, Jüni P et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. *EuroIntervention* 2016;**12**:1239–45.
49. Baber U, Dangas G, Cohen DJ, Gibson CM, Mehta SR, Angiolillo DJ et al. Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: rationale and design of the TWILIGHT study. *Am Heart J* 2016;**182**:125–34.
50. Sarafoff N, Martischni G, Wealer J, Mayer K, Mehili J, Sibbing D et al. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol* 2013;**61**:2060–6.
51. Wiviott SD, Antman EM, Gibson CM, Montalescot G, Riesmeyer J, Weerakkody G et al. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRIAL to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). *Am Heart J* 2006;**152**:627–35.
52. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–57.
53. Bonaca MP, Bhatt DL, Braunwald E, Cohen M, Steg PG, Storey RF et al. Design and rationale for the prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin-thrombolysis in myocardial infarction 54 (PEGASUS-TIMI 54) trial. *Am Heart J* 2014;**167**:437–44.e5.
54. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;**372**:1791–800.
55. Storey RF, Angiolillo DJ, Bonaca MP, Thomas MR, Judge HM, Rollini F et al. Platelet inhibition with ticagrelor 60 mg compared with 90 mg twice-daily in the PEGASUS-TIMI 54 study. *J Am Coll Cardiol* 2016;**67**:1145–54.
56. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T 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* 2017;**390**:1747–57.
57. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J* 2017;**38**:3070–8.
58. Kowalewski M, Suwalski P, Raffa GM, Stomka A, Kowalkowska ME, Szwed KA et al. Meta-analysis of uninterrupted as compared to interrupted oral anticoagulation with or without bridging in patients undergoing coronary angiography with or without percutaneous coronary intervention. *Int J Cardiol* 2016;**223**:186–94.
59. Kolh P, Windecker S, Alfonso F, Collet J-P, Cremer J, Falk V et al. ESC/EACTS myocardial revascularization guidelines 2014. *Eur Heart J* 2014;**46**:517–6.
60. Valgimigli M, Patialiakas A, Thury A, McFadden E, Colangelo S, Campo G et al. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. *J Am Coll Cardiol* 2015;**65**:805–15.
61. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrie D, Naber C et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;**373**:2038–47.
62. Naber CK, Urban P, Ong PJ, Valdes-Chavarri M, Abizaid AA, Pocock SJ et al. Biolimus-A9 polymer-free coated stent in high bleeding risk patients with acute coronary syndrome: a Leaders Free ACS sub-study. *Eur Heart J* 2017;**38**:961–9.
63. Garot P, Morice MC, Tresukosol D, Pocock SJ, Meredith IT, Abizaid A et al. 2-Year outcomes of high bleeding risk patients after polymer-free drug-coated stents. *J Am Coll Cardiol* 2017;**69**:162–71.
64. Carrie D, Menown I, Oldroyd K, Copt S, Talwar S, Maillard L et al. Safety and efficacy of polymer-free biolimus A9-coated versus bare-metal stents in orally anticoagulated patients: 2-year results of the LEADERS FREE oral anticoagulation substudy. *JACC Cardiovasc Interv* 2017;**10**:1633–42.
65. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrie D et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet* 2018;**391**:41–50.
66. Byrne RA, Serruys PW, Baumbach A, Escaned J, Fajadet J, James S et al. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. *Eur Heart J* 2015;**36**:2608–20.
67. Byrne RA, Stefanini GG, Capodanno D, Onuma Y, Baumbach A, Escaned J et al. Report of an ESC-EAPCI Task Force on the evaluation and use of bioresorbable scaffolds for percutaneous coronary intervention: executive summary. *EuroIntervention* 2018;**13**:1574–86.
68. Cassese S, Byrne RA, Juni P, Wykrzykowska JJ, Puricel S, Ndrepepa G et al. Midterm clinical outcomes with everolimus-eluting bioresorbable scaffolds versus everolimus-eluting metallic stents for percutaneous coronary interventions: a meta-analysis of randomised trials. *EuroIntervention* 2018;**13**:1565–73.
69. Rodes-Cabau J, Dauerman HL, Cohen MG, Mehran R, Small EM, Smyth SS et al. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. *J Am Coll Cardiol* 2013;**62**:2349–59.
70. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–607.
71. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–98.
72. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;**370**:1790–8.
73. Hamm CW, Mollmann H, Holzhey D, Beckmann A, Veit C, Figulla HR et al. The German Aortic Valve Registry (GARY): in-hospital outcome. *Eur Heart J* 2014;**35**:1588–98.
74. Gargiulo G, Sannino A, Capodanno D, Barbanti M, Buccheri S, Perrino C et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement: a systematic review and meta-analysis. *Ann Intern Med* 2016;**165**:334–44.
75. Siontis GC, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. *Eur Heart J* 2016;**37**:3503–12.
76. Ussia GP, Scarabelli M, Mule M, Barbanti M, Sarkar K, Cammalleri V et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. *Am J Cardiol* 2011;**108**:1772–6.
77. Stabile E, Pucciarelli A, Cota L, Sorropago G, Tesorio T, Salemm L et al. SAT-TAVI (single antiplatelet therapy for TAVI) study: a pilot randomized study comparing double to single antiplatelet therapy for transcatheter aortic valve implantation. *Int J Cardiol* 2014;**174**:624–7.
78. Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR et al. 2012 ACCF/AATS/SCA/STS expert consensus document on transcatheter aortic valve replacement. *J Am Coll Cardiol* 2012;**59**:1200–54.
79. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;**33**:2451–96.
80. Webb J, Rodés-Cabau J, Fremes S, Pibarot P, Ruel M, Ibrahim R et al. Transcatheter aortic valve implantation: a Canadian Cardiovascular Society position statement. *Can J Cardiol* 2012;**28**:520–8.

81. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e576S–600S.
82. Gargiulo G, Collet JP, Valgimigli M. Antithrombotic therapy in TAVI patients: changing concepts. *EuroIntervention* 2015;**11**(Suppl W):W92–5.
83. Dangas GD, Lefevre T, Kupatt C, Tchetché D, Schafer U, Dumonteil N et al. Bivalirudin versus heparin anticoagulation in transcatheter aortic valve replacement: the randomized BRAVO-3 trial. *J Am Coll Cardiol* 2015;**66**:2860–8.
84. Nijenhuis VJ, Bennaghmouch N, van Kuijk JP, Capodanno D, ten Berg JM. Antithrombotic treatment in patients undergoing transcatheter aortic valve implantation (TAVI). *Thromb Haemost* 2015;**113**:674–85.
85. Di Mario C, Eltchaninoff H, Moat N, Goicolea J, Ussia GP, Kala P et al. The 2011-12 pilot European Sentinel Registry of Transcatheter Aortic Valve Implantation: in-hospital results in 4, 571 patients. *EuroIntervention* 2013;**8**:1362–71.
86. Gilard E, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J et al. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012;**366**:1705–15.
87. Sannino A, Gargiulo G, Schiattarella GG, Perrino C, Stabile E, Losi MA et al. A meta-analysis of the impact of pre-existing and new-onset atrial fibrillation on clinical outcomes in patients undergoing transcatheter aortic valve implantation. *EuroIntervention* 2016;**12**:e1047–e56.
88. Rodes-Cabau J, Masson JB, Welsh RC, Garcia Del Blanco B, Pelletier M, Webb JG et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve: the ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) randomized clinical trial. *JACC Cardiovasc Interv* 2017;**10**:1357–65.
89. Capodanno D, Angiolillo DJ. Antithrombotic therapy for prevention of cerebral thromboembolic events after transcatheter aortic valve replacement: evolving paradigms and ongoing directions. *JACC Cardiovasc Interv* 2017;**10**:1366–9.
90. Windecker S, Tjissen J, Giustino G, Guimaraes AH, Mehran R, Valgimigli M et al. Trial design: rivaroxaban for the prevention of major cardiovascular events after transcatheter aortic valve replacement: rationale and design of the GALILEO study. *Am Heart J* 2017;**184**:81–7.
91. Nijenhuis VJ, Bennaghmouch N, Hassell M, Baan J Jr, van Kuijk JP, Agostoni P et al. Rationale and design of POPular-TAVI: antiPlatelet therapy fOr Patients undergoing Transcatheter Aortic Valve Implantation. *Am Heart J* 2016;**173**:77–85.
92. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ et al. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. *J Am Coll Cardiol* 2015;**66**:2844–54.
93. Whitlow PL, Feldman T, Pedersen WR, Lim DS, Kipperman R, Smalling R et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. *J Am Coll Cardiol* 2012;**59**:130–9.
94. Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Schofer N, Eschenbach L et al. Transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed annuloplasty rings. *J Am Coll Cardiol* 2017;**70**:1121–31.
95. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996;**61**:755–9.
96. Peritz DC, Chung EH. Left atrial appendage closure: an emerging option in atrial fibrillation when oral anticoagulants are not tolerated. *Cleve Clin J Med* 2015;**82**:167–76.
97. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–42.
98. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;**64**:1–12.
99. Mandrolia J, Foy A, Naccarelli G. Percutaneous left atrial appendage closure is not ready for routine clinical use. *Heart Rhythm* 2018;**15**:298–301.
100. Fauchier L, Cinaud A, Brigadeau F, Lepillier A, Pierre B, Abbey S et al. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:1528–36.
101. Landmesser U, Schmidt B, Nielsen-Kudsk JE, Lam SCC, Park JW, Tarantini G et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. *EuroIntervention* 2017;**13**:867–76.
102. Tzikas A, Shakir S, Gafoor S, Omran H, Berti S, Santoro G et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *EuroIntervention* 2016;**11**:1170–9.
103. Urena M, Rodes-Cabau J, Freixa X, Saw J, Webb JG, Freeman M et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. *J Am Coll Cardiol* 2013;**62**:96–102.
104. Lakkireddy D, Afzal MR, Lee RJ, Nagaraj H, Tschopp D, Gidney B et al. Short and long-term outcomes of percutaneous left atrial appendage suture ligation: results from a US multicenter evaluation. *Heart Rhythm* 2016;**13**:1030–6.
105. Lip GYH, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. *Thromb Haemost* 2017;**117**:1230–9.
106. Fauchier L, Lecoq C, Ancedy Y, Stamboul K, Saint Etienne C, Ivanov F et al. Evaluation of 5 prognostic scores for prediction of stroke, thromboembolic and coronary events, all-cause mortality, and major adverse cardiac events in patients with atrial fibrillation and coronary stenting. *Am J Cardiol* 2016;**118**:700–7.
107. Capodanno D, Rossini R, Musumeci G, Lettieri C, Senni M, Valsecchi O et al. Predictive accuracy of CHA2DS2-VASc and HAS-BLED scores in patients without atrial fibrillation undergoing percutaneous coronary intervention and discharged on dual antiplatelet therapy. *Int J Cardiol* 2015;**199**:319–25.
108. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc* 2013;**2**:e000250.
109. Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. *BMJ* 2013;**346**:f2573.
110. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;**37**:1582–90.
111. Rivera-Caravaca JM, Roldan V, Esteve-Pastor MA, Valdes M, Vicente V, Lip GYH et al. Long-term stroke risk prediction in patients with atrial fibrillation: comparison of the ABC-stroke and CHA2DS2-VASc scores. *J Am Heart Assoc* 2017;**6**:e006490.
112. Roldan V, Rivera-Caravaca JM, Shantsila A, Garcia-Fernandez A, Esteve-Pastor MA, Vilchez JA et al. Enhancing the 'real world' prediction of cardiovascular events and major bleeding with the CHA2DS2-VASc and HAS-BLED scores using multiple biomarkers. *Ann Med* 2018;**50**:26–34.
113. Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW et al. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:122–32.
114. Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS et al. Dynamic changes of CHA2DS2-VASc score and the risk of ischaemic stroke in Asian patients with atrial fibrillation: a Nationwide Cohort Study. *Thromb Haemost* 2018;**118**:1296–1304.
115. Pisters R, Lane DA, Nieuwlaar R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**:1093–100.
116. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N et al. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol* 2011;**58**:395–401.
117. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015;**36**:3258–64.
118. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet* 2016;**387**:2302–11.
119. Roldan V, Marin F, Manzano-Fernandez S, Gallego P, Vilchez JA, Valdes M et al. The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2013;**62**:2199–204.
120. Apostolakis S, Lane DA, Buller H, Lip GY. Comparison of the CHADS2, CHA2DS2-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. *Thromb Haemost* 2013;**110**:1074–9.
121. Guo YT, Zhang Y, Shi XM, Shan ZL, Wang CJ, Wang YT et al. Assessing bleeding risk in 4824 Asian patients with atrial fibrillation: the Beijing PLA Hospital Atrial Fibrillation Project. *Sci Rep* 2016;**6**:31755.
122. Guo Y, Zhu H, Chen Y, Lip GYH. Comparing bleeding risk assessment focused on modifiable risk factors only versus validated bleeding risk scores in atrial fibrillation. *Am J Med* 2018;**131**:185–92.
123. Wang C, Yu Y, Zhu W, Yu J, Lip GYH, Hong K. Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: a systematic review and meta-analysis. *Oncotarget* 2017;**8**:109703–11.

124. Rivera-Caravaca JM, Roldan V, Esteve-Pastor MA, Valdes M, Vicente V, Lip GYH et al. Importance of time in therapeutic range on bleeding risk prediction using clinical risk scores in patients with atrial fibrillation. *Sci Rep* 2017;**7**:12066.
125. Proietti M, Senoo K, Lane DA, Lip GY. Major bleeding in patients with non-valvular atrial fibrillation: impact of time in therapeutic range on contemporary bleeding risk scores. *Sci Rep* 2016;**6**:24376.
126. Proietti M, Hijazi Z, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD et al. Comparison of bleeding risk scores in patients with atrial fibrillation: insights from the RE-LY trial. *J Intern Med* 2018;**283**:282–92.
127. Esteve-Pastor MA, Rivera-Caravaca JM, Roldan V, Vicente V, Valdes M, Marin F et al. Long-term bleeding risk prediction in 'real world' patients with atrial fibrillation: comparison of the HAS-BLED and ABC-Bleeding risk scores. The Murcia Atrial Fibrillation Project. *Thromb Haemost* 2017;**117**:1848–58.
128. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres 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* 2017;**389**:1025–34.
129. Lip GYH, Skjoth F, Nielsen PB, Kjeldgaard JN, Larsen TB. The HAS-BLED, ATRIA, and ORBIT bleeding scores in atrial fibrillation patients using non-vitamin K antagonist oral anticoagulants. *Am J Med* 2017;**131**:574.e13–27.
130. Ruiz-Nodar JM, Marín F, Roldán V, Valencia J, Manzano-Fernández S, Caballero L et al. Should we recommend oral anticoagulation therapy in patients with atrial fibrillation undergoing coronary artery stenting with a high HAS-BLED bleeding risk score? *Circ Cardiovasc Interv* 2012;**5**:459–66.
131. Smith JG, Wieloch M, Koul S, Braun OO, Lumsden J, Rydell E et al. Triple antithrombotic therapy following an acute coronary syndrome: prevalence, outcomes and prognostic utility of the HAS-BLED score. *EuroIntervention* 2012;**8**: 672–8.
132. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF et al. Incident risk factors and major bleeding in patients with atrial fibrillation treated with oral anticoagulants: a comparison of baseline, follow-up and delta HAS-BLED scores with an approach focused on modifiable bleeding risk factors. *Thromb Haemost* 2018;**118**:768–77.
133. Wilson PWF, D'Agostino R, Bhatt DL, Eagle K, Pencina MJ, Smith SC et al. An international model to predict recurrent cardiovascular disease. *Am J Med* 2012;**125**:695–703.e1.
134. Girisis C, Garg S, Räber L, Sarno G, Morel M-A, Garcia-Garcia HM et al. SYNTAX score and Clinical SYNTAX score as predictors of very long-term clinical outcomes in patients undergoing percutaneous coronary interventions: a substudy of SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization (SIRTAX) trial. *Eur Heart J* 2011;**32**:3115–27.
135. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;**333**:1091.
136. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF et al. Major bleeding and intracranial hemorrhage risk prediction in patients with atrial fibrillation: attention to modifiable bleeding risk factors or use of a bleeding risk stratification score? A nationwide cohort study. *Int J Cardiol* 2018;**254**:157–61.
137. Esteve-Pastor M, Rivera-Caravaca J, Shantsila A, Roldán V, Lip G, Marín F. Assessing bleeding risk in atrial fibrillation patients: comparing a bleeding risk score based only on modifiable bleeding risk factors against the HAS-BLED score. The AMADEUS trial. *Thromb Haemost* 2017;**117**:2261–6.
138. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;**367**:1903–12.
139. Fanola CL, Giugliano RP, Ruff CT, Trevisan M, Nordio F, Mercuri MF et al. A novel risk prediction score in atrial fibrillation for a net clinical outcome from the ENGAGE AF-TIMI 48 randomized clinical trial. *Eur Heart J* 2017;**38**: 888–96.
140. Rivera-Caravaca JM, Roldan V, Esteve-Pastor MA, Valdes M, Vicente V, Marin F et al. Prediction of long-term net clinical outcomes using the TIMI-AF score: comparison with CHA2DS2-VASc and HAS-BLED. *Am Heart J* 2018;**197**:27–34.
141. Rivera-Caravaca JM, Marín F, Esteve-Pastor MA, Raña-Míguez P, Anguita M, Muñiz J et al. Usefulness of the 2MACE score to predicts adverse cardiovascular events in patients with atrial fibrillation. *Am J Cardiol* 2017;**120**:2176–81.
142. Pastori D, Rivera-Caravaca JM, Esteve-Pastor MA, Roldan V, Marín F, Pignatelli P et al. Comparison of the 2MACE and TIMI-AF scores for composite clinical outcomes in anticoagulated atrial fibrillation patients. *Circ J* 2018;**82**:1286–92.
143. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–619.
144. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA et al. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016;**134**: e192–55.
145. Mazurek M, Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC et al. Regional differences in antithrombotic treatment for atrial fibrillation: insights from the GLORIA-AF Phase II Registry. *Thromb Haemost* 2017;**117**:2376–88.
146. Alsalamy S, Al-Sabhan A, Alassim N, Sadat M, Qasim EA, Tamim H et al. Management and outcomes of patients presenting with sepsis and septic shock to the emergency department during nursing handover: a retrospective cohort study. *BMC Emerg Med* 2018;**18**:3.
147. Fiedler KA, Maeng M, Mehili J, Schulz-Schupke S, Byrne RA, Sibbing D et al. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial. *J Am Coll Cardiol* 2015;**65**:1619–29.
148. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;**381**:1107–15.
149. Kiviniemi T, Airaksinen KE, Rubboli A, Biancarri F, Valencia J, Lip GY et al. Bridging therapy with low molecular weight heparin in patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation: the AFCAS study. *Int J Cardiol* 2015;**183**:105–10.
150. Baker NC, O'Connell EW, Htun WW, Sun H, Green SM, Skelding KA et al. Safety of coronary angiography and percutaneous coronary intervention via the radial versus femoral route in patients on uninterrupted oral anticoagulation with warfarin. *Am Heart J* 2014;**168**:537–44.
151. Vranckx P, Verheugt FW, de Maat MP, Ulmans VA, Regar E, Smits P et al. A randomised study of dabigatran in elective percutaneous coronary intervention in stable coronary artery disease patients. *EuroIntervention* 2013;**8**:1052–60.
152. Vranckx P, Leebeek FW, Tijssen JG, Koolen J, Stammen F, Herman JP et al. Periprocedural use of rivaroxaban in elective percutaneous coronary intervention to treat stable coronary artery disease. The X-PLOER trial. *Thromb Haemost* 2015;**114**:258–67.
153. Lahtela H, Karjalainen PP, Niemela M, Vikman S, Kervinen K, Ylitalo A et al. Are glycoprotein inhibitors safe during percutaneous coronary intervention in patients on chronic warfarin treatment? *Thromb Haemost* 2009;**102**:1227–33.
154. Pancholy SB, Ahmed I, Bertrand OF, Patel T. Frequency of radial artery occlusion after transradial access in patients receiving warfarin therapy and undergoing coronary angiography. *Am J Cardiol* 2014;**113**:211–4.
155. Niccoli G, Banning AP. Heparin dose during percutaneous coronary intervention: how low dare we go? *Heart* 2002;**88**:331–4.
156. Chang RJ, Doherty TM, Goldberg SL. How does warfarin affect the activated coagulation time? *Am Heart J* 1998;**136**:477–9.
157. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;**289**:853–63.
158. Kiviniemi T, Karjalainen P, Niemela M, Rubboli A, Lip GY, Schlitt A et al. Bivalirudin use during percutaneous coronary intervention in patients on chronic warfarin therapy. *Thromb Res* 2014;**133**:695–6.
159. Di Sciascio G, Patti G, Pasceri V, Gatto L, Colonna G, Montinaro A. Effectiveness of in-laboratory high-dose clopidogrel loading versus routine pre-load in patients undergoing percutaneous coronary intervention: results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) randomized trial. *J Am Coll Cardiol* 2010;**56**:550–7.
160. Hochholzer W, Trenk D, Frundi D, Blanke P, Fischer B, Andris K et al. Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. *Circulation* 2005;**111**:2560–4.
161. Awtry EH, Loscalzo J. Aspirin. *Circulation* 2000;**101**:1206–18.
162. Payne CD, Li YG, Small DS, Ernest CS, Farid NA, Jakubowski JA et al. Increased active metabolite formation explains the greater platelet inhibition with prasugrel compared to high-dose clopidogrel. *J Cardiovasc Pharmacol* 2007;**50**:555–62.

163. Dominguez-Rodriguez A, Abreu-Gonzalez P, Avanzas P, Bosa-Ojeda F, Samimi-Fard S, Marrero-Rodriguez F et al. Intracoronary versus intravenous abiximab administration in patients with ST-elevation myocardial infarction undergoing thrombus aspiration during primary percutaneous coronary intervention—effects on soluble CD40 ligand concentrations. *Atherosclerosis* 2009;**206**:523–7.
164. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–77.
165. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
166. Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015;**385**:2465–76.
167. Sarafoff N, Martischniig A, Wealer J, Mayer K, Mehilli J, Sibbing D et al. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol* 2013;**61**:2060–6.
168. Dewilde WJ, Janssen PW, Kelder JC, Verheugt FW, De Smet BJ, Adriaenssens T et al. Uninterrupted oral anticoagulation versus bridging in patients with long-term oral anticoagulation during percutaneous coronary intervention: subgroup analysis from the WOEST trial. *EuroIntervention* 2015;**11**:381–90.
169. Kang SH, Chae IH, Park JJ, Lee HS, Kang DY, Hwang SS et al. Stent thrombosis with drug-eluting stents and bioresorbable scaffolds: evidence from a network meta-analysis of 147 trials. *JACC Cardiovasc Interv* 2016;**9**:1203–12.
170. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–92.
171. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–104.
172. Gorenk B, Blomstrom Lundqvist C, Brugada Terradellas J, Camm AJ, Hindricks G, Huber K et al. Cardiac arrhythmias in acute coronary syndromes: position paper from the joint EHRA, ACCA, and EAPCI task force. *Europace* 2014;**16**:1655–73.
173. Zeymer U, Annemans L, Danchin N, Pocock S, Newsome S, Van de Werf F et al. Impact of known or new-onset atrial fibrillation on 2-year cardiovascular event rate in patients with acute coronary syndromes: results from the prospective EPICOR Registry. *Eur Heart J Acute Cardiovasc Care* 2018; doi: 10.1177/2048872618769057.
174. Rivera-Caravaca JM, Roldan V, Esteve-Pastor MA, Valdes M, Vicente V, Lip GYH et al. Cessation of oral anticoagulation is an important risk factor for stroke and mortality in atrial fibrillation patients. *Thromb Haemost* 2017;**117**:1448–54.
175. Rubboli A, Agewall S, Huber K, Lip GYH. New-onset atrial fibrillation after percutaneous coronary intervention with stent: updated proposal of an algorithm for the choice of oral anticoagulant and its dose. *Eur J Intern Med* 2017;**40**:e11–12.
176. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;**347**:969–74.
177. Hamon M, Lemesle G, Tricot O, Meurice T, Deneve M, Dujardin X et al. Incidence, source, determinants, and prognostic impact of major bleeding in outpatients with stable coronary artery disease. *J Am Coll Cardiol* 2014;**64**:1430–6.
178. Proietti M, Lip GYH. Impact of quality of anticoagulation control on outcomes in patients with atrial fibrillation taking aspirin: an analysis from the SPORTIF trials. *Int J Cardiol* 2018;**252**:96–100.
179. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt F, Wildgoose P et al. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). *Am Heart J* 2015;**169**:472–8.
180. Gibson CM, Kirtane AJ, Murphy SA, Rohrbach S, Menon V, Lins J et al.; TIMI Study Group. Early initiation of eptifibatide in the emergency department before primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: results of the Time to Integrilin Therapy in Acute Myocardial Infarction (TITAN)-TIMI 34 trial. *Am Heart J* 2006;**152**:668–75.
181. Bomicke T, Valina CM, Stratz C, Amann M, Neumann FJ, Hochholzer W. On-clopidogrel platelet reactivity as predictor for long-term clinical outcome in patients after planned discontinuation of clopidogrel. *Thromb Haemost* 2017;**117**:1644–50.
182. Reny JL, Fontana P, Hochholzer W, Neumann FJ, Ten Berg J, Janssen PW et al. Vascular risk levels affect the predictive value of platelet reactivity for the occurrence of MACE in patients on clopidogrel. Systematic review and meta-analysis of individual patient data. *Thromb Haemost* 2016;**115**:844–55.
183. Podda GM, Cattaneo M. High on treatment platelet reactivity as a risk factor for adverse left ventricular remodelling after STEMI. *Thromb Haemost* 2017;**117**:829.
184. Jamasbi J, Ayabe K, Goto S, Nieswandt B, Peter K, Siess W. Platelet receptors as therapeutic targets: past, present and future. *Thromb Haemost* 2017;**117**:1249–57.
185. Weitz JI, Harenberg J. New developments in anticoagulants: past, present and future. *Thromb Haemost* 2017;**117**:1283–8.
186. Dimitropoulos G, Rahim SMZ, Moss AS, Lip GYH. New anticoagulants for venous thromboembolism and atrial fibrillation: what the future holds. *Expert Opin Investig Drugs* 2018;**27**:71–86.
187. Weitz JI, Fredenburgh JC. 2017 Scientific Sessions Sol sherry distinguished lecture in thrombosis: factor XI as a target for new anticoagulants. *Arterioscler Thromb Vasc Biol* 2018;**38**:304–10.
188. Buller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med* 2015;**372**:232–40.