Triple antithrombotic therapy in atrial fibrillation patients with acute coronary syndromes or undergoing percutaneous coronary intervention or transcatheter aortic valve replacement

Davide Capodanno[1], MD, PhD; Gregory Y.H. Lip[2], MD; Stephan Windecker[3], MD; Kurt Huber[4], MD; Paulus Kirchhof[5], MD; Giuseppe Boriani[6], MD; Deirdre Lane[7], PhD; Martine Gilard[8], MD; Jean-Philippe Collet[9], MD, PhD; Marco Valgimigli[10], MD, PhD; Robert A. Byrne[11]*, MB, BCh, PhD

1. Ferrarotto Hospital, University of Catania, Catania, Italy; 2. University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; 3. Department of Cardiology, Bern University Hospital, Bern, Switzerland; 4. 3rd Department of Medicine, Cardiology and Emergency Medicine, Wilhelminen Hospital, Vienna, Austria; 5. Centre for Cardiovascular Sciences, University of Birmingham and SWBH NHS Trust, Birmingham, United Kingdom; 6. Institute of Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, S. Orsola-Malpighi University Hospital, Bologna, Italy; 7. University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; 8. Département de Cardiologie, CHRU La Cavale Blanche, Brest, France; 9. ACTION Study Group, Institut de Cardiologie Hôpital Pitié-Salpêtrière (APHP), Université Paris 6, INSERM, Paris, France; 10. Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; 11. Deutsches Herzzentrum, Technische Universität München and DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

Introduction

Oral anticoagulation (OAC) is indicated for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) and at least one risk factor for stroke[1]. However, managing OAC is a challenge in NVAF patients who also require dual antiplatelet therapy (DAPT) in the setting of a presentation with an acute coronary syndrome (ACS) or where percutaneous coronary intervention (PCI) is undertaken[2,3]. In 2010, the European Society of Cardiology (ESC) Working Group on Thrombosis, in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the European Heart Rhythm Association (EHRA), published an expert consensus document on antithrombotic management of NVAF patients presenting with ACS or undergoing PCI. Most of the recommendations from the 2010 consensus document were subsequently incorporated into the 2012 focused update of the ESC guidelines for patients with atrial fibrillation[1].

Since then, many new studies have been published, and considerable progress has been made in both drug-eluting stent (DES) and transcatheter aortic valve implantation (TAVI) technologies. As a result, a new updated joint consensus document was recently published by the ESC Working Group on Thrombosis, EAPCI, EHRA, and the European Association of Acute Cardiac Care (ACCA), and endorsed by the Heart Rhythm Society (HRS) and the Asia-Pacific Heart Rhythm Society (APHRS)[4]. This editorial introduces some key recommendations of that document, discusses additional very recently presented trial data, and highlights ongoing and upcoming studies.

New studies driving reappraisal of existing recommendations

Aside from patients in need of concomitant OAC, the optimal duration of DAPT after coronary stenting in general and DES in particular remains unclear[5]. Prior recommendations for prolongation of DAPT after DES implantation to 12 months were non-evidence-based[6], and accumulating evidence suggests that a shorter duration of DAPT may suffice in many patients[7-9]. Recent joint ESC/ European Association of Cardio-Thoracic Surgeons (EACTS)

---

guidelines now recommend six months of DAPT in stable patients after stenting with DES[10], though United States guidelines continue to recommend at least 12 months of DAPT[11].

In relation to patients receiving OAC who undergo stenting and are in need of additional DAPT with aspirin and clopidogrel, the optimal duration of triple therapy, i.e., OAC plus DAPT, is unknown. On the one hand, the bleeding risks associated with triple therapy are increasingly recognised. A recent registry report from Denmark examined the outcomes of 8,700 hospitalised patients with AF and stable coronary artery disease between 2002 and 2011[12]. An analysis of these patients showed that, relative to OAC monotherapy (approximately 37% of the study population) the risk of bleeding increased when aspirin (hazard ratio [HR] 1.50, 95% confidence interval [CI]: 1.23-1.82), clopidogrel (HR 1.84, 95% CI: 1.11-3.06) or both aspirin and clopidogrel (HR 2.81, 95% CI: 1.82-4.33) were added to OAC. On the other hand, the risk of thromboembolism was comparable in all regimens that included OAC.

One recently examined option to reduce the risk of bleeding in patients receiving OAC who undergo coronary stenting is to omit aspirin therapy and continue OAC and single agent antiplatelet therapy with clopidogrel. This approach was evaluated in the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST) trial, which randomised 573 patients receiving OAC to either clopidogrel (study treatment) or clopidogrel plus aspirin (control treatment)[13]. Treatment was continued for one month after bare metal stent (BMS, used in ~31% of patients) and for one year after DES placement (used in ~65%). At one year, the primary endpoint of any Thrombolysis In Myocardial Infarction (TIMI) bleeding was significantly lower in the dual therapy arm (19.4% vs. 44.4%; HR 0.36, 95% CI: 0.26-0.50, p<0.001), though the rates of major bleeding were not different (3.2% vs. 5.6%; HR 0.56, 95% CI: 0.25-1.27, p=0.16). The ischaemic composite of myocardial infarction, stroke, target vessel revascularisation, or stent thrombosis was decreased in the dual therapy arm (11.1% vs. 17.6%; HR 0.60, 95% CI: 0.38-0.94, p=0.025). Interestingly, all-cause mortality was 61% lower in the triple therapy arm versus the dual therapy arm (2.5% vs. 6.3%; HR 0.39, 95% CI: 0.16-0.93, p=0.027), although this observation must be interpreted with caution due to the modest size of the study, the primary endpoint being driven by minor bleeds, the long treatment duration in the triple therapy arm (hence, more bleeding), and the lack of difference in bleeding events likely to have been prognostically important.

Data sources for understanding the role of non-vitamin K antagonist oral anticoagulants (NOACs) as part of a triple antithrombotic regimen include trials conducted in patients with NVAF and trials conducted in patients with ACS/PCI. In NVAF trials, the use of aspirin on top of OAC represented one third of the study population (with clopidogrel use in 0-5% of patients) **(Table 1)**[14-17]. In an ACS trial of low-dose rivaroxaban (2.5 mg BID or 5 mg BID), a triple antithrombotic regimen (i.e., low-dose rivaroxaban plus DAPT) was found to reduce the combined ischaemic endpoint at the price of increased bleeding (HR 3.96, 95% CI: 2.46-6.38, p<0.001)[18].

Table 1. Use of antiplatelet drugs in atrial fibrillation trials of NOACs.

	RE-LY[14] Dabigatran	ROCKET-AF[15] Rivaroxaban	ARISTOTLE[16] Apixaban	ENGAGE[17] Edoxaban
Concomitant use of aspirin alone	32%	≈37%	≈31%	≈29%
Concomitant use of clopidogrel alone	≈2%	<2%	≈2%	≈2%
Concomitant use of dual antiplatelet therapy	≈5%	Excluded	Excluded	Excluded

Percentages refer to use of antiplatelet drugs at some time during the study period, including discontinuation at enrolment and non-consecutive use.

Conversely, a phase III ACS trial of apixaban, where the same dose tested in NVAF was used, demonstrated no efficacy benefit of adding apixaban to DAPT, but increased bleeding (HR 2.59, 95% CI: 1.50-4.46, p=0.001)[19]. Overall, these findings emphasise the need for specifically designed studies to investigate the role of NOACs in patients who also have an indication for DAPT.

Key points from the 2014 consensus document
ACUTE CORONARY SYNDROME OR PERCUTANEOUS CORONARY INTERVENTION

General considerations for periprocedural management of antithrombotic therapies in NVAF patients with ACS or undergoing PCI include the following. First, although specific randomised trial data are lacking for this patient subgroup, radial access might be preferred for coronary angiography/PCI to minimise the risk of access-related bleeding depending on operator expertise and preference. Second, new-generation DES should be preferred over BMS, especially in patients at low risk of bleeding. Third, more potent adenosine diphosphate (ADP) receptor antagonists such as prasugrel and ticagrelor should not be part of a triple therapy regimen in patients with NVAF. Fourth, gastric protection with proton pump inhibitors should be advised in patients on OAC plus antiplatelet therapy. Scenario-specific considerations are summarised below.

– In vitamin K antagonist (VKA)-treated patients undergoing elective PCI, an uninterrupted anticoagulation strategy with no additional heparin boluses in case of therapeutic anticoagulation (INR >2, preferably coupled with radial access) is the preferred strategy in patients at moderate to high risk of thromboembolism, whereas NOACs should be discontinued 48 hours before PCI and periprocedural parenteral anticoagulation used as per standard practice. When the procedure requires OAC interruption for >48 hours, heparin bridging may be considered.

– In patients with NSTE-ACS, an early invasive strategy (i.e., within 24 hours) should be preferred in order to expedite treatment allocation and for delineation of the optimal antithrombotic regimen. Pre-treatment with P2Y$_{12}$ inhibitors and glycoprotein IIb/IIIa inhibitors is discouraged. In view of the multiple antithrombotic medications used in this setting, it seems prudent to stop OAC and administer unfractionated heparin or bivalirudin only as bail-out or if INR is ≤2 in a patient on VKA, balancing the acute need for additional antithrombotic therapy with the

excess bleeding risk and the "thrombus burden". Bridging with heparin may be considered in low-risk NSTE-ACS patients who are not referred for an early invasive strategy.

– In patients with STEMI, regular or even "routine" use of glycoprotein IIb/IIIa inhibitors is discouraged.

A key part of the document concerns long-term antithrombotic management in patients undergoing elective PCI or presenting with an ACS; recommendations are summarised in **Figure 1**, where a four-step approach is proposed. The combination and duration of antithrombotic therapies should be tailored according to the individual baseline characteristics based on: i) the risk of stroke (CHA_2DS_2-VASc score=1 or ≥2), ii) the risk of bleeding (HAS-BLED=0-2 or ≥3), and iii) the clinical presentation (stable coronary artery disease undergoing PCI versus ACS). The ESC Task Force felt that there is no strong evidence to suggest that NOACs behave differently from well-controlled adjusted-dose VKAs in the setting of ACS or PCI, although specific data are limited. Therefore, the principle of continuing an existing OAC and – in case of NOACs – the use of the lower tested dose for stroke prevention in AF is judged to be reasonable at present until new trials are available. Where a VKA is used in combination with antiplatelet

therapy, a desired target INR range of 2.0-2.5 should be considered, but particular attention is needed to the quality of INR control, as reflected by a high (>70%) average time in therapeutic range (TTR) given the close relationship of TTR to thromboembolism and bleeding risks[20,21]. In a patient with NVAF and stable vascular disease (arbitrarily defined as being free from any acute ischaemic event or repeat revascularisation for ≥one year) OAC alone should be preferred, although adding an antiplatelet agent may be considered in patients at very high risk of coronary events (i.e., stenting of the left main, proximal bifurcation, recurrent myocardial infarction, etc.). The Task Force concluded that the evidence was too weak to provide clear guidance on duration of therapy, but emphasised that the duration of a triple antithrombotic regimen should be as short as possible.

TRANSCATHETER AORTIC VALVE IMPLANTATION

Transcatheter aortic valve implantation (TAVI) is an area where information on the efficacy/safety balance of different periprocedural and long-term antithrombotic strategies is limited. Notably, the burden of atrial fibrillation in TAVI is ~40-50%, with ~30% of patients having a history of paroxysmal or chronic atrial fibrillation,
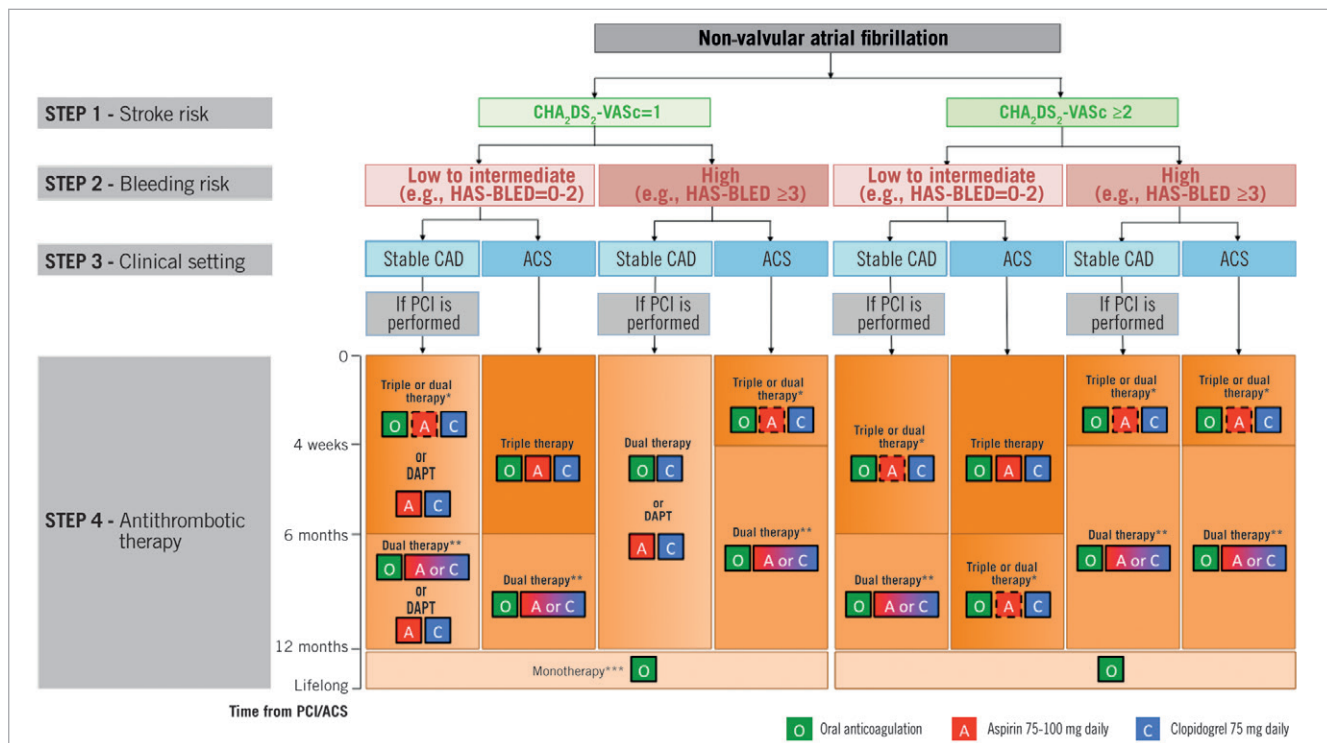

Figure 1. *Choice of antithrombotic therapy, including combination strategies of oral anticoagulation (O), aspirin (A) and/or clopidogrel (C). For Step 4, background colour and gradients reflect the intensity of antithrombotic therapy (i.e., dark background colour=high intensity; light background colour=low intensity). Solid boxes represent recommended drugs. Dashed boxes represent optional drugs depending on clinical judgement. New-generation DES are generally preferable over bare metal stents, particularly in patients at low bleeding risk (HAS-BLED 0-2). When vitamin K antagonists are used as part of triple therapy, INR should be targeted at 2.0-2.5 and the time in the therapeutic range should be >70%. *Dual therapy with oral anticoagulation and clopidogrel may be considered in selected patients. **Aspirin as an alternative to clopidogrel may be considered in patients on dual therapy (OAC plus single antiplatelet). ***Dual therapy with oral anticoagulation and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events. DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention. Reproduced with permission from Lip GY et al. Eur Heart J. 2014 [4].*

and an additional 10-15% of patients with new-onset episodes of atrial fibrillation after the procedure. Routine use of triple antithrombotic therapy is not recommended after TAVI. Although DAPT is otherwise recommended after TAVI in patients without NVAF, if OAC is indicated, then DAPT should not be prescribed unless another indication for DAPT exists, e.g., concomitant PCI. No data exist on the use of NOACs in the TAVI setting. Procedural anticoagulation trials in TAVI are warranted to select drugs that have the potential to limit bleeding complications (e.g., bivalirudin) compared with heparin, and to investigate different strategies of bridging and long-term management for patients with NVAF on OAC.

New studies/evidence since the publication of the 2014 consensus document

Two recent trials that have yet to be published have studied outcomes of OAC-treated patients who underwent stenting with DES. The ISAR-TRIPLE trial is the largest randomised trial comparing different durations of triple therapy[22]. Overall, 614 patients were randomised to either a six-week clopidogrel therapy (n=307) or a six-month clopidogrel therapy (n=307). The study tested the hypothesis that shortening clopidogrel therapy from six months to six weeks would be associated with superior net clinical outcomes, defined as a composite of death, myocardial infarction, definite stent thrombosis, stroke or TIMI major bleeding at nine months. The main finding was that six weeks of treatment was not superior to six months (9.9% versus 8.9%; HR 1.14, 95% CI: 0.68-1.91, p=0.63) (Sarafoff et al presented at: Transcatheter Cardiovascular Therapeutics; September 15, 2014; Washington, DC, USA). Moreover, cardiac death, definite stent thrombosis or TIMI major bleeding did not differ between treatment groups. Although there was no evidence that a six-week therapy was superior, the comparable outcomes between the groups may be clinically important and tentatively support a role for either treatment duration based on the individual ischaemic and bleeding risks of the patient.

The Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) trial recently demonstrated that the use of a second-generation DES, followed by a DAPT duration regimen dictated by patients' characteristics and not by stent type, is superior to conventional BMS implantation in patients at increased risk of thrombosis and bleeding (Valgimigli et al presented at: American College of Cardiology/i2 Scientific Session; March 31, 2014; Washington, DC, USA). The study included a subgroup of patients receiving OAC who were recommended for a 30-day course of DAPT[23]. Although the primary comparison was between two stents (BMS versus early-generation zotarolimus-eluting stents) there was no obvious signal of hazard in the patients who received DES and short duration DAPT.

A recent joint EHRA/EAPCI expert consensus document addresses the use of left atrial appendage (LAA) occlusion in patients with NVAF, prior stroke and potential contraindications to OAC[24]. The authors acknowledge that OAC remains the standard-of-care in these patients at present, though LAA occlusion therapy should be considered. Moreover, although randomised control trial

data exist only for patients who are eligible for both OAC and LAA occlusion[25], patients with a high risk of bleeding on OAC or those with contraindications to OAC represent the most accepted clinical indication for LAA occlusion. The authors clarify that patients who require prolonged triple therapy after transcatheter intervention may fall into these categories and become candidates for this treatment though intervention for this indication is not supported by specific trial data.

Upcoming studies in an evolving field

The new ESC joint consensus document provides a framework for clinical decision making in a field where data are sparse. A set of new studies is expected to expand our knowledge on treatment strategies for NVAF patients who need a combination of OAC and antiplatelet therapy in the coming years.

The LEADERS-FREE trial is testing the potential benefit of a newer-generation drug-coated, polymer-free stent (BioFreedom™; Biosensors, Morges, Switzerland) in 2,456 patients considered at high risk of bleeding (including patients on OAC) using a BMS (Gazelle™; Biosensors) as control and recommending short duration (one month) DAPT[26]. The primary safety endpoint is a composite of cardiac death, myocardial infarction and stent thrombosis according to a non-inferiority design, whereas the primary efficacy endpoint (clinically driven target lesion revascularisation) will be analysed according to a superiority analysis. This trial should help to characterise better a subset of PCI patients at high risk for bleeding, with the potential to support one-month duration of DAPT in DES-treated patients. However, the potential advantage of this strategy in patients with NVAF, compared with current high-efficacy new-generation DES combined with either clopidogrel and OAC (a WOEST approach) or a six-week duration of triple therapy (an ISAR-TRIPLE approach), may be difficult to demonstrate.

The merits (or otherwise) of NOACs in the landscape of NVAF patients undergoing PCI will be clarified by ongoing studies comparing multiple antithrombotic regimens, including PIONEER AF-PCI for rivaroxaban (NCT01830543) and RE-DUAL PCI for dabigatran (NCT02164864), as well as the recently announced EVOLVE AF-PCI for edoxaban and AAA for apixaban **(Table 2)**. In a landscape which is constantly changing, the impact of data from recently presented large-scale randomised controlled trials concerning the optimal duration of DAPT in patients without an indication for OAC (late-breaking at time of going to press) will also have knock-on effects for the management of patients with concomitant NVAF[27,28].

Finally, in the field of TAVI, the POPular-TAVI trial (NCT02247128) is comparing clopidogrel plus VKA versus VKA alone in patients undergoing TAVI with a concurrent indication for OAC, and aspirin versus DAPT in patients without an indication for OAC. Conversely, more insights into the appropriate use of NOACs will come from the ongoing ATLANTIS trial, where apixaban is compared with VKA in TAVI patients with an indication for OAC, and versus DAPT or single antiplatelet therapy in patients without an indication for OAC.

Table 2. Ongoing trials of NOACs in patients undergoing percutaneous coronary intervention.

	RE-DUAL PCI	PIONEER AF-PCI	EVOLVE AF-PCI	AAA
Status	Enrolling	Enrolling	Announced	Announced
Study type	Open-label, randomised	Open-label, randomised	Open-label, randomised	Open-label, randomised
Investigational drug	Dabigatran	Rivaroxaban	Edoxaban	Apixaban
ClinicalTrials.gov identifier	NCT02164864	NCT01830543	–	–
Patients	8,520 patients with atrial fibrillation who undergo a PCI with stenting (elective or due to an ACS)	2,169 patients with atrial fibrillation who undergo a PCI with stenting	~3,500 patients with atrial fibrillation who undergo a PCI with stenting	~4,500 patients with atrial fibrillation, and ACS or PCI or both
Follow-up	30 months	12 months	12 months	6 months
Experimental arm(s)	1) Dabigatran etexilate 110 mg plus clopidogrel 75 mg OD or ticagrelor 90 mg BID 2) Dabigatran etexilate 150 mg plus clopidogrel 75 mg OD or ticagrelor 90 mg BID	1) Rivaroxaban 2.5 mg BID plus aspirin ≤100 mg OD plus clopidogrel 75 mg OD or prasugrel 10 mg OD or ticagrelor 90 mg BID followed by rivaroxaban 15 mg (or 10 mg for subjects with moderate renal impairment) OD plus aspirin ≤100 mg 2) Rivaroxaban 15 mg (or 10 mg for subjects with moderate renal impairment) OD plus clopidogrel 75 mg OD or prasugrel 10 mg OD or ticagrelor 90 mg BID	Edoxaban 60 mg OD (or reduced dose of 30 mg OD in subjects with CrCl ≤50 mL/min, body weight ≤60 kg, or concomitant therapy with P-GP inhibitors [except amiodarone]) plus $P2Y_{12}$ inhibition (clopidogrel 75 mg OD preferably, or ticagrelor 90 mg BID, or prasugrel 10 mg OD)	Apixaban 5 mg BID (or reduced dose of 2.5 mg BID for patients with 2 out of the following features: age >80 years, weight <60 kg, Cr >1.5 mg/dL) plus clopidogrel. 2×2 factorial plan for aspirin
Control arm	Warfarin plus clopidogrel 75 mg OD or ticagrelor 90 mg BID plus aspirin ≤100 mg	Warfarin plus clopidogrel 75 mg OD or prasugrel 10 mg OD or ticagrelor 90 mg BID plus aspirin ≤100 mg	Warfarin plus clopidogrel 75 mg OD or prasugrel 10 mg OD or ticagrelor 90 mg BID plus aspirin ≤100 mg	Warfarin plus clopidogrel 75 mg
Primary efficacy endpoint	Death or first thrombotic event (all-cause death, myocardial infarction, stroke/systemic embolism)	–	–	Death, myocardial infarction, stroke or stent thrombosis
Primary safety endpoint	International Society of Thrombosis and Haemostasis major bleeding event	Clinically significant bleeding (Thrombolysis In Myocardial Infarction major bleeding, minor bleeding, and bleeding requiring medical attention)	International Society of Thrombosis and Haemostasis major or clinically relevant non-major bleeding event	International Society of Thrombosis and Haemostasis major or clinically relevant non-major bleeding event
Comment	Open-label, randomised, multicentre clinical study assessing the safety of 2 dabigatran treatment strategies and a warfarin treatment strategy	Open-label, randomised, multicentre clinical study assessing the safety of 2 rivaroxaban treatment strategies and a warfarin treatment strategy. The randomisation will be stratified by the intended duration of DAPT (1, 6, or 12 months)	Open-label, randomised, multicentre clinical study assessing the safety of an edoxaban-based antithrombotic treatment strategy and a vitamin-K antagonist-based antithrombotic treatment strategy	Open-label, randomised, multicentre clinical study assessing the safety of an apixaban-based antithrombotic treatment strategy and a vitamin-K antagonist-based antithrombotic treatment strategy

ACS: acute coronary syndromes; DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention

Conflict of interest statement

D. Capodanno reports receiving speaker's honoraria from Eli-Lilly/Daiichi Sankyo, AstraZeneca, Bayer and serving as an advisory board member for Eli-Lilly, Daiichi Sankyo and AstraZeneca. G. Lip reports serving as a consultant for Bayer, Astellas, Merck, Sanofi, Bristol-Myers Squibb /Pfizer, Daiichi Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and on a speakers bureau for Bayer, Bristol-Myers Squibb /Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Medtronic. S. Windecker reports receiving lecture fees from Biosensors, Biotronik, Boston Scientific, Medtronic, Edwards Lifesciences, Eli Lilly and AstraZeneca and research grants to the institution from Biotronik and St. Jude Medical. K. Huber reports receiving lecture fees from Bayer, Boehringer Ingelheim, Daiichi Sankyo and Pfizer, and Bristol-Myers Squibb. P. Kirchhof reports receiving consulting fees and honoraria from Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, MSD, Medtronic, Pfizer, Sanofi, Servier and research grants from Bristol-Myers Squibb, Pfizer Cardiovascular Therapeutics, Daiichi Sankyo, Sanofi, and St. Jude Medical. G. Boriani reports receiving speaker's fees from Boehringer Ingelheim, Boston Scientific and Medtronic. D. Lane has received investigator-initiated educational grants from Bayer Healthcare and Boehringer Ingelheim and served as a speaker for Boehringer Ingelheim, Bayer Healthcare, and BMS/Pfizer. In addition, Dr Lane is on the Steering Committee of a Phase IV apixaban study (AEGEAN) and has participated in various clinical trials of stroke prevention in atrial fibrillation. M. Gilard reports receiving lecture fees from Bayer, Daiichi Sankyo and AstraZeneca. J. Collet reports receiving research grants from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Medtronic, Boston Scientific, Cordis, and Stago, consulting fees from Sanofi-Aventis, Eli Lilly, and Bristol-Myers Squibb, and lecture fees from

Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, and AstraZeneca. R. Byrne reports receiving lecture fees from Biotronik and B. Braun. The other authors have no conflicts of interest to declare.

References

1. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P. ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J.* 2012;33:2719-47.

2. Capodanno D, Angiolillo DJ. Management of antiplatelet and anticoagulant therapy in patients with atrial fibrillation in the setting of acute coronary syndromes or percutaneous coronary interventions. *Circ Cardiovasc Interv.* 2014;7:113-24.

3. Dewilde WJ, Janssen PW, Verheugt FW, Storey RF, Adriaenssens T, Hansen ML, Lamberts M, Ten Berg JM. Triple therapy for atrial fibrillation and percutaneous coronary intervention: a contemporary review. *J Am Coll Cardiol.* 2014;64:1270-80.

4. Task Force Members, Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, Haeusler KG, Boriani G, Capodanno D, Gilard M, Zeymer U, Lane D, Storey RF, Bueno H, Collet JP, Fauchier L, Halvorsen S, Lettino M, Morais J, Mueller C, Potpara TS, Rasmussen LH, Rubboli A, Tamargo J, Valgimigli M, Zamorano JL. 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.

5. Kastrati A, Byrne RA, Schulz S. Will we ever know the optimal duration of dual antiplatelet therapy after drug-eluting stent implantation? *JACC Cardiovasc Interv.* 2011;4:1129-32.

6. King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, Jacobs AK, Morrison DA, Williams DO; 2005 WRITING COMMITTEE MEMBERS, Feldman TE, Kern MJ, O'Neill WW, Schaff HV, Whitlow PL, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation.* 2008;117:261-95.

7. Schulz S, Schuster T, Mehilli J, Byrne RA, Ellert J, Massberg S, Goedel J, Bruskina O, Ulm K, Schomig A, Kastrati A. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. *Eur Heart J.* 2009;30:2714-21.

8. Cassese S, Byrne RA, Tada T, King LA, Kastrati A. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials. *Eur Heart J.* 2012;33:3078-87.

9. Stefanini GG, Siontis GC, Cao D, Heg D, Jüni P, Windecker S. Short versus long duration of DAPT after DES implantation: a meta-analysis. *J Am Coll Cardiol.* 2014;64:953-4.

10. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A; Authors/Task Force members. 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). *EuroIntervention.* 2015;10:1024-94.

11. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH; American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2011;58:e44-122.

12. Lamberts M, Gislason GH, Lip GY, Lassen JF, Olesen JB, Mikkelsen AP, Sorensen R, Kober L, Torp-Pedersen C, Hansen ML. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: a nationwide cohort study. *Circulation.* 2014;129:1577-85.

13. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen JG, van 't Hof AW, ten Berg JM; WOEST study investigators. 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.

14. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139-51.

15. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM;

ROCKET AF Investigators. Rivaroxaban versus warfarin in non-valvular atrial fibrillation. *N Engl J Med.* 2011;365:883-91.

16. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981-92.

17. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369: 2093-104.

18. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012;366:9-19.

19. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, Huber K, Liaw D, Husted SE, Lopez-Sendon J, De Caterina R, Jansky P, Darius H, Vinereanu D, Cornel JH, Cools F, Atar D, Leiva-Pons JL, Keltai M, Ogawa H, Pais P, Parkhomenko A, Ruzyllo W, Diaz R, White H, Ruda M, Geraldes M, Lawrence J, Harrington RA, Wallentin L; APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med.* 2011;365:699-708.

20. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. *Thromb Haemost.* 2013;110:1087-107.

21. Gallego P, Roldan V, Marin F, Romera M, Valdes M, Vicente V, Lip GY. Cessation of oral anticoagulation in relation to mortality and the risk of thrombotic events in patients with atrial fibrillation. *Thromb Haemost.* 2013;110:1189-98.

22. Fiedler KA, Byrne RA, Schulz S, Sibbing D, Mehilli J, Ibrahim T, Maeng M, Laugwitz KL, Kastrati A, Sarafoff N. Rationale and design of The Intracoronary Stenting and Antithrombotic

Regimen-Testing of a six-week versus a six-month clopidogrel treatment Regimen In Patients with concomitant aspirin and oraL anticoagulant therapy following drug-Eluting stenting (ISAR-TRIPLE) study. *Am Heart J.* 2014;167:459-65.e1.

23. Valgimigli M, Patialiakas A, Thury A, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Airoldi F, Ferlini M, Liistro F, Dellavalle A, Vranckx P, Briguori C. Randomized comparison of Zotarolimus-Eluting Endeavor Sprint versus bare-metal stent implantation in uncertain drug-eluting stent candidates: rationale, design, and characterization of the patient population for the Zotarolimus-eluting Endeavor Sprint stent in uncertain DES candidates study. *Am Heart J.* 2013;166:831-8.

24. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C, Glikson M. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *EuroIntervention.* 2015;10:1109-25.

25. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators. 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.

26. Urban P, Abizaid A, Chevalier B, Greene S, Meredith I, Morice MC, Pocock S. Rationale and design of the LEADERS FREE trial: A randomized double-blind comparison of the BioFreedom drug-coated stent vs the Gazelle bare metal stent in patients at high bleeding risk using a short (1 month) course of dual antiplatelet therapy. *Am Heart J.* 2013;165:704-9.

27. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med.* 2014;371:2155-66.

28. Byrne RA, Schulz S, Mehilli J, Iijima R, Massberg S, Neumann FJ, ten Berg JM, Schömig A, Kastrati A; Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) Investigators. Rationale and design of a randomized, double-blind, placebo-controlled trial of 6 versus 12 months clopidogrel therapy after implantation of a drug-eluting stent: The Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) study. *Am Heart J.* 2009;157:620-4.e2.