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CURRENT OPINION

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)

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Introduction

Atrial fibrillation (AF) confers a substantial risk of mortality and morbidity from stroke and thrombo-embolism, and this common cardiac arrhythmia represents a major healthcare burden in Europe.[1] Stroke prevention is central to the management of AF patients, with the 2012 focused update of the European Society of Cardiology (ESC) guidelines[2] recommending oral anticoagulation (OAC) using well-controlled adjusted dose vitamin K antagonists (VKAs, e.g. warfarin) or non-VKA oral anticoagulants (NOACs, previously referred to as new or novel OACs[3]) for patients with AF and $\geq$1 stroke risk factor(s). Also, these guidelines strongly advocate a clinical practice shift so that the initial decision step now is the identification of 'truly low risk' patients, essentially those aged $<$65 years without any stroke risk factor (both male and female), who do not need any antithrombotic therapy.[2] The ESC guidelines also recommend the use of the CHA_2DS_2-VASc score[4] for stroke risk assessment, and define 'low-risk' patients as those with a CHA_2DS_2-VASc score = 0 (males) or score = 1 (females). Subsequent to this initial step of identifying the low-risk patients, effective stroke prevention (which is essentially OAC) can then be offered to AF patients with $\geq$1 stroke risk factor(s), with treatment decisions made in consultation with patients and incorporating their preferences.

In everyday clinical practice, over 80% of all patients with AF have an indication for OAC, and vascular disease co-exists in ~30% of them.[5–7] With an estimated prevalence of AF of 1–2% and ~20% of these requiring percutaneous cardiovascular interventions over time,[8] ~1–2 million AF patients in Europe who are on OAC may undergo percutaneous coronary interventions (PCI), usually including stenting. Almost all of these patients will have an indication for continuous OAC. Considerable variation in European clinical practice for the management of such patients is evident.[9]

Acute coronary syndromes (ACS), including unstable angina/non-ST segment elevation myocardial infarction (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI), constitute another cardiovascular disease entity with associated risks of mortality and morbidity from myocardial infarction (MI), heart failure, and ventricular arrhythmias. Antithrombotic therapy, with dual antiplatelet therapy consisting of low-dose acetylsalicylic acid and $P2Y_{12}$ inhibitors with ticagrelor or prasugrel being recommended as first line, is the mainstay to reduce the risk of recurrent ischaemic events during the first year after the acute event. In addition, an early invasive strategy in case of NSTE-ACS and primary PCI in case of STEMI with revascularization of culprit lesions are the current standard of care in the management of patients with ACS.[10] A particular challenge in terms of antithrombotic treatment are patients who present with both AF and ACS,[11] especially since such patients are at high risk for cardiovascular mortality and morbidity.[12]

As with the use of any antithrombotic drug, clinicians need to balance the risks of ischaemic stroke and thrombo-embolism, recurrent cardiac ischaemia or MI and/or stent thrombosis, and bleeding. In 2010, the European Society of Cardiology (ESC) Working Group on Thrombosis published a consensus document, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Coronary Intervention (EAPCI), to address the management aspects of this complex clinical scenario.[11] This was followed by a North American consensus document, which had many similarities in management approaches.[13,14]

Since 2010, substantial changes are now evident in stroke prevention in AF, with the introduction of NOACs and greater attention to quality of anticoagulation control [as reflected by average time in the therapeutic range (TTR) of the international normalized ratio (INR)].[15] Also, new generation drug-eluting stents (DESs) are available which may be less thrombogenic, and additional interventional procedures are being undertaken, such as transcathether aortic valve implantation (TAVI) or percutaneous mitral valve repair, whereby the presence or development of AF can predispose to thrombo-embolism.[16,17] Bridging therapy and the management of anticoagulated AF patients undergoing surgical or other procedures remains a management issue with expert guidance substituting for controlled trial data especially in patients taking NOACs.[18,19]

For this update, the Working Group on Thrombosis of the ESC convened a Task Force, with representation from EHRA, EAPCI, and the Acute Cardiovascular Care Association (ACCA), endorsed by the Heart Rhythm Society (HRS), and the Asia-Pacific Heart Rhythm Society (APHRS), with the remit to comprehensively review the published evidence available since the 2010 document, to publish a joint consensus document on the optimal antithrombotic therapy management in AF patients presenting with ACS and/or undergoing percutaneous coronary or valve interventions and to provide up-to-date recommendations for use in clinical practice.

For the purposes of this consensus document, AF will be defined as 'non-valvular AF',—that is, AF in the absence of prosthetic mechanical heart valves, or 'haemodynamically significant valve disease'. The latter refers to where the valve lesion (e.g. mitral stenosis) is severe enough to warrant intervention (e.g. surgery or percutaneous) or where it would have an impact on the patient's survival or well-being. Indeed, haemodynamically significant valve disease was generally excluded from the recent randomized trials of stroke prevention in AF: for example, the RE-LY trial excluded patients with 'severe heart valve disorder', whereas the ROCKET-AF trial excluded those with 'haemodynamically significant mitral valve stenosis' and the ARISTOTLE trial excluded those with 'moderate or severe mitral stenosis'.[20–22]

Overview of additional published data since 2010 on the topic of management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting

To address additional published data, we performed an overview of data published since the 2010 consensus document. These data are summarized in this section, which should be considered as complementary to the evidence tables published in the 2010 consensus document.[11]

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Cohort studies

Since 2010, various registries have again demonstrated the considerable heterogeneity in the combinations (and duration) of different antithrombotic drugs used in AF patients[23–52](*Table 1*). Notably, these patients are at high risk of both thrombotic and bleeding complications.[53] Most of the available data are still based on small, often single-centre and retrospective patient cohorts, or derive from subgroup analyses of patients enrolled in controlled trials of OAC.

Despite these limitations, some guidance can be taken from the available data. In general, there is a benefit of continued OAC in preventing thrombotic events, and in some studies even reductions in mortality. Furthermore, there is evidence that continuation of OAC used for chronic therapy, rather than switching or 'bridging' to other anticoagulants, confers a lower risk for severe bleeding events. Despite the heterogeneity, there is sufficient evidence that OAC should not be interrupted in patients with AF suffering from an ACS. This benefit is maintained despite good evidence of an increased bleeding rate in patients taking OAC and antiplatelet agents compared with those on OAC alone,[43,54] illustrating the higher relative risk of thrombo-embolic and thrombotic complications in these cohorts. Hence, 'dual therapy' (OAC + one antiplatelet agent) seems required, and possibly 'triple therapy' might be advisable, mainly in patients at high risk for thrombo-embolic ischaemic complications.[11,13] Many retrospective analyses have compared triple therapy [OAC plus dual antiplatelet therapy (DAPT)] against 'dual therapy' (OAC + one antiplatelet), and the results are consistent in showing an increase in the risk of bleeding with triple therapy, that is ~50% higher compared with 'dual therapy' and were evident for early and delayed bleeding risk as well (*Table 1*).

Some studies merit additional comment. In a retrospective analysis of the nationwide Danish registry,[38] early bleeding risk was increased on triple therapy compared with OAC plus single antiplatelet therapy at 90 days [hazard ratio (HR) 1.47, 95% confidence interval (CI) 1.04–2.08], with a trend to significance at 360 days (HR: 1.36, 95% CI: 0.95–1.95), without differences in thrombo-embolic events (HR: 1.15, 95% CI: 0.95–1.40). A more recent publication,[29] based on the same nationwide Danish registry, suggests that warfarin plus clopidogrel resulted in a non-significant reduction in major bleeding (HR: 0.78, 95% CI: 0.55–1.12) compared with triple therapy. There was also a non-significant reduction in MI or coronary death with warfarin plus clopidogrel compared with triple therapy (HR: 0.69, 95% CI: 0.48–1.00). When compared with triple therapy, bleeding risk was non-significantly lower for OAC plus clopidogrel (HR: 0.78, 95% CI: 0.55–1.12) and significantly lower for OAC plus aspirin and aspirin plus clopidogrel. These data suggest that both early (within 90 days) and delayed (90–360 days) bleeding risk with triple therapy exposure in relation to VKA + antiplatelet therapy was increased. Thus, even when the high risk of bleeding with recommended triple therapy after MI or PCI in AF patients decreases over time, the risk remains elevated in comparison with less intense antithrombotic regimens.[29,54]

Nonetheless, many unanswered questions remain resulting from the limitations of these types of registries, such as changes in the antithrombotic regimen over time, unknown duration of each type of antithrombotic drug, and unknown INR control (for those receiving VKAs), or even potential residual confounding arising from clinical characteristics, cessation of antithrombotic therapies in case of bleeding and different antithrombotic therapy indications.

Randomized controlled trials

Since publication of the 2010 consensus document, one controlled trial, the WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial[55] compared dual therapy (VKA plus clopidogrel) to triple therapy (VKA plus aspirin and clopidogrel) in 573 patients taking long-term OAC who received a coronary stent. The trial was powered to detect differences in the primary end-point of any (e.g. TIMI major plus minor) bleeding event within 1 year of follow-up. Combination therapy with OAC and clopidogrel was associated with less total bleeding complications (without significant differences in major bleeds), with no detectable increase in the rate of thrombotic events, especially stent thrombosis. Furthermore, there was a significant reduction in mortality at 12 months with dual therapy (*Table 1*).

There are some important issues that may limit the conclusions of the WOEST trial: only 69% of patients received OAC due to AF. Most of the patients underwent elective PCI (70–75%), and the femoral approach was used in 74%, increasing access site bleeding. Furthermore, the differences between dual and triple therapy for the primary end-point of 'all bleeding' were driven by minor bleeding events, proton pump inhibitors (PPIs) were not used routinely and triple therapy was continued for 12 months (and thus, the increased risk of bleeding is unsurprising). Both the European and North American consensus documents, in principle, recommend duration of triple therapy for the shortest time necessary, although there are some differences between European and North American guidelines.[53,56] Finally, the WOEST trial population size was too small to meaningfully assess major efficacy outcomes such as stent thrombosis or death.

Although it might be premature to abandon aspirin after stent implantation in AF patients requiring OAC based solely on the results of WOEST, dual therapy with OAC and clopidogrel may be considered as an alternative to triple therapy in selected AF patients at low risk of stent thrombosis/recurrent cardiac events.

Ongoing randomized controlled trials and registries

Two randomized trials and one multinational registry are currently testing different antithrombotic combinations for patients on OAC therapy who require stent implantation.

The ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation, clinicaltrials.gov id NCT00776633 [(http://clinicaltrials.gov/show/NCT00776633)] trial will address the hypothesis that reducing the length of clopidogrel therapy (75 mg o.d.) from 6 months to 6 weeks (in addition to aspirin and OAC) following implantation of a DES is associated with a reduced net composite end-point of death, MI, definite stent thrombosis, stroke, or major bleeding at 9 months.

The MUSICA-2 [Anticoagulation in Stent Intervention, clinical trials.gov id NCT01141153 (http://clinicaltrials.gov/ct2/show/NCT01141153)] trial[57] is investigating the safety and efficacy of a triple antithrombotic regimen of acenocoumarol, low-dose (100 mg o.d.) aspirin and clopidogrel vs. high-dose (300 mg o.d.)

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Table 1 Additional published data since 2010 on the topic of management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting

Study	*n*	Design	Outcomes	Follow-up (months)	Population	Comparison	Bleeding	Ischaemic end-point
Cohort studies								
Mutuberria *et al.*[23]	585	Prospective observational Multi-centre	Thrombotic events Bleeds	12	AF + PCI-S	TT vs. DAT regarding CHA_2DS_2-VASc score	CHA_2DS_2-VASc <2: TT increased risk of bleeding (all) (19.5 vs. 6.9%) and major bleeds (5 vs. 0%) CHA_2DS_2-VASc ≥2: TT increased major bleeds (8.4 vs. 3.1%)	CHA_2DS_2-VASc <2: no differences CHA_2DS_2-VASc ≥2: TT showed fewer embolisms (1.5 vs. 7.5%) No differences in MACE
Schlitt *et al.*[24]	963	Prospective observational Multi-centre	Adverse ischaemic events Bleeds	12	Registry, AFCAS High-risk patients with wide variation in ATT use	No comparisons among ATT groups	[a]	[a]
Pilgrim *et al.*[25]	323	Prospective observational Single-centre	MACE	48	ACS + DES	AF presence and events TT vs. DAT	AF increases risk of ICH TT associated with higher risk of bleeding	AF increases risk of death, ischaemic stroke & intracranial bleeding TT associated with higher risk of death
Rubboli *et al.*[26]	411	Prospective observational Multi-centre	MACE Bleeds	In-hospital	OAC + PCI AF 79%	Variables associated with DES implantation and TT at discharge	In-hospital major bleed rate was 2.1%. Complications limited	In hospital MACE rate 2.7%
Bernard *et al.*[27]	417	Retrospective observational single-centre	Thrombotic events (death, stroke and embolism) Bleeds	22	AF + PCI-S CHA_2DS_2-VASc ≥ 2	VKA vs. non-VKA at discharge	No differences in major bleeding HR 1.32 (0.70–2.63)	VKA reduces death-stroke-systemic embolism HR 0.45 (0.22–0.91) No differences in MAE or MACE
Sarafoff *et al.*[28]	377	Prospective observational Multi-centre	TIMI-bleeding Major, minor MACCE	6	OAC + PCI-S 36.9% ACS	VKA + ASA + prasugrel ($n = 21$) vs. VKA + ASA + clopidogrel ($n = 356$)	TIMI-bleeding Adjusted HR 3.2 (1.1–9.1, $P = 0.03$)	MACCE Adjusted HR 1.1 (0.2–5.1, $P = 0.91$)
Lamberts *et al.*[29]	12165	Retrospective Registry Nationwide	Bleeding and all-cause mortality Thrombotic composite event	12	OAC + MI/PCI-S 90.2% MI	OAC + clopidogrel ($n = 548$) vs. OAC + ASA + clopidogrel ($n = 1896$)	Any bleeding HR: 0.78 (0.55–1.12)	All-cause mortality HR: 0.87 (0.56–1.34) MI/coronary death HR: 0.69 (0.48–1.00)
Saheb *et al.*[30]	6296	Meta-analysis of 10 observational studies	MACE events, Stroke and major bleeds	12–24	Patients with indication for OAC	TT vs. DAT	TT increased major (HR 1.47;1.22–1.78) and minor (HR 1.55; 1.07–2.24) bleeds	TT reduced ischaemic stroke HR: 0.27 (0.13–0.57)

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Donze *et al.*[31]	515	Prospective observational Single-centre	Major and fatal bleeding	12	OAC + antiplatelet users No data on ACS	OAC + clopidogrel ($n = 11$) vs. OAC + ASA + clopidogrel ($n = 42$)	Major bleeding 9.1 vs. 2.4% No fatal bleeding	[a]
Ho *et al.*[32]	602	Retrospective single centre Database	Composite end-point death, ischaemic stroke, or TIA	24	OAC + PCI 69.6% ACS	OAC + ASA + clopidogrel ($n = 382$) ≥ACS: $n = 270 = 70.7\%$ vs. ASA + clopidogrel ($n = 220$)≥ ACS: $n = 149 = 67.7\%$ No reported data on subgroup ACS.	GI- bleeding 2.6% vs. 0.5% ($P = 0.045$) Any bleeding 3.7% vs. 1.8% ($P = 0.20$)	Composite end-point $CHADS_2 \leq 2$ HR 0.43 [0.14–1.3] $CHADS_2 > 2$: HR 1.0 [0.42–2.36]
Caballero *et al.*[33]	604	Retrospective Database Two-centres	Major bleeds, embolisms and MACE	17	AF + PCI-S Octogenarians ($n = 95$)	Octogenarians vs. <80 years VKA vs. non VKA at discharge	Octogenarians suffered higher major bleeds (20.0 vs. 10.9%) In octogenarians no significant increase in major bleeds with VKA	Octogenarians suffered higher all-cause mortality rate (33.3 vs. 19.3%) and embolism (12.6 vs. 3.5%) In octogenarians, VKA associated with less MACE, MI and MAE
Chan[34]	162	Prospective registry Multi-centre	Variables associated with AF Influence of AF on prognosis	30 days	PCI registry	AF vs. non AF patients	AF associated with in-hospital bleeds	AF associated with 4-increase in 30 day mortality
Lopes[35]	6925	Retrospective registry Multi-centre	Variables associated with AF and antithrombotic therapy	In-hospital	AMI registry	<50% received warfarin at discharge. TT indicated in only 14.6%	AF associated with increased risk of major bleeds (14.6 vs. 9.9%)	AF associated with increased risk of death (9.9 vs. 4.2%) and stroke (1.3 vs. 0.7%)
Lahtela *et al.*[36]	963	Prospective registry AFCAS Multi-centre	Bleeding events Composite major cardiovascular and cerebrovascular events	30d	AF + PCI-S Long-term OAC: 529	Uninterrupted OAC vs. bridging therapy in long-term OAC	No differences in major bleeds (2.6 vs. 2.6%)	No differences in death rate or MACCE
Ruiz-Nodar *et al.*[37]	590	Restrospective database Two centres	Major bleeds Embolic events Composite major events	12	AF + PCI- with CHA_2DS_2-VASc >1 and HAS-BLED ≥3	Use of VKA at discharge in patients with HAS-BLED score ≥3	HAS-BLED ≥3 VKA showed increased major bleeding rate (11.8 vs. 4.0%)	HAS-BLED ≥3 VKA showed lower mortality rate (9.3 vs. 20.1%) and MACE (13.0 vs. 26.4%)
Lamberts *et al.*[38]	11480	Retrospective nationwide registry	Primary end-point of fatal or nonfatal bleeding Composite secondary end-point of CV death, MI, and ischaemic stroke	12	OAC + MI/PCI-S 76.4% MI	OAC + ASA + clopidogrel vs. OAC + (ASA or clopidogrel)	Bleeding HR: 1.41 (1.10–1.81) Early (0–3 months) HR: 1.47 (1.04–2.08) Late (3–6 months) HR: 1.36 (0.95–1.95)	Composite end-point of CV death, MI, and ischaemic stroke HR: 1.15 (0.95–1.40)

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Table 1 *Continued*

Study	n	Design	Outcomes	Follow-up (months)	Population	Comparison	Bleeding	Ischaemic end-point
Fauchier *et al.*[39]	833	Retrospective registry Single centre	Major bleeds, embolism and MACE	24	AF + PCI stenting 62.4% ACS	DES ($n = 155$) vs. BMS ($n = 678$)	Similar rate of major bleeds (HR: 0.94)	Similar rates of MACE (HR: 1.24) and all-cause mortality (HR: 1.02)
Manzano-Fernandez *et al.*[40]	285	Retrospective analysis Single centre	Major bleeding	12	AF $CHADS_2 \geq 2$ and PCI-S ACS-STEMI 24.6% ACS-NSTEMI 59.6%	Moderate-severe kidney disease (KD) ($n = 91$) Mild KD ($n = 139$) No KD ($n = 55$) Significant differences between groups found for age, heart failure, haemoglobin and $CHADS_2$ score)	HR: 2.43 (1.11–5.34) HR: 7.96 (1.07–62.1) DES use: 61 vs. 42% major bleeds TT use 61 vs. 29% major bleeds	[a]
Rubboli *et al.*[41]	632	Prospective observational Multi-centre	MACE Bleeding events	12	OAC + PCI-S AF 58% ACS 63%	DAT 48% TT 32% W + aspirin 18%	No significant differences among three groups	No significant differences among three groups
Smith *et al.*[42]	159	Retrospective observational Single centre	Major bleeds	12	ACS 159 patients on VKA at discharge AF = 39.6%	TT vs. DAT Analysis between TT and DAT paired group performed	Higher major bleeds with TT (13.4 vs. 3.8%)	No differences in mortality rate, embolism or coronary events observed
Hansen[43]	82854	Retrospective nationwide registry	Non-fatal and fatal bleeding	40	Survivors of first hospitalization for AF	Different antithrombotic regimen at discharge	W + clopidogrel and TT carried greater than three-fold higher risk than W monotherapy	[a]
Zhao[44]	1996	Meta-analysis	MACE Bleeds	>3	OAC + stent implantation	Comparison of different antithrombotic regimen at discharge	TT increased risk of major bleeding (OR: 2.12; 1.05–4.29)	TT reduced MACE (OR: 0.60; 0.42–0.86)
Brugaletta *et al.*[45]	138	Prospective observational Multicenter	MACE	17	AF 67% All patients on OAC	Premature discontinuation DAT vs. DAT	Premature DAT discontinuation associated with increased MACE	No differences between TT vs. OAC + 1 antiplatelet drug
Gao *et al.*[46]	622	Prospective observational Single-centre	Bleeding MACCE (major adverse cardiac & cerebral events)	12	AF + DES implantation Acute MI 12.2%	OAC (+ 1 or 2 antiplatelets) Vs. DAT	Major bleeds HR 1.1 (0–57–1.32) TT only increased minor bleeds	MACCE HR 0.50 (0.33–0.78)
Uchida *et al.*[47]_	575	Prospective observational Single-centre	Major bleeding MACE	15	DES implantation AF = 29	TT vs. DAT	TT associated with higher risk of major bleeds (18.0 vs. 2.7%)	No differences in MACE

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Pasceri *et al.*[48]	165	Prospective observational Two-centres	Combination of MACE plus major bleedings	12	OAC + PCI-S AF 78.8%	DES vs. BMS	Non significant increase in major bleeds	Reduction in MACE with DES [0.35 (95% CI: 0.14–0.85)], based on a significant reduction in TVR [HR 0.33 (95% CI: 0.14–0.77)]. No differences in MI, stroke, or death
Rubboli *et al.*[49]	163	Prospective observational Multi-centres	MACE Bleeds	In hospital events	OAC indication + PCI-S AF = 137	Variables associated with events	No variables associated with bleeds	No variables associated with thrombotic complications
Gilard *et al.*[50]	359	Prospective observational STENTICO Multi-centre	Ischaemic stroke Bleeds	12	OAC + PCI-s AF = 248	Influence of OAC cessation at discharge vs. TT	TT associated with increased major bleeds (5.6 vs. 2.1%)	No significant differences in thrombotic events
Sambola *et al.*[51]	405	Prospective observational Multi-centre	Bleeding rate Thrombotic events	6	OAC + PCI-S AF = 274	Comparison among different ATT regimens	TT associated with higher minor bleeding events No differences in major bleeds	VKA + 1 antiplatelet associated with higher cardiovascular thrombotic events
Randomized controlled trials								
De Wilde *et al.*[55]	573	RCT Open-label Multi-centre	Any bleeds Composite end-points	12	OAC + PCI 27.5% ACS	OAC + clopidogrel ($n = 279$) vs. OAC + ASA + clopi ($n = 284$)	Any bleeding HR 0.36 (0.26–0.50, $P < 0.0001$) TIMI-bleeding HR 0.40 (0.27–0.58, $P < 0.0001$)	Composite ischaemic end-point HR 0.60 (0.38–0.94, $P = 0.025$) All-cause mortality HR 0.39 (0.16–0.93, $P = 0.027$)

ACS, acute coronary syndrome; ACS-NSTEMI, acute coronary syndrome non-ST elevation myocardial infarction; ACS-STEMI, acute coronary syndrome ST elevation myocardial infarction; AF, atrial fibrillation; ATT, Antithrombotic therapy; ICH, intracranial haemorrhage. BMS, bare metal stent; DES, drug eluting stent. MACE, major adverse cardiovascular events. MACCE, major adverse cardiovascular and cerebral events; MAE, major adverse events; MI, myocardial infarction; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; S, with stent; RCT, randomized controlled trial; TT, triple therapy; VKA, vitamin K antagonist therapy.
[a]Not reported.

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aspirin and clopidogrel in patients with AF and low-to-moderate risk of stroke ($CHADS_2 \leq 2$) referred for PCI.

The prospective, multi-centre LASER [Real Life Antithrombotic Stent Evaluation Registry, clinicaltrials.gov id NCT00865163 (http://clinicaltrials.gov/ct2/show/NCT00865163)] registry, sponsored by the ESC Working Group on Thrombosis, included 1000 patients who had stent implantation half of whom had the background of full OAC with VKAs and the other half without an indication for OAC. The final results are pending. In light of the relatively low rates of clinically relevant bleeding events in recent published registries such as management of patients with atrial fibrillation undergoing coronary artery stenting,[52,58] and the increased use of radial access for PCI, very large trials are needed to detect small differences between antithrombotic regimes in this patient cohort.

The use of NOACs in the antithrombotic management of AF patients undergoing coronary stenting is a subject of continued interest, with clinical trials ongoing or being planned, as will be discussed further in the section 'Non-VKA oral anticoagulants'.

Non-VKA oral anticoagulants

The potential role of NOACs for patients with ACS and AF has not been directly assessed, since AF patients requiring OAC were systematically excluded from recent ACS trials, and conversely, patients with recent ACS were likely to have been excluded from phase III stroke prevention trials in AF patients.

The data available in the literature dealing with the most appropriate management of patients with AF and ACS and/or undergoing PCI come from different sources.

First, there are data on the effects of concomitant prescription of NOACs and antiplatelet drugs derived from *post hoc* analyses of randomized controlled trials (RCTs) of NOACs in non-valvular AF patients,[59] as well as data on patient outcomes from RCTs of NOACs and antiplatelets in ACS/PCI patients[60–64] (*Table 2*). Where a NOAC is used in combination with clopidogrel and/or low-dose aspirin, the lower tested dose for stroke prevention in AF (that is, dabigatran 110 mg b.i.d., rivaroxaban 15 mg o.d. or apixaban 2.5 mg b.i.d.) should be considered, to minimize the risks of bleeding. However, dabigatran 110 b.i.d. was one intervention arm of the RE-LY trial, and thus, was tested among all eligible patients and may be considered on its own merits. On the other side, rivaroxaban 15 mg o.d. or apixaban 2.5 mg b.i.d. were given as a dose adjustment based on patient characteristics, and hence, prescribed to only a minority subset of the NOAC intervention arm. Thus, the lower doses may not necessarily provide adequate antithrombotic protection for AF in patients without the clinical features used for dose adjustment.

Secondly, further evidence comes from data on the risk of MI associated with NOACs, derived from RCTs of NOACs vs. warfarin or aspirin in non-valvular AF, including the original analyses from primary reports of the RCTs,[20–22,65,66] *post hoc* analyses or meta-analyses (the latter, pooling some data from RCTs, were not related to non-valvular AF patients), and 'real-life' nationwide AF patient data[67–69] (see Supplementary material online, *Table w1*). In the meta-analysis of dabigatran trials reported by Uchino and Hernandez,[67] a significantly higher rate of MI was reported by using dabigatran vs. warfarin (HR: 1.33, 95% CI: 1.03–1.71). In the RE-LY data, the absolute increase of MI risk reported in the first analysis was very low (0.19–0.21%/year)[20] and was not confirmed to be significant after re-analysis of the data with the inclusion of silent MIs.[70] Moreover, the net clinical benefit of dabigatran over warfarin was maintained in AF patients with a previous MI, and no significant increase in the risk of the composite end-point of coronary and cardiac events (MI, unstable angina, cardiac arrest, and cardiac death) was found in patients treated with dabigatran vs. warfarin.[71]

The most recent meta-analysis[72] of NOACs trials of AF, including the ENGAGE-AF trial,[66] found no significant difference in MI between NOACs (dabigatran and oral Factor Xa inhibitors in combination) and warfarin, but low dose regimes (dabigatran 110 mg b.i.d. and low-dose edoxaban) were associated with a 25% increase in MIs compared with warfarin in populations at low risk of recurrent events. It is unclear whether these effects also pertain to cohorts of ACS patients, where reinfarction is a common entity (e.g. ATLAS,[62] APPRAISE II[64]).

The debate on the small difference in MIs with dabigatran as reported in the first RE-LY analysis and the meta-analysis from Uchino and Hernandez[67] in patients who were stable at therapy initiation may simply be a reflection of the better protective effect of well-controlled warfarin against MI compared with NOACs.[73] The rates of MI in randomized trials in AF patients treated with NOACs, as well as the TTR of warfarin-treated patients is summarized in the Supplementary material online, *Table w2*. In ACTIVE-W, for example, there were numerically more MIs in aspirin-clopidogrel treated AF patients compared with warfarin.[74] In the North American subgroup of ROCKET-AF (mean TTR 64%), there were numerically more MIs in the rivaroxaban-treated patients (see Supplementary material online, *Table w2*). In the RE-LY trial, the annual rates of MI in the warfarin arm were 0.72 and 0.49%, with TTRs of <65 and ≥ 65%, respectively.[75] A numerical increase in MI was also noted in AF patients from the ENGAGE TIMI 48 trial with low-dose edoxaban vs. warfarin (0.89 vs. 0.75%), but not with high dose edoxaban (0.70 vs. 0.75%) (see Supplementary material online, *Table w2*).[66] The HOKUSAI trial of edoxaban for venous thombo-embolism treatment found a numerical increase in MIs in edoxaban treated patients compared with those on warfarin (0.5 vs. 0.3%) (see Supplementary material online, *Table w2*).[76] While conducted in non-AF patients, both ATLAS-TIMI 51 (comparing rivaroxaban in a low-dose BID regimen to placebo[62]) and APPRAISE II (full-dose apixaban vs. placebo[64]) demonstrated that adding a NOAC to dual antiplatelet therapy reduces reinfarction rates (APPRAISE II: 0.4%; ATLAS: 1.1%) compared with DAPT alone.

An analysis of the current literature (see Supplementary material online, *Tables w1* and *w2*) allows some considerations on the potential role and risk–benefit ratio of NOACs in patients with ACS and/or PCI/stenting with subsequent need for additional anti-platelet therapy:

- Historical data suggest that VKAs provide better protection against re-infarction than aspirin, albeit in a pre-statin and largely pre-PCI era.
- Dabigatran increases the risk of bleeding, especially lower gastrointestinal tract bleeding, in the setting of ACS, and this occurs even at doses below those proven to be beneficial by reducing the risk of stroke in AF patients (e.g. below 110 mg b.i.d.). However, the overall benefit of dabigatran in patients undergoing PCI or those

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Table 2 **Randomized controlled trials on NOACs and antiplatelet agents in AF and/or ACS**

Author/year	Study design	Size	Summary of findings	Comment
(a) Concomitant NOAC and antiplatelets in RCTs on NOAC in non valvular AF				
Dans *et al.*[59]	*Post hoc* analysis of RE-LY RCT, PROBE design (prospective, warfarin (INR 2.0 to 3.0) vs. dabigatran 110 mg b.i.d. or 150 mg b.i.d. non-valvular AF patients	6952 patients (38.4% of 18 113 RE-LY patients) received concomitant aspirin or clopidogrel at some time during the study	Concomitant APT (aspirin or clopidogrel) increased risk of major bleeding without affecting the advantages of dabigatran over warfarin. In the time-dependent analysis, concomitant use of a single APT increased risk of major bleeding (HR, 1.60; 95% CI: 1.42–1.82) Dual APT increased this risk even more (HR: 2.31; 95% CI: 1.79–2.98), but number of patients with TT was limited Absolute risks lowest with dabigatran 110 mg b.i.d. compared with dabigatran 150 mg bid or warfarin (annual risk of major bleeding in association with APTs 3.9, 4.4, and 4.8% per year, respectively)	Underestimation of the risks associated with full use of APT is likely, since mean duration of use was only 66% of the total study duration (2 years) Thrombo-embolic benefit of dabigatran 150 mg b.i.d. compared with warfarin was attenuated in patients with additional (dual) APT. However, dabigatran substantially lowers the risk of ICH even in combination with APTs
(b) RCTs on NOAC and antiplatelets in STEMI/NSTEMI/PCI				
Oldgren *et al.*[60]	RE-DEEM, Multi-centre, RCT, double-blind, placebo-controlled, dose-escalation trial with dabigatran	1861 patients (99.2% on dual APT) enrolled at mean 7.5 days after an STEMI (60%) or NSTEMI (40%) Randomized to dabigatran 50 mg ($n = 369$), 75 mg ($n = 368$), 110 mg ($n = 406$), 150 mg ($n = 347$) b.i.d., or placebo ($n = 371$)	Dabigatran, in addition to dual APT associated with a dose-dependent increase in bleeding in patients with recent MI 6-month incidence of primary end-point (composite of major or clinically relevant minor bleeding events) was 3.5, 4.3, 7.9, and 7.8% in the respective 50, 75, 110, and 150 mg b.i.d. dabigatran groups, compared with 2.2% with placebo ($P < 0.001$ for linear trend) Compared with placebo, HR (95% CI) for the primary outcome were 1.77 (0.70–4.50) for 50 mg, HR: 2.17 (0.88–5.31), for 75 mg 3.92 (1.72–8.95) for 110 mg, and 4.27 (1.86–9.81) for 150 mg b.i.d., respectively	Total number of ischaemic CV events was low; minor differences between treatment groups

Continued

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Table 2 *Continued*

Author/year	Study design	Size	Summary of findings	Comment
Mega *et al.*[61]	ATLAS ACS-TIMI 46 RCT, double-blind, dose-escalation, phase II study, with rivaroxaban in patients stabilized after ACS	3491 patients stabilized after STEMI (52%), NSTEMI (30%) or UAP (18%) randomized to placebo or rivaroxaban (at doses 5, 10, 15 or 20 mg) given q.d. or the same total daily dose given b.i.d. according to 2 strata (aspirin alone or with thienopyridine)	Clinically significant bleeding with rivaroxaban vs. placebo increased in a dose-dependent manner, HR (95% CI) ranged from 2.21, (1.25–3.9) for 5 to 5.06 (3.45–7.42) for 20 mg doses; $P < 0.0001$ irrespective of q.d. vs. b.i.d. dosing Rates of primary efficacy end-point (death, MI, stroke, or severe recurrent ischaemia requiring revascularization) were 5.6% for rivaroxaban vs. 7.0% for placebo (HR: 0.79, 95% CI: 0.60–1.05, $P = 0.10$) Rivaroxaban reduced the main secondary efficacy end-point of death, MI, or stroke compared with placebo (3.9 vs. 5.5%, HR: 0.69, 95% CI: 0.50–0.96, $P = 0.027$) irrespective of q.d. or b.i.d. dosing or thienopyridine use	
Mega *et al.*[62]	ATLAS ACS 2–TIMI 51 Prospective RCT, double-blind, placebo-controlled trial with rivaroxaban	15 526 ACS patients (50% STEMI, 26% NSTEMI, 24% UAP randomized to 2.5 or 5 mg rivaroxaban b.i.d. or placebo for a mean of 13 months	Rivaroxaban significantly reduced the primary efficacy end-point (a composite of CV death, MI, or stroke) compared with placebo; respective rates of 8.9% and 10.7% (HR: 0.84; 95% CI: 0.74–0.96; $P = 0.008$), with significant improvement for both rivaroxaban 2.5-mg b.i.d. (9.1 vs. 10.7%, $P = 0.02$) and rivaroxaban 5 mg b.i.d. (8.8 vs. 10.7%, $P = 0.03$). Rivaroxaban 2.5 mg b.i.d. reduced CV death rates (2.7 vs. 4.1%, $P = 0.002$) and all-cause mortality (2.9 vs. 4.5%, $P = 0.002$), a survival benefit that was not seen with rivaroxaban 5 mg b.i.d. Compared with placebo, rivaroxaban increased rates of major bleeding not related to CABG (2.1 vs. 0.6%, $P < 0.001$) and ICH (0.6 vs. 0.2%, $P = 0.009$), without a significant increase in fatal bleeding (0.3 vs. 0.2%, $P = 0.66$) or other adverse events Rivaroxaban 2.5 mg b.i.d. resulted in fewer fatal bleeds than the 5 mg b.i.d. dose (0.1 vs. 0.4%, $P = 0.04$)	Lower doses of rivaroxaban were tested when compared with non-valvular AF trials

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Alexander *et al.*[63]	APPRAISE Phase 2, double-blind, placebo-controlled, dose-ranging study with apixaban in recent STEMI and NSTEMI ACS with ≥1 additional risk factor for recurring events (including age ≥65 years, elevated cardiac biomarkers, heart failure, diabetes, or prior MI)	1715 ACS patients (63% STEMI in 63, 30% NSTEMI, and 8% UAP). randomized to 6 months of placebo ($n = 11$) or 1 of 4 doses of apixaban: 2.5 mg b.i.d. ($n = 317$), 10 mg q.d. ($n = 318$), 10 mg b.i.d. ($n = 248$), or 20 mg q.d. ($n = 221$)	Apixaban 10 mg b.i.d. and 20 mg b.i.d. arms discontinued due to excess total bleeding Dose-dependent increase in major or clinically relevant non-major bleeding compared with placebo, HR (95% CI) for apixaban 2.5 b.i.d., 1.78 (0.91–3.48); $P = 0.09$ and for 10 mg q.d. , 2.45 (1.31–4.61); $P = 0.005$) Lower ischaemic event rates with apixaban 2.5 mg b.i.d. 0.73(0.44–1.19; $P = 0.21$) and 10 mg q.d., 0.61 (0.35–1.04; $P < 0.07$) compared with placebo Increase in bleeding more pronounced and reduction in ischaemic events less evident in those taking aspirin plus clopidogrel than those on aspirin alone	Doses of rivaroxaban proved effective in stroke prevention in non-valvular AF caused higher bleeding rates
Alexander *et al.*[64]	APPRAISE-2 RCT, double-blind, placebo-controlled with in recent ACS patients with ≥2 risk factors for recurrent ischaemic events	$n = 7392$ ACS patients (40% STEM, 42% NSTEMI, 18% UAP) within the previous 7 days randomly assigned to apixaban 5 mg b.i.d. or placebo	Terminated prematurely after 74% recruitment due to increased major bleeding events with apixaban, without reduction in recurrent ischaemic events Primary outcome (CV death, MI, or ischaemic stroke) in 7.5% vs. 7.9% with apixaban or placebo, respectively, (HR: 0.95; 95% CI: 0.80–1.11; $P = 0.51$) Primary safety outcome (major bleeding) occurred in 1.3% vs. 0.5% of patients assigned to apixaban or placebo, respectively, (HR: 2.59; 95% CI: 1.50–4.46; $P = 0.001$) More ICH and fatal bleeding with apixaban vs. placebo Increased bleeding risk irrespective of APT regimen or revascularization, and consistent among all other key subgroups	Doses of apixaban proved effective in stroke prevention in non-valvular AF caused higher bleeding rates

ACS, acute coronary syndrome; APT, antiplatelet therapy; CABG, coronary artery bypass graft surgery; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PROBE, prospective, randomized, open, blinded end-point; RCT, randomized controlled trial; STEMI, ST elevation myocardial infarction; TT, triple therapy; UAP, unstable angina pectoris.

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AF patients with concomitant aspirin use was maintained in the RE-LY trial population.

- Apixaban at the dose that is beneficial in stroke prevention in AF patients (5 mg b.i.d.) increases the risk of bleeding when added to dual antiplatelet therapy and does not exert additional benefits against recurrent coronary events. However, the overall benefit of apixaban vs. warfarin was maintained in the ARISTOTLE trial irrespective of concomitant aspirin use.[77]
- In ROCKET AF, AF patients with prior MI assigned to rivaroxaban had a numerical (non-significant) reduction of ischaemic cardiac events.[78] Rivaroxaban at low doses (2.5 or 5.0 mg b.i.d.; e.g. three- to four-fold lower than the 15–20 mg q.d. dose that was proved to be effective in stroke prevention in AF) decreases the risk of recurrent ischaemic events, but increases the bleeding risk, including intracranial haemorrhage, compared with placebo.[62] Low-dose rivaroxaban (2.5 mg b.i.d.) that was useful in ACS (2.5 mg b.i.d.) has not been tested for stroke prevention in AF patients.
- There have been no head-to-head comparisons for one of the NOACs and a VKA in AF patients with ACS. Significantly lower intracranial bleeding rate of NOACs vs. warfarin are observed in the recent phase III trials in AF patients with or without additional antiplatelet therapy.
- There is a paucity of data on the use of the NOACs in combination with dual antiplatelet therapy with aspirin and the new $P2Y_{12}$ inhibitors, prasugrel or ticagrelor. This combination would be expected to expose the patients to an even higher risk of major bleeding with prasugrel or ticagrelor, compared with clopidogrel.[28]
- The ACS trials were underpowered to demonstrate a reduction in stroke risk by using NOACs in combination with (dual) antiplatelet therapy in non-AF patients.
- Given the absence of new data from RCTs and the outcome data coming from 'real-world' registries,[79,80] it appears questionable to consider the potential risk of MI as a criterion for selecting the most appropriate NOAC agent in a patient with non-valvular AF. The available data do not suggest that there is a need to switch patients on dabigatran to one of the other NOACs in the event of an ACS developing in a patient with AF.
- Conversely, in an ACS patient who develops new onset AF, and is at high stroke risk, OAC should be started, whether with a VKA or NOAC. Limited data suggest that use of the new $P2Y_{12}$ inhibitors would increase the risk of major bleeding, and thus, clopidogrel would be the preferred $P2Y_{12}$ inhibitor.

A recent meta-analysis, including seven published phase II and III RCTs on NOACs in patients with a recent ACS, showed that the addition of dabigatran to antiplatelet therapy led to a reduction (30%) in major adverse cardiovascular events (MACE) (HR: 0.70, 95% CI: 0.59–0.84) but a substantial increase in bleeding (HR: 1.79, 95% CI: 1.54–2.09).[81] The reduction in MACE events was attenuated (HR: 0.87, 95% CI: 0.80–0.95) and the risk of major bleeding more pronounced (HR: 2.34, 95% CI: 2.06–2.66) when NOACs were used in combination with dual anti-platelet therapy with aspirin and clopidogrel.

In general, in the setting of ACS, triple therapy with dual antiplatelet therapy and NOACs is associated with at least a doubling of the risk of major bleeding,[19] as similarly reported for VKAs in the WOEST trial[55] and consistent with the nationwide registry data from Denmark.[29] Thus, there is no strong evidence to suggest that NOACs behave differently to VKAs in the setting of ACS or stenting. Data are limited, but the principle of continuing an existing OAC seems reasonable at present. In ACS patients who develop new-onset AF while on dual antiplatelet therapy, OAC should also be started with a VKA (INR: 2.0–2.5) or NOACs. The duration of triple therapy depends on the individual risk for ischaemic and bleeding events (as discussed below). Details of the dosing of antithrombotic therapy in patients undergoing PCI have been proposed elsewhere.[11,19]

A series of measures can be applied to reduce the risk of bleeding in this setting in general, such as using low doses of aspirin (75–100 mg o.d., which is the standard of care in Europe anyway); use of clopidogrel as the preferred $P2Y_{12}$ inhibitor instead of the more potent ticagrelor or prasugrel; use of bare-metal stents (BMS), thus minimizing the required duration of triple therapy, and the use of the radial approach, thus minimizing the risk of access site bleeding.[19] However, it is uncertain whether BMS use requires a shorter duration of dual antiplatelet therapy than new generation DES. Indeed late stent thrombosis (1–12 months) is a recognized issue with BMS similar to DES.[82,83] New data on dual antiplatelet therapy cessation also shows no difference between BMS and DES, especially with new generation stents.[84,85] New generation DES (or BMS) would also be preferred over first generation DES, the latter being least preferred.[86]

While it is impossible to extrapolate the results of the ACS trials in non-AF patients to patients with AF and ACS, an improved assessment of the role of NOACs in AF patients with ACS and/or PCI with stenting can be obtained from prospective trials. At present, the optimal NOAC regimen for patients with AF and ACS or undergoing PCI has not been addressed by a RCT.

At the time of writing, two NOAC trials are ongoing or planned. The PIONEER AF-PCI trial [NCT01651780 (http://clinicaltrials.gov/ct2/show/NCT01651780)] mainly addresses safety in terms of clinically significant bleeding of two different treatment strategies and doses of rivaroxaban (2.5 mg b.i.d. followed by 15 mg q.d. or 10 mg q.d. in subjects with moderate renal impairment) in comparison with a dose-adjusted oral VKA treatment strategy in subjects with AF undergoing PCI. In addition, all patients will receive either single or dual antiplatelet therapy. This trial will also study the more potent platelet inhibitors prasugrel and ticagrelor in combination with OAC. However, PIONEER–AF-PCI is not powered to detect differences in stroke rates, and it will still remain uncertain if rivaroxaban 2.5 mg b.i.d. would adequately reduce strokes in AF, even when combined with antiplatelet agents. A similar but larger clinical trial with dabigatran (RE-DUAL PCI) has also been announced (http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2013/19_november_2013_dabigatranetexilate1.html).

Transcatheter aortic valve implantation

Parenteral antithrombotic treatment during TAVI aims to prevent thrombo-embolic complications related to large i.v. catheter manipulation, guidewire insertion, balloon aortic valvuloplasty and

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valve prosthesis implantation while minimizing the risk of bleeding particularly at the vascular access site.

Based on retrospective studies and randomized trials,[87–91] the most commonly used anticoagulant is unfractionated heparin (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[92–97] (*Table 3*). An alternative anticoagulant currently under investigation during TAVI is bivalirudin due to a favourable efficacy and safety profile compared with UFH during PCI.[98,99] The comparative safety of UFH and bivalirudin is the object of the ongoing Effect of Bivalirudin on Aortic Valve Intervention Outcomes 2/3 (BRAVO 2/3) trial (NCT01651780).

Long-term oral antithrombotic treatment after TAVI aims to prevent complications notably ischaemic stroke and MI as well as thrombo-embolism related to deep vein thrombosis, pulmonary embolism, valve thrombosis, and embolism owing to AF while minimizing bleeding risk. The baseline risk for ischaemic and thrombo-embolic complications is determined 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.[88,89,100,101]

Prospective data on antithrombotic therapy after TAVI are scarce (*Table 3*), and recommendations regarding pre-treatment, loading dose, 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 dual antiplatelet therapy consisting of low-dose acetylsalicylic acid (75–100 mg per day) and clopidogrel 75 mg o.d. (after loading dose of 300–600 mg) for a variable period of time ranging from a minimum of 1 month to a maximum of 6 months followed by indefinite aspirin monotherapy. The ongoing Aspirin vs. aspirin + clopidogRel following Transcatheter aortic valve implantation (ARTE) pilot trial [NCT01559298 (http://clinicaltrials.gov/show/NCT01559298)] comparing single with dual antiplatelet therapy after TAVI will provide important information regarding the balance of ischaemic and bleeding risk associated with additional clopidogrel treatment.

Among TAVI patients with AF but without CAD, OAC is recommended in accordance with recommendations for AF alone.[11] 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.[93] Indeed, OAC (essentially VKAs) use in biological aortic valves (surgical implantation) is generally recommended for only 3 months and could be stopped thereafter, except where patients have other reasons for prolonged or life-long OAC.

In the absence of solid data sets for TAVI patients with AF and recent PCI, these patients should be treated similar to patients receiving a stent without TAVI. The use of new $P2Y_{12}$ inhibitors in combination with acetylsalicylic acid or NOAC after TAVI has not been investigated and cannot be recommended at this time.

In patients with artificial mechanical valves, NOACs should not be used. In the Phase 2 RE-ALIGN trial,[102] dabigatran was associated with more thrombo-embolism and major bleeding, compared with warfarin, leading to early cessation of the trial.

Peri-operative/periprocedural strategy in patients on antithrombotic combination therapy: a brief overview

Patients treated with VKAs have an increased risk of peri- and post-procedural bleeding complications when receiving active anticoagulation but surgery is usually safe as soon as the INR is $\leq$2.0.[103] On the other hand, prolonged discontinuation of VKAs is associated with an increased MACE rate, especially in patients at high risk for thrombo-embolic events. There is no sufficient evidence to support heparin bridging in anticoagulated patients in general.[104]

Minor surgery can often be performed on continuous OAC.[19] If the peri-operative bleeding risk is moderate or high, VKAs should be discontinued between 3 and 5 days before surgery (dependent on the specific brand) with regular INR measurements. Surgery may be postponed if the INR is >2.0. Restarting VKA therapy depends on the individual peri- and post-operative bleeding risk and should be at the pre-procedural maintenance dose, and LMWH or UFH should be continued until the INR returns to therapeutic levels.[105] In surgical procedures with a low risk of bleeding (e.g. cataract surgery, minor skin surgery, or minor dental surgery) VKA therapy can be maintained in patients with or without prior stroke.[104]

In patients undergoing cardiac device implantation (see Supplementary material online, *Table w3*),[106–115] most studies are consistent in suggesting that uninterrupted OAC decreases the risk of peri-operative bleeding, including pocket haematomas, compared with heparin bridging. Since the 2010 consensus document, new studies have explored the impact of different strategies of anticoagulation management and/or bridging therapy in patients on VKAs undergoing surgical or invasive procedures[36,116–125](see Supplementary material online, *Table w4*).

In patients treated with NOACs bridging to surgery is usually not necessary, due to the fast-onset and offset action of these agents.[126,127] As a general recommendation, NOACs should be stopped 24 h before surgery in surgical interventions with low or 'normal' bleeding risk, and 48 h before surgery in surgical interventions with high-bleeding risk.[128] Patients with advanced chronic kidney disease may require longer stopping times, depending on the reliance of the NOAC on renal clearance. In the RE-LY study, dabigatran facilitated a shorter interruption of OAC in patients having urgent surgery, while rates of peri-procedural bleeding were similar in patients on dabigatran or warfarin, respectively.[129]

Whether continuation/administration of NOACs during left atrial catheter ablation is safe and effective is still a matter of debate, but recent meta-analyses have shown no differences in thrombo-embolism and bleeding between dabigatran and warfarin.[130,131] Observational data with rivaroxaban also seem reassuring.[132] Prospective controlled trials are ongoing.

Limitations of the current data and future areas of research

While patients discussed in this document are likely to be in need of both OAC and antiplatelet therapy, an adequate balance between

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Table 3 **Antiplatelet and antithrombotic therapy during and after transcatheter aortic valve interventions**

Study/year	Study design/treatment arm	Size	Device	Summary of findings	Comment
(a) Retrospective studies					
BRAVO I/2011 TCT 2011[87]	*Bivalirudin* (0.375–0.75 mg/kg bolus IV, followed by i.v. infusion at 1.75 mg/kg/h) vs. *UFH* (50 IU/kg bolus i.v. with supplemental boluses to maintain ACT between 200 and 250 s)	Bivalirudin ($n = 223$) UFH ($n = 205$)	Balloon aortic valvuloplasty	Significant reduction in in-hospital VARC 1 bleeding (life-threatening/major) for bivalirudin, when compared with UFH (3.6 vs. 10.7%; $P = 0.004$)	–
(b) Randomized trials					
PARTNER Trial/ 2010/2011[88,89]	*Anticoagulant regimen* UFH 5000 IU bolus IV, then as needed to achieve/maintain ACT $\geq$250 s	PARTNER B (TAVI $n = 179$, standard therapy $n = 179$) PARTNER A (TAVI $n = 348$, SAVR $n = 351$)	TAVI with the Edwards Sapien THV	PARTNER B (TAVI vs. standard therapy) at 30 days: Major bleeding (16.8 vs. 3.9%, $P < 0.001$) Major stroke (5.0 vs. 1.1%, $P = 0.06$) Death (5.0 vs. 2.8%, $P = 0.41$) PARTNER A (TAVI vs. SAVR) at 30 days Major bleeding (9.3 vs. 19.5%, $P < 0.001$) Major stroke (3.8 vs. 2.1%, $P = 0.20$) Death (3.4 vs. 6.5%, $P = 0.07$)	–
Ussia *et al.*[90]	*DAPT* ASA 100 mg/day AND clopidogrel 75 mg/day for 3 months followed by ASA 100 mg/day indefinite vs. *ASA* 100 mg/day indefinite	DAPT ($n = 40$) ASA ($n = 39$)	TAVI with the 3rd Generation Medtronic CoreValve	DAPT vs. ASA Outcomes at 30 days Life-threatening bleeding (5 vs. 5%, $P = 0.92$) Major bleeding (5 vs. 3%, $P = 0.61$) Major stroke (3 vs. 5%, $P = 0.49$) All-cause death (10 vs. 10%, $P = 0.63$)	Inconclusive due to small sample size
Stabile *et al.*[91]	*DAPT* ASA 100 mg/DAY AND clopidogrel 75 mg/day OR ticlopidine 250 mg/twice day) vs. *ASA* 100 mg/day indefinite	DAPT ($n = 60$) ASA ($n = 60$)	TAVI	DAPT vs. ASA Outcomes at 30 days: Major/minor vascular complication (13 vs. 5%, $P = 0.03$) Bleeding (15 vs. 10%, $P = 0.20$)	Inconclusive due to small sample size
PARTNER Trial/ 2010/2011[88,89]	*Antiplatelet regimen* Loading dose: at the discretion of the investigator (ASA 75–100 mg), clopidogrel 300 mg) Post-procedure: ASA 75–100 mg/day indefinite AND clopidogrel 75 mg/day for 6 months. If warfarin indicated, then only ASA 75–100 mg/day and warfarin (target INR 2–3)	Partner B (TAVI $n = 179$, standard therapy $n = 179$) Partner A (TAVI $n = 348$, SAVR $n = 351$)	TAVI with the Edwards Sapien THV	PARTNER B (TAVI vs. Standard therapy) at 12 months: Major bleeding (22.3 vs. 11.2%, $P = 0.007$) Major stroke (7.8 vs. 3.9%, $P = 0.18$) Death (30.7 vs. 49.7%, $P < 0.001$) PARTNER A (TAVI vs. SAVR) at 12 months Major bleeding (14.7 vs. 25.7%, $P < 0.001$) Major stroke (5.1 vs. 2.4%, $P = 0.07$) Death (24.2 vs. 26.8%, $P = 0.44$)	–

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Guidelines/consensus documents					
ACCF/AATS/SCAI/STS[92]	Expert consensus document	–	–	–	Anticoagulation initiated prior to placement of the delivery sheath into the vasculature UFH to maintain an ACT >300 s UFH can be reversed by the administration of protamine sulfate
ACCF/AATS/SCAI/STS[92]	Expert consensus document	–	TAVI	–	Antiplatelet therapy with ASA and clopidogrel is recommended In patients treated with warfarin, a direct thrombin inhibitor, or Factor Xa inhibitor it is reasonable to continue low-dose ASA, but other antiplatelet therapy should be avoided
ESC/EACTS[93]	Expert consensus document	–	TAVI	–	A combination of low-dose ASA and a thienopyridine is used early after TAVI followed by ASA or a thienopyridine alone In patients with atrial fibrillation, a combination of VKA and ASA or thienopyridine is generally used, but should be weighed against the increased risk of bleeding
Canadian Cardiovascular Society[94]	Expert consensus document	–	TAVI	–	Indefinite low-dose ASA is recommended along with 1–3 months of a thienopyridine (no evidence) For patients with indication for oral anticoagulants the need for adjunctive antiplatelet agents is controversial and triple therapy should be avoided unless definite indications exist
ACCP[95]	Expert consensus document	–	TAVI	–	In patients with transcatheter aortic bioprosthetic valves, we suggest ASA (50–100 mg/day) plus clopidogrel (75 mg/day) over VKA therapy and over no antiplatelet therapy in the first 3 months
DGK—German Society of Cardiology[96]	Expert consensus document	–	TAVI	–	Recommendation for DAPT for 1–6 months followed by indefinite ASA 100–300 mg/day In case there is an indication for oral anticoagulation, triple therapy (<3 months) might be considered

Continued

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Table 3 Continued

Study/year	Study design/treatment arm	Size	Device	Summary of findings	Comment
ESC/EACTS[93]	Expert consensus document	–	SAVR Bioprosthesis	–	Low-dose ASA (IIa C) VKA (INR 2–3) (IIb C)
ACC/AHA[97]	Expert consensus document	–	SAVR Bioprosthesis	–	Low risk ASA (75–100 mg/day) (Class I) VKA (INR 2–3) (Class IIa) High risk ASA (75–100 mg/day) (Class I) VKA (INR 2–3) (Class I)
ACCP[95]	Expert consensus document	–	SAVR Bioprosthesis	–	In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA, we suggest ASA (50–100 mg/day) over VKA in the first 3 months (Grade 2C)

ACT, activated clotting time; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; IV, intravenous; IU, International Units; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve; UFH, unfractionated heparin; VARC, Valve Academic Research Consortium; VKA, vitamin K antagonists.

ischaemic stroke, bleeding risk, recurrent coronary events, and stent thrombosis will require some degree of personalized management.[133] There are adequate historic data to suggest that a combination of OAC and antiplatelet agents is able to prevent AF-related strokes, stent thrombosis, and recurrent coronary events. The suggestions for antithrombotic therapy put forward in this consensus document are largely based on expert consensus and/or derived from extrapolation of data from patients in sinus rhythm, observational studies, subgroup analyses, and a few smaller controlled trials. We have data for the bleeding effects of combination therapy in non-AF populations for dabigatran,[60] apixaban,[64] and rivaroxaban,[62,134] although for rivaroxaban, this was generally at doses that are lower compared with those proven to provide stroke prevention in AF. Better assessment of bleeding and ischaemic risk in PCI patients with AF would be desirable.

A sizeable proportion of the anticoagulated AF population will be in need for transient combination therapy of OAC with antiplatelet therapy. Continuation of an existing anticoagulant and addition of carefully weighed antiplatelet therapy seem reasonable in most patients, as outlined in this document. Unfortunately, there is a lack of adequately powered, outcome-based controlled trials comparing different antithrombotic regimes in patients with AF undergoing coronary stenting procedures and/or experiencing an ACS, and in those developing a need for OAC (i.e. AF) during or shortly after ACS.

The clinical outcomes of ACS patients differ markedly from stable patients with AF and CAD (e.g. in the risk for reinfarction or access site/periprocedural bleeding). Importantly, ACS patients are at a higher risk of stroke and reinfarction than stable patients with AF and CAD, and the mechanisms of thrombotic events in a clinical situation of activated inflammatory and prothrombotic signalling cascades may differ from stable patients.

Thus, there is a clear need for high-quality-controlled clinical trials to define the optimal antithrombotic therapy in these patients. The patient population in need for optimized therapy is rather large, and the event rates seem sufficiently high to make such trials feasible and sufficiently important for the cardiovascular community.

Also, there is increasing recognition that the quality of INR control (as reflected by average individual TTR) in a VKA-treated patient is closely related to efficacy and safety outcomes.[135] A low TTR is associated with a high risk of thrombo-embolism and serious bleeding, while a high TTR is associated with low-adverse event rates.[136,137] A recent ESC anticoagulation working group position document[138] recommends a TTR of >70%, and such a 'high-TTR' anticoagulation strategy could be tested against 'usual care' in ACS patients with AF undergoing PCI/stenting. Also, a management strategy based on predicting those who would do well on a VKA with a high TTR, using a recently validated clinical score[139] [SAME-TT_2R_2 score (SAME-TT_2R_2 score: Sex (females), Age (<60 years), Medical history (at least two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), Treatment (interacting drugs, e.g. amiodarone for rhythm control) [all one point], as well as current Tobacco use (two points) and Race (non-Caucasian; two points)), e.g. 0–1] as recommended in the ESC anticoagulation consensus document,[138] could be tested against those where a VKA would be less suitable (with a high SAME-TT_2R_2 score, e.g. ≥2) and a NOAC

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would be a better alternative. The SAME-TT_2R_2 score has recently been shown to be predictive of patients with poorer TTR levels,[140] and identifies those with labile INRs, and consequently, more thrombo-embolism and serious bleeding events.[141]

Other areas in need of investigation via RCTs are listed below

(1) Safety and effectiveness of combination therapy of NOACs with different antiplatelet therapies in AF patients undergoing PCI.
(2) Safety and effectiveness of combining the newer $P2Y_{12}$ receptor inhibitors (prasugrel, ticagrelor) with OACs in AF patients with ACS.
(3) Comparative effectiveness and safety of a VKA and a NOAC as the basis for combination therapy in AF patients undergoing PCI.
(4) Comparison of different durations of dual antiplatelet therapy, or of monotherapy with aspirin, clopidogrel, prasugrel, or ticagrelor, in combination with OAC in patients with elective PCI and (possibly as a separate trial) in patients with ACS.
(5) Evaluation of a strategy where patients with AF after stent implantation, no matter whether acute or planned, and with a low CHA_2DS_2-VASc-score (0–1) are treated with dual antiplatelet therapy only (including the more effective $P2Y_{12}$-receptor blockers for the shortest necessary time), then followed by dual antithrombotic therapy (an antiplatelet agent and OAC), compared with a conventional OAC-based triple/dual therapy regime.
(6) Evaluation of the optimal anticoagulant regime in patients undergoing AF ablation.

Until these studies are available, we will have to rely on more information from contemporary observational programmes. Such programmes will need adequate follow-up rates, good information on duration and type of therapy, and adequate adjudication of events to generate meaningful new information in addition to the available data sets.

Consensus recommendations

Consensus recommendations on the management of AF patients with ACS and/or undergoing PCI/stenting are summarized in *Table 4* and *Figure 1*.

In general, the period of triple therapy should be as short as possible, followed by OAC plus a single antiplatelet therapy (preferably clopidogrel 75 mg/day, or as an alternative, aspirin 75–100 mg/day). The duration of triple therapy 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). In these consensus recommendations for patients with non-valvular AF, where we refer to OAC, this can either be with well-controlled adjusted dose VKA (with TTR >70%) or with a NOAC.

General

(i) In AF patients, stroke risk must be assessed using the CHA_2DS_2-VASc score, and bleeding risk assessed using the HAS-BLED score.[2] Risk stratification is a dynamic process, and must be performed at regular intervals (i.e. on a yearly basis) (Class I, level of evidence C).
  (a) The HAS-BLED score should be used to 'flag up' the patients potentially at risk of bleeding, and to help identify and correct the potentially reversible bleeding risk factors (e.g. uncontrolled hypertension, labile INRs, concomitant use of aspirin or NSAIDs, alcohol excess/abuse, etc.).[2,142]
  (b) Risk stratification for ACS should be performed using the GRACE score, as per current guidelines.[143]
(ii) Where adjusted dose VKA is used, good quality anticoagulation control is recommended, with a TTR >70% (Class I, level of evidence A).
(iii) 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 (Class IIa, level of evidence C).
(iv) Where a NOAC is used in combination with clopidogrel and/or low-dose aspirin, the lower tested dose for stroke prevention in AF (that is, dabigatran 110 mg b.i.d., rivaroxaban 15 mg o.d. or apixaban 2.5 mg b.i.d.) may be considered (Prescribing information for edoxaban awaited.) (Class IIb, level of evidence C).
(v) In a patient with AF and stable vascular disease (arbitrarily defined as being free from any acute ischaemic event or repeat revascularization for >1 year) the patient should be managed with OAC alone (i.e. whether NOAC or a VKA) (Class IIa, level of evidence B).
(vi) Radial access should be considered as the default for coronary angiography/intervention to minimize the risk of access-related bleeding depending on operator expertise and preference (Class IIa, level of evidence C).
(vii) New generation DES may be preferred over BMS in patients at low risk of bleeding (i.e. HAS-BLED 0–2) (Class IIb, level of evidence C).
(viii) Novel $P2Y_{12}$ receptor inhibitors (prasugrel and ticagrelor) should not be part of a triple therapy regimen in patients with AF (Class III, level of evidence C).

Stable CAD

(i) In patients with stable CAD and AF undergoing PCI at low-bleeding risk (HAS-BLED 0–2), triple therapy (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 dual therapy with OAC (i.e. whether NOAC or a VKA) and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) should be continued for up to 12 months (Class IIa, level of evidence C).
  (a) In selected patients with a CHA_2DS_2-VASc score = 1 (by virtue of their vascular disease only) at low-bleeding risk (HAS-BLED 0–2), dual antiplatelet therapy consisting of aspirin 75–100 mg and clopidogrel 75 mg/day; or dual therapy consisting of OAC (i.e. whether NOAC or a VKA) and clopidogrel 75 mg/day should be considered (Class IIa, level of evidence C).
  (b) Dual therapy of OAC (i.e. whether NOAC or a VKA) and clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients with CHA_2DS_2-VASc score ≥2 (Class IIb, level of evidence C).

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Table 4 Recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to-high thrombo-embolic risk (in whom oral anticoagulation therapy is required)

Haemorrhagic risk	Stroke risk	Clinical setting	Recommendations
Low or moderate (HAS-BLED 0–2)	Moderate (CHA_2DS_2-VASC = 1 in males)	Stable CAD	*At least 4 weeks (no longer than 6 months):* triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day[a] *Up to 12th month*: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day)[b] *Lifelong*: OAC[c]
	High (CHA_2DS_2-VASC ≥2)	Stable CAD	*At least 4 weeks (no longer than 6 months):* triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day[d] *Up to 12th month*: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) *Lifelong*: OAC[c]
	Moderate (CHA_2DS_2-VASC = 1 in males)	ACS	*6 months*: triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day *Up to 12th month*: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) *Lifelong*: OAC[c]
	High (CHA_2DS_2-VASC ≥2)	ACS	*6 months*: triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day *Up to 12th month*: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) *Lifelong*: OAC[c]
High (HAS-BLED ≥3)	Moderate (CHA_2DS_2-VASC = 1 in males)	Stable CAD	*12 months*: OAC and clopidogrel 75 mg/day[b] *Lifelong*: OAC[c]
	High (CHA_2DS_2-VASC ≥2)	Stable CAD	*4 weeks*: triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day[a] *Up to 12th month*: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) *Lifelong*: OAC[c]
	Moderate (CHA_2DS_2-VASC = 1 in males)	ACS	*4 weeks*: triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day[d] *Up to 12th month*: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) *Lifelong*: OAC[c]
	High (CHA_2DS_2-VASC ≥2)	ACS	*4 weeks*: triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day[d] *Up to 12th month*: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) *Lifelong*: OAC[c]

PPI should be considered in all patients, particularly where aspirin is used. Newer generation drug-eluting stents should be preferred over bare metal stents in patients at low risk for bleeding. New generation drug-eluting stent is generally preferable over bare-metal stent, particularly in patients at low bleeding risk (HAS-BLED 0–2). OAC, oral anticoagulation, either warfarin (INR: 2.0–2.5) or non-VKA oral anticoagulant at the lower tested dose in AF (dabigatran 110 mg b.i.d., rivaroxaban 15 mg o.d. or apixaban 2.5 mg b.i.d.). INR, international normalized ratio; PPI, proton pump inhibitors; ACS, acute coronary syndrome.
[a]Combination of OAC + clopidogrel 75 mg/day or dual antiplatelet therapy consisting of aspirin 75-mg/day and clopidogrel 75 mg/day may be considered as an alternative.
[b]Dual antiplatelet therapy consisting of aspirin 75 mg/day and clopidogrel 75 mg/day may be considered as an alternative.
[c]Alone or combined with single antiplatelet therapy only in very selected cases (e.g. stenting of the left main, proximal bifurcation, recurrent MIs etc).
[d]Combination of OAC and clopidogrel 75 mg/day may be considered as an alternative.

(ii) In patients with stable CAD and AF undergoing PCI at high-bleeding risk (HAS-BLED >3), triple therapy (OAC, aspirin 75–100 mg daily, clopidogrel 75 mg daily) or dual therapy consisting of OAC (i.e. whether NOAC or a VKA) and clopidogrel 75 mg/day should be given for 4 weeks after PCI following which dual therapy with OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) should be continued for up to 12 months (Class IIa, level of evidence C).

(a) In selected patients with a CHA_2DS_2-VASc score = 1 at high-bleeding risk (HAS-BLED >3), dual antiplatelet therapy consisting of aspirin 75–100 mg and clopidogrel 75 mg/day; or dual therapy consisting of OAC (i.e. whether NOAC or a VKA) and clopidogrel 75 mg/day may be considered (Class IIb, level of evidence C) for 12 months.

(iii) Long-term antithrombotic therapy with OAC (i.e. whether NOAC or a VKA) (beyond 12 months) is recommended in all patients (Class I, level of evidence B).

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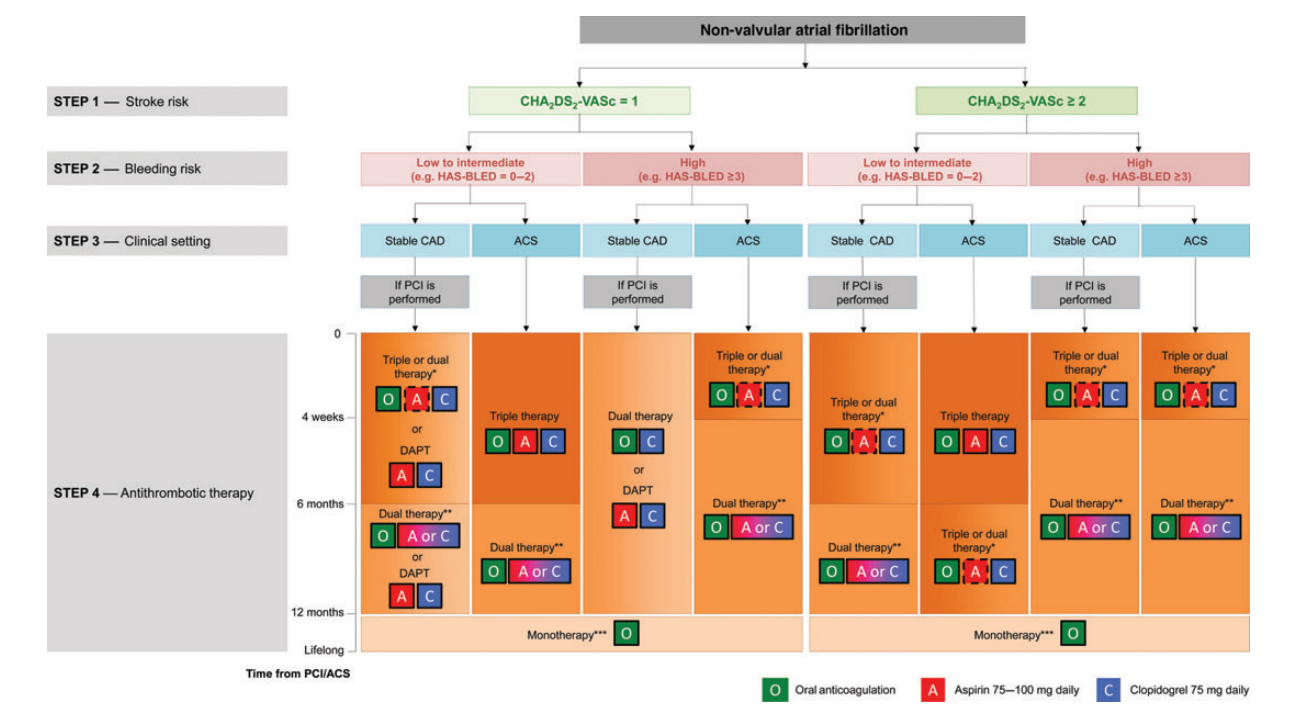

Figure 1 Choice of antithrombotic therapy, including combination strategies of oral anticoagulation (O), aspirin (A) and/or clopidogrel (C). For Step 4, background colour and gradients reflect the intensity of antithrombotic therapy (i.e. dark background colour = high intensity; light background colour = low intensity). Solid boxes represent recommended drugs. Dashed boxes represent optional drugs depending on clinical judgement. New generation drug-eluting stent is generally preferable over bare-metal stent, particularly in patients at low bleeding risk (HAS-BLED 0–2). When vitamin K antagonists are used as part of triple therapy, international normalized ratio 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 (i.e. oral anticoagulation plus single antiplatelet). ***Dual therapy with oral anticoagulation and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at very high risk of coronary events. ACS, acute coronary syndromes; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

(a) Combination OAC plus single antiplatelet therapy [preferably clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day)] may be considered in only very selected cases, e.g. stenting of the left main, proximal left anterior descending, proximal bifurcation, recurrent MIs, etc. (Class IIb, level of evidence C).

(iv) Gastric protection with PPIs should be considered in patients with OAC plus antiplatelet therapy (Class IIa, level of evidence C).

(v) Where OAC patients are at moderate-to-high risk of thrombo-embolism (i.e. CHA2DS$_2$-VASc ≥2), an uninterrupted anticoagulation strategy with no additional heparin boluses during PCI is the preferred strategy and radial access used as the first choice during therapeutic anticoagulation with a VKA (INR 2–3). This strategy might reduce periprocedural bleeding and thrombo-embolic events (Class IIa, level of evidence C).

(vi) Where NOAC patients are at moderate-to-high risk of thrombo-embolism (i.e. CHA$_2$DS$_2$-VASc ≥2), cessation of the drug for 48 h and parenteral anticoagulation as per standard practice during PCI may be prudent in a non-emergency situation (Class IIb, level of evidence C).

(vii) 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. Pharmacodynamic data suggest that enoxaparin might be a better option than UFH, because of the more predictable and stable level of anticoagulation. Such 'bridging' therapies may actually 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 on the basis of renal function and the pharmacokinetics of the specific NOAC (Class IIb level of evidence C).

NSTE-ACS including unstable angina and NSTEMI

(i) Patients with moderate-to-high-risk NSTE-ACS and AF at low risk of bleeding (HAS-BLED 0–2) should receive dual antiplatelet therapy with aspirin plus clopidogrel and OAC (i.e. whether NOAC or a VKA) should also be given/continued (Class IIa, level of evidence C).

(ii) An early invasive strategy (within 24 h) should be preferred among patients with moderate-to-high-risk NSTE-ACS in

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order to expedite treatment allocation (medical vs. PCI vs. CABG) and to determine the optimal antithrombotic regimen (Class IIa, level of evidence C).

(a) Pre-treatment with glycoprotein (GP) IIb/IIIa inhibitors should be avoided in such patients.

(b) Pre-treatment with $P2Y_{12}$ receptor antagonists may be withheld until the time of coronary angiography in case of an early invasive strategy within 24 h.

(iii) In the ACS setting, patients are often given aspirin, clopidogrel, heparin (whether UFH or enoxaparin) or bivalirudin and/or a GP IIb/IIIa inhibitors. Given the risk of ischaemia and bleeding it may be prudent to stop OAC (i.e. whether NOAC or a VKA) therapy, and where a VKA or NOAC is used, administer UFH or bivalirudin only as bailout (but avoiding GP IIb/IIa 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' (Class IIb, level of evidence C).

(a) in low-risk ACS patients with delayed transfer for an invasive strategy at >24 h of admission, it may be prudent to stop OAC therapy and bridge the patient with unfractionated heparin or enoxaparin (class IIb level of evidence C). For a NOAC, cessation of the drug for 36–48 h (based on the biological half-life of the respective agents and the actual kidney function) may be prudent (Class IIb, level of evidence B).

(b) When a parenteral anticoagulant is needed to support PCI in a patient at high risk of bleeding, bivalirudin should be considered as an alternative to unfractionated heparin (class IIa, level of evidence A).

(c) When a parenteral anticoagulant is needed to support PCI in a patient at low risk of bleeding, bivalirudin should be considered as alternative to unfractionated heparin (class IIa, level of evidence B).

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

(a) In selected patients with a CHA_2DS_2-VASc score ≥ 2 at low risk of bleeding (HAS-BLED 0–2), continuation of triple therapy or dual antiplatelet therapy consisting of OAC (i.e. whether NOAC or a VKA) and clopidogrel 75 mg/day may be considered (Class IIb, level of evidence C) between 6 and 12 months (Class IIb, level of evidence C).

(v) In patients with ACS and AF at high risk of bleeding (HAS-BLED ≥ 3), the initial use of triple therapy (OAC, aspirin, and clopidogrel) should be considered for 4 weeks following PCI irrespective of stent type; this should be followed by long-term therapy (up to 12 months) with OAC and a single antiplatelet drug (preferably clopidogrel 75 mg/day, or as an alternative, aspirin 75–100 mg/day) (Class IIa, level of evidence C).

(a) As an alternative to initial triple therapy in selected patients at high risk of bleeding (e.g. HAS-BLED ≥ 3) and low risk of stent thrombosis/recurrent ischaemic events, dual therapy consisting of OAC and clopidogrel 75 mg/day may be considered (Class IIb, level of evidence C).

(vi) Long-term antithrombotic therapy (beyond 12 months) is recommended with OAC whether with VKA or a NOAC in all patients (Class I, level of evidence B).

(a) Combination OAC plus single antiplatelet therapy (preferably clopidogrel 75 mg/day, or as an alternative, aspirin 75–100 mg/day) may be considered in very selected cases, e.g. stenting of the left main, proximal left anterior descending, proximal bifurcation, recurrent MIs, etc. (Class IIb, level of evidence B).

(vii) 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) (Class IIb, level of evidence C).

Primary PCI

(i) In the acute setting, a patient with AF and STEMI may be treated with primary PCI, aspirin, clopidogrel, and heparin (UFH) or bivalirudin, while GP IIb/IIIa inhibitors in bailout situations might be useful in some cases. Given the risk of bleeding with such combination antithrombotic therapies, it may sometimes be prudent to temporarily stop OAC therapy. Regular or even 'routine' use of GP IIb/IIIa inhibitors is discouraged, as are the novel $P2Y_{12}$ inhibitors (Class IIb, level of evidence B).

(ii) In the setting of STEMI, radial access for primary PCI is the best option to avoid procedural bleeding depending on operator expertise and preference (Class I, level of evidence A).

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

(a) In selected patients with STEMI and a CHA_2DS_2-VASc score ≥ 2 at low risk of bleeding (HAS-BLED 0–2), continuation of triple therapy or dual antiplatelet therapy consisting of OAC (i.e. whether NOAC or a VKA) and clopidogrel 75 mg/day may be considered (Class IIb, level of evidence C) between 6 and 12 months.

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

(a) As an alternative to the initial triple therapy in selected patients at high risk of bleeding (e.g. HAS-BLED ≥ 3) and low risk of stent thrombosis/recurrent ischaemic events, dual therapy consisting of OAC and clopidogrel 75 mg/day may be considered (Class IIb, level of evidence B).

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(v) Long-term antithrombotic therapy (beyond 12 months) is recommended with OAC in all patients (Class I, level of evidence B).

(a) Combination OAC plus single antiplatelet therapy (preferably clopidogrel 75 mg/day, or as an alternative, aspirin 75–100 mg/day) may sometimes be continued in very selected cases, e.g. stenting of the left main, proximal bifurcation, recurrent MIs, etc. (Class IIb, level of evidence B).

(vi) The routine use of ticagrelor or prasugrel in combination with OAC is not recommended (Class III, level of evidence B).

(a) The use of ticagrelor or prasugrel in combination with OAC may only be considered under very circumstances (e.g. definite stent thrombosis while on clopidogrel, aspirin, and OAC) (Class IIb, level of evidence C).

Application to general anticoagulated patients, who may or may not have AF

The recommendations for non-valvular AF patients largely apply to 'general' anticoagulated populations, with some notable exceptions.

(i) Where patients have AF and a prosthetic mechanical heart valve, such patients would be at substantial risk of thromboembolism and/or prosthetic valve thrombosis during interruption of anticoagulation using a VKA. These patients should undergo percutaneous procedures during anticoagulation with VKA with the lowest possible median INR within the therapeutic range based on risk factors and prosthesis thrombogenicity (Class IIa, level of evidence B).

(ii) NOACs must not be used in patients with mechanical heart valves or valvular atrial fibrillation (Class III, level of evidence B).

(iii) Patients with recent (3–6 months) or recurrent venous thrombo-embolism are at risk of recurrent events if anticoagulation is interrupted. Arterial access via the radial route should be preferred in such patients, especially during therapeutic anticoagulation (VKA, with INR 2–3; or NOACs) depending on operator expertise (Class IIa Level of Evidence: C).

(iv) In patients with stable vascular disease (e.g. with no acute ischaemic events or PCI/stent procedure in the preceding 1 year), OAC monotherapy (well-controlled VKA or a NOAC) should be used, and concomitant antiplatelet therapy should not be prescribed on a routine basis (Class IIa, Level of Evidence: B).

(a) Combination of OAC plus single antiplatelet therapy (preferably clopidogrel 75 mg/day, or as an alternative, aspirin 75–100 mg/day) may be sometimes continued in very selected cases, e.g. stenting of the left main, proximal left anterior descending, proximal bifurcation, recurrent MIs, etc. (Class IIb, level of evidence B).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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