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REVIEW

Novel therapeutic concepts

Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting: executive summary—a Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI)

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There remains uncertainty over optimal antithrombotic management strategy for patients with atrial fibrillation (AF) presenting with an acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting. Clinicians need to balance the risk of stroke and thromboembolism against the risk of recurrent cardiac ischaemia and/or stent thrombosis and the risk of bleeding. The full consensus document comprehensively reviews the published evidence and presents a consensus statement on a 'best practice' antithrombotic therapy guideline for the management of antithrombotic therapy in such AF patients. This executive summary highlights the main recommendations from the consensus document.

Keywords Atrial fibrillation • Antithrombotic therapy • Acute coronary syndrome • Percutaneous coronary intervention • Stenting • Warfarin

Preamble

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia, with a substantial risk of mortality and morbidity from stroke and thromboembolism. Antithrombotic therapy is central to the management of AF patients, with oral anticoagulation (OAC) with the vitamin K antagonists being recommended as

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thromboprophylaxis in patients with AF at moderate–high risk of thromboembolism.[1] Approximately 70–80% of all patients in AF have an indication for continuous OAC, and coronary artery disease co-exists in 20–30% of these patients.[2,3] With an estimated prevalence of AF in 1–2% of the population,[4] one to two million anticoagulated patients in Europe are candidates for coronary revascularization, often in the form of percutaneous coronary interventions (PCI), usually including stents.

The long-term results of stent usage have been blighted by the dual problem of in stent restenosis (ISR) and stent thrombosis. In particular, the increasing use of drug-eluting stents (DES) to minimize ISR necessitates long-term dual antiplatelet therapy with aspirin plus a thienopyridine (at present most frequently clopidogrel) to reduce the risk of early and late stent thrombosis. Combined aspirin–clopidogrel therapy, however, is less effective in preventing stroke compared with OAC alone[5]—although a *post hoc* retrospective analysis suggests that this may be dependant upon quality of INR control[6]—and OAC alone is insufficient to prevent stent thrombosis.[6–9] The management of AF patients presenting with an acute coronary syndrome (ACS) poses similar management complexities. Acute coronary syndrome patients presenting with acute ST-elevation myocardial infarction (STEMI) are increasingly managed with primary PCI with additional combined antithrombotic therapy regimes. Those presenting with non-ST-elevation acute myocardial infarction (NSTEMI) are also managed with combined antithrombotic therapy, and frequently an early invasive revascularization strategy is recommended by guidelines and more commonly used. Current guidelines for ACS and/or PCI broadly recommend the use of aspirin–clopidogrel combination therapy after ACS (12 months irrespective of PCI) and after a stent [4 weeks for a bare metal stent (BMS), up to 12 months for a DES].[8,9] Clearly, in subjects with AF at moderate–high risk of stroke (essentially $CHADS_2$ score of 0 = low risk, 1 = medium risk, >1 = high risk, *vide infra* for acronym), where there is the requirement for long-term OAC, there is the need to balance stroke prevention against stent thrombosis following PCI stenting vs. the harm of bleeding with combination antithrombotic therapy. Thus, in AF patients who present acutely with an ACS—as well as those who undergo elective PCI stenting—who are already on OAC, the management now would in theory lead to so-called 'triple (oral) therapy' consisting of dual oral antiplatelet agents plus OAC, with the potential harm of bleeding. It has to be stated clearly that the use of DES of first and second generation, due to the prolonged need of dual antiplatelet therapy, should be avoided in patients with an indication for long-term OAC. Unfortunately, this situation is not always known when stents are implanted or might become evident after stent implantation.

Moreover, there is a lack of published evidence on what is the optimal management strategy in such AF patients. Current published clinical guidelines on antithrombotic therapy use in AF and PCI do not adequately address this issue.[8–14] In recognizing this deficiency, the Working Group on Thrombosis of the European Society of Cardiology (ESC) convened a Task Force, with representation from the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) with the remit to comprehensively review the published evidence and to publish a consensus statement on a 'best practice' guideline for the management of antithrombotic therapy in AF patients presenting with ACS and/or undergoing PCI stenting. The Task Force was charged with the task of performing an assessment of the evidence and acting as an independent group of authors to develop or update written recommendations for clinical practice.

This consensus document is intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for management, and reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence with the aim of improving patient care. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and the patient in light of all of the circumstances presented by that patient.

The full consensus document—that includes a systematic review of the published literature—has been published in *Thrombosis and Haemostasis*, the official journal of the Working Group on Thrombosis.[15] Recommendations in this consensus document are evidence-based and derived primarily from published data. In the majority of cases, these recommendations represent level of evidence C due to lack of prospective randomized studies and/or registries. The present article represents an executive summary of the main points debated and the recommendations from this consensus document.

Periprocedural issues

It is estimated that ~5% of patients undergoing PCI require long-term OAC due to AF.[16,17] Accordingly, patients with ACS and on home warfarin are significantly less likely to undergo coronary angiography and PCI and their waiting times for these procedures are longer than in patients not on warfarin.[16] The general perception that warfarin should be discontinued a few days prior to PCI and the periprocedural INR level should fall below therapeutic range (<2.0) may contribute to these delays.

A simple strategy of temporary replacement of warfarin by dual antiplatelet drug therapy is not a good option, as shown by more adverse events in recent observational studies on coronary stenting.[18,19] This view is supported by data showing that non-use of OAC markedly increases mortality in patients with AF after acute myocardial infarction.[20–22] Another potential strategy is a temporary adjustment of warfarin dosing to reach a perioperative INR of 1.5–2.0. The latter has been shown to be safe and effective in the prevention of thromboembolism after orthopaedic surgery, but the low INR level is inadequate for PCI or stroke prevention in AF.[1,23]

Current guidelines recommend bridging therapy with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) to cover the temporary discontinuation of OAC, if the risk of thromboembolism is considered high.[8] These recommendations are based on circumstantial evidence and there are no large randomized trials to support the recommendations. The specific problems and advantages/disadvantages of bridging with LMWH and UFH are beyond the scope of this executive summary, but have been discussed in the full version of this consensus document[15] and other expert consensus documents.[24] Indeed, there are no randomized trials comparing different strategies to manage long-term OAC during PCI. Reports focusing on PCI are limited, but MacDonald *et al.*[25] reported that 4.2% of 119 patients developed

enoxaparin-associated access site complications during LMWH bridging therapy after cardiac catheterization.

Supporting this view, recent findings suggest that uninterrupted anticoagulation with warfarin could replace heparin bridging in catheter interventions with a favourable balance between bleeding and thrombotic complications.[26–30] In these studies, this simple strategy was at least as safe as that of more complicated bridging therapy. The incidence of bleeding or thrombotic complications was not related to periprocedural INR levels, and propensity score analyses suggested that the bridging therapy may lead to increased risk of access site complications after PCI.[27] Similarly, therapeutic (INR 2.1–4.8) periprocedural warfarin led to the lowest event rate with no increase in bleeding events in 530 patients undergoing balloon angioplasty through the femoral route.[31] In line with these PCI studies, no major bleeding events were observed in patients randomized to therapeutic periprocedural warfarin in a small study of diagnostic coronary angiography, although all procedures were performed using transfemoral access. Of importance, a median of 9 days was required for INR to return to the therapeutic level in the patients where warfarin was stopped.[32]

Performing PCI without interrupting warfarin has several theoretical advantages. Wide fluctuations in INR are known to be common and long lasting after interruption necessitating prolonged bridging therapy. Secondly, warfarin re-initiation may cause a transient prothrombotic state due to protein C and S suppression.[33] The fear for fatal bleedings with uninterrupted OAC may also be overemphasized, since the anticoagulant effect of warfarin can be rapidly overcome by a combination of activated blood clotting factors II, VII, IX, and X or by fresh frozen plasma. Finally, interruption of OAC only seems to be mandatory in coronary procedures with a relatively high risk for perforation, e.g. the more aggressive interventional treatment of chronic total occlusions.[30]

In the light of limited data, the simple strategy of uninterrupted OAC treatment is an alternative to bridging therapy and may be most useful for the patients with high risk of thrombotic and thrombo-embolic complications, since OAC cessation and re-initiation may cause a transient prothrombotic state. If this strategy is chosen, radial access is recommended in all patients to decrease the rate of procedural bleedings. Furthermore, in planned or non-urgent procedures and when patients have a therapeutic OAC (INR 2–3), the additional use of UFH is not necessary and might potentially trigger bleeding complications. This is different in patients with acute STEMI, when INR is frequently not known: in this situation, regardless of INR values, UFH should be added in moderate doses (e.g. 30–50 U/kg).[31]

Aspirin and clopidogrel

Aspirin reduces periprocedural ischaemic complications and should be administered in all patients prior to any PCI procedures. On the basis of randomized trials and *post hoc* analyses, pretreatment with clopidogrel is also recommended whenever it can be accomplished.[12] Even if there are no randomized trials on the efficacy and safety of this antiplatelet policy in patients on OAC, analyses from retrospective studies also support this recommendation in this patient group.[7]

Glycoprotein IIb/IIIa inhibitors

There is a modest increase (2.4 vs. 1.4%) in bleeding risk associated with glycoprotein IIb/IIIa inhibitor (GPI) use during ACS.[34] There are no safety data from clinical trials on warfarin-treated patients, since this patient group has been excluded from all randomized GPI studies. In 'real world' clinical practice, warfarin-treated patients are less often treated with GPI drugs. In recent PCI studies, the GPI use was associated with a 3–13-fold risk of early major bleeding in warfarin-treated patients.[26,27,35] In general, GPIs seem to increase major bleeding events irrespective of periprocedural INR levels and should be used with some caution in this patient group and probably avoided if use is not indicated due to massive intraluminal thrombi. Furthermore, GPIs add little benefit in terms of reduction of ischaemic events in patients with stable angina and troponin-negative ACS.[36,37]

Bivalirudin

Increasing data for the intravenous direct thrombin inhibitor, bivalirudin, are available in the setting of primary PCI and non-ST-elevation (NSTE) ACS,[38,39] with a similar incidence in MACE but lower bleeding events, when compared with heparin plus GPI. However, there are no published data on bivalirudin in AF patients, especially in the setting of concomitant anticoagulation with an OAC.

Access site

In addition to the choice of antithrombotic strategy, vascular access site selection may also have a great impact on bleeding complications. Radial artery access has been associated with a reduced risk of access site bleeding and other vascular complications in meta-analyses of randomized trials and registry studies.[40–43] In line with these reports, femoral access was an independent predictor (hazard ratio of 9.9) of access site complications in 523 warfarin-treated patients.[27] On the basis of current evidence, a radial approach should be always considered in anticoagulated patients, since haemostasis is rarely an issue with this access site.

Stent thrombosis

Early randomized trials showed that dual antiplatelet therapy is superior to the combination of aspirin and warfarin in the prevention of stent thrombosis.[7,44–46] In the ACS setting, it has been estimated that stent thrombosis can occur in 1 of 70 cases.[47]

Reports on the incidence of stent thrombosis in patients with AF are limited and the diagnostic criteria applied have varied, since uniform criteria have only recently been published.[48] Stent thrombosis seems to be rare in this patient group in real-life practice, especially with triple therapy.[20,21,49] However, a warfarin plus aspirin regimen seems to be suboptimal in the prevention of myocardial infarction.[20,21] A trend towards worse outcomes was observed in patients with AF receiving warfarin and a single antiplatelet agent.[49]

At present, in patients on OAC therapy, the additional use of dual antiplatelet therapy (triple therapy) seems to be the best option to prevent stent thrombosis and thromboembolism. Data on the safety of warfarin plus clopidogrel combination are limited, but this combination may be an alternative in patients with high bleeding risk and/or absent risk factors for stent thrombosis.[49] In patients with very high bleeding risk, DES should be

avoided[50] and balloon angioplasty (without stenting) is an option if an acceptable result can be achieved. In this case, OAC might be combined with aspirin or a thienopyridine ADP receptor antagonist in the usual dose. If, however, a stent is needed, bare metal stents (BMS), especially 'less thrombogenic stents' (carbon- or titanium-nitride-oxide-coated stents, stents with biodegradable coating, or antibody-coated stents capturing endothelial progenitor cells) may perhaps need a shorter duration of combination antiplatelet therapy.[51–54]

Stroke

The ACTIVE-W trial[6] showed that dual antiplatelet therapy cannot replace OAC in stroke prevention in patients with AF and recent observational studies on clinical practice support this conclusion also after coronary stenting.[20,21] The incidence of stroke has rarely been reported in these studies, but triple therapy has generally been more effective than both dual antiplatelet treatment and the combination of OAC and a single antiplatelet agent.[18,20,21,50]

With triple therapy, thrombo-embolic events are infrequent,[18] although a much higher incidence (15.2%) has been reported in patients while on treatment with the combination of warfarin and aspirin.[18,21] Interestingly, the ACTIVE-A trial that studied aspirin–clopidogrel combination vs. aspirin alone for stroke prevention in moderate–high risk patients with AF for whom OAC therapy was unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events by 11%, especially stroke (by 28%), but increased the risk of major haemorrhage by 54%.[55]

Bleeding risk

The annual risk of haemorrhagic stroke or of other major bleeds among 'real world' AF patients taking OAC who attend anticoagulation management services is estimated around 3%.[56,57] Elderly non-valvular AF patients (≥75 years) who are able to comply to oral anticoagulant therapy appear to benefit significantly from moderate-intensity OAC compared with aspirin alone, with an annual risk of any stroke or of arterial embolism of 1.8 vs. 3.8%, and without an increase in major bleeding events.[58]

Overall, the annual frequency of major bleeding ranges from 2 to 15% across the spectrum of ACS and depends greatly on the type of antithrombotic treatment and use of invasive procedures. The widely accepted predictors of major bleedings include advanced age, female gender, history of bleeding, use of PCI, renal insufficiency, and use of GPIs.[59,60] Excessive doses of antithrombotic drugs especially in elderly female patients and those with renal failure increase the risk of bleeding events. There are no studies specifically focusing on the risk prediction of bleeding events in AF patients with ACS or undergoing PCI, but the in-hospital incidence of major bleeds, among contemporary 'real life' ACS patients without AF ranges from 4–6% up to 9%.[17,50,61]

In patients with high bleeding risk the duration of dual antiplatelet therapy should be minimized by avoiding DES or at least strictly limiting DES to those clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc. where a significant benefit is expected when compared with BMS. Sometimes even the plain old balloon angioplasty should be considered when the angiographic result after balloon angioplasty is acceptable and in some cases also coronary artery bypass graft (CABG) might be favoured over PCI. In patients under 'triple' therapy, bleeding rates are lowest when INR is frequently controlled and targeted close to the lower limit of efficacy (2.0–2.5).[16,62] To avoid gastrointestinal bleeding due to this combination therapy gastric protection with proton pump inhibitors (PPIs) is considered useful during triple therapy.[63] A potential attenuation by PPIs of the clopidogrel effect on platelet inhibition has been reported recently. However, such an inhibitory effect on clopidogrel action by different PPIs (mainly omeprazole), which has been demonstrated by the use of *ex vivo* platelet function assays or retrospective analyses of registries[64–67] had no impact on clinical outcome in a *post hoc* analysis of a prospective ACS trial[68] and the first prospective trial randomized for the use or non-use of omeprazole,[69] and seems, therefore, clinically irrelevant. If patients are prone to develop gastrointestinal bleeding complications (elderly, patients with a history of ulcer disease or prior gastrointestinal bleeding) gastric protection is indicated[63] and can be performed by the use of any PPI. Major bleeding events should be treated aggressively, but inadvertent stopping of antithrombotic treatment due to minor bleeding events is not wise (*Table 1*). Stroke risk factors are listed in *Table 1*, which also shows similarities to many risk factors for bleeding.[70]

What to do if patients need CABG or staged percutaneous coronary intervention procedures?

There is only limited experience on CABG during therapeutic OAC or timing of cessation of OAC before surgery. In the light of this limited information, bridging therapy with LMWHs or UFH is recommended for AF patients under long-term OAC referred for CABG.[14,71] However, a clear protocol for warfarin cessation and bridging for cardiac surgery is lacking. It is possible that poorly managed warfarin cessation can increase bleeding after coronary bypass surgery, since preoperative warfarin use has been cited as a risk factor for increased post-operative haemorrhage if warfarin is stopped within 7 days before surgery.[71]

Elective or urgent CABG is frequently performed in patients on dual antiplatelet therapy due to previous PCI or in patients with ACS. Perioperative management of antiplatelet therapy is problematic in view of the long elimination time required for the antiplatelet effect and individualized balancing between the increased perioperative bleeding risks and proven antithrombotic benefits caused by the drugs should be undertaken. In the CURE trial analyses, exposure to clopidogrel within 5 days before CABG increased the risk of major bleeding 50% and later retrospective analyses have shown the risk to be comparable even when using off-pump surgery.[72] Later retrospective analyses have, however, suggested that CABG during dual antiplatelet therapy is safer than previously thought and in a recent large single-centre cohort clopidogrel stopped within 5 days before CABG did not increase the risk of reoperation, blood transfusion, or haematocrit drop ≥15%.[73] In view of this limited information, aspirin is recommended to be continued throughout the perioperative period in patients who require CABG within 6 weeks after placement of BMS and within 6–12 months after DES implantation even in patients on OAC. In patients scheduled for elective CABG, it is common policy to interrupt clopidogrel at least 5 days before CABG, unless the risk of interruption is deemed unacceptably high. In patients with ACS, the risks of delaying the surgery and withdrawing the evidence-based antiplatelet therapy should be

Table 1 Clinical factors associated with an increased risk for stroke/thromboembolism and an increased risk of severe bleeding in atrial fibrillation patients

Risk factors for thromboembolism	Bleeding risk factors
Previous stroke, transient ischaemic attack, or embolism	Cerebrovascular disease
Age ≥ 75 years (Age 65–74 years)	Advanced age (>75 years)
Heart failure or moderate–severe left ventricular dysfunction on echocardiography (e.g. ejection fraction ≤40%)	History of myocardial infarction or ischaemic heart disease
(Vascular disease)	
Hypertension	Uncontrolled hypertension
Diabetes mellitus	(Female gender)
(Female gender)	(Low body weight)
Mitral stenosis prosthetic heart valve	
	Anaemia
[Renal dysfunction (stage III–V)]	[Renal dysfunction (stage III–V)]
	History of bleeding
	Concomitant use of other antithrombotic substances such as anti-platelet agents

Note that most factors pose patients at risk for both types of events. In AF patients in general, thrombo-embolic events (strokes) are approximately one magnitude more likely than severe bleeds. Less validated factors are given in brackets. Adapted from Kirchoff *et al.*, *Europace* 2009;**11**:860–885.[70] TIA, transient ischaemic attack; TE, thromboembolism; GI, gastrointestinal; MI, myocardial infarction; LVEF, left ventricular ejection fraction.

balanced against the bleeding risks of ongoing dual antiplatelet therapy during CABG. In case of emergent CABG in ACS while anticoagulated with OAC, fresh frozen plasma and vitamin K administration might be needed before CABG to reverse anticoagulation and UFH started. During revascularization by CABG, the opportunity to treat AF by surgical measures (e.g. occlusion of left atrial appendage or surgical ablation by Cox-Maze or radical Maze) during the surgical procedure might be considered.

Staged PCI is not an issue when the procedures are performed during uninterrupted therapeutic OAC. Repeated bridging therapy during staged operations is likely to lead to instability in the effective anticoagulation level. Hence, the preferential strategy is probably the uninterrupted strategy. Therefore, in the case of staged procedure, each procedure will be performed while being anticoagulated with an OAC.

Systematic review of published data on anticoagulated atrial fibrillation patients with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting

A systematic review of published data on patients undergoing PCI who are either on OAC or have AF was performed as part of this consensus document with full details available in the full version.[15] The following factors were associated with increased bleeding risk in at least one of the published series on PCI in OAC patients.[16, 74–81]

- 'Triple therapy' using an oral anticoagulant and dual platelet inhibition (most often aspirin and clopidogrel, in the earlier studies also aspirin plus ticlopidine).
- OAC when compared with non-anticoagulated patients
- Use of a GPIIb/IIIa inhibitor
- Left main or three-vessel disease
- Older age (e.g. >75 years)
- Female gender
- Smoking
- Chronic kidney disease
- A high INR value (>2.6).

In addition, radial access was associated with less access site bleeding events in a recent cohort study of PCI 'all-comers'.[40] Interestingly, femoral closure devices were not well associated with reduced bleeding events: of the devices used, only one (a fibrin plug) appeared to reduce access site bleeding.[40–43] An earlier meta-analysis of femoral closure devices suggested no prevention of access site bleeding with one device and even an increase of bleeding events with another (older) device.[82]

Expert consensus recommendations of a practical, pragmatic approach to management of patients with atrial fibrillation who need anticoagulation with vitamin K antagonists

Elective

(i) In elective PCI, DES should be avoided or strictly limited to those clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc. (*Table 2*), where a significant benefit is expected when compared with BMS; triple therapy

Table 2 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	Clinical setting	Stent implanted	Recommendations
Low or intermediate	Elective	Bare metal	1 month: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Lifelong: warfarin (INR 2.0–3.0) alone
	Elective	Drug eluting	3 (-olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)[a]
			Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	Bare metal/drug eluting	6 months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)[a]
			Lifelong: warfarin (INR 2.0–3.0) alone
High	Elective	Bare metal[b]	2–4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	Bare metal[b]	4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day); mg/day);[a]
			Lifelong: warfarin (INR 2.0–3.0) alone

INR, international normalized ratio; ACS, acute coronary syndrome.
[a]Combination of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day may be considered as an alternative.
[b]Drug-eluting stents should be avoided.

(OAC, aspirin, clopidogrel) should be used for 4 weeks following PCI with BMS in patients with AF and stable coronary artery disease; this should be followed by long-term therapy (12 months) with OAC plus clopidogrel 75 mg daily (or alternatively aspirin 75–100 mg daily, plus gastric protection with a PPI, depending on the bleeding and thrombotic risks of the individual patient) (Class IIa, level of evidence: B).

(ii) Clopidogrel 75 mg daily should be given in combination with OAC plus aspirin 75–100 mg daily for a minimum of 1 month after implantation of a BMS, but longer with a DES [at least 3 months for a '-limus' (sirolimus, everolimus, and tacrolimus) type eluting stent and at least 6 months for a paclitaxel-eluting stent] following which OAC and clopidogrel 75 mg daily (or alternatively aspirin 75–100 mg daily, plus gastric protection with a PPI) may be continued (Class IIa, level of evidence: C).

(iii) Where OAC patients are at moderate–high risk of thromboembolism, an uninterrupted anticoagulation strategy can be the preferred strategy and radial access used as the first choice even during therapeutic anticoagulation (INR 2–3). This strategy might reduce periprocedural bleeding and thrombo-embolic events during bridging therapy (Class IIa, level of evidence: C).

(iv) When the procedures require interruption of OAC for longer than 48 h in high thrombo-embolic risk patients, unfractionated heparin may be administered. Low molecular weight heparin (enoxaparin, dalteparin) given by subcutaneous injection is an alternative, although the efficacy of this strategy in this situation is uncertain. There may actually be an excess bleeding risk associated with such 'bridging' therapies, possibly due to dual modes of anticoagulation in the overlap periods. In many patients, performing PCI after a short interruption of OAC (e.g. at an INR close to the lower border of the therapeutic range) will be adequate. (Class IIa, level of evidence: C).

(v) When OAC is given in combination with clopidogrel and/or low-dose aspirin, the dose intensity must be carefully regulated, with a target INR of 2.0–2.5. (Class IIa, level of evidence: C).

NSTE-ACS including unstable angina and non-ST-elevation acute myocardial infarction

(i) Following presentation with a non-ST segment elevation acute coronary syndrome (NSTE-ACS) with or without PCI in patients with AF, dual antiplatelet therapy with aspirin plus clopidogrel is recommended, but in an AF patient at moderate–high risk of stroke, anticoagulation therapy should also be given/continued (Class IIa, level of evidence: B).

(ii) In the acute setting, patients are often given aspirin, clopidogrel, heparin (whether UFH or an LMWH, enoxaparin) or

bivalirudin and/or a GPI. Given the risk of bleeding with such combination antithrombotic therapies, it may be prudent to stop OAC therapy, and administer antithrombins or GPIs only if INR ≤ 2. Many such patients will undergo cardiac catheterization and/or PCI stenting, and DES should be avoided or be strictly limited to those clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc. where a significant benefit is expected when compared with BMS. However, in anticoagulated patients at very high risk of thromboembolism, uninterrupted strategy of OAC can be the preferred strategy and radial access used as the first choice even during therapeutic anticoagulation (INR 2–3). This strategy might reduce periprocedural bleeding and thrombo-embolic events during bridging therapy (Class IIa, level of evidence: C).

(iii) For medium to chronic management, triple therapy (OAC, aspirin, clopidogrel) should be used in the short term (3–6 months) or longer in selected patients at low bleeding risk. In patients with a high risk of cardiovascular (thrombotic) complications (e.g. patients carrying a high GRACE or TIMI risk score), long-term therapy with OAC may be combined with clopidogrel 75 mg daily (or alternatively, aspirin 75–100 mg daily, plus gastric protection with either PPIs, H2 antagonists, or antacids) for 12 months (Class IIa, level of evidence: C).

(iv) When OAC is given in combination with clopidogrel and/or low-dose aspirin, the dose intensity must be carefully regulated, with a target INR of 2.0–2.5 (Class IIa, level of evidence: C).

Primary percutaneous coronary intervention

(i) In the setting of acute STEMI with primary PCI and AF, patients are often given aspirin, clopidogrel, and heparin (UFH). Where patients have a high thrombus load, GPIs (preferably abciximab) may be given as a 'bail out' option. As an alternative to heparin plus GPI, bivalirudin might be used. Mechanical thrombus removal (e.g. thrombus aspiration) is encouraged. Given the risk of bleeding with such combination antithrombotic therapies, it may be prudent to stop OAC therapy. Ideally, GPIs, or bivalirudin, would not be considered if INR is >2, except in a 'bail out' option (Class IIa, level of evidence: C).

(ii) The dose of periprocedural heparin may be adjusted to achieve a low-therapeutic activated clotting time (ACT 200–250 s in patients receiving a GPI, or 250–300 s in patients not receiving a GPI), where available (Class IIa, level of evidence: C).

(iii) If the presentation with acute STEMI occurs, radial access for primary PCI is probably the best option to avoid procedural bleeding depending on operator expertise and preference (Class IIa, level of evidence: B).

(iv) For medium to long-term management, triple therapy (OAC, aspirin, clopidogrel) should be used in the short term (3–6 months) or longer in selected patients at low bleeding risk, followed by more long-term therapy (up to 12 months) with OAC plus clopidogrel 75 mg daily (or alternatively, aspirin 75–100 mg daily, plus gastric protection with a PPI) (Class IIa, level of evidence: C).

What to do in patients at high risk of bleeding

(i) Arterial access via the radial route should be used especially during therapeutic anticoagulation (INR 2–3). Fondaparinux is an alternative to enoxaparin (in NSTE-ACS, but not for STEMI) but limited data are available in anticoagulated patients.

(ii) Bivalirudin is an alternative to heparin plus GPIs peri-PCI, but there are no available data in anticoagulated patients.

(iii) Medium- to long-term triple therapy should be avoided, and the use of DES strictly limited to those clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc. where a significant benefit is expected when compared with BMS. After BMS, triple therapy should be used for 2–4 weeks, followed by OAC monotherapy. After DES, triple therapy is currently recommended for 3–6 months, followed by OAC monotherapy, depending on the stent type used. Second and third generation DES might possibly be associated with shorter re-endothelialization times and therefore less extended need for triple therapy. In selected patients at high risk for cardiovascular events, clopidogrel 75 mg/day may be added to OAC despite a higher bleeding risk of the anticoagulant-clopidogrel combination.

Application to non-atrial fibrillation populations (general anticoagulated populations)

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. These patients should undergo percutaneous procedures during anticoagulation in the low therapeutic range (Class IIa, level of evidence: C).

(ii) Similarly, patients with recent (3–6 months) or recurrent venous thromboembolism would be at risk of recurrent events should anticoagulation be interrupted. Arterial access via the radial route has to be preferred in such patients, especially during therapeutic anticoagulation (INR 2–3) depending on operator expertise and preference (Class IIa, level of evidence: C).

(iii) Medium- to long-term management would be as described above, for elective and acute settings.

Miscellaneous

(i) In patients with stable vascular disease (e.g. with no acute ischaemic events or PCI/stent procedure in the preceding 1 year), OAC monotherapy should be considered and concomitant antiplatelet therapy may not be prescribed (Class IIa, level of evidence: B).

(ii) In patients with AF younger than 65 years without heart disease or risk factors for thromboembolism (essentially lone AF, $CHADS_2$ score = 0), the risk of thromboembolism is low without treatment and the effectiveness of aspirin for primary prevention of stroke relative to the risk of bleeding has not been established. Thus, such patients would not need OAC therapy, and management for elective PCI stenting can follow routine management strategies (Class IIa, level of evidence: B).

(iii) Following acute presentations with ACS, aspirin plus clopidogrel should be used for 12 months, irrespective of whether PCI stenting is performed, followed by single antiplatelet therapy with aspirin, as indicated by guidelines (Class IIa, level of evidence: C).

Areas for further studies

Current recommendations in this consensus document are largely based on limited evidence obtained from small, single-centre and retrospectively analyzed cohorts. Thus, there is a definite need for large scale registries and prospective clinical studies to determine the optimal antithrombotic management of patients with AF at intermediate or high thrombo-embolic risk undergoing coronary interventions. This scenario will also change with the availability of more potent antiplatelet agents (e.g. prasugrel, etc.) that in current ACS trials show improved efficacy but greater bleeding risk, when compared with clopidogrel.[83] However, data on prasugrel in anticoagulated patient populations are lacking. Post-hoc subgroup analyses from other ongoing stroke prevention trials with new oral anticoagulants (e.g. RELY, ROCKET-AF, ARISTOTLE, ENGAGE-AF TIMI48, etc) may possibly provide additional information given that some patients included within these studies may be taking aspirin (or have undergone PCI stenting).[83]

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