Consensus Document

Management of Antithrombotic Therapy in Atrial Fibrillation Patients Presenting With Acute Coronary Syndrome and/or Undergoing Percutaneous Coronary Intervention/ Stenting

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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Summary

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. This 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.

1. 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 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 es-

timated prevalence of AF in 1–2% of the population (4, 5), one to two million anticoagulated patients in Europe are candidates for coronary revascularisation, 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 minimise 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 to OAC alone (6) and OAC alone is insufficient to prevent stent thrombosis (7). The management of AF patients presenting with an acute coronary syndrome (ACS) poses similar management complexities. ACS 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 revascularisation 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, 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 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, versus 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 inhibition 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) (see Supplementary Table 1 available online at www.thrombosis-online.com).

In recognising 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 document on a 'best practice' antithrombotic therapy management guideline for 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.

The ESC Committee for Practice Guidelines have made every effort to avoid any actual, potential, or perceived conflict of interest that might arise as a result of an outside relationship or personal interest of the writing committee. Specifically, all members of the Writing Committee and peer reviewers of the document were asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. Writing committee members were also encouraged to declare a previous relationship with industry that might be perceived as relevant to guideline development.

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.

Literature searches were conducted in the following databases: PubMed/MEDLINE and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Registry). Searches focused on English-language sources and studies in human subjects. Articles related to animal experimentation were cited when the information was important to understanding pathophysiological concepts pertinent to patient management and comparable data were not available from human studies. Additional information was requested from the authors where necessary. Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA/ESC format as follows and described in Supplementary Table 2 (available online at www.thrombosis-online.com). 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 randomised studies and/or registries.

2. Overview of pathophysiology of thrombogenesis in AF and in ACS/PCI/stents as relevant to clinical observations

2.1. Thrombogenesis in AF in relation to stroke and other systemic thromboembolism

Subjects with non-valvular AF who are not receiving antithrombotic drugs have an annual rate of ischaemic stroke or other systemic thromboembolism (TE) of 5%, compared to 0.5–1% in age-matched controls without AF (1). The risk of TE with AF increases over five-fold in the presence of rheumatic heart disease, especially mitral valve stenosis. Rheumatic heart disease is observed in 15% of Western AF patients, but this is even a larger problem world-wide. Approximately one in three patients with AF not receiving anticoagulants will develop an ischaemic stroke in their lifetime, with roughly two-thirds being cardioembolic and one-third being atherothrombotic (1). Cardioembolic strokes are more disabling than atherothrombotic strokes, with a higher early mortality rate (1, 15).

The risk of TE is similar among subjects with paroxysmal, persistent or permanent AF, and is increased by the presence of clinical risk factors, especially where there is a history of prior stroke or mitral stenosis/prosthesis (1). The CHADS$_2$ score (**C**ongestive heart failure; **H**ypertension; **A**ge; **D**iabetes; previous ischemic **S**troke) is the simplest and most commonly used schema for predicting the risk of TE in patients with non-valvular AF, whereby patients with a score of ≥2 are 'high risk' and merit anticoagulation with warfarin (16) (see Table 1). Excellent overviews of stroke risk factors and published stroke risk stratifi-

Table 1: Clinical factors associated with an increased risk for stroke/thromboembolism and an increased risk of severe bleeding in AF patients. Note that most factors pose patients at risk for both types of events. In AF patients in general, thromboembolic 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. TIA transient ischaemic attack, TE thromboembolism, GI gastrointestinal, MI myocardial infarction, LVEF left ventricular ejection fraction.

Risk factors for thromboembolism	Bleeding risk factors
Previous stroke, transient ischemic attack, or embolism	Cerebrovascular disease,
Age =75 years (Age 65 to 74 y)	Advanced age (>75 years).
Heart failure or moderate-severe left ventricular dysfunction on echocardiography [eg. Ejection fraction =40%] (Vascular disease)	History of myocardial infarction or ischemic heart disease
Hypertension	Uncontrolled hypertension
Diabetes mellitus	?
(Female gender)	?
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 antiplatelet agents.

cation schemata have been published by the Stroke in AF Working Group (17, 18), as well as by the UK National Institute for Health and Clinical Excellence (NICE) (19). Risk factors for bleeding and bleeding risk assessment scores have also been recently reviewed (20, 21), but it is worth remembering that as stroke risk increases, bleeding risk also increases, often leading to discontinuation of OAC therapy (22).

Increasing evidence suggests that the thrombogenic tendency in AF is related to several underlying pathophysiological mechanisms, which can be discussed in relation to Virchow's triad for thrombogenesis (23). The type of thrombus in AF is mainly fibrin-rich where platelets play a smaller role, consistent with the superior prophylactic effect of OAC in comparison with antiplatelet therapy for stroke prevention in AF (1, 6, 23, 24).

'Abnormal changes in blood flow' are evident by stasis in the left atrium (LA), and seen as spontaneous echocontrast on transesophageal echocardiography (TEE). The loss of synchronous atrial systolic function, with sluggish/stagnant flow, results in stasis, mostly within the LA appendage. Indeed, residual thrombus within the LA appendage can be detected by TEE in over 40% of AF patients with acute TE (25). 'Abnormal changes in vessel wall' usually refer to underlying structural heart disease (which can be observed in about 70% of AF patients) that includes LA enlargement, poor systolic and/or diastolic left ventricular (LV) function, mitral annulus calcification, etc. Ultrastructurally, a 'prothrombotic' LA endocardial surface has been described, with endocardial denudation and oedematous/fibroelastic infiltration of the extracellular matrix (23, 26). Moreover, sources of TE other than the LA appendage (such as LA, LV, ascending aorta, carotid and intracerebral arteries) may exist in AF patients (23). There is also increased local expression in the dysfunctional atrial endocardium of prothrombotic molecules, such as tissue factor (27) and von Willebrand factor (VWF) (28). The third component of Virchow's triad, that is, 'abnormal changes in blood constituents' are well described, involving haemostasis and platelet activation, as well as fibrinolysis, inflammation and growth factors (23, 29–31). This triad of abnormalities increasing the propensity to thrombogenesis in AF has led to AF being described as a prothrombotic or hypercoagulable state, a concept first proposed in 1994 (32). Of note, many circulating prothrombotic biomarkers, including those related to inflammation, have prognostic implications in AF (33–35).

The relative role of coagulation versus platelet activation in the pathogenesis of TE in patients with AF can roughly be inferred from the results of antithrombotic drug interventions that have been tested in randomised clinical trials. Among non-valvular AF patients, the relative risk reduction (RRR) for stroke that is achieved with moderate intensity OAC [international normalised ratio (INR) = 2–3] compared to placebo is approximately 65%, as opposed to the 20% RRR achieved with aspirin versus placebo (1, 36). Consistently, moderate intensity OAC produces a RRR for stroke of 40% compared to aspirin, and of 30% compared to aspirin + clopidogrel (6, 36). Interestingly, among medium-high risk non-valvular AF patients not eligible to take warfarin, aspirin + clopidogrel was superior to aspirin alone for stroke prevention (37).

Taken together, these results indicate that inhibition of coagulation remains the mainstay in preventing AF-related TE. The lesser but significant role of platelets – best inhibited by a combined antiplatelet drug regimen – is presumably related to the prominent involvement of platelets in the pathogenesis of atherothrombotic (that is, non-cardioembolic) events.

Thrombogenesis in ACS/PCI/stenting

The ACS, which include unstable angina, NSTEMI and STEMI, share common pathophysiological processes that are characterised by coronary plaque disruption/erosion with superimposed thrombus formation, leading to myocardial ischaemia.

Patients with ACS at high risk of complications, especially those with STEMI and high-risk NSTEMI patients, derive significant benefit from urgent PCI, in terms of reduced major adverse cardiovascular events (MACE) (12). PCI with stenting requires not only dual antiplatelet therapy with aspirin and a thienopyridine ADP-receptor antagonist, but often an "upgraded" triple antiplatelet regimen in the periprocedural phase, through the administration of a glycoprotein IIb/IIIa antagonist. Moreover, in patients receiving DES, re-endothelialisation of the inner surface of stents is slow, which explains the longer need for combined antiplatelet therapy due to the pro-thrombogenic surface of non-reendothelised stents with DES versus bare metal stents (BMS).

Thrombogenesis in ACS/PCI-stenting

In most cases, ACS is ultimately brought about by localised damage of the endothelial surface of the coronary arteries, usually as a consequence of an underlying atherosclerotic lesion (38). In about 25% of cases the damage consists of a superficial erosion or denudation of the endothelial cells covering the atherosclerotic plaque, whereas in about 75% it is caused by plaque rupture. PCI results in additional 'trauma' to the vessel wall, that triggers local prothrombotic activation. The implantation of a stent to secure the initial dilatation and prevent restenosis gives rise to further (and often chronic) prothrombotic/proinflammatory reaction(s) towards this 'foreign substance' (39).

With the use of DES, covered with antiproliferative agents aimed at inhibiting restenosis but also delaying re-endothelialisation, this prothrombotic/proinflammatory activation will last for months and years and may contribute to stent thrombosis even after one year (40, 41). Chronic activation of coagulation may also be present, as microscopic examination has reported fibrin deposition at the stent ends (40, 41).

Prothrombotic/proinflammatory state in ACS/PCI-stenting

Under normal circumstances the endothelium is antithrombotic by expressing inhibitors of platelet activation, like nitric oxide (NO) and prostacyclin (PGI2), coagulation inhibitors, like tissue factor pathway inhibitor and heparan sulphate, in addition to tissue-type plasminogen activator promoting fibrinolysis. However, when superficial erosions occur, the endothelium is activated towards haemostasis, becoming pro-thrombotic with expression of VWF and plasminogen activator inhibitor-1, in addition to reduced expression of NO and PGI2 (38). This promotes platelet activation which in turn can activate coagulation on the platelet surface. When spontaneous or PCI-induced plaque rupture occurs, circulating blood gets in contact with the subendothelium and with constituents of the atherosclerotic plaque; thus, collagen will further increase the activation of platelets, and most importantly, tissue factor will be available for activation of coagulation (38). In a short time, a potentially occlusive thrombus may form (38).

The pathogenesis of coronary thrombosis amongst patients with coronary artery disease (CAD) and in those undergoing PCI is considered to be largely platelet driven. Indeed, antiplatelet therapy compared to placebo is effective in reducing the incidence of MACE in CAD (9, 14); also, PCI-related thrombosis is best prevented by a combination of antiplatelet drugs rather than by an antiplatelet drug combined with OAC (12, 42), and among ACS patients, aspirin + clopidogrel vs aspirin alone given for 9–12 months reduces the rate of MACE from 11% to 9%, while increasing major bleeds from 2.7% with aspirin alone to 3.7% with the dual antiplatelet drug regimen (42).

Yet, in men at high risk of cardiovascular disease (CVD) (43) and among patients with manifest CAD, the RRR of MACE with aspirin therapy alone is similar to that achieved with OAC alone (about 20%) (44). This suggests that the plaque rupture (that presumably triggers most spontaneous ACS) induces a thrombogenic state that involves both platelets and coagulation. Indeed, aspirin + OAC (whether warfarin or a direct thrombin inhibitor) are superior to aspirin alone in the management of ACS patients (44) and, in theory, both are not inferior to dual antiplatelet therapy (45). Additionally, procoagulant polymorphisms of the Factor II, Factor V and PAI-1 genes but none of the platelet gene polymorphism explored to date have shown significant associations with clinically manifest CAD (46).

Thromboembolic risk in stable and acute CAD, with and without PCI treatment

The annual rate of MACE during the first year after an ACS is in the order of 9–10%, with most events occurring in the first three months (47). The risk is considerably lower for patients with stable CAD, with an estimated 2% annual incidence of MACE (48). As mentioned above, PCI with stenting compared to balloon angioplasty alone has markedly reduced the rates of restenosis, but is associated with a risk of stent thrombosis. The latter has received special attention in virtue of its high associated mortality and morbidity (49). In randomised trials, the incidence of ACS attributable to definite, possible or probable stent thrombosis (using the Academic Research Consortium definitions [50]) is approximately 0.5–1% per year, for up to four years after PCI ("definite" = with angiographic or autopsy evidence; "probable" = related to stented vessel or to unexpected death within 30 days of PCI; "possible" = related to unexpected sudden death beyond 30 days of PCI) (51, 52).

Most stent thromboses occur early (<30 days) or very late (>1 year) (49–51). The incidence of early stent thrombosis (<30 days) is considerably increased among unstable ACS patients (1.4%) (53). With DES, compared to BMS, fewer thromboses are observed during first year but more are seen beyond one year after PCI (51, 52). Stopping treatment with a thienopyridine ADP-receptor antagonist causes a >10-fold increase of stent thrombosis (49). Recent data also show that polymorphisms in the cytochrome P450 gene, that regulates thienopyridines metabolic activation, are significantly linked with lower antiplatelet response to certain therapies and with an approximately threefold higher incidence of stent thrombosis (54). These observations make dual antiplatelet drug treatment mandatory for all contemporary PCI-treated patients, with durations ranging from four weeks for BMS up to one year or more for all DES.

3. Periprocedural issues

It is estimated that around 5% of patients undergoing PCI require long-term OAC due to AF (55–57). Accordingly, patients with ACS and on home warfarin are significantly less likely to under-

go coronary angiography and PCI and their waiting times for these procedures are longer than in patients not on warfarin (55). The general perception that warfarin should be discontinued a few days prior to PCI and the periprocedural INR level should be < 1.5–1.8 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 (57, 58). This view is supported by data showing that non-use of oral anticoagulation markedly increases mortality in patients with AF after acute myocardial infarction (59–61). 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, 62).

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 randomised trials to support the recommendations. Indeed, there are no randomised trials comparing different strategies to manage long-term OAC during PCI. The safety and feasibility of heparin bridging therapy has been evaluated in patients who receive long-term OAC and require interruption of OAC for elective surgery or an invasive procedure (63–67). Spyropoulos et al. (64) showed a major bleeding rate of 3.3% with UFH and 5.5% with LMWH in 901 patients with bridging therapy for an elective surgical or invasive procedure. Another recent study (65) reported a 6.7% incidence of major bleeding with LMWH bridging therapy in patients at risk of arterial embolism undergoing elective non-cardiac surgery or an invasive procedure, but also lower (2.9%) rates of major bleeding have been reported. Reports focusing on PCI are limited, but MacDonald et al. (68) reported that 4.2% of 119 patients developed enoxaparin-associated access site complications during LMWH bridging therapy after cardiac catheterisation. Thus, there is some suggestion that UFH is better than LMWH for bridging to manage OAC for PCI.

Patients undergoing PCI require procedural anticoagulation not only to avoid thromboembolic complications, but also thrombotic complications of the intervention, and only highly selected low-risk procedures may be safe without anticoagulation (69). Periprocedural anticoagulation has traditionally been performed with UFH or more recently with LMWHs or direct thrombin inhibitors. Theoretically, warfarin may also be used to facilitate PCI, since warfarin is known to increase activated coagulation time in a predictable fashion (70).

Supporting this view, recent findings suggest that uninterrupted anticoagulation with warfarin could replace heparin bridging in catheter interventions with a favorable balance between bleeding and thrombotic complications (71–75). 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 (72). 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 (76). In line with these PCI studies, no major bleeding events were observed in patients randomised 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 nine days was required for INR to return to the therapeutic level in the patients where warfarin was stopped (77).

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 (78). 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 (75).

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 thromboembolic 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) (76).

Aspirin and clopidogrel

Aspirin reduces periprocedural ischaemic complications and should be administered in all patients prior to any PCI procedures. Based on randomised trials and posthoc analyses, pretreatment with clopidogrel is also recommended whenever it can be accomplished (80). Even if there are no randomised 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 (57, 72).

Glycoprotein IIb/ IIIa inhibitors (GPI)

There is a modest increase (2.4% versus 1.4%) in bleeding risk associated with GPI use during ACS (81). There are no safety data from clinical trials on warfarin-treated patients, since this patient group has been excluded from all randomised GPIIb/IIIa studies.

In 'real-world' clinical practice, warfarin-treated patients are less often treated with GPIIb/IIIa drugs. Not surprisingly, bleeding complications seem to represent a significant limitation to the effectiveness of GPIs, as shown by the CRUSADE Registry (82). In the latter, GPI use was associated with increased in-hos-

pital risk of major bleeding (13.8% versus 9.0%) and transfusions (10.8% versus 9.1%) in the patients on home warfarin treatment even if only one third of the patients underwent PCI. In patients under OAC, the additional use of GPIs in the cath lab varies between 3% and 71% (57). In recent PCI studies, the GPI use was associated with a three- to 13-fold risk of early major bleeding in warfarin-treated patients (71, 72, 83). A recent analysis on 10 clinical trials assessing the efficacy and safety of various antithrombotic medications in ACS reported that new AF developed in 7% of the randomised patients during hospitalisation, and resulted in a four-fold increase in the incidence of moderate or severe bleeding in patients with NSTEMI, mainly randomised to GPI (84).

Thus, there is a wide variation in the use of GPIs in warfarin-treated AF patients in real-life setting. 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 (85, 86).

Bivalirudin

Increasing data for the intravenous direct thrombin inhibitor, bivalirudin, in the ACS setting are available in the setting of primary PCI and ACS (87, 88), with a similar reduction in MACE but lower bleeding events, when compared to heparin plus GPIIb/IIIa. However, there are limited data on bivalirudin in AF patients, especially in the setting of concomitant anticoagulation with a 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-analysis of randomised trials and registry studies (89–91). 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 (72).

Continuing randomised trials (CURRENT substudy and RIVAL) will ultimately give an answer to the selection of access site. In addition, vascular closure devices are an alternative to mechanical compression in order to achieve vascular haemostasis after femoral artery puncture, but the meta-analysis could not demonstrate significant effects on haemorrhagic or vascular complications (92). 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 randomised trials showed that dual antiplatelet therapy is superior to the combination of aspirin and warfarin in the prevention of stent thrombosis (7, 93, 94). In the STARS trial, the rate of stent thrombosis in these trials was unacceptably high without dual antiplatelet therapy (95). In the ACS setting, it has been estimated that stent thrombosis can occur in one out of 70 cases (96).

Reports on the incidence of stent thrombosis in patients with AF are scarce (54) and the diagnostic criteria have varied, since the uniform criteria has only recently been published (88). Stent thrombosis seems to be rare in this patient group in real-life practice, especially with triple therapy (59, 60, 97). However, a warfarin + aspirin regimen seems to be suboptimal in the prevention of myocardial infarction (60). A trend towards worse outcomes was observed in patients with AF receiving warfarin and a single antiplatelet agent (98). However, the small number of adverse events and limited information should be taken into account when considering these results.

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 + 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. In patients with very high bleeding risk, DES should be avoided (99) 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, BMS, especially "less thrombogenic stents" (carbon- or titanium-nitric-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 (100–103). In general, DES should be avoided in patients under OAC at present. However, new third generation DES seem to have accelerated re-endothelialisation and might therefore become of interest in the near future. Respective registries (e.g. the Italian MATRIX registry) and trials to test their usefulness are currently performed.

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 on coronary stenting (59, 60). 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 (57, 59, 60, 98).

With triple therapy, thromboembolic events are infrequent (57), although a much higher incidence (15.2%) has been reported in patients while on treatment with the combination of warfarin and aspirin (60). Interestingly, the ACTIVE-A trial which studied aspirin-clopidogrel combination therapy 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 (RR with clopidogrel, 0.89; 95%CI, 0.81–0.98; P=0.01), especially stroke (RR 0.72; 95%CI, 0.62–0.83; P<0.001), but increased the risk of major haemorrhage (RR 1.57; 95% CI, 1.29–1.92; P<0.001) (37). However, the definition of 'non suitable' also included patients who did not want to take OAC and doctors who did not want to put their patients on OAC although they would have had benefit from OAC therapy compared to dual antiplatelet therapy. Indeed, many patients legitimately judged not to be candidates

for warfarin therapy, will not have the same relative contraindication to warfarin a year later.

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% (20). 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 to aspirin alone, with an annual risk of any stroke or of arterial embolism of 1.8 versus 3.8%, and without an increase in major bleeding events (104).

Bleeding complications are the most frequent non-ischaemic complications in the management of ACS. Several definitions are used to grade the severity of bleeding events, which may render cross-comparisons between studies difficult. Overall, it is estimated that 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 incidence of bleeding events seems to be even higher in patients with AF and especially those treated with OAC.

The widely accepted predictors of major bleedings include advanced age, female gender, history of bleeding, use of PCI, renal insufficiency and use of GPIs (105). 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 on the basis of several registry studies it is conceivable the same risk factors are valid also in this patient group. The in-hospital incidence of major bleeds, including haemorrhagic stroke, among contemporary "real-life" ACS patients without AF ranks from 4–6% up to 9% (56, 98, 106).

Several bleeding scores have been developed and proposed in order to quantify the risk of bleeding in ACS patients (106). One of the best validated is that based on patient databases from the REPLACE-2 and REPLACE-1 trials (107). Another bleeding risk assessment is proposed according to the following criteria: creatinine clearance < 30 ml/min, history of prior bleeding, female gender, age >75, and (femoral versus radial) access site (108). The latter criterion has been chosen given the fact that >85% of major bleeds are related to catheterisation access site. High risk for bleeding has been defined as ≥2 the above criteria. An bleeding risk index for outpatients based on the same risk factors has been developed for the evaluation of long-term bleeding risk in warfarin treated patients, but it is not known whether this index is also useful for the patients with concomitant need for antiplatelet therapy (109).

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 as compared to 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 fa-

vorised 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 (110, 111). To avoid gastrointestinal bleeding due to this combination therapy gastric protection with proton pump inhibitors (PPIs) is considered useful during triple therapy (112). However, a potential attenuation of PPIs on the clopidogrel effect on platelet inhibition has been shown recently. Whether such an effect on clopidogrel action is due to all PPIs or mainly to omeprazole (113–116) is still matter of discussion and more data on this potential attenuation effect are awaited. If patients are prone to develop gastrointestinal bleeding complications (elderly, patients with a history of ulcer disease or prior gastrointestinal bleeding) at least omeprazole should be avoided and H2-receptor antagonists (e.g. ranitidine) or antacids should be used. Major bleeding events should be treated aggressively, but inadvertent stopping of antithrombotic treatment due to minor bleeding events is not wise.

What to do if patient needs CABG or staged PCI procedure?

There is only limited experience on CABG during therapeutic oral anticoagulation 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, 106). However, 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 postoperative haemorrhage if warfarin is stopped within seven days before surgery (117).

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 individualised balancing between the increased perioperative bleeding risks and proven antithrombotic benefits caused the drugs. In the CURE trial analyses, exposure to clopidogrel within five day before CABG increased the risk of major bleeding 50% and later retrospective analyses have shown the risk be comparable even when using off-pump surgery (42). 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 within five days before CABG did not increase the risk of reoperation, blood transfusion, or haematocrit drop ≥15% (118). In view of this limited information aspirin is recommended to be continued throughout the perioperative period in patients who require CABG within six weeks after stent 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 five days before CABG, unless the risk of interruption is deemed unacceptable high. In patients with ACS, the risks of delaying the surgery and withdrawing the evidence-based antiplatelet therapy should be balanced against the bleeding risks of ongoing dual antiplatelet therapy during CABG.

In case of emergent CABG in ACS whilst anticoagulated with OAC, fresh frozen plasma and vitamin K administration

might be needed before CABG to reverse anticoagulation, and UFH started. During revascularisation by CABG, the opportunity to treat AF by surgical measures (e.g. occlusion of left atrial appendix or surgical ablation by Cox-Maze or radical Maze) during the surgical procedure could be considered.

Staged PCI is not an issue when performing all the procedures 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 whilst being anticoagulated with an OAC.

4. Systematic review of published data on anticoagulated AF patients with ACS +/- undergoing PCI/stents

As part of the systematic review for this consensus document, we reviewed what other published guidelines have stated in relation to this topic. A summary of recommendations has been depicted in Supplementary Table 1 (available online at www.thrombosis-online.com).

4.1. Review of published data on patients undergoing PCI who are either on oral anticoagulation or have AF

In a systematic review of published data on patients undergoing PCI who are either on oral anticoagulation or have AF as part of this consensus document, we identified 18 studies that reported outcomes of anticoagulated and/or AF patients undergoing PCI (57, 60, 83, 97, 98, 99, 110, 119–127) (see Supplementary Tables 3 (a) and (b) available online at www.thrombosis-online.com). These reported on approximately 3,500 patients. The patients in some of the publications certainly overlap, so that the number of published patients is probably slightly lower. Most publications reported retrospective analyses of single-center consecutive patient series receiving PCIs in different settings. One report stratified patients to anticoagulation withdrawal or to continuation of anticoagulant therapy by the perceived need for anticoagulation based on prosthetic valves, recent presence of thrombus, recent pulmonary embolism, low ejection fraction or large atria, or prior stroke (127). The data are heterogeneous, and more so are the reporting of clinical parameters associated with thrombotic or bleeding events.

Reporting of potential factors involved in bleeding or thrombotic events during PCI

In a first step, we analysed the number of studies that reported several of the known factors associated with bleeding and/or thrombotic events. This analysis summarizes which factors were estimated as relevant by the investigators and authors, and by exclusion identifies factors that may be neglected by some. In descending order, the studies reported on the following known clinical factors associated with bleeding or thrombotic events: female sex (15/18 publications), presence of AF (15/18 publications), diabetes or hypertension and use of a stent (14/18 publications), prior stroke (9/18), renal dysfunction (6/18), and a history of bleeding events (3/18). In addition, the following procedural details potentially associated with bleeding or thrombotic events were reported: PCI in the setting of acute coronary syndrome (15/18), use of a GPI (12/18), no use of anticoagulation (12/18), use of DES (11/18), radial or femoral access site (7/18), and use of a closure device for femoral access patients (4/18 studies).

Factors associated with bleeding in published reports of PCI in OAC patients

The following factors were associated with increased bleeding risk in at least one of the published series on PCI in OAC patients.

– "Triple therapy" using an oral anticoagulant and dual platelet inhibition, most often aspirin and clopidogrel, in the earlier studies also aspirin plus ticlopidine (83, 97)
– oral anticoagulation when compared to non-anticoagulated patients (59)
– use of a GP IIb/IIIa inhibitor (83, 123),
– left main or three-vessel disease (83),
– older age (e.g. >75 years) (59),
– female gender (123),
– smoking (123),
– chronic kidney disease (83), and
– a high INR value (> 2.6) (123).

In addition, radial access was associated with less access site bleeding events in a recent cohort study of PCI "all-comers" (90). Interestingly, femoral closure devices were not well associated with reduced bleeding events: of the devices used in that study, only one (a fibrin plug) appeared to reduce access site bleeding (90). 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 (128).

Outcome of PCI in OAC or AF patients

Major long-term outcomes, usually assessed after one year or a few months of follow-up, were reported as follows: Death occurred in 12% of the patients, major bleeding events in 6%, stent thrombosis in 2%, stroke in 4%, myocardial infarction in 7% (nine studies). The combination of all MACE was only reported in five publications and is therefore not summarised in this analysis.

Event rates in trials that compared different antithrombotic regimes after stenting

We also assessed similar information in the main publications of four of the major early PCI trials in which the optimal antithrombotic therapy after PCI with stenting was investigated, often by comparing anticoagulation arms and/or patient arms without a thienopyridine (i.e. clopidogrel or ticlopidine) (7, 129–131). These trials reported on a total of 3,008 patients. The major outcomes of these trials and the patient characteristics are summarised in Table 2. The main outcome of these trials is that dual platelet inhibition is required to prevent stent thrombosis after PCI-stenting. In the context of this document, it is well worth noting that factors associated with bleeding were often not reported (Table 2). Also, major complication rates were lower in these trials, while reported bleeding rates were higher, albeit in the setting of a controlled clinical trial with rigorous follow-up.

Interestingly, the rate of major cardiovascular complications

and the rate of stent thrombosis was similar in these trials when compared to the MACE and stent thrombosis rate in published OAC-PCI cohorts. Similarly, and a bit surprisingly, the rate of major bleeding events was not that markedly elevated in the OAC patients when compared to the PCI study patients (Table 2). The rates of severe outcomes, namely stroke and death, in contrast, was markedly higher in the OAC patients than in the PCI study patients, again highlighting the relevance of thrombotic (rather than bleeding) events for survival in patients that require OAC.

5. Expert consensus recommendations of a practical, pragmatic approach to management of patients with AF who need anticoagulation with Vitamin K antagonists [Table 3]

5.1. 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. where a significant benefit is expected as compared to BMS and triple therapy (OAC, aspirin, clopidogrel) used for four 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 either PPIs, H2-receptor antagonists or antacids 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 one month after implantation of a BMS, but longer with a DES [at least three months for a '-limus' (sirolimus, everolimus and tacrolimus) type eluting stent and at least six 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 either PPIs, H2-receptor antagonists or antacids may be continued (Class IIa Level of Evidence: C).

Table 2: Summary of the published clinical, procedural and outcome information on anticoagulated patients or AF patients undergoing PCI. For abbreviations, see text. For comparison, the same information – if available – is also given from four major PCI studies that included an OAC arm. Bold numbers indicate that there is a relevant numerical difference between the groups. All of these differences favour bleeding in the OAC cohort studies. It is well worth noting that bleeding rates were comparable between these studies, while other outcomes, mainly stroke and death, were more prevalent in the OAC reports. These differences may be due to selection bias (controlled trials vs. cohort studies) and probably in part reflect that populations at low risk for death or stroke were included in the early controlled PCI studies. [*indicates inferred information].

	Reports on PCI in anticoagulated patients (n=18 publications)		PCI studies including OAC and antiplatelet arms (n=4 publications)	
	Percent of patients	Number of studies reporting data	Percent of patients	Number of studies reporting data
Patients on OAC	72%	18	41%	4
Patients with AF	**67%**	14		
Acute coronary syndrome	**82%**	15	**45%**	3
Radial access	20%	7		
Femoral access	**80%**	7	100%*	
Closure device	31%	4		
GPI inhibitor	**36%**	12	**0%***	
POBA only	1%	12		
Stent	98%	13		
Drug-eluting stent	46%	11		
Mean age (yrs)	69,0	16	71,0	16
Females	**28%**	15	**9%**	4
Prior stroke	**13%**	9	**2%**	1
Diabetes	**32%**	14	**9%**	4
Hypertension	**71%**	14	**16%**	4
Heart failure	23%	7		
Prior relevant bleed	9%	3		
Renal dysfunction	26%	6		
No OAC	47%	11	50%	2
Major Outcomes				
Death (n)	12%	9	1%	4
Major bleed n	6%	13	6%	3
Stent thrombosis	2%	10	2%	2
Stroke	4%	8	0%	1
Infarctions	7%	9	3%	4

Table 3: Recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to- high thromboembolic 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 + gastric protection
			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 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day* (or aspirin 100 mg/day);
			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 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day* (or aspirin 100 mg/day);
			lifelong: warfarin (INR 2.0–3.0) alone.
High	Elective	Bare metal#	*2 to 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#	*4 weeks:* triple therapy of warfarin (INR 2.0–2.5) + aspirin ≥100 mg/day + clopidogrel 75 mg/day ;
			up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day*(or aspirin 100 mg/day); mg/day);
			lifelong: warfarin (INR 2.0–3.0) alone.

* combination of warfarin (INR 2.0–3.0) + aspirin =100 mg/day (with PPI, if indicated) may be considered as an alternative. # drug eluting stents should be avoided. INR = international normalized ratio; PPI = proton pump inhibitors; ACS = acute coronary syndrome.

(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 thromboembolic event during bridging therapy (Class IIa Level of Evidence: C)

(iv) When the procedures require interruption of OAC for longer than 48 hours in high-risk patients, UFH may be administered. LMWH (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 oral anticoagulation (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 IIb, Level of Evidence: C).

5.2. NSTE-ACS including unstable angina and NSTEMI

(i) Following presentation with a NSTE ACS with or without PCI in patients with AF, dual antiplatelet therapy with aspirin + 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 a 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 catheterisation 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 as compared to 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 peri-procedural bleeding and thromboembolic event 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-receptor 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).

5.3. Primary PCI

(i) In the acute setting following presentation with acute STEMI with primary PCI in a patient with AF, patients are often given aspirin, clopidogrel and heparin (UFH). Where patients have a high thrombus load, bivalirudin or GPIs may be given as a 'bail out' option. As an alternative to heparin + GPI, bivalirudin can 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 peri-procedural heparin may be adjusted to achieve a low-therapeutic activated clotting time (ACT 200–250 seconds in patients receiving a GPI, or 250–300 seconds 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 either PPIs, H2-receptor antagonists or antacids) (Class IIa Level of Evidence: C).

5.4. 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 non-STE-ACS, but not for acute interventions) but limited data are available in anticoagulated patients.

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

(iii) Medium to long-term management should possibly avoid, and anyway strictly limit DES to those clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc. where a significant benefit is expected as compared to BMS. Triple therapy should be used for 2–4 weeks, followed by OAC monotherapy. In selected patients at high risk for cardiovascular events and for bleeds, clopidogrel 75 mg/day may be added despite a high bleeding risk of the anticoagulant-clopidogrel combination (also see recommendation 5.6.).

5.5. Application to non-AF populations i.e. 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.

5.6. Miscellaneous

(i) In patients with stable vascular disease (e.g. with no acute ischaemic events or PCI/stent procedure in the preceding one year), OAC monotherapy should be used, and concomitant antiplatelet therapy should 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 + clopidogrel should be used for 12 months, irrespective of whether PCI-stenting is performed, following which single antiplatelet therapy (e.g. aspirin) can be used, as indicated by guidelines (Class IIa, Level of Evidence: C).

6. Areas for further studies

Current recommendations in this consensus document are largely based on limited evidence obtained from small, single-center and retrospectively analyzed cohorts. Thus, there is a definite need for large scale registries and prospective clinical studies appear to determine the optimal antithrombotic management of patients with AF at intermediate or high thromboembolic risk undergoing coronary interventions. Until then, the debates over the optimal antithrombotic management strategy for AF patients presenting with acute coronary syndrome and/or undergoing PCI-stenting is likely to continue (132, 133), especially in the presence of stroke risk factors – and whether AF is paroxysmal, persistent or permanent (134, 135). This scenario will change with the availability of more potent antiplatelet agents (e.g. prasugrel, etc) that in current ACS trials shows im-

proved efficacy but greater bleeding risk, when compared to clopidogrel (136). However, data on prasugrel in anticoagulated patient populations are lacking.

A prospective, multi-center registry AFCAS (Management of patients with *A*trial *F*ibrillation undergoing *C*oronary *A*rtery *S*tenting), aiming at prospectively evaluating the antithrombotic strategies currently adopted in this patient subset, and at investigating the potential benefit or harm of OAC and/or antiplatelet treatments, has been launched in several European countries. The first results of this study (expected in late 2009) will hopefully contribute to shed light on this common issue (137). Another registry sponsored by the Working Group on Thrombosis, the LASER registry has just started.

The ISAR-TRIPLE trial will give an answer to the hypothesis that reducing the duration of clopidogrel therapy from six months to six weeks after DES implantation is associated with improved clinical outcomes in patients on acetylsalicylic acid

and an oral anticoagulant (127). The What is the Optimal antiplatElet and anticoagulant in patients with oral anticoagulation and StenTing (WOEST) study (139) will assess the hypothesis that the combination warfarin + clopidogrel 75 mg/day is superior to triple therapy (warfarin + clopidogrel 75 mg/day + aspirin 80 mg/day) with respect to bleeding complications while equally safe with respect to the prevention of thrombotic complications in patients with both indications for warfarin use and dual antiplatelet (clopidogrel 75 mg/day + aspirin 80 mg/day) treatment. These trials are expected to run until 2011–2012.

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), but these trials will only report their findings over the next few years (140) (see www.clinicaltrials.gov).

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