Management of Antiplatelet and Anticoagulant Therapy in Patients With Atrial Fibrillation in the Setting of Acute Coronary Syndromes or Percutaneous Coronary Interventions

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Atrial fibrillation (AF), the most common cardiac arrhythmia, occurs in 1% to 2% of the general population, with a prevalence varying from 0.5% in subjects 40 to 50 years old to 5% to 15% in the elderly who are >80 years old.1-3 Stroke is the most feared complication of AF, resulting in death or disabling symptoms in a vast proportion of cases.4 In the Framingham study, the age-adjusted incidence of stroke was 5-fold higher in subjects with AF, and the attributable risk raised from 1.5% at 50 to 59 years to 23.5% at 80 to 89 years.5

Chronic oral anticoagulation (OAC) therapy is the mainstay of stroke prevention in patients with AF at high risk for cardioembolic sequelae; ≈70% to 80% of all patients with AF have an indication for OAC, and coronary artery disease coexists in 20% to 30% of them.6,7 With an estimated prevalence of AF in 1% to 2% of the population, it may be projected that ≈1 to 2 million patients on OAC in both the United States and Europe are candidates for coronary revascularization, often in the form of percutaneous coronary interventions (PCI). Patients undergoing PCI, as well as those who present with an acute coronary syndrome (ACS), also require dual antiplatelet therapy (DAPT), usually aspirin in combination with a platelet adenosine diphosphate P2Y12 receptor antagonist, with the goal of reducing the risk of ischemic recurrences, including stent thrombosis.8 However, the efficacy and safety of combining OAC with DAPT (triple antithrombotic therapy) in these patients is a topic of debate. In fact, although this combination can potentially prevent both thromboembolism and atherothrombotic events, it is also associated with an increased risk of severe bleeding. In a large nationwide registry of 40,812 patients hospitalized with myocardial infarction (MI), the risk of subsequent hospitalizations for bleeding increased with the number of antithrombotic drugs used, being 1.8-fold in patients on vitamin K antagonists (VKAs) and aspirin, 3.5-fold in patients on VKAs and clopidogrel, and 4-fold in patients on triple therapy, with numbers needed to harm of 45.4, 15.2, and 12.5, respectively.9 On this background, treatment with OAC and antiplatelet agents requires careful consideration of the risks and benefits associated with each drug and their combination.

On one hand, the challenge of balancing the risk of thromboembolism (ie, stroke) and atherothrombotic events (ie, stent thrombosis) and, on the other, the risk of bleeding demand for a timely review of the literature on using various combinations of OAC and antiplatelet therapies in patients with coexisting AF and coronary artery disease. This is also underscored by the recent availability of newer antithrombotic agents, including oral anticoagulants (ie, dabigatran, rivaroxaban, apixaban) and antiplatelets (ie, prasugrel, ticagrelor). This article reviews the evidence supporting antithrombotic agents for AF and ACS/PCI, and describes contemporary antithrombotic regimens and practical recommendations for patients with both conditions, with focus on new data and ongoing development of novel oral anticoagulant (NOAC) and antiplatelet drugs.

Epidemiology of Relevant Clinical Scenarios

Triple antithrombotic therapy may be required as the result of several commonly encountered clinical scenarios in daily practice. First, patients with paroxysmal, persistent, long-standing, or permanent AF on OAC may experience an ACS, either non–ST-segment elevation ACS (NSTE-ACS) or ST-segment elevation MI, or undergo elective PCI. In a prospective series of 261 consecutive patients with AF undergoing coronary angiography, the overall incidence of coronary artery disease was relatively high at 34%, and revascularization by either PCI or coronary artery bypass grafting was needed in 21%.10 Second, new-onset AF may occur within 7 days during or after hospitalization in ≈6% to 8% of patients after an ACS or PCI.11-14 In a meta-analysis of 120,566 patients from 10 clinical trials, AF occurred in 8% of patients with a ST-segment elevation MI and in 6.4% of patients with NSTE-ACS.15 Importantly, 7-day mortality was higher in patients with AF (5.1%) than in those without AF (1.6%), with adjusted hazards of 1.65 in ST-segment elevation MI and 2.30 in NSTE-ACS. At present, the underlying mechanisms of AF in myocardial ischemia remain poorly understood.16

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113
Stroke/Embolic Risk in Patients With AF on Anticoagulation With VKAs or NOACs

In patients with AF, adjusted-dose warfarin and antiplatelet agents reduce the risk for stroke by ≈65% and by ≈20%, respectively.17 However, oral antiplatelet agents do not perform as well as OAC with warfarin in this context. The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) trial performed in patients with AF plus ≥1 risk factor for stroke was stopped prematurely because of a clear evidence of superiority of OAC compared with DAPT with aspirin and clopidogrel, particularly in those already receiving OAC at study entry, with no increase in bleeding complications.18 In a meta-analysis of 6 contemporary randomized clinical trials published between 2002 and 2012, focusing on patients with AF on warfarin therapy, the stroke rates were found to be higher in elderly, female, subjects who were VKAs naïve or those with previous stroke or transient ischemic attack, renal impairment, previous aspirin use, or high CHADS2 score (cardiac failure, hypertension, age, diabetes mellitus, stroke [doubled]) score.19 However, even in the highest risk subgroup (previous stroke), the annualized risk of stroke with warfarin therapy was relatively low (≈2.5% per year). These results have corroborated the role of OAC with warfarin as the mainstay of cardioembolic prevention in patients with AF. In contrast, despite its undeniable benefits, warfarin is affected by a number of known limitations, including bleeding complications, dietary or drug interactions, and need for international normalized ratio (INR) monitoring and dose adjustment. These limitations may contribute to explain why only approximately half of patients who would benefit from OAC actually receive warfarin.20 Patients deemed unsuitable for warfarin therapy may benefit from DAPT with aspirin and clopidogrel, which in the ACTIVE-A trial was shown to reduce the risk of major vascular events and stroke, compared with aspirin alone, at the price of an increased risk of major bleeding.21

NOACs, which act by directly and selectively inhibiting key coagulation factors such as thrombin (ie, dabigatran) or factor Xa (ie, rivaroxaban and apixaban), have recently entered the market and clinical practice guidelines for the management of patients with nonvalvular AF.22 NOACs hold several favorable characteristics, including good availability, rapid onset of action, minimal drug/food interaction, no need for coagulation monitoring or dose adjustment, established efficacy and low risk of bleeding.23 In meta-analyses of warfarin-controlled trials, NOACs have been shown to reduce mortality significantly by 11% to 12%, the combination of stroke and systemic embolism by 18% to 23%, and intracranial hemorrhage by 21% to 54%.21-24 The annualized absolute risks of stroke or systemic embolism in these pooled analyses have been estimated at 2.4% to 2.8% with NOACs and 3.1% to 3.5% with warfarin.24,25

Ischemic Risk in Patients With ACS and/or Undergoing PCI on Antiplatelet Therapy With Aspirin and P2Y12 Receptor Inhibitors

DAPT with aspirin and a P2Y12 receptor inhibitor is the cornerstone of pharmacological ischemic prevention after an ACS or PCI.26-29 Clopidogrel, the most studied P2Y12 receptor inhibitor, was shown to reduce by 20% the incidence of cardiovascular death, nonfatal MI, or stroke in aspirin-treated patients with ACS from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial.30 Despite a 38% relative increase of major bleeding at 1 year with clopidogrel in the entire cohort, the benefit of clopidogrel treatment outweighed the risk of bleeding. This benefit was irrespective of patient management (invasive or noninvasive) as well as revascularization strategy (PCI or coronary artery bypass grafting).

In the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, long-term (1-year) clopidogrel therapy was shown to reduce the risk of adverse ischemic events selectively in patients undergoing PCI.31 However, numerous pharmacodynamic investigations have consistently demonstrated that individual responsiveness to clopidogrel is not uniform in all patients and is subject to interindividual and intra-individual variability.32 In parallel, a growing degree of evidence underscores that recurrence of atherothrombotic complications, including stent thrombosis, may be attributed to poor response to clopidogrel.33 Novel platelet P2Y12 inhibitors approved by regulatory authorities in both the United States and Europe (prasugrel, ticagrelor) have generally been shown to improve clinical outcomes in patients with ACS when compared with clopidogrel, particularly those undergoing PCI.33

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial, during a median follow-up of 15 months, prasugrel reduced the combined risk of cardiovascular mortality, MI, or stroke by 19% in patients with ACS and scheduled PCI (9.9% versus 12.1%; P<0.001), at the price of an increased risk of bleeding, including fatal bleeding.34 Subsequent risk–benefit analyses suggested that in patients with a history of stroke or transient ischemic attack, prasugrel may actually be harmful, whereas neutral effects have been observed in patients ≥75 years old or those with a body weight <60 kg.35 On the contrary, patients with ACS <75 years old who are treated conservatively were not found to gain any anti-ischemic benefit from prasugrel over clopidogrel in the Targeted platelet inhibition to clarify the optimal strategy to medically manage Acute Coronary Syndromes (TRILOGY-ACS) trial, during a median follow-up of 17 months (13.9% versus 16.0%; P=0.21), and similar risks of bleeding were observed.36 Compared with clopidogrel, ticagrelor was found to reduce the risk significantly of cardiovascular mortality, MI, or stroke at 12 months by 16% in the Platelet Inhibition and Patient Outcomes (PLATO) trial (9.8% versus 11.7%; P<0.001), which included patients across the broad spectrum of ACS referred to invasive or noninvasive management.37 Although there were no differences in the risk of protocol-defined major bleeding, non–coronary artery bypass grafting–related major bleedings were more common with ticagrelor than clopidogrel, and there was also an increased risk of fatal intracranial hemorrhage.38

VKAs Plus Antiplatelet Therapy With Aspirin and/or P2Y12 Receptor Inhibitors

Many trials are available to guide the care of patients with either AF or those with ACS and/or PCI; however, there is a limited amount of randomized data focusing on patients with both conditions. The risk of bleeding linked to concurrent use of aspirin, clopidogrel, and OAC, however, has been well
Importantly, this combination seems to increase the hazard of bleeding regardless of whether a good control of percentage of time in the therapeutic range of warfarin is achieved. Two different meta-analyses have reached similar conclusions in showing that triple antithrombotic therapy is associated with a 2-fold increased risk of major bleeding compared with nontriple antithrombotic regimens. The most frequent site of serious bleed in patients on triple antithrombotic therapy is the gastrointestinal tract. Importantly, bleeding may impact on mortality with multiple suggested mechanisms, including premature discontinuation of antithrombotic therapies, immunosuppression, and platelet activation by blood transfusion and hemodynamic compromise.

In contrast to the striking evidence on the safety hazard with triple therapy, data on efficacy are mixed, likely as the reflection of differences in combinations and doses of antithrombotic drugs, study design, follow-up durations, bleeding definitions, and indications for therapy in mostly retrospective and observational series. Accordingly, the 2 above-mentioned meta-analyses yielded conflicting results, with Zhao et al reporting fewer major adverse cardiovascular events and mortality with triple therapy compared with DAPT, and Gao et al reporting similar outcomes between patients on triple therapy and those on alternative regimens. Both meta-analyses, however, demonstrated a similar benefit of triple therapy in reducing stroke.

Although there are no adequate clinical data on which to base firm recommendations, both United States and European expert consensus documents suggest that triple therapy should be used depending on the balance of ischemic and bleeding risk, favoring a combination of low-dose aspirin (plus a gastric acid suppressing agent, preferably a proton pump inhibitor), clopidogrel as the P2Y12 inhibitor of choice, and OAC with warfarin, targeting an INR between 2.0 and 2.5. The safety of this approach, particularly regarding the importance of keeping a low-intensity anticoagulation, has been demonstrated in a small series.

Novel treatment strategies aimed at reducing the risk of bleeding by varying the combination of antithrombotic agents administered are a matter of ongoing interest. Dropping aspirin is one of them. Recently, the results of the open-label, multicenter What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) trial have been published, in which 573 patients on oral anticoagulants (69% for AF) and undergoing PCI were randomized to clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy). The trial showed a large reduction in the primary end-point of overall TIMI bleeding at 12 months in patients receiving double therapy compared with those receiving triple therapy (hazard ratio, 0.36; 95% confidence interval [CI], 0.26–0.50; P<0.001), particularly confined to minimal and minor bleeding, with a numeric, albeit not statistically significant reduction of major bleeding. In addition, there was no increase in the rate of thrombotic events, including MI, target vessel revascularization, and stroke. Lower rates of the composite efficacy end-point (11.3% versus 17%; P=0.025) and mortality (2.6% versus 6.4%; P=0.027) were noted among patients on double therapy; however, it should be noted that the trial was not powered for neither noninferiority nor superiority in any of the efficacy end-points. The results of the WOEST trial demonstrate that a strategy of OAC plus clopidogrel, with drop of aspirin, is associated with less bleeding and similar or even superior ischemic protection, but other investigations are warranted to better elucidate the risk-benefit of dropping aspirin in patients on triple antithrombotic therapy. Recently, in a large (n=12165) nationwide real-world study of patients with AF with indication for multiple antithrombotic drugs after ACS/PCI, the combination of OAC and clopidogrel was equal or better on both benefit and safety outcomes compared with triple therapy.

Data on combination of VKAs with aspirin and/or novel P2Y12 inhibitors are scarce. In the TRITON-TIMI 38 and TRILOGY-ACS studies, patients were not enrolled if they were on OAC that could not be safely discontinued. Therefore, no meaningful information can be drawn from these trials on patients on triple therapy including prasugrel. Recently, a single-center, observational study of 377 patients with indication for OAC who underwent drug-eluting stent (DES) implantation reported the bleeding and ischemic outcomes of 21 patients (5.6%) who received prasugrel in combination with aspirin and VKAs. At 6 months, TIMI major and minor bleeding were more frequently observed among patients on triple antithrombotic treatment who received prasugrel compared with those who received clopidogrel (28.6% versus 6.7%; P=0.001), with an adjusted hazard ratio of 3.2 (95% CI, 1.1–9.1; P=0.03) after correcting for baseline confounders. There was no significant difference regarding the composite ischemic end-point between the prasugrel and clopidogrel groups. These findings raise a note of caution over the use of prasugrel in patients who need OAC. This is in line with the product label of prasugrel, as well as that of ticagrelor. In fact, although outcomes of patients on treatment with ticagrelor and OAC have not yet been reported, and those patients were excluded from enrollment in the PLATO and the ongoing Prevention of Cardiovascular Events (eg, Death From Heart or Vascular Disease, Heart Attack, or Stroke) in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin - TIMI 54 (PEGASUS-TIMI 54, clinicaltrials.gov identifier NCT01225562), a large ongoing secondary prevention trial of ticagrelor in patients with history of MI, ticagrelor is associated with potent platelet inhibition, increased risk of non–coronary artery bypass grafting-related bleeding, including fatal intracranial hemorrhage, raising concerns if concomitantly used with OAC.

**NOACs Plus Single or Dual Antiplatelet Therapy**

Because many patients already use NOACs, and many others will be likely treated in the future, management of concomitant antiplatelet therapy in patients with newly onset ACS or treated by PCI is a topic of growing interest. However, currently available data on oral antiplatelet agents (mostly aspirin alone) in addition to NOACs are scarce and limited to relatively small subgroups of patients from trials of dabigatran or apixaban, as described below. In addition, of the 4 pivotal phase III AF trials of NOACs, 3 (rivaroxaban, apixaban, and edoxaban) did not allow the inclusion of patients with
concomitant clopidogrel use.62–64 The only phase III AF trial that allowed concomitant use of clopidogrel was the one of dabigatran, although given the limited number of patients any inference on the efficacy and safety of combination with DAPT, at present, remains speculative.60,65

In the phase 2 Prevention of Embolic and Thrombotic Events in Patients with Persistent AF (PETRO) study, 502 patients with AF at high risk for thromboembolic events based on qualifying inclusion criteria were assigned to a total of 10 treatment groups to identify a safe dose of dabigatran etexilate for subsequent clinical development.59 Adding to a total of 10 treatment groups to identify a safe dose of dabigatran etexilate for subsequent clinical development.59 Adding to a comparator arm of patients receiving INR-adjusted warfarin alone, 3 doses of dabigatran etexilate (50-, 150-, and 300-mg bid) were investigated in a 3×3 factorial modality with no aspirin or aspirin 81- or 325-mg once daily. With such design characteristics, the PETRO study provides meaningful early insights on the safety of combining aspirin and dabigatran. Major bleeding episodes (n=4) within 12 weeks occurred only in patients treated with dabigatran 300-mg bid plus aspirin (6.3% versus 0% in patients treated with dabigatran 300-mg bid alone; P<0.02). In addition, there was a significant increase in major plus clinically relevant bleeding events (17.2% versus 5.7%; P=0.03) and total bleeding episodes (39.1% versus 13.3%; P=0.0003) in patients on dabigatran 300-mg bid plus aspirin compared with those on dabigatran 300-mg bid alone. Overall, 13 patients assigned to dabigatran plus aspirin stopped receiving aspirin during the trial (2 receiving dabigatran 50-mg bid, 3 receiving dabigatran 150-mg bid, and 8 receiving dabigatran 300-mg bid).

In the phase 3 Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, 2 blinded fixed doses of dabigatran etexilate (110- and 150-mg bid) were compared with open-label warfarin in 18113 patients with AF and ≥1 risk factor for stroke.65 After a median follow-up of 3 years, the lower dabigatran dose was shown to be noninferior to warfarin in terms of the primary end-point of stroke and systemic embolism, with a lower risk of major bleeding. In contrast, the higher dabigatran dose was shown to be superior to warfarin in reducing stroke or systemic embolism, with a similar risk of major bleeding. In the RE-LY trial, concomitant use of antiplatelet agents, including clopidogrel, was allowed at the discretion of the attending physician. A post hoc analysis from the RE-LY trial recently targeted 6952 (38.4%) patients with concomitant antiplatelet treatment (aspirin alone in 5789, clopidogrel alone in 351, and both aspirin and clopidogrel in 812 patients) at some time during the study (with only 27% of patients on concomitant antiplatelets at 6-month landmark periods).66 The effect of dabigatran 110-mg bid versus warfarin on the primary efficacy and safety end-points was not significantly modified in patients who received antiplatelet agents (P for interaction=0.738 and 0.794, respectively). Conversely, the effect of dabigatran 150-mg bid on stroke and systemic embolism seemed mitigated among patients who used antiplatelets versus those who did not (relative risk reduction, 20% versus 48%; P for interaction=0.058), although the effect on major bleeding remained unmodified (P for interaction=0.875). The use of antiplatelet treatment was associated with increased risk of major, minor, and extracranial bleeding in each of the treatment groups, with the few observed episodes of intracranial hemorrhage possibly explaining the lack of a similar pattern with antiplatelets use on this end point. The risk of major bleeding was 2.3 higher among patients who received DAPT, and 1.6 higher in those who only received a single antiplatelet agent, with relative increases consistent whether patients were on dabigatran 110- or 150-mg bid, or warfarin, but absolute risks lowest with the lower dabigatran dose. No relationship was noted between the dose of aspirin and the risk of various forms of bleeding. Although informative, the results of this post hoc analysis must be judged with caution, because the use of antiplatelet agents in the RE-LY was neither randomized nor stratified, and only a minority of patients was using an antiplatelet agent (even less were those who used it continuously throughout the study). In addition, most patients were taking aspirin, whereas the use of clopidogrel or DAPT was infrequent, and prasugrel or ticagrelor were not used. Despite these limitations, these findings provide added support for the understanding that concomitant use of antiplatelets with warfarin or NOACs increases risk without significant benefit. Based on the above, in patients who need OAC but are at high risk for bleeding, one may consider choosing to stop antiplatelet therapy, use the lower dose of dabigatran or do both, with the strategy depending on a careful assessment of the relative need for either drug.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, a total of 18201 patients with AF and ≥1 additional risk factor for stroke were randomized to a twice-daily dose of apixaban 5-mg or warfarin.63 At a median of 1.8 years, apixaban was shown to be superior to warfarin in reducing the primary ischemic end-point, causing less major bleeding and resulting in lower rates of death from any cause. Concomitant aspirin use was left at the discretion of the treating physician, being detected on day 1 from randomization in 4433 cases (24%). In a dedicated subanalysis, there was no significant interaction between the treatment effect of apixaban versus warfarin on the primary end-point between patients on aspirin and those who were not (P for interaction=0.10), although the relative risk reduction in stroke or systemic embolism was higher in patients on aspirin (relative risk reduction, 42%) compared with those without aspirin (relative risk reduction, 16%).64 Similarly, no interaction on major bleeding was noted (P for interaction=0.29), with apixaban shown to be safer than warfarin in both patients treated with aspirin and those without. Because this analysis addressed only aspirin, and use of clopidogrel was not allowed in the ARISTOTLE trial, additional randomized clinical trials are needed to determine the impact of the combination of apixaban and DAPT.

**Recommendations on the Management of Patients on Oral Anticoagulation With ACS and/or Undergoing PCI**

**Risk Stratification and Balance**

Management of patients who require antiplatelet therapy on top of OAC cannot be reduced to a series of rules that fit in all cases, but it necessarily requires careful decision-making focused on individual characteristics. Risk scores may assist in identifying subsets at risk of recurrent ischemic events or bleeding, for which antithrombotic strategies must inevitably
be personalized. Unfortunately, the hazard for ischemic and bleeding events frequently coexists in the same patient, because these complications share multiple risk factors. In such cases, one should carefully weigh the risk and benefit of each drug choice, taking into account the preference of the patient. In addition, the length of triple therapy should be sized in proportion to the bleeding risk, the clinical scenario, and tight control of INR values should be achieved in any case.

The CHADS2 risk score is advocated by the European guidelines as a rapid, bedside means of assessing the risk of stroke.66 Patients with CHADS2 ≥2 should be prescribed OAC indefinitely, unless contraindicated, because of higher adjusted risk of stroke per year compared with those with CHADS2 scores of 0 or 1, for whom DAPT is preferable.67 However, these latter continue to experience a certain degree of stroke risk, which underscores the need for more precise assessment of stroke risk factors in this population. An updated scheme expressed as CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, stroke [doubled], vascular disease, age 65–74, and sex category [female]) has been proposed to fulfill this aim by incorporating additional stroke risk factors that influence whether or not to use OAC into the simpler CHADS2 scheme.66 With such approach, OAC should be prescribed only in patients with CHA2DS2-VASc ≥2, whereas those with a score of 1 should be prescribed either OAC (preferred) or aspirin, and those with a score of 0 should be prescribed no antithrombotic therapy for AF (preferred) or aspirin alone.

Similarly, risk stratification tools are available to estimate the individual risk of bleeding.34 The European guidelines formally endorse the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [>65], drugs/alcohol concomitantly) as a simple method to assess bleeding risk in patients with AF, with scores ≥3 indicating high risk. The HAS-BLED score has been found to predict bleeding significantly also in patients on triple antithrombotic therapy, with a relatively good discrimination (c statistic, 0.67).66 In a study of 590 patients with AF and CHA2DS2-VASc ≥1 undergoing PCI, 71% had a HAS-BLED ≥3.70 In these patients, OAC was found to reduce the risk of death at 12 month independently, whereas the use of DES, with subsequent need for prolonged DAPT, independently predicted the risk of major bleeding. Interestingly, similar results have been demonstrated in octogenarian patients with AF undergoing PCI (mean HAS-BLED, 3.05).71 Overall, these findings underscore that the benefit of using VKAs on top of DAPT to reduce ischemic events may overshadow the bleeding risk even in patients with HAS-BLED ≥3. This is also in line with registry data showing that patients with AF undergoing PCI have a CHADS2 score ≥2 in ≈70% of cases, so that OAC treatment should not be withdrawn even when combined anticoagulant and antiplatelet treatment is warranted.72

**Procedural Considerations for Minimizing the Risk of Bleeding With Triple Antithrombotic Therapy**

A series of procedural aspects need to be taken into consideration when dealing with a patient in need of triple antithrombotic therapy. Given the complexity and risk associated with management of these patients, it is first important to define whether there is an indication to be on triple antiplatelet therapy. In fact, there are subgroups of patients with AF with a low annual risk of thromboembolic events (ie, CHA2DS2-VASc 0 or 1) that do not require OAC. Also, the reduction in stroke with well-controlled warfarin therapy versus DAPT in patients at lower risk of stroke is likely outweighed by the increased risk of bleeding.28 It is also important to note that compliance with treatment is pivotal for demonstrating efficacy with OAC and to minimize bleeding complications. In fact, patients with a time in the therapeutic range <65% derive no significant advantage from OAC over DAPT in reducing vascular events (relative risk, 0.93; 95% CI, 0.70–1.24; P=0.61).73 With the above considerations in mind, if a patient does require OAC, the below items should be considered for optimal management of antithrombotic therapy.

**Avoiding Unnecessary Revascularization**

In context of the incremental bleeding risk associated with combining OAC with antiplatelet therapies, the appropriateness of PCI particularly for patients who present with stable ischemic heart disease must be clearly ascertained and consistent with current appropriate use criteria.

**Vascular Access**

In a meta-analysis of randomized clinical trials, the radial approach for PCI has been found to reduce access-site complications by 73% compared with the femoral approach, with a trend toward a significant reduction in death, MI, or stroke combined.72 Similarly, in the more recent, large Radial versus Femoral Access for Coronary Intervention (RIVAL) trial of patients with ST-segment elevation MI, major vascular complications, including large hematomas, were less frequently observed in the radial compared with the femoral arm (1.4% versus 3.7%; P<0.001).73 A radial access may be of potential use in patients on OAC (either warfarin or NOACs), particularly if OAC cannot be withdrawn, or INR exceeds the normal range at the time of an emergent procedure.76 In the PCI subgroup of a small randomized trial, patients on uninterrupted warfarin therapy were found to experience a lower rate of access-site complications with the radial access compared with the femoral access (0% versus 37.5%; P=0.034).77

**Stent Selection**

Current North American and European expert consensus documents on the management of antithrombotic therapy in patients with AF undergoing PCI with stenting suggest that when placement of a coronary stent is necessary in patients undergoing elective PCI who need chronic OAC, a bare metal stent (BMS) should be preferred whenever possible over a DES attributable to the shorter need for DAPT.48,49 However, many interventionalists still favor DES in patients with high-risk coronary presentations, and DES were used in about two thirds of patients included in the WOEST trial.52 In addition, that recommendation may be outdated in light of multiple recent sources of data suggesting that second-generation everolimus-eluting stents are associated with lower rates of definite stent thrombosis than other DES and even lower than BMS.78–80 Importantly, this benefit has also been observed in subsets of patients at high risk for stent thrombosis, including those undergoing primary PCI and those with diabetes mellitus,
where the safety gain is paralleled by the superior efficacy of DES in reducing the need for repeat revascularization.81–83

On this background, the benefit of a DES over a BMS should be balanced against the increased risk of bleeding with a prolonged triple therapy. The optimal duration of DAPT after DES implantation is still a controversial issue, with large ongoing trials (clinicaltrials.gov identifiers NCT00977938 and NCT00661206) aimed at shedding more light on this topic.84 As noted above, second-generation devices, including stents eluting everolimus or zotarolimus, might offer ideal features such as less thrombogenicity and no need for long-term DAPT.78,79 The Xience and Promus everolimus-eluting stents have recently gained European CE Mark approval for use with DAPT for ≥3 months, and the Resolute Integrity zotarolimus-eluting stent for 1 month.85,86 These data have been supported by studies and presentations at major cardiovascular congresses demonstrating that discontinuation of DAPT after either 1, 3, or 6 months duration was not associated with a significant increase in stent thrombosis with these newer stents among low-risk all-comers populations.87–89 This is also in line with a recent large registry supporting the relative safety of DES versus BMS should DAPT discontinuation be required early (ie, between 6 weeks and 6 months).92

Overall, the net clinical benefit of treatment with BMS and OAC in conjunction with either mono (clopidogrel) or dual (aspirin plus clopidogrel) antiplatelet therapy remains to be determined when compared with treatment using a second-generation DES (specifically Xience/Promus and/or Resolute Integrity) in conjunction with an abbreviated (1–3 months) duration of DAPT, but could clearly weigh in favor of the newer generation DES in conjunction with an abbreviated DAPT regimen. Bioreabsorbable coronary scaffolds may have the potential for reducing late thrombotic events in patients undergoing PCI, but the scaffold persists 1 to 2 years, and large-scale studies are needed to characterize the safety of this new technology.93

Intraprocedural Anticoagulation
Management of anticoagulant therapy during PCI is mostly empirical in patients on OAC because of lack of a solid evidence base. In the multicenter Atrial Fibrillation undergoing Coronary Artery Stenting (AFCAS) registry, uninterrupted anticoagulation was shown to be similar to conventional bridging therapy with heparin, after adjustment for propensity score, in terms of both major adverse cardiac and cerebrovascular events (1.16; 95% CI, 0.44–3.05; P = 0.76) and bleeding complications (1.38; 95% CI, 0.77–2.48; P = 0.28).94 However, whether continuation of OAC is a safe option in the peri-PCI period remains unproven without confirmation from a dedicated randomized clinical trial.

Current US guidelines consider enoxaparin a reasonable option in patients either treated with upstream subcutaneous enoxaparin in the context of an NSTE-ACS (to whom additional dose of 0.3 mg/kg IV should be administered at the time of PCI to patients who have received <2 therapeutic subcutaneous doses (ie, 1 mg/kg) or received the last subcutaneous enoxaparin dose 8–12 hours before PCI) or those who have not received previous antithrombin therapy and are administered intravenously enoxaparin at the time of PCI (to whom a 0.5–0.75 mg/Kg IV bolus can be given). However, switching from unfractionated heparin to enoxaparin (and vice versa) may increase the risk of bleeding and should be discouraged.95,96

Avoidance of intraprocedural drugs that increase the risk of bleeding (ie, glycoprotein IIb/IIIa inhibitors on top of unfractionated heparin) and preference toward anticoagulant regimens with proven benefits in reducing bleeding complications (ie, bivalirudin) may be prudent in patients who are orally anticoagulated. Bivalirudin has consistently shown to reduce the bleeding risk of patients with coronary artery disease undergoing PCI compared with heparin and glycoprotein IIb/IIIa inhibitors, particularly those presenting with an ACS.97–99 A recent meta-analysis has confirmed the safety benefit of bivalirudin over unfractionated heparin alone.100 However, there are no studies exploring whether such benefit is enhanced, similar, or blunted in patients who are orally anticoagulated. Because PCI practice moves toward other bleeding-avoidance strategies, such as a broader use of the radial approach, as noted above, a reassessment of the relative benefit of bivalirudin versus the choice of the access site is underway in the ongoing Minimizing adverse hemorrhagic events by transradial access site and systemic implementation of Angiox (MATRIX) trial (clinicaltrials.gov identifier NCT01433627).

Selection of Oral Antithrombotic Drugs
Which Oral Antiplatelet Agent(s)?
Based on current evidence, clopidogrel (75 mg/d) should be the preferred P2Y12 receptor antagonist in patients with AF with ACS, and used in combination with a low dose (<100 mg/d) of aspirin. DAPT with clopidogrel and aspirin also remains the current standard for patients undergoing elective PCI. Prasugrel and ticagrelor should be avoided in patients concomitantly treated with OAC.

Which Oral Anticoagulant?
The evidences on the efficacy and safety of NOACs are rapidly accumulating. However, despite the theoretical advantages of NOACs over VKAs, in particular the consistent finding of reduced intracranial hemorrhage, there is a lack of data on the impact of their combination with DAPT in patients undergoing PCI. In addition, there has been some concern surrounding the lack of reversing agents for NOACs, although various compound are under investigation to account for this limitation.101 Lack of a readily available method to determine the degree of anticoagulation is deemed as another important limitation of NOACs, particularly in patients with hemorrhagic complications and death resulting from closed head injuries or trauma.102,103 As such, warfarin (targeting low-intensity OAC with an INR between 2.0 and 2.5) remains the standard of care for patients with AF who also require DAPT because of the larger experience accumulated to date, the availability of monitoring, and an established antidote. The results of newer studies of NOACs targeting patients with AF undergoing PCI might change rapidly this recommendation and guidelines in the future.

How Many Antiplatelet Agents, and for How Long in Elective PCI?
The North American expert consensus document on the management of antithrombotic therapy in patients with AF
undergoing PCI with stenting provides recommendations based on the individual risk for stent thrombosis (ie, low, high, any) and the risk of bleeding (ie, low, high). Patients at low risk of both stent thrombosis and bleeding should receive triple therapy for ≥1 month after placement of a BMS and for ≥6 months after placement of a DES, followed by OAC plus 1 antiplatelet agent (ie, aspirin or clopidogrel) up to 12 months, with OAC only continued thereafter. In contrast, patients at high risk of stent thrombosis and low risk of bleeding should receive triple therapy for ≥6 months after a BMS, and for 12 months after a DES. After 12 months, continuation of a single antiplatelet agent in addition to OAC should be considered in patients at high risk for stent thrombosis. Finally, regardless of the risk of stent thrombosis, patients at high bleeding risk should receive a BMS and maintain triple therapy for ≥1 month, followed by OAC plus 1 antiplatelet agent up to 12 months and OAC indefinitely thereafter.

The parallel European expert consensus document provides recommendations following a different approach that take into consideration bleeding on one hand, and clinical presentation on the other. In elective PCI patients who receive BMS and are at low or intermediate risk of bleeding (HAS-BLED <3), triple antithrombotic therapy with warfarin (with lower dose intensity, targeting an INR between 2.0 and 2.5), low-dose aspirin, and clopidogrel 75-mg daily should be given for 1 month in association with gastric protection, followed by warfarin lifelong (targeting the usual INR between 2.0 and 3.0). If patients who receive a BMS are deemed at high risk of bleeding (HAS-BLED ≥3), triple therapy as above should be prescribed for 2 to 4 weeks, followed by warfarin alone indefinitely thereafter. In patients who receive DES, the duration of triple antithrombotic therapy should be customized according to the type of stent implanted and the individual risk of bleeding, with paclitaxel-eluting stents requiring ≥6 months, and limus-eluting stents requiring ≥3 months of DAPT. As noted above, second-generation DES may be a safe option to shorten the window of triple antithrombotic therapy. If a DES is implanted, in the period between 3 (or 6) and 12 months, warfarin (INR, 2.0–2.5) should be given in combination with clopidogrel or aspirin (single platelet inhibitor). After 12 months, administration of warfarin alone (INR, 2.0–3.0) is advised.

How Many Antithrombotic Agents, and for How Long in ACS?

Clinical guidelines both in North America and in Europe recommend 12 months of DAPT after an ACS irrespective of treatment, whether medical or by PCI with implantation of a BMS or a DES. This recommendation should be tempered and tailored in patients on OAC, according to the risk of bleeding with prolonged triple therapy. The North American document cited above supports (may be reasonable) the use of DAPT for 12 months in patients undergoing stenting after an ACS who are at high risk of thrombotic events and at low risk of bleeding. Differently, according to the European document, patients with ACS with low or intermediate bleeding risk should be on triple therapy for ≥6 months, followed by dual therapy with warfarin (INR, 2.0–2.5) and clopidogrel (or low-dose aspirin) up to 12 months, and warfarin alone (INR, 2.0–3.0) lifelong thereafter. Also, the European consensus recommend that patients with ACS at high risk of bleeding should be prescribed triple therapy as above for 4 weeks, then drop aspirin (or clopidogrel) up to 12 months, and continue warfarin (INR, 2.0–3.0) indefinitely thereafter. In patients undergoing PCI, high priority should be given to the implantation of a BMS. During primary PCI, use of glycoprotein IIb/IIIa inhibitors should be reserved to bailout situations and avoided as much as possible in patients with INR >2.0.

Use of Proton Pump Inhibitors

According to an expert consensus document and the American College of Cardiology/the American Heart Association PCI guidelines, use of proton pump inhibitors should be encouraged in patients on DAPT therapy to reduce the risk of gastrointestinal bleeding, particularly in case of concurrent use of OAC. However, pharmacokinetic and pharmacodynamic studies suggest that concomitant use of clopidogrel and omeprazole reduces the antiplatelet effects of clopidogrel, possibly through competitive metabolic effects of cytochrome CYP2C19 or reduced biological action of clopidogrel related to genetic polymorphisms, leading to a box warning from drug regulating agencies in the United States and Europe. Although retrospective studies and post hoc analysis have suggested a potential for an increased risk of ischemic events attributable to this drug–drug interaction, this has not proven to translate into meaningful differences at the clinical level in a randomized clinical trial. It should be noted that the interaction of clopidogrel with proton pump inhibitors is not class specific because it applies to only those drugs (ie, omeprazole and esomeprazole) interfering with the CYP2C19. Therefore, in line with PCI guidelines, non-CYP2C19 interfering proton pump inhibitors (ie, pantoprazole, dexlansoprazole) should be preferred.

Managing Bleeding Complications

In case of bleeding or in asymptomatic patients with excessively high INR values, strategies aimed at reversing the effect of oral antithrombotic drugs may be necessary. Antagonizing the effect of warfarin requires suspending the drug and eventually administering a dose of vitamin K (phytonadione) or blood derivatives, including fresh frozen plasma or prothrombin complex concentrates. There are currently no specific antidotes to neutralize the effect of NOACs, although several different drugs and compounds are under investigation as potential reversing agents. Clopidogrel, prasugrel, and ticagrelor have no antidotes. When an antidote is not available and bleeding continues despite the usual hemostatic techniques, platelet transfusion has the potential to reverse bleeding by restoring normal hemostasis, even if platelet count is normal, at the price of a slightly increased risk of platelet activation and aggregation. If deemed necessary in patients treated with novel P2Y12 inhibitors, platelets should be administered ≥6 hours after administration of the loading dose of prasugrel or 4 hours after the administration of the maintenance dose, to avoid interference by the circulating active metabolite of the drug. No data exist on the hemostatic benefit of platelet transfusion in patients treated with ticagrelor.
Future Directions

Two randomized clinical trials are currently testing different antithrombotic combinations for patients on OAC who require stent implantation. The Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE, clinicaltrials.gov id NCT00776633) trial will address the hypothesis that reducing the length of clopidogrel therapy from 6 months to 6 weeks after implantation of DES is associated with a reduced net composite of death, MI, definite stent thrombosis, stroke, or major bleeding at 9 months on top of treatment with aspirin and an oral anticoagulant. The Anticoagulation in Stent Intervention (MUSICA-2, clinicaltrials.gov id NCT01141153) trial is investigating the safety and efficacy of a triple antithrombotic regimen of acenocoumarol, low-dose (100 mg/d) aspirin, and clopidogrel versus high-dose (300 mg/d) aspirin and clopidogrel in patients with AF and low-to-moderate risk of stroke (CHADS2 ≤ 2) referred to PCI.

After an ACS, patients remain at risk for recurrent atherothrombotic events despite the use of DAPT.114,115 This risk may be partly related to excess thrombin generation, supporting the rationale for use of an anticoagulant on top of DAPT at long-term after an ACS. This strategy was shown to be of potential use with warfarin (but challenges related with drug administration and bleeding concerns have limited its use for this indication) and ximelagatran (but the drug is no longer on the market because of reported hepatotoxicity).115,116 The advent of NOACs has renewed the interest toward the long-term use of oral anticoagulants in ACS. However, dabigatran and dar- exaban were associated with a dose-dependent increased risk of bleeding in their respective phase II trials.117,118 And apixaban increased the number of major bleeding events without a significant reduction in the rate of ischemic events in a phase III trial.119 Another phase III trial of low-dose rivaroxaban (2.5-mg bid) on top of aspirin and clopidogrel in patients with ACS showed a significant reduction in mortality at the price of a 4-fold increase in intracranial hemorrhage.120 Importantly, the 2.5-mg bid dose of rivaroxaban used in the trial was about one quarter of that tested in AF. Therefore, whether this regimen would be sufficiently safe and protective in AF versus warfarin or the combination of a higher dose of rivaroxaban plus a P2Y12 inhibitor only is unknown and will be assessed in a ≥2100-patient prospective trial (A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention [PIONEER AF-PCI], clinicaltrials.gov identifier NCT01830543). In this trial, patients with nonvalvular AF undergoing PCI with no history of previous transient ischemic attack or stroke will be randomized to 1 of 3 treatment arms: (1) triple antithrombotic therapy with aspirin (75–100 mg/d), clopidogrel (75 mg/d), and VKAs (INR, 2.0–3.0); at the discretion of the treating physician, patients will drop clopidogrel at 1, 6, or 12 months, which will be defined at time of randomization; (2) triple antithrombotic therapy with aspirin (75–100 mg/d), clopidogrel (75 mg/d), and rivaroxaban (2.5-mg bid); at the discretion of the treating physician, patients will drop clopidogrel at 1, 6, or 12 months, which will be defined at time of randomization; (3) dual antithrombotic therapy with rivaroxaban 15-mg/d (or 10-mg for subjects with moderate renal impairment) and clopidogrel (75 mg/d). In a small subgroup of patients, the novel P2Y12 receptor antagonists, prasugrel (10 mg/d), or ticagrelor (90 mg bid), will be allowed to be used in lieu of clopidogrel. The primary end-point will be the 12-month composite of TIMI major bleeding, TIMI minor bleeding, and bleeding requiring medical attention. The secondary end-point will be the composite of cardiovascular death, MI, stroke, and stent thrombosis. Most recently, a trial of dabigatran 150-mg or 110-mg twice-daily plus single antiplatelet therapy versus triple therapy with warfarin and DAPT (Randomized Evaluation of Dual Therapy with Dabigatran versus Triple Therapy Strategy with Warfarin in Patients with nonvalvular atrial fibrillation that have undergone PCI with Stenting [RE-DUAL PCI]) has been announced.121

Conclusions

Triple therapy with OAC, aspirin, and clopidogrel is recommended for patients with AF with ACS and/or PCI, but evidence mainly stems from observational series, mostly from single centers. For this reason, European and US guidelines assign a C level of evidence to this recommendation, and emphasize the need for balancing the thrombotic and the bleeding risks at the individual level. Incorporation of NOACs, prasugrel, and ticagrelor into a triple therapy scheme is challenging in a field where data are limited. Further investigation of less-is-more approaches (ie, WOEST-like trials) is crucial to confirm the effectiveness of adding 2 and not 1 antiplatelet agent on top of OAC.

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References

Capodanno and Angiolillo


Triplet Antithrombotic Therapy in ACS/PCI


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