Choices in antithrombotic management FOR patients with atrial fibrillation UNDERGOING PERCUTANEOUS CORONARY INTERVENTION. Questions (and answers) in CHRONOLOGICAL sequence

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ABSTRACT

 In accordance with the 2018 joint consensus document issued by the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA), and endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA), the management of antithrombotic therapy of patients with atrial fibrillation undergoing percutaneous coronary intervention requires that multiple and interconnected issues, including, duration of initial triple antithrombotic therapy, selection of P2Y12 inhibitor, choice of oral anticoagulant to be combined with antiplatelet therapy, intensity of oral anticoagulation throughout combination therapy, and choice of oral anticoagulant for indefinite therapy, are addressed. To assist the responsible physician in clinical decision making, a series of practical questions are proposed and discussed in chronological sequence.

KEY WORDS: percutaneous coronary intervention, oral anticoagulation, atrial fibrillation, warfarin, non-vitamin K-antagonist oral anticoagulants

CONFLICT OF INTERESTS

 None.

INTRODUCTION

 Based on the 2018 joint consensus document issued by the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA), and endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA), the management of antithrombotic therapy in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) should include an initial period of triple antithrombotic therapy (TAT) with oral anticoagulant (OAC), aspirin and clopidogrel, followed by double antithrombotic therapy (DAT) with OAC and clopidogrel until 12 months, and finally OAC monotherapy indefinitely (1) (Fig. 1). Immediate initiation of DAT following PCI may be considered when concern regarding bleeding complications is predominant over that of myocardial ischemic events (1) (Fig. 1)

 Once the above management suggestions are accepted, identification of the chronological sequence according to which the associated practical questions need to be answered may be helpful. As outlined in Fig. 2 and discussed below, the questions and the sequence may be as follows:

* For how long should TAT be continued?
* Which P2Y12 inhibitor, i.e., clopidogrel vs. ticagrelor or prasugrel, should be given in combination?
* Which OAC, i.e., vitamin K-antagonist (VKA) vs. non-vitamin K-antagonist (NOAC), should be chosen?
* Should a NOAC be chosen, is there anyone to be preferred?
* Which intensity of OAC, i.e., target International Normalized Ratio (INR) with VKA or drug dose with NOAC, should be pursued?
* Which OAC, i.e., VKA vs. NOAC, should be chosen for long-term monotherapy?

QUESTIONS AND ANSWERS

*Section 1.1. For how long should TAT be continued?*

 Across clinical trials comparing TAT to DAT, randomization took place from some hours to several days after PCI (2-5), which was carried out according to standard practice, including peri-procedural use of aspirin. Therefore, TAT was initially implemented in all patients, including those who were subsequently randomized to DAT. Based on consistent observations of an increased (early) risk of stent thrombosis (+50-60%) and myocardial infarction (+20-30%) with DAT (6-9), the immediate withdrawal of aspirin after PCI appears not justifiable. Considering that the risk of stent thrombosis (and associated myocardial infarction) is the highest within the first hours/days after PCI (10), a duration of TAT not shorter than 1 to few weeks is likely be warranted to all AF patients undergoing PCI, including those in whom the bleeding risk is predominant (11). Indeed, separation of the Kaplan-Meier curves of bleeding events in the PIONEER AF-PCI (2), RE-DUAL PCI (3), and AUGUSTUS (4) trials appears to occur not earlier than a few days/weeks after randomization, suggesting that the bleeding risk of TAT as compared to DAT is not substantially increased when its duration is limited. Of note, in the ENTRUST AF-PCI study (5) the early incidence of bleeding events was higher with DAT than with TAT.

 Appraising the risk of stent thrombosis and recurrent myocardial ischemic events, by using clinical judgment, including indication to the PCI procedure, such as, acute coronary syndrome (ACS) vs. stable coronary artery disease (CAD), diabetes mellitus or presence of uncontrolled cardiovascular risk factors (12), and procedural characteristics, including treatment of at least 3 vessels and/or 3 lesions and/or bifurcation lesion with 2 stents and/or total chronic occlusion, implantation of at least 3 stents, and total length of stented lesion > 6 cm (13), TAT can then be extended from the initial minimum of 1 to few weeks up to a maximum of 6 months (1, 11) (Fig. 1). Of note, the individual risk of stroke does not need to be taken into account when selecting the duration of initial TAT, given that standard therapy for stroke prevention, i.e., OAC, is part of both TAT and DAT.

*SECTION 2.1. Which P2Y12 inhibitor, i.e., clopidogrel vs. ticagrelor vs. prasugrel, should be given in combination?*

 Given the lower bleeding risk with clopidogrel compared to ticagrelor or prasugrel in the seminal PLATO (14) and TRITON-TIMI 38 (15) trials in non-AF ACS patients, and the reported more than two-fold increase of bleeding risk with a prasugrel-based vs. clopidogrel-based TAT (16), the P2Y12 inhibitor of choice to be used in triple combination with OAC and aspirin should be clopidogrel (1, 17). The limited evidence ifor triple as well as double therapy combination with the more potent P2Y12 inhibitors ticagrelor and prasugrel, which in clinical trials comparing TAT (with VKA) and DAT (with NOAC) were used in the range of 4-12% and 1%, respectively, needs to be acknowledged (2-5). Switching to clopidogrel should always be performed according to current recommendations (17) when a patient in need for TAT is already on ticagrelor or prasugrel. Ticagrelor or prasugrel may possibly be considered in triple combination when TAT is anticipated to be limited to very few days and/or the in-hospital period (18) and the patient’s risk of bleeding is very low (i.e., young age, standard body weight, no previous history of bleeding, no renal dysfunction and/or hypertension and/or diabetes). DAT with OAC and ticagrelor or prasugrel may be possibly taken into consideration (19), especially in patients at increased risk of bleeding but deemed at persistent risk of stent thrombosis and/or recurrent myocardial events. Whether in these latter patients the decision on the use of clopidogrel instead may be guided by platelet function tests is currently unknown. As a routine policy, platelet function testing is currently discouraged (17).

 Of note, neither single (SAPT) nor dual antiplatelet therapy (DAPT) should be used for stroke prevention given the significant lower efficacy compared to OAC, even amongst patients with a single non-sex stroke risk factor, in the absence of significant differences in the occurrence of major or intracranial bleeding (20).

*SECTION 3.1. Which OAC, i.e., VKA vs. NOAC, should be chosen?*

 The OAC of choice in either TAT or DAT should be a NOAC because of the superior overall safety as compared to VKA in AF patients (21-24), the lower absolute incidence of bleeding with both dabigatran doses (and proportional to the dose) vs, VKA in combination with either SAPT or DAPT (25), and the unique evidence deriving from the AUGUSTUS trial (4) with apixaban, which allows to disentangle the contribution on safety of a NOAC versus VKA. Whereas this conclusion may be straightforward for AF patients already on a NOAC at the time of PCI, the decision on what OAC to choose may be more complex for patients who are instead on VKA. Given the increased risk of bleeding associated with the addition of either SAPT or DAPT (26), the potential harmful effects of a significant bleeding event in a patient who has recently undergone PCI (including those related to inappropriate withdrawal of one of more antithrombotic agents) (27), and the observation that the safety benefit of dabigatran-based DAT compared to VKA-based TAT is preserved regardless of whether patients were previously on VKA or not (28), switching from VKA to a NOAC appears generally advisable. This also for the entire lifespan of the patient who will receive a safer OAC also when combination therapy is over. An exception may be represented by those patients who derive from VKA the best possible treatment, i.e., a time in therapeutic range (TTR) of at least 70%, are at low risk of bleeding, and in whom combination therapy is anticipated to be limited to a rather short time (i.e., 1 week to 3-6 months).

*SECTION 3.2. Should a NOAC have been chosen, is there anyone to be preferred?*

In the absence of head-to-head comparisons between the different NOAC, and therefore the lack of clear demonstration of superior safety of any NOAC vs. another (21-24), the largely comparable treatment strategies evaluated in major trials (2-5), as well as the questionable rationale of changing an agent which was previously chosen as the optimal for the patient lifespan and has worked fine during previous time (if this is the case), the ongoing NOAC at the time of PCI may, and actually should, generally be confirmed. An exception may be when TAT is programmed since the beginning to be given for 6 months, a duration for which evidence is available only for apixaban (4), which therefore may be the NOAC to prefer. At variance, routine switching from another NOAC to apixaban whenever an initial, even short, course of TAT is chosen after PCI appears highly debatable (29). In fact, in the absence of specific reasons for not doing so, the original NOAC that has been previously deemed the optimal for the lifespan of the patient should actually be restarted when the course of TAT is finished and DAT, for which every NOAC has solid evidence (2-5), is initiated (29). The switching from one anticoagulant to another may be associated with an increased risk of both hemorrhagic and ischemic events (30), and therefore is not generally advised. Selection of the individual NOAC in AF patients undergoing PCI should likely be better guided by lifelong considerations, such as, risk of stroke and bleeding, patient compliance, co-morbidities, etc., rather than just the need to combine antiplatelet agents for a few weeks/months.

*Section 4.1. Which intensity of OAC, i.e., target International Normalized Ratio (INR) with VKA or drug dose with NOAC, should be pursued?*

 *Based on* observational data reporting a comparable incidence of bleeding events after PCI with TAT of VKA, aspirin, and clopidogrel and standard DAPT with aspirin and clopidogrel when the INR in the TAT cohort was maintained between 2.0-2.5 (31), the lower end of therapeutic range should generally be aimed for when TAT is carried out with VKA. What has never been addressed however, is whether such narrow INR range allows to obtain good quality OAC, commonly defined as a TTR above 70% (1). Of note, such target was not even accomplished in the rigorous experimental context of the most recent trials with NOAC in AF patients undergoing PCI, where moreover the optimal INR range in the TAT arm had been set 2.0-3.0 (2-5), The importance of having an adequate TTR should not go overlooked in these patients, given the observation of an inverse relationship between tTTR values and risk of major bleeding (32).

 When NOAC are used in either TAT or DAT, the issue of OAC intensity is related to the drug dose. All four NOAC are available in two doses, and their biological effect should be considered linearly proportional to the dose because of the first-order kinetic of these drugs. However, the significance of the two doses of dabigatran as compared to those of factor Xa-inhibitors apixaban, edoxaban, and rivaroxaban appears different given the different design of the phase III trials comparing the four NOAC to VKA for stroke prevention in AF patients (33). In the RE-LY trial dabigatran was given at the dose of either 110 or 150 mg twice daily in a same population (21). Hence, the intensity of OAC was lower with 110 mg and higher with 150 mg, as confirmed by the comparable efficacy and superior safety to VKA of the lower dose and the superior efficacy and comparable safety to VKA of the higher dose (21). At variance, in the factor Xa-inhibitors ROCKET AF (22), ARISTOTLE (23) and ENGAGE AF (24) trials, the two doses of NOAC were administered to two different populations, and the lower dose was given aiming at not increasing the intensity of OAC in those patients with clinical characteristics ultimately leading to an increase in exposure to, and therefore effect of, the drug as compared to patients without the above characteristics and receiving the higher dose (33). Thus, the higher and lower dose of dabigatran can be chosen by the physician based on the objective, i.e., superior safety on bleeding events vs. superior efficacy on stroke prevention, pursued (33). As a word of caution, it should be noted that an increased risk of stent thrombosis and/or myocardial infarction may be present when the lower dabigatran dose of 110 mg is used in DAT (3). The full vs. reduced dose of factor Xa-inhibitors should be mandatorily given only based on the absence vs. presence respectively, of specific clinical factors mandating dose reduction in clinical trials (33). Inappropriate use of reduced doses of factor Xa-inhibitors in real-world settings has been shown to likely provide an increase in safety without properly protecting against stroke (34). With the possible exception of rivaroxaban that has been tested in the PIONEER- AF PCI trial (2) at the off-label reduced dose of 15 mg once daily, with no apparent harm in terms of stroke prevention, all factor Xa-inhibitors in both TAT (for which however only apixaban has adequate evidence) (4) or DAT should always be given at the appropriate dose, that is, full in the absence and reduced in the presence respectively, of the established clinical variables.

*Section 5.1. Which OAC, i.e., VKA vs. NOAC, should be chosen for long-term monotherapy?.*

 Based on historical data in patients with ACS (35, 36), as well as more recent evidence in patients with stable CAD (defined as freedom from myocardial infarction and/or coronary revascularization > 1 year) (37), there is comparable efficacy on recurrent cardiovascular events of OAC monotherapy with VKA and either aspirin alone or combination of VKA and aspirin; hence, indefinite VKA monotherapy is the option after 12 months of combined antithrombotic therapy when VKA is the ongoing OAC (1).

Because of the overall superior safety of NOAC vs. VKA in AF patients (21-24), as well as the superior safety of NOAC monotherapy vs. combination of NOAC and aspirin recently reported in AF patients with stable CAD (38, 39), switching to a NOAC may be considered for indefinite therapy in patients previously on VKA. When NOAC is already part of combination therapy during the first 12 months after PCI, then NOAC monotherapy should be confirmed indefinitely. In the lack of direct comparisons of different NOAC in AF patients with stable CAD, no specific agent appears to be preferred and the ongoing drug should generally be continued, unless specific reasons, i.e., side effects, adherence, etc., suggest switching to another agent.

CONCLUSIONS

 While acknowledging the persistence of gaps in evidence, especially regarding efficacy, in the antithrombotic management of AF patients undergoing PCI, it must be recognized that a large body of data is nowadays available, and guidelines and consensus papers are consistent in addressing current clinical practice. Given the numerous aspects to be considered when arranging the antithrombotic therapy in these patients, the practical questions and sequence of answering proposed and discussed above may be of use to assist decision-making by the responsible physician.

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LEGEND OF FIGURES

Figure 1: Algorithm for the management of antithrombotic therapy in AF patients undergoing PCI: agents and durations suggested (1). AF: atrial fibrillation; PCI: percutaneous coronary intervention; O: oral anticoagulant; A: aspirin; C; clopidogrel; mo.: months.

Figure 2. Questions to be answered in sequence when arranging antithrombotic therapy in AF patients undergoing PCI. AF: atrial fibrillation; PCI: percutaneous coronary intervention; TAT: triple antithrombotic therapy; OAC: oral anticoagulant; VKA: vitamin K-antagonist; NOAC: non-vitamin K-antagonist oral anticoagulant; DAT: double antithrombotic therapy