Antithrombotic therapy and bleeding risk in atrial fibrillation. Fewer unanswered questions

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Atrial fibrillation (AF) is associated with increased risk of stroke and thromboembolism, and oral anticoagulation (OAC) with coumarin derivatives is indicated in patients considered at “moderate-high risk”. The current European Society of Cardiology (ESC) guidelines recommend the CHA2DS2-VASc score for stroke risk stratification in patients with AF (1, 2), given the limitations associated with the older CHADS2 score (3, 4). Of note, the net clinical benefit favours OAC for almost all AF patients, with the exception being patients who are at very low risk of ischaemic stroke, with a CHA2DS2-VASc score =0 (5, 6). Accordingly, when the CHA2DS2-VASc score is applied, the proportion of patients with an indication for OAC could raise almost to 94% (7).

The use of OAC is associated with an increased risk of major bleeding, with intracranial haemorrhage, the most dangerous complication associated with warfarin. Although rates of intracranial bleeding are considerably lower than in the past (<1% in contemporary reports), its development is often fatal (8, 9). An increased risk of bleeding may also occur with aspirin, and or dual-antiplatelet therapy using aspirin plus clopidogrel (10), or with concomitant OAC with antiplatelet therapy (6).

Bleeding risk plays an important role on prognosis, and such risk should be assessed before starting OAC, or even more when combined antithrombotic therapy is used (11). How do we assess bleeding risk? The HAS-BLED bleeding risk score has been proposed as a practical tool to assess the individual bleeding risk in AF patients, potentially supporting clinical decision-making regarding antithrombotic therapy in AF patients (11, 12), whereby a score of ≥3 indicates ‘high risk’. Although the prognosis of patients with high risk of bleeding using the HAS-BLED score is worse (13), the ‘net clinical benefit’ of OAC by balancing ischaemic stroke balanced against intracranial haemorrhage is greater even in those patients with a HAS-BLED score ≥3, given that the absolute benefit of ischaemic stroke reduction would outweigh the increase in serious bleeding (6, 14).

In this issue in Thrombosis and Haemostasis, Azoulay et al. provide us with valuable information on the risk of bleeding in patients with AF whilst taking various antithrombotic regimens (15). Based on a study population of over 70,000 patients newly-diagnosed with chronic AF, they conclude that while all antithrombotic therapies are associated with an elevated risk of bleeding, the risk increases in an additive fashion with dual and triple antithrombotic therapy, particularly in combinations containing warfarin. They use those patients not exposed to any antithrombotic therapy in the year prior to index date, as their primary comparator group. Secondly, the authors give the crude and adjusted increased bleeding risk compared to the warfarin arm.

These comparisons demonstrated the burden associated with the use of different antithrombotic therapy combinations. Indeed, warfarin monotherapy was associated with an over-two-fold increased risk of any bleeding event. On the contrary, monotherapy with aspirin or clopidogrel had similar bleeding event rates as the “no use of any antithrombotic therapy” arm. Although the use of antiplatelet therapy monotherapy in patients with AF is highly debatable, the present study suggests that aspirin (or clopidogrel) monotherapy could be safer than warfarin in terms of bleeding.

The information provided about the dual antithrombotic therapy by Azoulay et al. (15) is also remarkable given the scarce data on the different antithrombotic combinations. Dual antithrombotic therapy containing warfarin was associated with a three-fold increased risk of bleeding in warfarin-aspirin or warfarin-clopidogrel combinations. Interestingly, the risk of bleeding seemed similar with either of combinations. On the other hand dual-antiplatelet therapy showed a risk of any bleeding slightly inferior to OAC (1.68 fold increased risk of any bleeding event). While dual-antiplatelet therapy may have a limited role in everyday clinical practice, Azoulay et al. (15) did not find significant differences in the intracranial haemorrhage between dual antiplatelet therapy and no-antithrombotic arm.

Triple therapy (TT) and the other combinations of OAC plus one antiplatelet drug are basically indicated in patients with AF with acute coronary syndrome (ACS) and/or coronary stenting (16-18). Importantly, coronary artery disease is present in around 20-30% of patients with AF (19). Besides, many more patients with AF are undergoing coronary angioplasty and stenting.

Nonetheless, patients with AF presenting with an ACS or with chronic ischaemic heart disease undergoing percutaneous coronary intervention with stent implantation represent a complex management problem (17, 18, 20). It is recognised that TT increases the risk of bleeding, and Azoulay et al. (15) confirm this, by show-
ing an 80% increased risk of bleeding when compared to warfarin monotherapy.

When TT is indicated, we should try to have the shortest possible time exposed to such a regimen. The duration of TT is mainly determined by two variables: the clinical setting (non-modifiable variable) and the type of stent (modifiable variable). Knowing that the benefit of dual antiplatelet therapy in patients with ACS is mainly obtained during the first months, the type of stent may be the variable that influences the length duration of triple therapy. There is unanimity in that drug-eluting stents (DES) use should be avoided or strictly limited to those clinical and anatomical situations such as long lesions, small vessels, diabetic patients, where a significant benefit is expected as compared to bare-metal stent (BMS) (21). Although we should prioritise the use of BMS, revascularisation with DES can be an option in patients with a high restenotic risk, diabetes, multiple vessel disease, etc - but always with newer second or third generation DES (that requires much shorter dual antiplatelet therapy use) and adapting the duration of TT to the bleeding risk. Indeed, TT could be prolonged six or 12 months in patients with high thrombotic risk and low bleeding risk, or (alternatively) be reduced to three months in those patients at high bleeding risk.

The management algorithm that we have recently proposed (22) (▶ Figure 1) is based on the recommendations from the Consensus Document by the European Society of Cardiology Working Group on Thrombosis, giving a very important weight to bleeding risk (16). The use of BMS should be recommended in patients with high haemorrhagic risk. Nevertheless, DES use should have a place, even in these high-bleeding-risk patients. In particular cases, the use of TT could be used during the first six months followed by the OAC plus one antiplatelet drug during the first year. The duration of antiplatelet therapy must also take into account the thrombotic risk (e.g. ‘high risk’ ACS; several DES; treatment of proximal left anterior descending or left main coronary artery; long lesions, etc.). The recent European and North American consensus documents

**Figure 1: Recommendations for the duration of triple therapy and antithrombotic strategies in patients with atrial fibrillation at moderate-to-high thromboembolic risk and coronary stenting.** AF, atrial fibrillation; BMS, bare-metal stent; DES, drug-eluting stent; OAC, oral anticoagulation; TR, thrombotic risk; TT, triple therapy (oral anticoagulation+acetylsalicylic acid [100 mg/day]+clopidogrel [75 mg/day]). Reprinted with permission from Rev Esp Cardiol 2013; 66: 12-16.
(16-18) both agree that warfarin alone should be given indefinitely after 12 months and that concomitant antiplatelet therapy should be used in patients with high risk of thrombotic events with a low risk of bleeding.

The findings of the present study should be interpreted in the setting of the study design and its limitations, as the authors recognise (15). When considering the balance of risk and benefit, not every major complication (major bleeding, embolism, cardiac events) can be weighted equally (23), and depending upon patient’s values and preferences, some may wish to avoid thrombotic complications (or even death) compared to reducing major bleeding complications, or vice versa. For these reasons, it is crucial to try to quantify the severity of bleeding events (11). Another limitation is that changes of antithrombotic regimens in these patients may have occurred during the follow-up period, sometimes in relation with the presence of thrombotic or haemorrhagic complications. Also, we do not have unequivocal information about the quality of anticoagulation control for warfarin; a fact that could have a high impact on stroke and major haemorrhagic events, but that on the other hand reflects the reality of the clinical management of these patients whereby the recommendations about an strict control of the international normalised ratio may not be entirely optimal.

**Conflicts of interest**

Dr. Ruiz-Nodar has received research grants and speaker fees from Medtronic, Boston Scientific and AstraZeneca. Dr. Marin has received research grants from and served in the speakers bureau of Bayer, Boehringer Ingelheim and Pfizer.

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