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Atrial fibrillation and ischaemic heart disease: should we use acetylsalicylic acid beside anticoagulants?

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Coexistence of atrial fibrillation and ischaemic heart disease is very common and patients affected by these conditions are exposed to both a high ischaemic and haemorrhagic risk. The choice of an appropriate combination of anticoagulant therapy with single or dual antiplatelet treatment is indeed one of the most relevant and contemporary challenges in clinical practice. Several studies and meta-analyses pointed out that 1 year after an acute coronary syndrome or percutaneous revascularization, the use of the sole anticoagulant therapy is not associated with increased risk of major cardiovascular events, whereas there is a substantial reduction of clinical significant bleeding events, as compared to patients treated also with antiplatelet medications. However, there are no clear-cut data regarding the possibility to implement this strategy in each patient, regardless the cardiovascular risk class. Furthermore, for patients requiring a combined anticoagulant and antiplatelet treatment, the available data seem to favour an association of direct anticoagulant and inhibitors of P2Y12, rather than regimens including aspirin. These data are derived mainly from observational studies, with all their limitations. The use of aspirin could be beneficial in patients with significant comorbidities, such as diabetes mellitus, or with severe peripheral atherosclerotic disease, involving the carotids and other large arteries.

Introduction

The coexistence of atrial fibrillation (AF) and ischaemic heart disease is a very frequent condition, requiring complex therapeutic strategies and representing a real clinical challenge for physicians. About 30% of patients with AF have coronary artery disease and undergo percutaneous myocardial revascularization (PCI). Conversely, 15% of subjects with ischaemic heart disease experience at least one episode of AF during their lifetime.[1] Considering that the estimated prevalence of AF worldwide is ~33.5 million people, 10 million individuals may be the candidate for combination therapy with antiplatelet and anticoagulant drugs during their lifetime. These patients present both a high ischaemic and haemorrhagic risk (two-fold higher than those not on antiplatelet therapy), related to the underlying pathologies and to the need to receive both antiplatelet, sometimes in dual therapy, and anticoagulant drugs.[2] Moreover, it has been shown that bleeding events that occur after percutaneous or surgical revascularization are often associated with a worse prognosis.[3] At the same time, the fear of an increased rate of serious bleedings, particularly intracranial, leads to an insufficient prescription of anticoagulant therapy in patients who are already taking antiplatelet agents, exposing them to an unacceptable risk of thromboembolic events, especially at brain level, without significant benefit in the reduction of haemorrhagic events.

Indeed, it has been widely demonstrated that prescribing an anticoagulant therapy is mandatory in patients with CHA_2DS_2-VASc [congestive heart failure, hypertension, age

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≥ 75 years, diabetes mellitus, prior stroke of transient ischaemic attack or thromboembolism, vascular disease, age 65–74 years, and sex category (female)] ≥2. At the same time, it is also important to underline that therapy with antiplatelet agents is fundamental in secondary prevention [re-infarctions, recurrent myocardial infarction (MI), and more specifically acute and late stent thrombosis][4] in patients with ischaemic heart disease.

Since the available evidence is heterogeneous and somehow conflicting, the choice of the most appropriate combination of an anticoagulant therapy with a single or double antiplatelet therapy, with the aim to adequately match ischaemic and haemorrhagic risk, represents a real challenge in clinical practice, especially in patients undergoing PCI.

The general consensus, also endorsed by the main international guidelines, is to maintain anticoagulant therapy and to modify the intensity and duration of the antiplatelet therapy.[5] Several studies and meta-analyses have shown that, 1 year after an acute coronary syndrome or a PCI procedure, the use of single anticoagulant therapy does not increase the risk of major cardiovascular events (MI, ischaemic stroke, systemic embolism) and mortality from all causes (regardless of the type of stent, medicated or metallic, implanted), but it is associated with a significant reduction of major bleedings (based on the Thrombolysis in Myocardial Infarction score), compared to patients treated also with a single antiplatelet therapy.[6,7] The AFIRE study (Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease), conducted in 2236 patients with AF and stable coronary artery disease, has demonstrated the non-inferiority of a direct oral anticoagulant (DOAC), rivaroxaban alone, compared to combination therapy with a single antiplatelet agent, in the primary composite efficacy endpoint (stroke, systemic embolism, MI, unstable angina with the need for revascularization, death from all causes), against fewer major bleeds.[8]

These studies, however, were not able to clarify whether this type of strategy can be adopted for all patients, or restricted to those who have a reduced risk of ischaemic events or, vice versa a prohibitive bleeding risk. Furthermore, these studies enrolled only patients with acute coronary syndromes, excluding the large group of subjects with stable coronary artery disease. For this reason, due to the lack of additional evidence, it is not possible to provide general recommendations, and further randomized trials are required.[9]

In patients with high haemorrhagic risk (e.g. elderly, HASBLED > 3), the European guidelines on myocardial revascularization suggest to combine anticoagulant therapy with a dual antiplatelet therapy (aspirin and clopidogrel) for 1–3 months, to continue with a single antiplatelet drug up to 12 months from revascularization and finally to maintain anticoagulant therapy only. Otherwise, in those subjects who have a low bleeding risk, a triple therapy should be proposed for the first 6 months after coronary angioplasty.[10]

Although it is well established that the use of DOAC reduces the risk of bleeding events compared to vitamin K antagonists (VKA), probably as a consequence of their direct action on the coagulation cascade (inhibition of factor Xa or prothrombin), the evidence on which antiplatelet regimen to administer still remains inconclusive. In both PIONEER AF-PCI (Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention)[11] and RE-DUAL PCI (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting)[12] trials, combination therapy with a DOAC (rivaroxaban 15 mg and dabigatran 150 or 110 mg twice daily, respectively) and a P2Y12 inhibitor (mostly clopidogrel) has been demonstrated to be equally effective in reducing mortality, MI, and stroke compared to triple therapy based on warfarin, aspirin, and P2Y12 inhibitors, against a significant reduction (∼40%) of major bleeding events, in patients undergoing coronary angioplasty (in >50% of cases for acute coronary syndromes). These studies, however, did not evaluate the effects of a triple therapy with DOAC, aspirin, and P2Y12 inhibitors, which would probably have been associated with fewer major and minor bleedings than VKA.

More recently, in the AUGUSTUS trial (Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation), a two-by-two factorial design study, 4614 patients with AF who underwent PCI following an acute coronary syndrome were randomized to receive P2Y12 inhibitor in association with apixaban or VKA and aspirin or placebo for 6 months. The apixaban-based regimen without aspirin was associated with the smallest number of clinically relevant bleeds (16.1% vs. 9%) and hospitalizations, in the absence of significant differences in the incidence of ischaemic events (MI, stroke, stent thrombosis, and urgent revascularization).[13] However, it should be noted that there was no significant increase in the risk of intracranial bleedings in the aspirin group. A 2018 meta-analysis conducted in 5317 patients showed that a combination therapy based on DOAC and P2Y12 inhibitors represented a more adequate strategy than triple therapy in terms of reduction of major and minor bleedings (47%), with a comparable efficacy in the prevention of atherothrombotic events. However, it should be emphasized that a significant difference in the number of intracranial bleeds were not demonstrated.[14]

These data were confirmed by a subsequent meta-analysis published in 2019, which demonstrated that, in 9924 patients suffering from AF and undergoing PCI, therapeutic strategies that did not include the use of aspirin were associated with a lower bleeding risk and with a comparable ischaemic risk, including stent thrombosis (which is one of the main reasons for the use of dual antiplatelet therapy in the months following a percutaneous revascularization). However, it should be noted that the absolute number of atherothrombotic events was higher in the placebo group than in the aspirin group. The authors therefore suggested to prefer a combination regimen of DOAC and P2Y12 inhibitors, avoiding triple VKA-based therapy and dual antiplatelet therapy.[15]

According to these results, the use of aspirin should be considered a second choice, since the small benefit in terms of efficacy outcomes would correspond to a

significant increase in the absolute risk of clinically relevant bleeding.

However, many of the studies analysed are observational and suffer of important limitations which should be highlighted:[16]

(1) In most cases, precise information on antiplatelet therapy, including the types of drugs and their dosages, was available only at the time of enrolment and eventual therapeutic changes were not recorded during follow-up, nor data about the antithrombotic regimen actually taken at the time of onset of ischaemic or haemorrhagic events.
(2) Subgroup analyses according to comorbidities and main cardiovascular risk factors, including diabetes mellitus, the presence of carotid atherosclerosis, and peripheral artery disease of the lower limbs have not been performed.
(3) The use of new generation drug-eluting stents, characterized by a very low incidence of thrombosis (<1%), could have played a role in the absence of significance in the reduction of ischaemic events.
(4) The increased number of bleedings, even minor, related to the use of a triple therapy could have led to the withdrawal of one of the two antiplatelet drugs and consequently to a greater number of ischaemic events in the triple therapy group.
(5) Dual therapy regimens based on DOAC and aspirin have not been analysed.
(6) Clopidogrel has a lower gastrointestinal detrimental effect, which could have led to fewer bleedings than aspirin.
(7) Proton pump inhibitors, which received a Class IA recommendation by the latest guidelines and which might have a role in reducing and almost eliminating gastrointestinal bleedings (the most frequent cause of aspirin-related bleedings) were not used in most studies.[17]
(8) It has been recently suggested that the dosage of aspirin should be adjusted for body weight in order to maintain therapeutic efficacy.[18] However, no subgroup analyses based on this parameter have been performed.

For these reasons, further trials, possibly randomized and double-blinded, exploring differences in the intensity of anticoagulation and antiaggregation in groups treated with double or triple therapy are certainly desirable in the future.

European guidelines on chronic coronary syndromes recommend the use of triple therapy with aspirin, clopidogrel, and an anticoagulant (preferably DOAC) for over a month after coronary revascularization if the risk of stent thrombosis exceeds the haemorrhagic thrombosis (Class IIa, level of evidence C).

Furthermore, insufficient data are available regarding the treatment of patients with stable coronary artery disease who have not undergone PCI and who are treated conservatively with medical therapy alone. No prospective studies have yet been carried out regarding the addition of aspirin on top of DOAC therapy, thus it is not possible to provide an exhaustive and definitive answer. Within this category, the use of aspirin could be particularly beneficial for those patients with a high or very high-risk profile, such as those with diabetes and severe atherosclerotic disease, both at coronary (e.g. involvement of three vessels) and peripheral artery (carotid arteries and arterial circulation of the lower limbs) levels. In this regard, European guidelines suggest the use of aspirin in addition to anticoagulant therapy for patients at high risk of recurrent ischaemic events (in particular with history of MI) in the absence of a considerable risk of bleeding (Class IIb, level of evidence B).[17] In patients with high atherothrombotic risk (previous MI, multivessel disease, age over 65 years), the COMPASS study (Cardiovascular Outcomes for People Using Anticoagulation Strategies) has shown that the combination of aspirin with rivaroxaban at the very low dosage of 2.5 mg twice daily is associated with a significant reduction in mortality (23%) and stroke (44%) incidence.[19]

Another category to consider with caution is certainly represented by patients undergoing surgical revascularization by coronary artery bypass grafting.[20] In these subjects, indeed, coronary artery disease is particularly widespread and the risk of occlusion of the grafts or vessels downstream of the anastomoses can be very high and could be reduced by adding aspirin to anticoagulant therapy. However, up to now, no clinical trials have specifically analysed this category of patients. In addition, it should be also underlined that the effectiveness of aspirin in secondary prevention has been largely demonstrated by several prospective randomized trials, characterized by large sample sizes, and subsequently proven by relevant meta-analyses.[21]

In the absence of more precise recommendations from international guidelines and future or ongoing trials, physicians should evaluate each patient individually and carefully establish the risk/benefit ratio between an increased bleeding risk and the efficacy of secondary prevention of major cardiovascular events.[22] An initial more tight and rigorous follow-up strategy is also of fundamental importance, with the aim to adequately modify ongoing therapies in the case of occurrence of symptoms or adverse events.

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