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(CASE REPORT)

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Antithrombotic management in patients with atrial fibrillation, coronary artery disease, and intracranial hemorrhage: A case report and critical review of the literature

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Abstract

The coexistence of atrial fibrillation (AF), coronary artery disease (CAD) and the onset of intracranial haemorrhage (ICH) presents a complex therapeutic challenge, given the need to prescribe triple antithrombotic therapy to patients at high risk of bleeding and thrombosis. International guidelines advocate an individualized approach based on risk stratification.

This case study presents the case of an octogenarian male with permanent atrial fibrillation (AF) and coronary artery disease (CAD), who underwent percutaneous revascularization and required sequential antithrombotic therapy. During his clinical course, he experienced an acute hemorrhagic cerebrovascular event, raising challenges regarding the timing of restarting appropriate antithrombotic therapy to provide the best efficacy and safety profile. Considering scientific evidence published up to 2024 and guidelines published by the ACC/AHA/ESC in 2024, we discuss sequential anticoagulation and antiplatelet restart strategies in patients with multiple cardiovascular comorbidities and central nervous system bleeding. Our case study highlights the importance of adopting a balanced therapeutic strategy tailored to each patient, incorporating thrombotic and hemorrhagic risk stratification tools to facilitate the most appropriate therapeutic decision and optimize efficacy and safety.

Keywords: Atrial Fibrillation; Intracranial Hemorrhage; Anticoagulation; Antiplatelet; Coronary Stent

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia of clinical significance. In adjusted models, AF is associated with increased morbidity, especially stroke and heart failure, as well as increased mortality. AF and coronary artery disease (CAD) are two common cardiovascular conditions that have many shared risk factors and pathophysiological mechanisms. AF affects approximately 2–3% of the general population and its prevalence increases with age, affecting around 10% of people over 80(1). Conversely, CAD is the leading cause of cardiovascular disease and mortality worldwide. It is estimated that around 30% of patients with AF also have CAD. The combination of AF with CAD is the area where use of multiple antithrombotic drugs is most frequently indicated, consisting of antiplatelet agents plus direct oral anticoagulant (DOAC). There is a general trend to decrease the duration of dual antiplatelet therapy (DAPT) to reduce bleeding; however, this may increase ischaemic events and stent thrombosis, which complicates therapeutic decision-making due to the need to combine anticoagulants and antiplatelet agents(2).

AF is a powerful risk factor for stroke, independently increasing risk ≈5-fold throughout all ages. The percentage of strokes attributable to AF increases steeply from 1.5% at 50 to 59 years of age to 23.5% at 80 to 89 years of age(3). The

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situation worsens in cases that begin with intracranial hemorrhage (ICH), an event that constitutes one of the most feared complications of antithrombotic therapy, especially in elderly patients. Despite therapeutic advances, there is no absolute consensus on the ideal timing and optimal combination of drugs that offer an adequate safety and efficacy profile in this group of patients who debut concomitantly with these 3 diseases.

We present a complex case, which raises therapeutic challenges in which the three entities coexist concomitantly: AF, revascularized CAD with stent implantation, and traumatic ICH. Through the presentation of this case, we illustrate the therapeutic decisions taken, based on the most updated scientific literature.

2. Presentation of the case

An 81-year-old male, with a history of hypertension, permanent atrial fibrillation under management with direct oral anticoagulants (ACOD) and type 2 diabetes mellitus, who presented with sudden loss of consciousness and spontaneous recovery before 30 seconds, causing cranioencephalic trauma, accompanied by anterograde amnesia, without signs of neurological focalization.

Physical examination showed blood pressure: 150/90 mmHg, heart rate 55 beats per minute, respiratory rate 16 breaths per minute, peripheral oxygen saturation 99% without oxygen therapy, temperature: 37 degrees Celsius. On cardiovascular examination with arrhythmic heart sounds, no signs of intravascular or interstitial congestion. On neurological examination without sensory or motor focalization. 12-lead electrocardiogram in atrial fibrillation rhythm with a rate ventricular of 50 bpm, left atrial dilatation, preserved intraventricular conduction, without data of myocardial injury or ischemia. Blood biochemistry shows pancytopenia without absolute neutropenia with WHO grade II macrocytic anemia, mild thrombocytopenia, coagulation times not prolonged, creatinine, urea nitrogen, aspartate aminotransferase, alanine aminotransferase and bilirubins in normal range.

Complementary studies were performed and vitamin B12 levels were found to be 106 picograms/milliliter. This established vitamin B12 deficiency as the cause of pancytopenia, and supplementation was initiated. In addition, a doppler ultrasound of the carotid arteries was performed, revealing: Atheromatosis of the bilateral extracranial cerebral arteries due to intimal thickening without the formation of atherosclerotic plaques. A transesophageal echocardiogram revealed evidence of a left ventricle with slightly depressed systolic function (43%) and diffuse hypokinesia. There was also aortic valve sclerosis with mild to moderate insufficiency, as well a dilatation of the left atrium with an area of 44 ml/m^2 accompanied by spontaneous echo contrast. However, the left atrial appendage was free of thrombus.

Taking the clinical presentation and paraclinical findings into account, coronary angiography was performed. This showed that the right coronary artery was the dominant vessel and that there was a 70% ulcerated lesion in the middle third. Angioplasty and implantation of an Ultimaster Tansei 3.5 x 18 mm medicated stent was performed, resulting in final angiographic flow of TIMI III. The patient presented with extreme bradycardia at 20 beats per minute. This required the administration of atropine and the placement of a transient pacemaker as an emergency measure.

Evaluated by electrophysiology considering slow atrial fibrillation, debuted with syncope episode that led to hospitalization, presenting extreme bradycardia after cardiac catheterization requiring transient pacemaker placement. Concluding data of sick sinus syndrome, conduct implantation of definitive unicameral pacemaker, implanted ASSURITY MRI ABBOTT ST. JUDE MEDICAL performing programming of the device a ventricular rate of 60 bpm.

During his evolution, the patient showed a deterioration in consciousness, expressed as drowsiness with a tendency towards stupor and disorientation in all three spheres, without any motor or sensory neurological focalization. Cranial tomography revealed left frontal cerebral contusions with laminar subdural haemorrhage and a preserved midline, with no evidence of hydrocephalus. The neurosurgery service evaluated this and considered it to be of traumatic origin. They recommended maintaining clinical surveillance of the neurological status and performing a control tomography scan. His state of consciousness improved during his recovery, but disorientation persisted in all three spheres. A control cranial tomography scan five days after the bleeding revealed a resolving haematoma without mass effect or midline displacement. The neurosurgery group maintained conservative management.

We have a patient with permanent atrial fibrillation and traumatic intracranial haemorrhage who has had a coronary stent implanted within the last month. He requires triple antithrombotic therapy for 7–30 days to reduce the risk of ischemia and stent thrombosis.

The patient was categorized as being at high risk of major bleeding using the HAS-BLED and DOAC scores, with scores of 4 and 10 respectively, in addition to being at high cardioembolic and thrombotic risk, with a CHA_2DS_2-VA score of 6.

An interdisciplinary approach involving the neurology, neurosurgery, cardiology and internal medicine services was adopted, with the aim of controlling the bleeding mechanism and reducing the volume of the haematoma. Taking these data into account, dual antiplatelet therapy was initiated for 30 days to avoid stent restenosis. After this period, the patient will continue with simple antiplatelet therapy with clopidogrel until the one-year treatment period is complete. Regarding anticoagulation, after carrying out neuroimaging control, apixaban 5 mg twice daily will be started 3 weeks after the index bleeding event and continued indefinitely. The patient made a satisfactory recovery without evidence of new neurological focality or acute coronary events and was discharged from hospital with a follow-up appointment with cardiology and neurosurgery.

3. Discussion

The coexistence of AF and CAD is frequent and poses extremely important clinical challenges. It is estimated that up to 30% of patients with AF also have CAD (1). This association increases the risk of adverse cardiovascular events, such as ischemic stroke and myocardial infarction. In fact, the risk of cerebral ischemic attack, doubling compared to those patients with only one of the two conditions. The management of patients with AF and CAD involves the appropriate use of antithrombotic strategies, including anticoagulation and antiplatelet therapy (2).

The use of oral anticoagulants and antiplatelet agents is supported by a strong scientific evidence base. The PIONEER AF-PCI study published in 2016, was a multicenter clinical trial that compared three treatment strategies in patients with atrial fibrillation who underwent percutaneous coronary intervention (PCI), who were randomized to receive rivaroxaban 15 mg dud plus P2Y12 inhibitor (clopidogrel) or rivaroxaban 2.5 mg bid plus dual antiplatelet therapy, (DAPT), and Warfarin plus DAPT, in which the objective was to evaluate the safety and efficacy of these three strategies. The aim of the study was to evaluate whether a dual-therapy strategy with rivaroxaban would reduce the risk of bleeding without increasing the risk of thromboembolic events compared with standard triple therapy. The results showed that the dual-therapy strategy with rivaroxaban significantly reduced the risk of major bleeding and clinically relevant nonmajor bleeding compared with standard therapy, without a significant increase in the risk of thromboembolic events. The results demonstrated that the use of rivaroxaban in combination with a P2Y12 inhibitor reduced major bleeding and did not increase the risk of thrombotic events compared with triple anticoagulation therapy(4).

One of the main pillars of evidence collection in the case of management of patients requiring antithrombotic therapy after a bleeding complication in coronary artery disease and/or atrial fibrillation is the expert consensus document of the Working Group on Thrombosis of the European Society of Cardiology. The first thing the consensus defines is thrombotic risk stratification into 5 categories: low, low to moderate, moderate, high and very high. The second element considered in the choice of therapy in these patients is the risk of recurrent bleeding, for which characteristics are defined according to the severity of bleeding and clinical onset(5).

According to the expert consensus of the European Society of Cardiology Working Group on Thrombosis, recommendations have been proposed for antiplatelet management after an episode of extracranial bleeding in patients who have received a coronary device in the last 12 months. First, the importance of an individualized assessment of thrombotic risk and bleeding risk in each patient is emphasized.

In patients at low risk of recurrent bleeding and high thrombotic risk, it is recommended that dual antiplatelet therapy, consisting of a combination of aspirin and a P2Y12 receptor inhibitor, be restarted early. This strategy is based on the evidence that dual antiplatelet therapy significantly reduces the risk of thrombotic events in patients with coronary artery disease and has demonstrated solid clinical benefits in previous studies. However, in patients with an increased risk of recurrent bleeding, a reduction in antiplatelet therapy to antiplatelet monotherapy, preferably with a P2Y12 receptor inhibitor, should be considered(5).

The European Heart Rhythm Association Practice Guideline establishes recommendations regarding the duration of triple therapy in patients with AF after PCI. Triple therapy with DAPT and an DOAC for up to 30 days may be advisable in patients at high atherothrombotic risk, as was the case in our patient. In contrast, continuation of triple therapy beyond 30 days rarely seems justified(6).

Therefore, the choice of anticoagulant, as well as the duration of triple and dual therapy, should be personalized based on atherothrombotic, cardioembolic, and bleeding risk. It is strongly recommended to formally assess the risk of stroke and cardiac ischemic events using validated tools such as the CHA_2DS_2-VA scores and the Global Registry of Acute Coronary Events (GRACE)(7).

Estimation of bleeding risk should lead to efforts to correct or reduce reversible bleeding risk factors. The use of proton pump inhibitors should be encouraged in all patients with a combination of antiplatelet and anticoagulants. In patients with acute coronary syndrome (ACS) at high risk of bleeding, the duration of DAPT may be shorter (3 to 6 months). If concomitant AF is present or develops during the first year after an ACS and there is an indication for anticoagulation, an ACOD should be initiated and the need for continued TAPD carefully weighed against the increased risk of bleeding, beyond 1 month after the index event, aspirin can be discontinued in most of these patients(8).

Regarding the impact of intracranial hemorrhage, it should be considered that approximately 0.2-0.6% of patients with coronary syndrome develop intracranial hemorrhage (ICH) annually while on antiplatelet therapy and up to 0.5-1.0% of patients treated with oral anticoagulant. The big question in these patients is: when is it indicated to safely restart anticoagulation?

In addition to its immediate prognosis, ICH in the setting of AF is also associated with subsequent ischemic stroke and mortality, in part due to discontinuation of anticoagulation after ICH. However, a history of spontaneous ICH constitutes a contraindication to anticoagulation as labeled for vitamin K antagonists (VKAs) and DOACs, unless the cause of bleeding (such as uncontrolled hypertension, aneurysm or arteriovenous malformation, or triple medical therapy) has been reversed.

There are no evidence-based guidelines on the use of OAC in patients with AF after ICH. Current knowledge is based on observational data (mainly retrospective) with varying proportions of patients with ICH and AF restarting DOACs predominantly or exclusively with VKA. (9) Observational studies involving patients with AF and a history of ICH showed that restarting oral anticoagulation with an DOACs versus VKA was associated with similar or lower rates of ischemic stroke with no (or even lower) differences in recurrent ICH.

In randomized controlled trials, the incidence of subdural and epidural hematomas in AF patients on DOACs therapy was <0.2% and <0.1% per year, respectively. Although specific data are lacking, it appears to be safe to initiate or restart DOACs approximately 4 weeks after (surgical removal of traumatic epidural or subdural hematoma (HSD), particularly in the absence of drug/alcohol abuse or substantial risk of falls. Depending on the clinical presentation and extent of hematoma, brain imaging (using CT or MRI) is recommended before restarting OAC. (10)

The optimal management of patients who have experienced intracerebral bleeding and require subsequent anticoagulation therapy remains a clinical challenge. The decision to restart anticoagulation in these cases is based on a careful assessment of the balance between the benefits of preventing thromboembolic events and the potential risks of recurrent bleeding. Among the key studies supporting the possibility of restarting anticoagulation therapy in this setting: the RESTART study, conducted in 2019, evaluated restarting anticoagulation therapy after intracranial bleeding in patients who were receiving oral anticoagulants. The results showed that restarting anticoagulant therapy after an adequate 3- to 4-week break did not significantly increase the risk of recurrent intracranial hemorrhage compared with those who did not restart therapy. Furthermore, it was observed that the benefits in reducing the risk of thromboembolic events outweighed the risks of bleeding. (11). The duration of discontinuation of oral anticoagulant therapy may vary, but a break of at least 3 to 4 weeks is generally suggested.

Given the complexity of the case presented and the multiple comorbidities of patients with high thrombotic risk but also high bleeding risk, one of the management possibilities is surgical treatment of atrial fibrillation, thus avoiding long-term anticoagulation in these patients with a high risk of bleeding recurrence. Percutaneous occlusion of the left atrial appendage is another option that may be considered for those patients with contraindications to long-term anticoagulation; however, it also requires dual antiplatelet therapy for at least 1 to 3 months, which establishes a bleeding risk similar to that of anticoagulation (12).

Surgical management, including pulmonary vein isolation (PVI), has been widely investigated as a therapeutic option to control symptoms and improve outcomes in patients with AF. Several studies, such as FIRE AND ICE (2016), RAAFT-2 (2017), and STAR-AF II (2017), have demonstrated the effectiveness of PVI with different modalities of radiofrequency, catheter ablation and cryotherapy in maintaining sinus rhythm and reducing ablation-related adverse cardiovascular events. In addition, the CASTLE-AF study (2018) showed that PVI in patients with heart failure and AF resulted in a significant reduction in the combined events of cardiovascular death or hospitalization for heart failure compared with optimal medical therapy (10).

4. Conclusion

The antithrombotic management of patients with atrial fibrillation and revascularized coronary artery disease who have experienced an intracranial haemorrhage is a highly complex clinical challenge.

It is necessary to evaluate the benefits of preventing thromboembolic events against the risks of major bleeding. This should be supported by validated tools that can guide decision-making and risk stratification for complications. Current literature and international guidelines recommend staggered reinitiation of antithrombotic therapy after intracranial haemorrhage, particularly when the underlying cause has been treated and controlled, as was the case here.

The reintroduction of oral anticoagulation three weeks after ICH, following brain imaging, aligns with current guidelines. However, the optimal timing for resuming dual platelet antiplatelet therapy in this context remains undefined, particularly within the first 30 days following elective percutaneous coronary intervention. In this scenario, patient safety should be a top priority without compromising the effectiveness of treatment.

This case highlights the importance of continuous clinical surveillance and reassessment, coupled with collaboration across specialties, to optimize outcomes for patients with complex cardiovascular and neurological conditions.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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