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Oral anticoagulation – current knowlegde

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Summary

Vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC) are two groups of drugs used in the prevention of thromboembolic events. Although DOACs are currently the preferred option in such prophylaxis, there are still indications for the use of VKAs. Thromboembolic episodes may occur as a result of many cardiovascular diseases, inter alia cardiac dysrhythmias. Atrial fibrillation is an arrhythmia that may be asymptomatic or manifested by chest pain, syncope, dyspnea or fatigue. Moreover, it is associated with a high risk of serious complications. An ischemic stroke or myocardial infarction can result from poorly treated AF and may sometimes be the only symptom of an arrhythmia. Therefore, the assessment of a patient's eligibility for anticoagulation therapy is an important element in the prevention of thromboembolic events. Demographic aging and the associated comorbidity may pose a clinical problem in the treatment of atrial fibrillation. The selection of an appropriate anticoagulant therapy should be individualized to the patient's needs.

Key words: anticoagulant treatment, vitamin K antagonists, direct oral anticoagulants, atrial fibrillation

Introduction and purpose

Atrial fibrillation is one of the most common arrhythmias worldwide.[1] Its symptoms include palpitations, syncope, dyspnea, vertigo or anxiety. [2,3] Complications of this condition, such as myocardial infarction or ischemic stroke, can be fatal or associated with severe disability.[4] The current approach to patients with atrial fibrillation is based on the ABC - atrial fibrillation better care - regimen. "A" stands for anticoagulation/avoiding the stroke, "B" for better symptom management and "C" for cardiovascular and comorbidity optimization.[5] Therefore, in addition to treatment aimed at restoring sinus rhythm or maintaining normal heart rate, anticoagulant treatment is introduced when indicated.[2] Drugs used in the prevention of thromboembolic episodes can be

divided into vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs).[6] Both groups have their advantages and disadvantages. The purpose of the following article is to review the current knowledge of anticoagulant treatment in atrial fibrillation.

State of knowledge

Atrial fibrillation (AF) occurs when the atria contract in an uncoordinated manner, independent of the rhythm transmitted by the sinoatrial node. [4] This leads to irregular contractions of the ventricles of the heart, whose work may be accelerated, remain normal or be slowed down. [2] This arrhythmia can be associated with quality of life-degrading symptoms such as palpitations, dyspnea, chest pain, fatigue or syncope, although it can also be asymptomatic. [3] The risk of developing atrial fibrillation increases with age. [7] It is also associated with genetic factors [8], and is more common in the male gender [4]. People with type 2 diabetes [9], hyperthyroidism [10] or obstructive sleep apnea [11] are particularly prone to this arrhythmia. Sedentary lifestyles [12], smoking [13] and obesity [14] also increase the risk of AF. Atrial fibrillation is associated with the risk of severe complications, such as ischemic stroke [15], transient ischemic attack (TIA)[16], myocardial infarction [17] and extracerebral thromboembolic complications [4].

Atrial fibrillation leads to ineffective atrial contraction and thus to the stasis of certain amounts of blood in the atria. Particular attention should be paid to the left atrial appendage, where blood often accumulates and forms thrombi. Such a thrombus can detach from the wall of the appendage and move into the bloodstream and, along with the blood stream, reach the brain or other organs, causing their ischemia.[4,18]

The use of prophylaxis of thromboembolic episodes is based on the evaluation of the patient on the CHA₂DS₂-VASc score. This scale considers gender, age, history of stroke or TIA or other thromboembolic episode, diabetes mellitus, hypertension, symptoms of heart failure or decreased left ventricular ejection fraction, or hypertrophic cardiomyopathy, vascular disease. With ≥ 1 in men and ≥ 2 points in women, anticoagulant treatment should be considered, while with ≥ 3 points in women and ≥ 2 in men, anticoagulants should be instituted. [2,19] Patient qualification should also include an assessment of bleeding risk. This is performed using the HAS-BLED scale, which assesses the presence of factors such as hypertension, abnormal renal or hepatic function, a history of ischemic or hemorrhagic stroke, a history of major bleeding or a predisposition to bleeding, unstable INR values in patients who take VKAs, frailty syndrome or age over 65 years, alcohol abuse or concomitant use of antiplatelet drugs or nonsteroidal anti-inflammatory drugs. [2] It is important to regularly assess the risk of bleeding even after anticoagulant treatment is introduced and to control modifiable risk factors. [19]

Oral anticoagulant treatment options are vitamin K antagonists (VKAs) such as acenocoumarol or warfarin, or direct oral anticoagulants (DOACs), including dabigatran, apixaban, rivaroxaban, edoxaban.

The anticoagulant effect of vitamin K antagonists is based on inhibiting the synthesis of vitamin K-dependent coagulation factors II, VII, IX and X. It should be remembered that vitamin K antagonists, likewise inhibit the production of anticoagulation factors - protein S and protein C, which may, especially at the beginning of treatment, increase the risk of thromboembolic episodes. [20] The effect of VKAs is individually variable, depending on diet, genetic factors, comorbidities or liver function. [21] Furthermore, many commonly taken medications can affect the metabolism of vitamin K antagonists, weakening or enhancing their effects. Among them is amiodarone, an antiarrhythmic drug also used in AF, which enhances the effects of VKAs.[22] VKA treatment requires regular monitoring of INR. The therapeutic range for AF is 2.0 -3.0 and should be monitored monthly. [2] However, studies show that patients taking VKAs stay within the therapeutic range less than half the time of treatment. [23] VKAs are not eliminated by the kidneys, which may favor their use in patients with chronic kidney disease.[20] Nevertheless, VKAs carry a high risk of hemorrhagic complications, and some may impair renal function. [24,25] Recent guidelines indicate a safety advantage for the use of DOACs in this case. [26] Currently, anticoagulant treatment with VKAs is indicated only in AF patients who have mechanical valves in

the heart and in patients with AF and moderate to severe mitral valve stenosis, usually with a rheumatic background. [19] Nevertheless, VKAs remain frequently used drugs, mainly because of their lower cost in comparison to DOACs. [20]

Taking anticoagulants is inherently associated with an increased risk of bleeding. A higher risk of intracerebral hemorrhages has been reported with VKA treatment than with DOAC use. [27] Moreover, when hemorrhage did occur, the size of intracerebral hematomas was significantly smaller in patients on DOACs.[28]

Severe hemorrhage or the need for emergency surgery require reversal of anticoagulants action. Vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC) or recombinant factor VII are used to reverse the effects of VKAs. [29] Vitamin K abolishes the effects of VKA, but the full effect after intravenous administration does not occur until after a minimum of 24 hours.[30] Fresh frozen plasma is a fairly readily available non-specific reversal agent for VKA, although its administration should be compatible with the patient's blood type, which further delays its action, there is a risk of cardiovascular overload, clotting factor concentrations are lower than with PCC, and its use may be associated with complications such as transfusion-related acute lung injury (TRALI) [29,31]. Highly purified PCC combined with vitamin K administration is the preferred way to reverse the effects of VKAs. [32] The effect is very rapid and reaches full efficacy within 10 minutes. [29] However, administration of an excessive dose may be associated with a potential risk of thrombosis. [32] Combining vitamin K with PCC or FFP is important because the half-life of vitamin K antagonists is longer than that of PCC or FFP, thus a sudden rise in INR may occur once their effect is complete. Administering vitamin K reverses the effect of warfarin or acenocoumarol in a more long-term manner.[29,30,33] Recombinant factor VII is sometimes used for sudden bleeding in VKA takers, but these are exceptional situations and it is not universally recommended. [30]

Direct oral anticoagulants are a fairly new anticoagulant treatment option. As previously mentioned, they include dabigatran, rivaroxaban, apixaban and edoxaban.

Dabigatran is a direct, potent thrombin inhibitor, which suppresses the conversion of fibrinogen to fibrin. It binds to free thrombin, as well as to the clot-bound one.

It is taken as a prodrug, which is converted to its active form in the liver. About 80% of the drug is excreted by the kidneys. [34,35] Therefore, its use is contraindicated in patients with creatinine clearance <30ml/min. [26]

Rivaroxaban is a direct inhibitor of both free and clot-associated factor Xa. It inhibits thrombin formation and thus has an anticoagulant effect. It is administered in the active form. It is partially excreted by the kidneys but can be used in patients with creatinine clearance in the range of 15-29 ml/min in reduced doses. [26,36]

Apixaban, similarly to rivaroxaban, is a direct inhibitor of factor Xa. It inhibits both free and clot-bound factor Xa. It is taken in its active form. Of the DOACs, it has the least renal excretion. [36]

Edoxaban is also a direct inhibitor of factor Xa. It is approximately in 50% excreted by the kidneys. [38]

DOACs, compared with VKAs, are associated with a lower risk of bleeding, including intracerebral hemorrhage. [25] At the same time, it is important to note that the use of DOACs reduces the risk of thromboembolic episodes to a greater extent than VKAs. [39] Moreover, there are indications that treatment with DOACs in patients who have not experienced an ischemic stroke may reduce the risk of dementia compared to patients taking VKAs. [40] The use of DOACs certainly has the advantage of not requiring anticoagulant action control.[34] Currently, DOACs are recommended as first-line drugs for the prophylaxis of thromboembolic episodes in AF, aside from the previously described exceptions requiring the use of VKAs.[19] There are also clinical situations in which the choice of anticoagulant treatment is a significant problem. End-stage renal failure is a contraindication to DOACs, and VKAs are associated with possibly severe complications. [41]

In addition to their many advantages, DOACs are not ideal drugs. They can interact with

other medications, as exemplified by the increased levels of dabigatran when taken together with amiodarone. [42] Rivaroxaban and apixaban, as substances metabolized with CYP3A4, can interact with drugs such as ketoconazole, rifampicin and phenobarbital [34]. Moreover, the costs associated with the purchase of DOACs are greater than those accompanying the purchase of VKAs. [20] Anticoagulant treatment in patients undergoing chemotherapy who suffer from atrial fibrillation is a serious problem. It is recommended to individualize the approach depending on the risk of bleeding, the risk of thromboembolic episodes and the patient's general health. It is preferable to maintain current anticoagulant treatment unless possible drug interactions pose a contraindication. [43]

In the event of severe bleeding or the need for emergency surgery, it is necessary to use agents that reverse the effects of DOACs. There are specific substances that reverse the anticoagulant properties of DOACs. In the case of dabigatran, such an agent is idarucizumab , a fragment of a monoclonal humanized antibody that binds to dabigatran with an affinity about 350 times greater than that of thrombin.[44] Its efficacy is very high, neutralizing the effect of dabigatran in 100% within an average of 4 hours. Severe and difficult-to-control bleeding as well as the need for emergency surgery in patients treated with dabigatran are indications for idarucizumab. [45] Andexanet alfa is a specific reversal agent of rivaroxaban and apixaban. It is a recombinant, modified factor Xa that binds factor Xa inhibitors while having no procoagulant activity. It acts in a dose-dependent manner. Importantly, andexanet alfa may also reverse the effects of enoxaparin and fondaparinux. After the initial bolus administration, it is necessary to administer a continuous infusion for 120 min to sustain the effect. The indication for its use is severe and life-threatening bleeding. [45,46]

If specific reversal agents for DOACs are unavailable or unapproved, as in the case of edoxaban, prothrombin complex concentrate (PCC) or activated prothrombin complex concentrate (aPCC) are often used in the event of severe bleeding or the need for emergency surgery. [45,46] APCC is more recommended for bleeding associated with dabigatran intake, while PCC is used for bleeding associated with Xa inhibitor therapy. [45] It is important to note that in cases of major bleeding, fresh frozen plasma is ineffective in patients taking DOACs.[47] Research continues on new reversal agents for DOACs. [44, 47]

Conclusion

As the population ages, the number of people suffering from cardiovascular diseases such as atrial fibrillation will increase. This arrhythmia is associated with serious complications, such as ischemic stroke. In many cases, prophylaxis of thromboembolic episodes is necessary, for which the patient is qualified on the basis of standardized scales. For many years, vitamin K antagonists were the only option for oral anticoagulant treatment; however, in recent years they have been superseded by direct oral anticoagulants (DOACs). DOACs are associated with a lower risk of hemorrhagic complications compared to VKAs, fewer drug interactions and a better safety profile. Current guidelines identify DOACs as first-line drugs for the prevention of thromboembolic episodes in AF. However, there are contraindications to their use, for example, the presence of a mechanical valve in the heart, when VKAs are the preferred treatment. Older age is often associated with comorbidities the treatment of which can often pose clinical problems. Such a situation can be end-stage renal failure, when the choice of an appropriate anticoagulant prophylaxis is significantly difficult. A situation of this kind requires an individual approach to the patient and interdisciplinary cooperation between specialists. Moreover, neoplastic diseases and anticoagulant therapy in patients with AF also pose clinical challenges. Each patient requires an individualized approach also in terms of socioeconomics, as sometimes the price of DOACs can result in the non-purchase of an anticoagulant and may be associated with serious consequences.

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