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ARTIGO DE REVISÃO

Non-vitamin K antagonist anticoagulants to cardioembolic ischemic stroke due to atrial fibrillation: a brief update to clinical practice

Key Words: ischemic stroke; anticoagulation; non-vitamin K antagonists anticoagulants; warfarin
Palavras Chave: acidente vascular cerebral isquêmico; anticoagulação; anticoagulantes não-antagonistas de vitamina K; varfarina

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ABSTRACT

Stroke is one of the most important disease and cause of mortality worldwide. Several clinical scenarios demand full dose of anticoagulants after stroke or to the treatment of some frequent comorbidity, namely most important the atrial fibrillation. Anticoagulation is intended both to primary and secondary prevention in stroke. However, controversy exists over many issues regarding mainly to type of agent, efficacy according to etiology, ideal time of anticoagulation and the use of novel anticoagulants. This latter consists mostly on the use of non-vitamin antagonists oral anticoagulants.

RESUMO

O acidente vascular cerebral (AVC) é uma das mais importantes doença e causa de mortalidade no mundo. Vários cenários clínicos exigem dose completa de anticoagulantes após o curso ou para o tratamento de algumas comorbidades frequentes, ou seja, dentre as mais importantes a fibrilação atrial. A anticoagulação é destinada tanto a prevenção primária e secundária de AVC. No entanto, existem controvérsias sobre muitas questões relativas principalmente ao tipo de agente, a eficácia de acordo com a etiologia, o tempo ideal de anticoagulação e a utilização de novos anticoagulantes. Este último tópico consiste principalmente na utilização de antagonistas não-vitamina anticoagulantes orais.

UPDATE

Atrial fibrillation (AF) is an independent risk factor for stroke[1]. AF consists of a thrombotic state with elevated factors of platelet adhesion, activation and aggregation, reduced blood flow in the left atrium and endothelial lesion with release of Von Willebrand factor[2]. In line with the demographic trend of population aging, the number of AF patients is set to increase in the coming decades while embolic ischemic stroke risk increases with age,

attaining 5.1% per year in patients aged 80-89 years[1]. Minor episodes of subclinical embolism may also occur, resulting in cognitive impairment and dementia[2,3].

Patients with AF in the acute phase of stroke or transient ischemic attack (TIA) have a high risk for recurrence of brain ischemia. Thus, a number of studies have been performed assessing the efficacy of early anticoagulation in the prevention of recurrent ischemic stroke[4,5]. In general, the administration of anticoagulants in the first hours after cardioembolic ischemic stroke is not recommended, since the effectiveness of this approach in preventing ischemic stroke recurrence has not been established and is associated with a greater risk of intracranial hemorrhaging. Moreover, the use of anticoagulants has proven no more effective than aspirin for reducing mortality and disability some months after stroke[6].

Guidelines of the American Heart Association, American Stroke Association and American College of Chest Physicians recommend delaying anticoagulation in the management of ischemic stroke due to AF[7]. However, the ideal timing for starting anticoagulation remains controversial. Anticoagulation should be delayed in extremely advanced age, large extension infarctions, extensive small vessel disease and uncontrolled hypertension[2]. It is generally advisable to postpone this therapy by 2-4 weeks.

Although commonly used in the long-term prevention of ischemic stroke in AF patients, the benefit of warfarin in the acute phase has yet to be confirmed, given its a delayed onset of action and theoretically transient hypercoagulability in the initial period of its administration[4]. In general, the early administration of aspirin is recommended, followed by warfarin for secondary prevention after calculating the risks of thromboembolism and hemorrhaging based on clinical assessment as well as CHA_2DS_2-VASc and HAS-BLED scores, respectively[8,9].

Oral anticoagulation with vitamin K antagonist (warfarin), maintaining INR at between 2 and 3, reduces stroke risk by over 60%[1]. However, the benefits of the therapy are highly dependent on the quality control of anticoagulation (INR), where the effective anticoagulation rate may vary. Around 30% of AF patients in use of warfarin have strokes[10,11]. The action of warfarin can vary according to patient vitamin K intake and interaction with other drugs, where constant control of INR is necessary[12]. In patients on oral anticoagulation that have recurrent cerebrovascular events, therapeutic orientations are unclear. Among patients using warfarin, thrombolysis is only indicated when INR is less than 1.7[13].

New oral anticoagulants can be safer (stable and predictable anticoagulant effect) and more effective (rapid onset of action) in cases of cardioembolic ischemic stroke, posing lower risks of intracranial hemorrhaging and offering comparable or superior efficacy to warfarin in log-term stroke prevention[4]. Compared to warfarin, these novel anticoagulants reduce the rate of stroke and systemic embolism by 19%, all-cause mortality by 10% and intracranial hemorrhaging by 52%[12]. In addition, these agents have few associated drug-drug interactions and dietary restrictions. Recent guidelines favor these anticoagulants over warfarin[12].

In the last 5 years, dabigatran, rivaroxiban and apixaban have been Food and Drug Administration (FDA) approved for use in patients with nonvalvular AF[14]. Mechanical heart valve, pregnancy and breast-feeding are factors contra-indicating the use of these anticoagulants[12] (Table 1).

Table 1: Below provides a summary of the results from the RE-LY, ROCKET-AF and ARISTOTLE trials involving novel oral anticoagulants.

	RE-LY	ROCKET-AF	ARISTOTLE
Treatment	Dabigatran, 110 or 150 mg, twice daily *vs* warfarin (INR 2-3)	Rivaroxiban 15 or 20 mg/day *vs* warfarin (INR 2-3)	Apixaban 2.5 or 5 mg, twice daily *vs* warfarin (INR 2-3)
Mean treatment duration	2 years	590 days	1.8 years
Sample	18,113	14,264	18,201
Main results	? Ischemic or hemorrhagic stroke, systemic embolism and major or minor bleeding; ? AMI and gastrointestinal bleeding	? Stroke and systemic embolism; no significant differences in relation to major bleeding; ? gastrointestinal bleeding	?Stroke/systemic embolism, bleeding and mortality

Note: RE-LY=Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF=Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE=Apixaban for Reduction In STroke and Other ThromboembоLic events in atrial fibrillation; INR=International Normalized Ratio; AMI= Acute Myocardial Infarction.

Dabigatran is a direct inhibitor of thrombin with efficacy in the primary and secondary prevention of stroke[1,15]. The recommended dose for patients with preserved renal function is 150mg every 12 hours. If creatinine clearance lies in the 15-30 ml/min range, this dose should be reduced to 75 mg. Dabigatran reaches peak plasma concentration in 2 hours after administration and has a half-life of 12-17 hours[14]. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, the most common adverse events were dyspepsia, diarrhea and abdominal pain. In addition, the agent showed a higher rate of gastrointestinal bleeding than warfarin[14,16] . The RE-LY trial involved 18,113 patients with AF from 951 clinical in 44 countries. The occurrence of stroke or systemic embolism was 1.53%, 1.11% and 1.69% per year, using 110mg of dabigatran, 150mg of dabigatran and warfarin, respectively. Neither of the doses were inferior to the efficacy of vitamin K antagonist. The rate of hemorrhagic stroke was 0.38%, 0.12% and 0.10% per year among patients receiving warfarin, 110mg dabigatran and 150mg dabigatran, respectively. Rates of major or minor bleeding, life-threatening bleeding or intracranial hemorrhaging were higher for warfarin. Only gastrointestinal bleeding and acute myocardial infarction were greater with the use of dabigatran. The only prevalent adverse effect of this anticoagulant was dyspepsia. The higher incidence of dyspepsia and gastrointestinal bleeding most likely stems from the added acid in the dabigatran capsule, given that it is best absorbed at low pH[16].

Rivaroxaban is a direct factor Xa inhibitor whose recommended dose is 20mg per day if creatinine clearance exceeds 50ml/min, and 15mg per day for a level in the 15-50ml/min range. The agent reaches peak plasma concentration in 2-4 hours after oral administration and has a half-life of 9-13 hours[14]. The Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) involved 14,264 AF patients, spanned from 18th December 2006 to 17th June 2009, and compared the use of rivaroxaban versus warfarin. Mean duration of treatment was 590 days and mean follow-up was 707 days. The incidence of stroke or systemic embolism was 1.7% per year in the group of patients receiving rivaroxaban versus 2.2% in those using warfarin. Decreases of 2g/dL or greater in hemoglobin and transfusions were more common among patients on rivaroxaban, whereas fatal bleeding or in bleeding at critical anatomical sites were less frequent. Intracranial hemorrrhaging was significantly lower with use of the direct factor Xa inhibitor. Gastrointestinal bleeding was more common with rivaroxaban. The trial concluded that the agent was not inferior to warfarin in the prevention of stroke and systemic embolism and exhibited relative safety[17].

The Triplo AXEL trial compared rivaroxaban versus warfarin for the prevention of recurrent ischemic injury and intracranial hemorrhaging in patients with AF and acute brain ischemia. Patients using rivaroxaban had fewer hemorrhages and less ischemic injury. Further investigations assessing the application of this factor Xa inhibitor were recommended[4].

The management of patients in use of rivaroxaban who present ischemic stroke is not well established. Considering that INR is ineffective for measuring the level of anticoagulation with rivaroxiban and that tests for measuring this value are not widely available, the safety of thrombolysis for patients in use of this anticoagulant has yet to be determined[18].

Switching from warfarin to rivaroxaban must be carried out with caution. Coagulation factors normalize several days after halting therapy with vitamin K antagonist. The synergism between the drugs peaks shortly after discontinuation of warfarin therapy, becoming less marked around 2-3 days later, if the therapy is interrupted at an INR of 2.5. When making this switch, the US Prescribing Information and European Summary of Product Characteristics recommend withdrawal of warfarin and then initiation of factor Xa inhibitor on the following day, if INR is lower than 3[19].

Apixaban is also a Factor Xa inhibitor, with a half-life of 8-15 hours and recommended dose of 5mg every 12 hours for patients with preserved renal function, and 2.5 mg every 12 hours if the patient meets 2 of the following criteria: age older than 80 years, weight under 60 kg, and blood creatinine level greater than 1.5mg/dL[14]. The Apixaban for Reduction In STroke and Other ThromboemboLic events in atrial fibrillation (ARISTOTLE) trial involved 18,201 participants from 1034 clinics in 39 countries. Individuals treated with apixaban had a lower rate of stroke or systemic embolism (21% reduction); less bleeding (31% reduction) intracranially or at other sites; and lower mortality (11% reduction)[14,20]. In an earlier comparison with other novel oral coagulants, apixaban was considered the safest option[21].

A meta-analysis of the ARISTOTLE, ROCKET-AF and Engage AF Timi 48 (assessing edoxaban, another direct factor Xa inhibitor) trials, found similar results for all the drug regimens in relation to hemorrhagic

stroke, with a risk ratio of 0.488 (95% CI 0.396-0.601)[22]. The absence of antidotes in cases of hemorrhagic complications remains a drawback. However, it is important to bear in mind that the half-life of these agents is relatively short and measures such as volume resuscitation and transfusion of RBCs can be taken in cases of bleeding[14].

Switching from warfarin to a novel anticoagulant is recommended only in patients with good adherence to treatment using vitamin K antagonist. Individuals previously presenting gastrointestinal bleeding should be warned of the risks[14].

Since AF patients may have concomitant vascular disease and the use of aspirin in the prevention of recurrent ischemic stroke may be necessary for its effect on atherosclerotic disease. Aspirin can be prescribed early in all ischemic stroke patients, unless there is an absolute contra-indication[2].

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