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Review article

Bridging anticoagulation therapy

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ABSTRACT

Oral anticoagulation therapy is used in patients with various diagnoses to reduce the risk of thromboembolic events or to induce a hypocoagulation state to facilitate dissolution of a thrombus. In clinical practice we often encounter anticoagulated patients, many of whom have been diagnosed with nonvalvular atrial fibrillation. Each year a significant number of these patients undergo a medical procedure, which, in some cases, requires temporary discontinuation of anticoagulation therapy. However without anticoagulation therapy, the patient is at increased risk of thromboembolic events. Therefore, parenteral anticoagulants with fast onset and rapid cessation of action can be used to reduce risk while patients are without adequate oral anticoagulation. Here we summarized the currently available data, which has been drawn from guidelines and other expert documents of European Society of Cardiology (ESC), American College of Cardiology (ACC) and American College of Chest Physicians (CHEST). The vast majority of available studies, including the only single randomized, double-blind, placebo-controlled BRIDGE trial, report an increased risk of major bleeding in patients on bridging therapy. A subanalysis of the RE-LY trial, also found that thromboembolic risk in patients with bridging therapy was significantly higher. The most detailed recommendation for use of bridging therapy in patients with nonvalvular atrial fibrillation was provided by the 2017 Expert Consensus of the ACC, while the ESC only marginally discusses bridging therapy in their expert documents. Bridging is not generally necessary in patients taking non-vitamin K oral anticoagulants (NOACs), but if clinical circumstances require it, the risks and benefits are the same as with vitamin K antagonist (VKA) anticoagulation. Data on the use of NOACs for bridging therapy are scarce.

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Introduction

Anticoagulation therapy significantly reduces the risk of systemic embolization in patients with atrial fibrillation and is currently an integral part of the treatment strategy in most patients with this diagnosis. Traditional anticoagulation in patients with atrial fibrillation used warfarin, since it was the only available vitamin K antagonist (VKA). In recent years, we have seen the emergence of a new group of anticoagulants called non-vitamin K oral anticoagulants (NOACs). Despite the clear benefits of this drug group, VKA are still widely used. Data from the GARFIELD-AF registry, which includes data from patients with atrial fibrillation from 35 countries, including the Czech Republic, shows that prescriptions of NOACs are growing steadily. In a cohort from 2010 to 2011, only 4.2% of patients were on NOACs, while 53.2% of patients were on VKAs. In a cohort of patients from 2014 to 2015, 37.0% of patients were taking NOACs and 34.0% were taking VKAs [1]. Based on practice, however, it can be assumed that in the Czech Republic the proportional representation of VKA to NOACs is higher.

VKAs act as inhibitors of the enzyme epoxide reductase, which catalyses formation of the reduced form of vitamin K, which is needed as a cofactor for γ-carboxylation of coagulation factors II, VII, IX, and X, which determines their efficacy. This mechanism of action results in a gradual onset of VKA anticoagulation, as well as slow cessation of anticoagulation. The slow cessation is caused by the persistence of preformed gamma-carboxylated coagulation factors in the blood that built up during VKA therapy, which leads to throttled increased in the formation of gamma-carboxylated coagulation factors II, VII, IX, and X by liver after VKA discontinuation [2].

In practice, we encounter situations where we have to consider interruption of VKA anticoagulation. These are mostly surgical situations or other invasive procedures, where full anticoagulation would burden the patient with a significant risk of bleeding. However, when the INR (International Normalized Ratio) falls below the therapeutic range, the patient is at increased risk of thromboembolic events. To reduce this risk, it is common practice to administer anticoagulants with a fast onset and rapid cessation of action. Currently low weight molecular heparin (LWMH) or unfractionated heparin (UFH) is used to bridge the period when the INR is in the subtherapeutic range. This procedure is called bridging anticoagulation therapy. In the periprocedural period, physicians must address 3 issues regarding anticoagulation:

- Is interruption of anticoagulation therapy necessary with respect to characteristics of the patient and procedure? If so, when should oral anticoagulation be stopped?
- Choice of an anticoagulant with rapid onset and cessation of action for use as a bridging therapy.
- When should oral anticoagulation be reinitiated?

In the present article, we summarize currently available data as well as the expert opinions on bridging therapy, which, despite its widespread use in clinical practice, is controversial. Interruption and reinitiation of anticoagulation in the periprocedural period is not the main focus of this article and if readers are interested in further information, we refer them to the documents of the respective professional societies.

Thromboembolic events vs. bleeding

The essence of bridging anticoagulation therapy is to minimize the risk of thromboembolic events in the periprocedural period while maintaining the lowest risk of bleeding events. To properly select patients who will benefit from bridging therapy, we need to estimate the risk of thromboembolic and bleeding events as accurately as possible.

Several scoring systems have been developed to predict the risk of thromboembolic events in patients with nonvalvular atrial fibrillation. The $CHADS_2$ score, which has good predictive value, was developed in 2001 using a combination of the AFI and SPAF scoring systems [3]. In subsequent observations, 1.4% of patients who were classified as low-risk patients ($CHADS_2$ 0–1), according to the $CHADS_2$ score, had a thromboembolic event within 1 year. Therefore, an effort was made to create a scoring system with even better predictive value. This effort culminated in 2009 with the Birmingham 2009 scoring system. This system is now better known by the CHA_2DS_2-VASc acronym [4]. Several observational registries and studies correlated CHA_2DS_2-VASc score with the incidence of ischemic stroke (IS) or thromboembolic events in general. The most extensive work of this kind was the Swedish Atrial Fibrillation cohort study. It was a prospective study with a sample of 90,490 patients who never used anticoagulant therapy, Table 1

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