Concerns over dosing oral anticoagulants in clinical practice

Atrial fibrillation (AF) is a heart condition characterized by an abnormal rhythm leading to irregular beat. An important consequence of AF is an incomplete emptying of the atria (upper heart chamber) leading to blood stasis and, potentially, blood clotting within the heart. These clots can eventually exit the heart with the blood flow and, given the vascular anatomy, tend to go to the brain circulation, when they can cause strokes. Strokes secondary to heart emboli are particularly large and tend to have severe consequences in terms of mortality and disability. Fortunately, anticoagulation is highly effective to prevent clotting and large studies have consistently shown that most patients derive a net benefit from anticoagulation; i.e., given the frequency of cardioembolism and its severity, anticoagulation is beneficial for a majority of patients, even if it increases bleeding as an unavoidable side effect. For many decades, vitamin K antagonists (VKA) have been the only drugs available for these patients. These drugs have the major downside of having a narrow therapeutic window (the ideal dose, effective but not too toxic) and a highly variable interindividual metabolism. This makes it imperative that patients under VKA treatment have the treatment effect monitored (the international normalized ratio [INR] test) periodically (often every 3 to 4 weeks) and the drug dose adjusted based on the results. Unfortunately, up to 20% of patients who would benefit from anticoagulation are not recommended or refuse it, largely over a fear of bleeding (the patient's or the physician's)

About a decade ago, a different class of drugs, direct oral anticoagulants (DOAC, because they inhibit clotting factors directly, unlike VKA which act by blocking their production) became available. Contrary to VKA, these agents had a wide therapeutic window and relatively little interindividual variation in plasma concentration. These drugs do not require monitoring and their doses are not adjusted based on blood tests but rather on a few simple clinical and analytical datapoints (largely, age, weight and kidney function).

In a recent letter to the editor in *Medicina Clinica* we caution physicians that recent data suggest that DOAC are commonly underdosed (almost 10% of patients in the largest study to date). Data supporting the use of DOAC in patients with AF are based on clinical trials, where patients are rigorously treated according to protocol. If patients in clinical practice are not dosed similarly, there is no evidence that they are protected against cardioembolism. In fact, some data suggest that they are not, which is in line with studies in patients treated with VKA finding that patients with a lower than optimal treatment effect according to the blood test had a higher risk of cardioembolism. Yet, receiving anticoagulation (even if at lower doses) still places these patients at some risk of bleeding.

We think it is safe to assume underdosing comes from the same fear of bleeding that has affected treatment with VKA for a long time. With DOACs, this fear seems to not only take the form of undertreatment, but also of underdosing.

We conclude, therefore, that it is essential to prescribe drugs at the appropriate dose and, more

specifically, that the evidence-based dose of DOAC should be recommended to ensure protection against cardioembolism.

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