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Improvement in Adherence to Guidelines for Anticoagulant Therapy of Atrial Fibrillation: We Can Still Do Better

Atriyal Fibrilasyonun Antikoagülan Tedavisi İçin Kılavuzlara Uyumdaki Artış: Hala Daha İyisini Yapabiliriz

EDITORIAL COMMENT
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Atrial fibrillation (AF) is a global health care problem with an increasing prevalence worldwide.[1] As it significantly increases the risk of stroke and systemic embolism, AF is associated with substantial morbidity and mortality. Therefore, anticoagulant therapy is the mainstay of management of patients with AF.[1] For decades, vitamin K antagonists were the first-choice anticoagulants in the prevention of thromboembolism in patients with AF. However, based on the results of pivotal randomized controlled trials (RCTs) and meta-analyses, current guidelines recommend direct oral anticoagulants (DOACs) in preference to vitamin K antagonists as first-line treatment for stroke prevention in patients with AF who are eligible for oral anticoagulants.[1]

Although it has been well demonstrated that adherence to these guidelines is associated with improved clinical outcomes,[2-4] there are some patient-related, physician-related, and health care system-related barriers to guideline-directed anticoagulant treatment of patients with AF.[1-5] This leads to a failure in the translation of evidence from RCTs to real-world outcomes. RCTs are the gold standard for evaluating the safety and efficacy of new therapeutic agents. On the other hand, real-world studies continue to provide valuable information about patient and physician preferences, tolerance, adherence, safety, and effectiveness of drugs in actual daily clinical practice.[6] In this issue of the journal, the ROTA study provides important real-world data from Turkey about anticoagulant treatment patterns in patients with AF. The rate of DOACs use was found to be as high as 79.4%. As in the rest of the world, the prescription rate of DOACs seems to have increased in our country despite restrictive criteria for reimbursement. However, 3.5% of patients with high stroke risks did not receive any anticoagulant treatment. On the other hand, 76.1% of patients with low stroke risks were treated with anticoagulants. Therefore, either the clinical judgements of stroke and bleeding risks in the real world include factors beyond the scores recommended by the guidelines or there are still gaps in translation of knowledge and education.

One of the most important findings of the study was that more than 25% of DOAC users were receiving reduced doses. However, the proportion of patients with inappropriate dose adjustments has not been reported. Reduced dosing of DOACs may impact the safety and/or effectiveness of treatment unless appropriately adjusted according to the guidelines. In daily clinical practice, off-label underdosing of DOACs is rather common with rates around 20%.[7,8] Patients receiving inappropriately reduced-dose DOACs had higher rates of stroke/systemic embolization and sometimes even death without a proportional reduction of bleeding risk.[9-11]

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There are two main reasons for prescribing inappropriately underdosed DOACs. First, it is related to the common perception that bleeding represents an iatrogenic event, whereas stroke is a possible result in the natural course of the disease.[12] Second, on-label dose adjustments according to the guidelines may be challenging in clinical practice as each DOAC has specific dose reduction criteria.[1]

Dose adjustment is important, especially in patients with chronic kidney disease. For rivaroxaban, edoxaban, and dabigatran, renal dosing adjustments are based on estimated creatinine clearance. However, apixaban dose adjustments are not based solely on creatinine clearance. Current ESC guideline recommends that the apixaban dose should be reduced when only ≥ 2 of the following criteria are met: age ≥ 80 years, total body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL.[1] In contrast, European Heart Rhythm Association practical guides still recommends dose reduction for apixaban if creatinine clearance is 15–29 mL/min.[13] Compared with the assessment of only creatinine clearance, evaluation of multiple factors and the discrepancies between the guidelines may complicate appropriate dose adjustments. Thus, underdosing with apixaban may be more frequent than it is anticipated. It has been reported that apixaban underdosing was five times more frequent than in the pivotal ARISTOTLE trial.[14] This finding may be related to failure in appropriate dose adjustments or its more frequent preference in higher-risk subgroups, as also demonstrated by the ROTA study. Therefore, the clinical consequences of underdosing a DOAC in relatively higher-risk groups may be more serious. A recent meta-analysis showed that while inappropriately reduced doses of dabigatran and rivaroxaban had no effect on major bleeding and all-cause mortality rates, inappropriately reduced doses of apixaban led to an increased risk of both major bleeding and all-cause mortality.[15] The association between inappropriate dose adjustments of DOACs and worse clinical outcomes reinforces the importance of evaluation of renal functions and appropriate dose adjustments. Serum creatinine level and creatinine clearance should be assessed carefully not only at baseline, but also periodically throughout the course of therapy. The awareness of the clinicians about the clinical consequences of inappropriate dosing and knowledge about appropriate DOAC dose adjustments should be enhanced.

The drug of choice according to the different risk groups in the ROTA study was also noteworthy. The most commonly prescribed DOAC was rivaroxaban in all thromboembolic risk groups with an average rate of 38.1%. The reason that makes rivaroxaban the most favorite DOAC irrespective of the risk profile was probably related to its early market entry and the concerns about adherence and compliance. It has been demonstrated that adherence to chronic cardiovascular medications was better with once-a-day dosing compared to twice-a-day dosing.[16] Likewise, compliance with therapy was found to be better with once-daily medications.[17] The ROTA study found that although apixaban was the drug of choice in only 8.4% of patients with low risk, the rate increased to 27% in the high-risk group. The clinicians seem to have a tendency to prescribe apixaban to patients having a higher-risk profile. There is no RCT that has performed a head-to-head comparison between the individual DOACs with respect to efficacy and safety. However, there are meta-analyses and observational studies indicating a lower risk of stroke/systemic embolism and/or major bleeding with the use of apixaban.[18-20] It seems that the participant physicians attempted to individualize treatment based on not only the net clinical benefit but also the patient characteristics and preferences, as the guidelines have recommended.[1] Although rivaroxaban was the most favorite DOAC in all risk groups due to the possible concerns about compliance, apixaban was preferred more frequently in high-risk individuals in accordance with the results of these observational studies. Therefore, the results of the real-world studies seem to be influencing physician preferences in daily clinical practice.

In summary, the ROTA study showed that adherence to guideline-based treatment recommendations for patients with AF has been improving in Turkey. Nevertheless, there is still a way to go to improve adherence to these guidelines. The integrated multidisciplinary management model proposed by the current ESC guideline (1) can help us overcome barriers to the implementation of evidence-based therapy in patients with AF.

Declaration of Interests: The authors declare that they have no competing interest.

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