Practical considerations on non-vitamin K oral anticoagulants in patients with high body weight

To the Editor,

I have read with keen interest the systematic review by Güler et al. (1) entitled "A review of the fixed dose use of new oral anticoagulants in obese patients: Is it really enough?" published in Anatol J Cardiol 2015:1020-9. This review is of importance in everyday practice where patients with high body weights are encountered much more commonly than in clinical trials. The authors summarized the current clinical data based on the efficacy and safety of non-vitamin K oral anticoagulants (NOAC) used in patients with atrial fibrillation (AF) and in the prevention and therapy of venous thromboembolism (VTE) with the emphasis on obesity, which is also a rapidly rising epidemic among subjects requiring long-term anticoagulation. The manufacturers of dabigatran, rivaroxaban, and apixaban currently suggest that no dose adjustments are necessary for patients with high body weights even if the present evidence to support such a recommendation is rather weak (2). Although clinical trials on NOAC showed no weight-associated differences in the outcomes of NOAC in AF or VTE, several reports indicate that clinical outcomes of anticoagulant therapy with NOAC could be unsatisfactory in extremely obese patients in part because of the increased clearance of anticoagulants and distribution volume with largely unaltered drug absorption (2). The authors of the current review (1) highlighted the intriguing concept that compared with factor Xa inhibitors, dabigatran, whose renal elimination is the largest (80%), is more prone to provide insufficient anticoagulation intensity in individuals with high body weights. Although no comprehensive subgroup analysis for rivaroxaban or apixaban administered in obese patients has been published to date, the influence of body weight on the anticoagulant effects of these agents appear small. In our cohort of patients with VTE, subjects with a body mass index (BMI) of >35 kg/m^2 represent approximately 10% patients, whereas those with BMI below 18 kg/m^2 represent 5%, with the predominance of young women (A. Undas, unpublished data). From our experience, low BMI is associated with a higher risk of bleeding, which is a more consistent feature than similar rate of VTE recurrences in patients with BMI of >35 kg/m^2 versus those with BMI of <35 kg/m^2. The choice of appropriate regimens of an NOAC in subjects with high body weights is difficult, particularly if the bleeding risk is increased for example in a form of heavy menstrual bleedings. Therefore, monitoring the anticoagulant effects of NOAC is important in this subset of anticoagulated patients; the need for anticoagulation at high body weights is considered one of the well-established indications to determine the blood concentrations of NOAC (3, 4). However, the association between the blood levels of NOAC measured using coagulation assays and thrombotic or bleeding complication is uncertain because of a large variability of the results (5).

Taken together, each patient on NOAC who weighs below 50 kg or above 100–120 kg requires regular visits to the outpatient clinic, particularly within the first weeks of the therapy. The appropriate supervision aims to minimize the risk of bleeding or thromboembolic events in particular individuals who at baseline are at a high risk of these complications. As suggested in the current review (1), more common control visits may increase the safety and efficacy of long-term anticoagulation at high body weights regardless of age and sex. In our opinion, laboratory monitoring of trough anticoagulant effects as well as creatinine clearance should be considered in selected patients. Further clinical studies, particularly registries, are needed to determine whether a fixed dose of NOAC is truly efficacious in patients with morbid obesity.

Anetta Undas
Institute of Cardiology, Jagiellonian University Medical College, and Center for Research and Medical Technology, John Paul II Hospital, Cracow-*Poland*

References

1. Güler E, Babur Güler G, Demir GG, Hatipoğlu S. A review of the fixed dose use of new oral anticoagulants in obese patients: Is it really enough? Anatol J Cardiol 2015: 1020-9.
2. Patel JP, Roberts LN, Arya R. Anticoagulating obese patients in the modern era. Br J Haematol 2011; 155: 137-49.
3. Undas A, Pasierski T, Windyga J, Crowther M. Practical aspects of new oral anticoagulant use in atrial fibrillation. Pol Arch Med Wewn 2014; 124: 124-35.
4. Baglin T, Hillarp A, Tripodi A, Elalamy I, Buller H, Ageno W. Measuring Oral Direct Inhibitors (ODIs) of thrombin and factor Xa: A recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2013 Jan 24. Epub of ahead of print.
5. Zalewski J, Rychlak R, Góralczyk T, Undas A. Rivaroxaban concentration in patients with deep vein thrombosis who reported thrombus progression or minor hemorrhagic complications: first Polish experience. Pol Arch Med Wewn 2014; 124: 553-5.

Address for Correspondence: Anetta Undas, MD, PhD
Institute of Cardiology Jagiellonian University Medical College
80 Pradnicka St., 31-202 Cracow-*Poland*
Phone: +48 12 6143004 Fax: +48 12 6142120
E-mail: mmundas@cyf-kr.edu.pl

DOI:10.14744/AnatolJCardiol.2016.6970

Author`s Reply

To the Editor,

We would like to thank the authors for their interest in our paper and their comments regarding our study entitled "A review of

the fixed dose use of new oral anticoagulants in obese patients: Is it really enough?" published in Anatol J Cardiol 2015; 15: 1020-9 (1).

Under-representation of obese patients in the subgroups of relevant studies raises concerns about the efficacy and safety of new oral anticoagulants (NOACs). The number of patients with high body weights is quite low in studies investigating the pharmacodynamics and pharmacokinetics of NOACs. In the context of data obtained from these studies, a fixed dose use of NOACs is recommended for obese or morbidly obese patients with no distinction from other patients. However, various recent case reports of pulmonary embolism or stroke under NOAC therapy have led to questions about the efficacy of fixed dose in this patient population. Increased creatinine clearance seems to be the most likely responsible mechanism. To overcome this problem, it is advisable to use drugs with less renal excretion in patients with increased creatinine clearance. Nevertheless, this hypothesis needs to be confirmed with randomized studies.

We would like to thank the authors for sharing their unpublished data about their patients with high body weights. Apart from the inefficiency problem with fixed dose use of NOACs in obese patients, concerns about bleeding risk in patients with a low body mass index or weight <50 kg are noteworthy as the authors stated. Similarly, rivaroxaban 15 mg was used in the J-ROCKET AF trial unlike the global ROCKET-AF trial, and this dose was recommended for the Japanese population (2). Routine monitorization of the plasma levels of NOACs in morbidly obese patients to decrease complications might be an alternative option. Although determination of activated partial thromboplastin time for dabigatran and factor Xa level for rivaroxaban was suggested for urgent conditions (3), methodological uncertainty prevents the recommendation of an ideal treatment dose in clinical practice as emphasized by the authors (4). Approval and marketing of unavailable antidotes for NOACs could be useful to some extent in patients suffering from bleeding complications.

Furthermore, frequent follow-up visits of patients under NOAC therapy might help the earlier detection of bleeding or embolic complications; however, it may not always prove useful because of the lack of instruments for monitorization of drug efficacy. Further studies are warranted for the determination of an ideal dose of NOACs in morbidly obese patients.

Ekrem Güler[1], Gamze Babur Güler[1], Gültekin Günhan Demir[1], Suzan Hatipoğlu[2]
[1]Department of Cardiology, Faculty of Medicine, Medipol University, İstanbul-*Turkey*
[2]Department of Cardiology, Ersoy Hospital, İstanbul-*Turkey*

References

1. Güler E, Babur Güler G, Demir GG, Hatipoğlu S. A review of the fixed dose use of new oral anticoagulants in obese patients: Is it really enough? Anatol J Cardiol 2015: 1020-9.
2. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. J-ROCKET AF study investigators. Rivaroxaban vs. Warfarin in Japanese Patients With Atrial Fibrillation – The J-ROCKET AF Study. Circ J 2012; 76: 2104-11.
3. Baglin T, Hillarp A, Tripodi A, Elalamy I, Buller H, Ageno W. Measuring Oral Direct Inhibitors (ODIs) of thrombin and factor Xa: A recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2013; 11: 756-60.
4. Zalewski J, Rychlak R, Góralczyk T, Undas A. Rivaroxaban concentration in patients with deep vein thrombosis who reported thrombus progression or minor hemorrhagic complications: first Polish experience. Pol Arch Med Wewn 2014; 124: 553-5.

Address for Correspondence: Dr. Ekrem Güler
TEM bağlantı yolu Medipolmega Üniversite Hastanesi
Bağcılar, İstanbul-*Türkiye*
Fax: +90 212 460 70 70 E-mail: ekgul@yahoo.com

The atrial conduction time in patients with normal atrial size

To the Editor,

We have read with great interest the manuscript by Hosseinsabet (1) entitled "Assessment of atrial conduction times in patients with mild diastolic dysfunction and normal atrial size," published in the Anatolian Journal of Cardiology 2015; 15: 925-31. In this study, Hosseinsabet (1) clearly demonstrated that there were no differences in atrial conduction times (ACTs) and atrial electromechanical delays (EMDs) in patients with mild diastolic dysfunction and normal left atrial volume compared with normal subjects.

We want to share further comments about the findings of the study. The evaluation of atrial EMD with tissue Doppler echocardiography fundamentally shows the time during the propagation of cardiac impulse through atria. If the atrial size increases, the pathway of the cardiac impulse and the required time for the propagation of the impulse will also increase. This situation has already been supported with the findings of recent studies that include patients of different diseases with atrial enlargement such as mitral stenosis or atrial septal defect (2, 3). These studies also revealed the association of increased atrial size and increased EMD (2, 3). On the other hand, a condition without atrial enlargement can be expected with similar EMD values as a normal control group. The findings of the study by Hosseinsabet supported this expectation (1). It seems that when the enlargement of the atria reaches a critical size, then the increase in atrial EMD can be appreciable. However, in the literature, there are conflicting findings of various studies evaluating the suspecibility for atrial fibrillation (AF) in many medical conditions without the enlargement of atria, such as atrial septal aneurysm or familial Mediterranean fever (4, 5). These studies documented the increase in EMD and ACT in patients with a similar size of atria compared with control groups by using the same method of tissue Doppler echocardiography as Hosseinsabet. It can be speculated that the underlying mecha-