Unsolved issues of the efficacy and safety of edoxaban

To the Editor,

We read with keen interest the study by Liang et al. (1), in which the authors evaluated data from five randomized clinical trials (RCTs) on edoxaban and warfarin performed with as many as 24,836 patients with atrial fibrillation (AF).

Their main finding was a 14% reduction in the incidence of cardiovascular death (CVD) in the edoxaban group as compared with the warfarin group. Furthermore, edoxaban reduced major bleeding by 35% and non-major bleeding by 20%, with no difference in the thromboembolic events such as stroke, systemic embolic events, and myocardial infarction.

This observation is in line with the results of the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction study 48) and the systematic review (2) of four pivotal RCTs for stroke prevention in patients with AF [the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation), ENGAGE AF-TIMI 48 (edoxaban), RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate), and ROCKET AF (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation) trials; n=71,683], which reported a lower risk of stroke, including hemorrhagic stroke and systemic embolism, along with all-cause mortality for non-vitamin K antagonist oral anticoagulants (NOACs) as compared with vitamin K antagonists [risk ratio (RR): 0.81, 95% CI: 0.73–0.91 and RR: 0.90, 95% CI: 0.85–0.95, respectively). Interestingly, NOACs reduced intracranial bleeding by 52% (RR: 0.48, 95% CI: 0.39–0.59) but increased gastrointestinal bleeding by 25% (RR: 1.25, 95% CI: 1.01–1.55). The authors should comment on the efficacy and safety of edoxaban as compared with three other NOACs from the paper by Ruff et al. (2).

As the authors stated, the main limitation of the current metanalysis was an extremely unbalanced sample size and substantial heterogeneity. Two studies [the ENGAGE AF-TIMI 48, n=21,105 and ENSURE-AF (Edoxaban vs. Warfarin in Subjects Undergoing Cardioversion of Nonvalvular Atrial Fibrillation) trials, n=2,149] accounted for more than 93% of the sample size, which might affect end points. CVD as the end point was evaluated in three studies. Taking into account that in the ENGAGE AF-TIMI 48 trial the annualized rate of strokes was similar in the edoxaban and warfarin groups, but hemorrhagic strokes were lower in the edoxaban group, it would be interesting to include hemorrhagic strokes in the current metanalysis. All-cause mortality was a component of the composite secondary end point in the ENGAGE AF-TIMI 48 trial and was analyzed by Ruff et al. (2).

Last but not least, the authors did not discuss the previous metanalysis by Chen et al. (3), published in 2015. This meta-analysis included four RCTs with 23,001 patients and showed edoxaban to be at least equal in efficacy to warfarin and superior regarding safety.

Finally, several subsets of AF populations characterized by elevated bleeding risk, including patients in advanced age, with a low body mass, advanced chronic kidney disease, liver disease, prior serious bleeding, thrombocytopenia, and cancer, were not specifically addressed by the authors, and the safety profile for such high-risk patients remains largely unknown (4, 5).

Taken together, edoxaban is an attractive anticoagulant for stroke prevention in patients with AF, as confirmed by the present meta-analysis; however, more research is needed to assess its relative value compared with other NOACs and in high-risk subgroups.

Leszek Drabik[1,*], Anetta Undas[1,]**
Department of *Pharmacology, and **Institute of Cardiology, Jagiellonian University Medical College; Krakow-*Poland*
[1]John Paul II Hospital; Krakow-*Poland*

References

1. Liang X, Xie W, Lin Z, Liu M. The efficacy and safety of edoxaban versus warfarin in preventing clinical events in atrial fibrillation: A systematic review and meta-analysis. Anatol J Cardiol 2021; 25: 77-88.
2. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383: 955-62. [Crossref]
3. Chen J, Zhuang X, Long M, Su C, Wang L. Efficacy and Safety of Edoxaban in Nonvalvular Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials. J Stroke Cerebrovasc Dis 2015; 24: 2710-9. [Crossref]
4. Undas A, Drabik L, Potpara T. Bleeding in anticoagulated patients with atrial fibrillation: practical considerations. Pol Arch Intern Med 2020; 130: 47-58. [Crossref]
5. Lodziński P, Gawałko M, Budnik M, Tymińska A, Ozierański K, Grabowski M, et al. Trends in antithrombotic management of patients with atrial fibrillation. A report from the Polish part of the EURObservational Research Programme - Atrial Fibrillation General Long-Term Registry. Pol Arch Intern Med 2020; 130: 196-205. [Crossref]

Editor's Note
Despite our repeated emails, we received no response from the authors.

Address for Correspondence: Anetta Undas, MD,
Institute of Cardiology, Jagiellonian University Medical College,
80 Pradnicka Street, 31-202 Kraków-*Poland*
Phone: +48 12 614 30 04
E-mail: mmundas@cyf-kr.edu.pl

DOI:10.5152/AnatolJCardiol.2021.81410